De-implementation of low-value care in hip and knee arthroplasty

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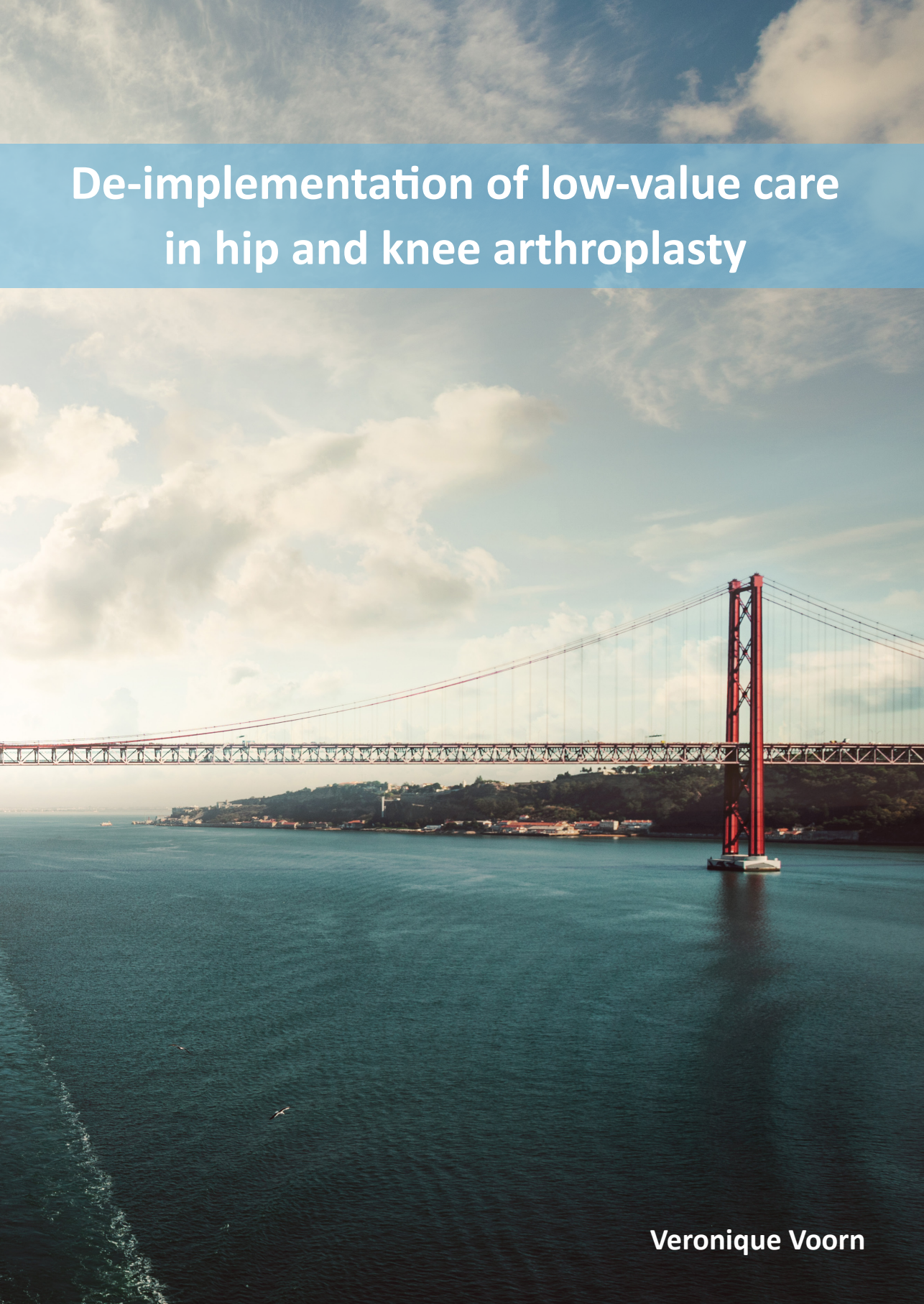

Veronique Voorn

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Contents

Chapter 1

General introduction

In the last decades, apart from the implementation of new diagnostic or therapeutic strategies, the abandonment of low-value care has become more important in many countries. Low-value care includes diagnostic and therapeutic strategies that have proven to be of limited benefit for patients, increase costs and/or may cause harmful effects. Evidence shows that e.g. in the United States of America an estimated 30% of all medical spending does not add value in care.[1,2] Abandonment or reduction of this value care (i.e. de-implementation) may lead to improved quality of care while reducing expenditures.[3] The importance for this is emphasized by initiatives such as the 'choosing wisely' campaign which started in 2012 in the USA and in the meanwhile spread to many other countries.[1,4] A key element of this campaign is that medical societies create 'better not to do' lists of tests, treatments and procedures in their field for which there is strong evidence of overuse, potential harm, or significant and unjustifiable costs. An example of low-value care that has not yet been addressed in research on de-implementation strategies is the use of blood salvage and the preoperative treatment with erythropoietin (EPO) in perioperative blood management in primary elective total hip arthroplasty (THA) and total knee arthroplasty (TKA).

Therefore, this thesis will focus on the de-implementation of blood salvage and pre-operative treatment with EPO in primary elective THA and TKA in order to improve quality of care for patients undergoing THA and TKA. In this introductory chapter, an introduction is given to primary THA and TKA, blood salvage and the preoperative treatment of EPO, as well as a description of a systematic approach to de-implement the use of blood salvage and preoperative treatment of EPO in primary THA and TKA. This chapter will conclude with the general aims and outline of this thesis.

Primary elective hip- and knee arthroplasties

Primary elective THA and TKA are two of the most performed procedures in orthopaedic surgery. In 2014 28,026 primary THA and 26,754 primary TKA were performed in the Netherlands.[5] It is expected that the number of these procedures will increase to more than 100.000 by the year of 2030.[6] Total joint replacement surgery including THA and TKA is, in addition to other risks, associated with perioperative blood loss and with anaemia in the direct postoperative period.[7] This can lead to high rates of allogeneic blood transfusions up to 69% depending on the transfusion threshold.[8] Although allogeneic transfusions are relatively safe, transfusion reactions, transmission of infectious diseases and immunomodulatory effects resulting in increased susceptibility of infections can affect the outcome of the surgery.[9-12] Therefore in the last two decades great efforts have been made to make transfusion policies more restrictive as opposed to the fairly liberal

haemoglobin threshold of 10 g/dL (6.2 mmol/L) by Adams and Lundy in 1942.[9,13-15] In addition to a more restrictive transfusion policy, there is an ongoing trend to aim for optimal patient blood management (PBM) to improve clinical outcomes and patient safety and to avoid the need of allogeneic transfusions by the optimization of the red cell mass, minimization of blood loss, and by optimization of tolerance of anaemia.[8-10,16-19]

Blood salvage and preoperative treatment with EPO

Blood salvage and preoperative treatment with EPO are two PBM techniques that are used in THA and TKA to avoid that postoperative haemoglobin levels drop below the threshold for allogeneic transfusions. Blood salvage includes two modalities: intra-operative autologous blood salvage, in which the shed blood collected, washed and concentrated before reinfused into a patient and postoperative autologous blood salvage with a device that postoperatively collects and re-infuses wound blood. In the Netherlands the postoperative blood salvage is used almost exclusively in primary joint arthroplasties. Intra-operative blood salvage is retained for more complex surgery such as revision arthroplasty[20].

In the Netherlands, EPO treatment in THA and TKA is used in mildly anaemic patients with a haemoglobin level between 10 to 13 g/dl (6.2 and 8.2 mmol/L) according to the indication for which EPO is registered in the Netherlands. Additionally EPO can be used to augment preoperative autologous blood donation.[21] The latter option should only be recommended in cases with multiple antibodies for whom no compatible blood is available.[22]

Many studies on the effectiveness of EPO and blood salvage have been performed. Systematic reviews showed that these studies had several limitations, such as a retrospective design, small patient numbers and poor methodological quality.[8,23] Therefore in 2014 So-Osman performed a multicentre RCT, the Transfusion 'Op Maat' (TOMaat) study, with adequate power on the effectiveness of the above mentioned blood salvage and EPO in elective hip and knee arthroplasties.[24,25] This study concluded that blood salvage is not effective to prevent exposure to allogeneic transfusion or to reduce the number of allogeneic red blood cell units transfused in primary elective total hip and knee arthroplasty. Concerning EPO it was concluded that, although EPO was effective to prevent exposure to allogeneic transfusion and to reduce the number of allogeneic red blood cell units transfused, the costs of EPO treatment are high so that it is considered not cost-effective in primary elective THA and TKA.[24] Given these findings, the use of blood salvage and EPO can be considered as low-value care.

Systematic approach for de-implementation

Despite the findings that blood salvage is not effective and EPO not cost-effective, this evidence did not automatically find its way into daily practice and the use of both techniques continued.[20] Therefore, additional efforts need to be taken to abandon this low-value care from clinical practice. Until now little is known about the process of de-implementation of long-established existing techniques or practice that might have become redundant or cause over-treatment.[1] Theory or empirical evidence on how to effectively de-implement is sparse, and only limited knowledge is available about the specific agents involved in the de-implementation of low-value care.[26-34] In addition, it has been suggested that there are fundamental differences between implementation and de-implementation, as it is harder to give up low-value care, than to adopt new and promising innovations.[28,33] Despite these fundamental differences it has been assumed that the model of Grol[35] for the systematic approach for implementation also applies to de-implementation.[36,37] In this thesis this systematic approach is used for 1) Setting concrete targets for the de-implementation of blood salvage and EPO. 2) An analysis of current performance, target group and setting for the use of blood salvage and EPO. 3) The development of a comprehensive strategy for de-implementation of blood salvage and EPO followed by 4 and 5) The execution and evaluation of this strategy. By using the model of Grol, we attempt to develop a de-implementation strategy that addresses existing barriers for abandoning blood salvage and EPO, is aimed at the relevant target group and effectively changes behaviour of physicians in blood management. The systematic approach will make it replicable to develop a de-implementation strategy in a different context and it will lead to insights on possible pitfalls in de-implementation research.

Aim and brief outlines of this thesis

The main aim of this thesis is to evaluate the effectiveness of a de-implementation strategy to reduce blood salvage and EPO in THA and TKA, based on the (de-)implementation model of Grol[35] as shown in figure 1.

The first step described in this thesis is the development of concrete targets for the de-implementation of blood salvage and EPO. For this purpose, the evidence that is currently available on the effectiveness of blood salvage and EPO is evaluated by means of meta-analyses in chapter 2 and chapter 3.

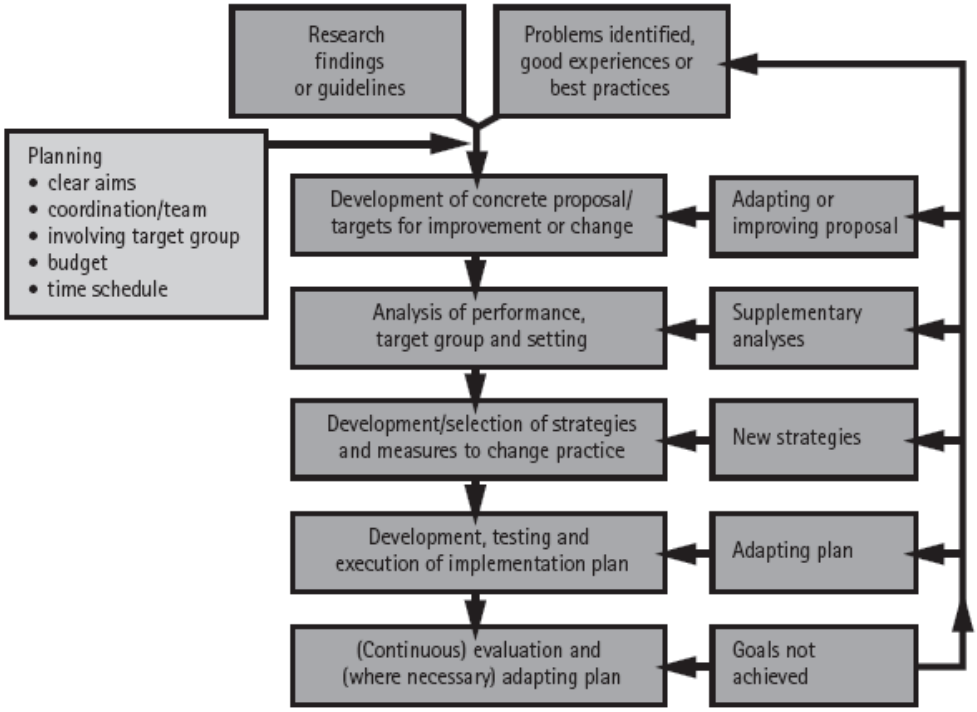

Figure 1: Implementation model by Grol (2005)

Subsequently, a problem analysis study is performed, in which current performance, target group and setting for the use of blood salvage and EPO is explored corresponding to step 2 of the Grol model. In chapter 4 the protocol for this problem analysis is described. In chapter 5 the current use of blood salvage and EPO within the Netherlands is assessed. Based on this current use, target groups were determined. In chapter 6 it is evaluated whether the outcome indicators 'allogeneic transfusion' and 'length of stay' of THA and TKA patients can be used to assess the differences in quality of care of hospitals for THA

and TKA patients and which factors are associated with differences of outcomes for the quality indicators 'allogeneic transfusion' and 'length of stay'. Chapter 7 describes an exploration of barriers that hinder the de-implementation of blood salvage and EPO in THA and TKA.

In step 3 a strategy to de-implement blood salvage and EPO in THA and TKA is developed based on the results of the problem analysis study (step 2). This de-implementation strategy is described in chapter 8.

Next the effectiveness of the de-implementation strategy is executed and evaluated in a cluster randomized clinical trial, corresponding to respectively step 4 and 5 of the model of Grol. Chapter 9 reports about the results of this cluster RCT.

References

1. Levinson W, Kallewaard M, Bhatia RS, et al. 'Choosing Wisely': a growing international campaign. BMJ Qual Saf. 2015;24(2):167-174.
2. Smith M, Saunders R, Stuckhardt L, et al. Best Care at Lower Cost: The Path to Continuously Learning Health Care in America. National Academies Press (US). 2013. doi:10.17226/13444.
3. Colla CH, Morden NE, Sequist TD, et al. Choosing wisely: prevalence and correlates of low-value health care services in the United States. J Gen Intern Med. 2015;30(2):221-228.
4. Wolfson D, Santa J, Slass L. Engaging physicians and consumers in conversations about treatment overuse and waste: a short history of the choosing wisely campaign. Acad Med. 2014;89(7):990-995.
5. Koot H, Schreurs W. LROI-Rapportage 2014: 'Orthopedische Implantaten in Beeld' Available: http://www.lroi.nl/.
6. Otten R, van Roermund PM, Picavet HS. Trends in the number of knee and hip arthroplasties: considerably more knee and hip prostheses due to osteoarthritis in 2030. Ned Tijdschr Geneeskd. 2010;154:A1534.
7. Goodnough LT, Maniatis A, Earnshaw P, et al. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. Br J Anaesth. 2011;106(1):13-22.
8. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiology. 2010;113(2):482-495.
9. So-Osman C. Red blood cell transfusion triggers and transfusion alternatives in elective orthopedic hip and knee replacement surgery - a review. International Journal of Clinical Transfusion Medicine. 2015;3:47-54.
10. Goodnough LT. Blood management: transfusion medicine comes of age. Lancet. 2013;381(9880):1791-1792.
11. Rohde JM, Dimcheff DE, Blumberg N, et al. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. JAMA. 2014;311(13):1317-1326.
12. Kim JL, Park JH, Han SB, et al. Allogeneic Blood Transfusion Is a Significant Risk Factor for Surgical-Site Infection Following Total Hip and Knee Arthroplasty: A Meta-Analysis. The Journal of arthroplasty. 2017;32(1):320-325.
13. Salpeter SR, Buckley JS, Chatterjee S. Impact of More Restrictive Blood Transfusion Strategies on Clinical Outcomes: A Meta-analysis and Systematic Review. The American Journal of Medicine. 2014;127(2):124-131.
14. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2012;4:CD002042.
15. Adams RC, Lundy JS. Anesthesia in cases of poor surgical risks. Some suggestions for decreasing the risk. Surg Gynecol Obstet. 1942;74:1011-1019.
16. Hofmann A, Farmer S, Towler SC. Strategies to preempt and reduce the use of blood products: an Australian perspective. Curr Opin Anaesthesiol. 2012;25(1):66-73.
17. Shander A, Van AH, Colomina MJ, et al. Patient blood management in Europe. British journal of anaesthesia. 2012;109(1):55-68.
18. Goodnough LT, Shander A. Patient blood management. Anesthesiology. 2012;116(6):1367-1376.
19. Gross I, Shander A, Sweeney J. Patient blood management and outcome, too early or not? Best Practice & Research Clinical Anaesthesiology Patient blood management 2013:161-172.
20. Struijk-Mulder MC, Horstmann WG, Verheyen CC, et al. Ten-year follow-up on Dutch orthopaedic blood management (DATA III survey). Arch Orthop Trauma Surg. 2014;134(1):15-20.
21. Alsaleh K, Alotaibi GS, Almodaimegh HS, et al. The use of preoperative erythropoiesis-stimulating agents (ESAs) in patients who underwent knee or hip arthroplasty: a meta-analysis of randomized clinical trials. J Arthroplasty. 2013;28(9):1463-1472.
22. Dutch Institute for Healthcare Improvement CBO. Guideline Bloodtransfusionpolicy (in Dutch). Available at: www.cbo.nl 2011.
23. Sharma R, Farrokhyar F, McKnight LL, et al. Quality of assessment of randomized controlled trials in blood conservation after joint arthroplasty. J Arthroplasty. 2011;26(6):909-913.
24. So-Osman C, Nelissen RG, Koopman-van Gemert AW, et al. Patient blood management in elective total hip- and knee-replacement surgery (Part 1): a randomized controlled trial on erythropoietin and blood salvage as transfusion alternatives using a restrictive transfusion policy in erythropoietin-eligible patients. Anesthesiology. 2014;120(4):839-851.
25. So-Osman C, Nelissen RG, Koopman-van Gemert AW, et al. Patient blood management in elective total hip- and knee-replacement surgery (part 2): a randomized controlled trial on blood salvage as transfusion

alternative using a restrictive transfusion policy in patients with a preoperative hemoglobin above 13 g/dl. Anesthesiology. 2014;120(4):852-860.
26. Niven DJ, Mrklas KJ, Holodinsky JK, et al. Towards understanding the de-adoption of low-value clinical practices: a scoping review. BMC Med. 2015;13:255.
27. Prasad V, Ioannidis JP. Evidence-based de-implementation for contradicted, unproven, and aspiring healthcare practices. Implement Sci. 2014;9(1):1.
28. Davidoff F. On the undiffusion of established practices. JAMA Intern Med. 2015;175(5):809-811.
29. Elshaug AG, Hiller JE, Tunis SR, et al. Challenges in Australian policy processes for disinvestment from existing, ineffective health care practices. Aust New Zealand Health Policy. 2007;4:23.
30. Montini T, Graham ID. "Entrenched practices and other biases": unpacking the historical, economic, professional, and social resistance to de-implementation. Implement Sci. 2015;10:24.
31. Polisena J, Clifford T, Elshaug AG, et al. Case studies that illustrate disinvestment and resource allocation decision-making processes in health care: a systematic review. Int J Technol Assess Health Care. 2013;29(2):174-184.
32. Roman BR, Asch DA. Faded promises: the challenge of deadopting low-value care. Ann Intern Med. 2014;161(2):149-150.
33. Ubel PA, Asch DA. Creating value in health by understanding and overcoming resistance to de-innovation. Health Aff (Millwood). 2015;34(2):239-244.
34. Willson A. The problem with eliminating 'low-value care'. BMJ Qual Saf. 2015;24(10):611-614.
35. Grol R, Wensing M, Eccles M. Improving Patient Care: The Implementation of Change in Clinical Practice. Oxford: Elsevier 2005.
36. van Bodegom-Vos L, Vermeulen H, Marang- van de Mheen P. Het terugdringen van onnodige verpleegkundige handelingen: hoe pak je dat aan? Nederlands Tijdschrift voor Evidence Based Practice. 2017;15(2):4-7.
37. van Bodegom-Vos L, Davidoff F, Marang-van de Mheen PJ. Implementation and de-implementation: two sides of the same coin? BMJ Qual Saf. 2017 Jun;26(6):495-501.

Chapter 2

Cell Salvage in Hip and Knee Arthroplasty: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Cell salvage is used to reduce allogeneic red blood-cell (RBC) transfusions in total hip arthroplasty (THA) and total knee arthroplasty (TKA). We performed a meta-analysis to assess the effectiveness of cell salvage to reduce transfusions in THA and TKA separately, and to examine whether recent trials change the conclusions from previous meta-analyses.

Methods: We searched MEDLINE through January 2013 for randomized clinical trials evaluating the effects of cell salvage in THA and TKA. Trial results were extracted using standardized forms and pooled using a random-effects model. Methodological quality of the trials was evaluated using the Cochrane Collaboration's tool for risk-of-bias assessment.

Results: Forty-three trials (5631 patients) were included. Overall, cell salvage reduced the exposure to allogeneic RBC transfusion in THA (risk ratio [RR], 0.66; 95% confidence interval [CI], 0.51 to 0.85) and TKA (RR, 0.51; 95% CI, 0.39 to 0.68). However, trials published in 2010 to 2012, with a lower risk of bias, showed no significant effect of cell salvage in THA (RR, 0.82; 95% CI, 0.66 to 1.02) and TKA (RR, 0.91; 95% CI, 0.63 to 1.31), suggesting that the treatment policy regarding transfusion may have changed over time.

Conclusions: Looking at all trials, cell salvage still significantly reduced the RBC exposure rate and the volume of RBCs transfused in both THA and TKA. However, in trials published more recently (2010 to 2012), cell salvage reduced neither the exposure rate nor the volume of RBCs transfused in THA and TKA, most likely explained by changes in blood transfusion management.

Introduction

Blood loss in total hip arthroplasty (THA) and total knee arthroplasty (TKA) may necessitate allogeneic red blood cell (RBC) transfusion. Concerns regarding the safety of allogeneic RBC transfusions have led to the use of perioperative cell salvage, intended to reduce allogeneic blood use.[1]

Previous meta-analyses of randomized controlled trials concluded that cell salvage is effective at reducing the need for allogeneic RBC transfusion, without adverse impact on clinical outcomes in orthopaedic surgery.[1-3] None of those meta-analyses compared the effectiveness of cell salvage in THA with those in TKA. However, it can be hypothesized that the effects in THA and TKA might be different, given differences in anatomy, size of the wound, and surgical technique. Furthermore, as there is less surrounding tissue that can absorb blood lost in TKA, reinfusion drains are likely to collect blood more effectively in TKA than in THA, leading to a larger reduction in the risk for allogeneic RBC transfusion in TKA

Furthermore, several large randomized controlled trials that have been published more recently indicated that cell salvage did not reduce the need for allogeneic RBC transfusion.[4-6] Various developments in orthopaedic surgery may have resulted in these different outcomes of recent trials. First, there has been a trend toward using more restrictive transfusion thresholds. In the last decade there has been an increased awareness that the traditional transfusion trigger, a haemoglobin concentration of <10 g/dL (~6.2 mmol/L),[7] is no longer tenable because of transfusion risks and escalating costs. Therefore, transfusion in many centres is now based on clinical symptoms, overall patient health, and a more restrictive haemoglobin level of 8 g/dL (~5.0 mmol/L) in uncomplicated cases.[8] Second, the treatment policy in control groups may be different in recent trials, particularly with respect to the routine use of closed suction drainage since Parker et al.[9] showed in 2007 that this was associated with higher transfusion rates in THA and TKA without any effect on the rates of wound infections or hematomas compared with using no drain. Third, changes in the timing of cell salvage potentially affected the outcomes of recent trials. Currently, cell salvage devices can reinfuse blood collected both intraoperatively and postoperatively (i.e., perioperatively), whereas the first cell salvage devices could only reinfuse blood collected during surgery. Finally, surgical techniques might have changed. For example, concerns have been raised about the use of tourniquet control in TKA as complications due to its use can delay recovery.[10] Because of these concerns, more recent studies may not have had routine tourniquet use, leading to lower effectiveness of cell salvage in TKA. All of these developments underline the need to update the available evidence.

The aims of the present study were 1) to assess the effectiveness of cell salvage in reducing allogeneic RBC transfusion in THA and TKA separately, and 2) to examine whether the addition of recent trials changes the conclusions regarding the effectiveness of cell salvage as described by Carless et al.[1] To our knowledge, the meta-analysis by Carless et al. was not only the largest meta-analysis but also the most complete one, as the other meta-analyses only reviewed specific types of cell salvage or patient groups.[2,3]

Materials and Methods

Study selection

All articles involving orthopaedic procedures identified by Carless et al.[1] were retrieved. Next, we searched MEDLINE from January 2009 through January 2013 using the same search strategy as Carless et al. (see Appendix 1). Furthermore, the references of included articles were checked and experts in the field were contacted for additional studies.

Articles were eligible for inclusion if they reported results of randomized controlled trials using cell salvage in THA and/or TKA in adult patients (at least eighteen years old). Studies with a combination of active comparisons were only included if both the intervention and control groups were equally exposed to the active treatment (active treatment plus cell salvage compared with active treatment only), as was done by Carless et al.[1] There were no language restrictions.

Data extraction and outcome measures

Study characteristics and outcomes were extracted for all thirty-five studies involving orthopaedic procedures from Carless et al.[1], using standardized forms, to show the results for THA and TKA separately. If data could not be extracted separately for THA and TKA, the authors of the study were contacted. If they did not respond, the article was placed in the category “not able to split or other orthopaedic procedures.”

Next, the titles of newly identified trials from our search strategy were screened by two reviewers, and full-text articles were retrieved. The reviewers independently selected trials that met the inclusion criteria, with disagreements resolved by consensus. For each selected trial, the reviewers independently extracted the following study characteristics: type of surgery (THA or TKA), transfusion threshold used (none, ≤8.0 g/dL [~5.0 mmol/L] [restrictive], or >8.0 g/dL [~5.0 mmol/L] [traditional]), treatment policy in the control group (no drain, use of closed suction wound drainage after surgery, or another active intervention), timing of cell salvage (intraoperative, perioperative, or postoperative), use

of tourniquet control (in TKA), and primary outcomes (the number of patients exposed to allogeneic RBC transfusion, and the volume of RBCs transfused per patient [with transfusion data expressed in millilitres converted to RBC units by dividing by 300]).

Risk of bias assessment

Included studies were assessed for methodological quality, using the Cochrane Collaboration's tool for assessing risk of bias, by two independent reviewers. The domains assessed were sequence generation, allocation concealment, and blinding[11]. Disagreement was resolved by consensus.

Statistical Analysis

Data were extracted and entered into Review Manager (RevMan) (version 5.2.13; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). Dichotomous and continuous data were pooled across trials using a random-effects model. Differences in outcome between the experimental group (receiving cell salvage) and the control group were expressed as a risk ratio (RR) for dichotomous outcomes and as a weighted mean difference (WMD) for continuous outcomes, along with a 95% confidence interval (CI). Thus, an RR of <1 indicates that cell salvage reduces the risk for allogeneic blood transfusion, and a negative WMD value indicates a reduction in the volume of RBCs transfused. If neither the standard deviation nor the standard error of the mean was reported for continuous data, the trial was not included. Differences were considered significant if $p < 0.05$. In addition, data in RevMan were arranged into three groups according to the decade of publication to assess changes in the effectiveness of cell salvage over time.

Subgroup Analysis and Investigation of Heterogeneity

Statistical heterogeneity was examined with the I^2 test. The I^2 test describes the percentage of the total variation across studies that is due to heterogeneity rather than chance (with 0% indicating no observed heterogeneity, and >50% indicating substantial heterogeneity)[11]. Four exploratory analyses of subgroups (defined prior to the study) were performed; these involved the transfusion threshold used, treatment policy in the control group, timing of cell salvage, and use of tourniquet control (in TKA).

Source of funding

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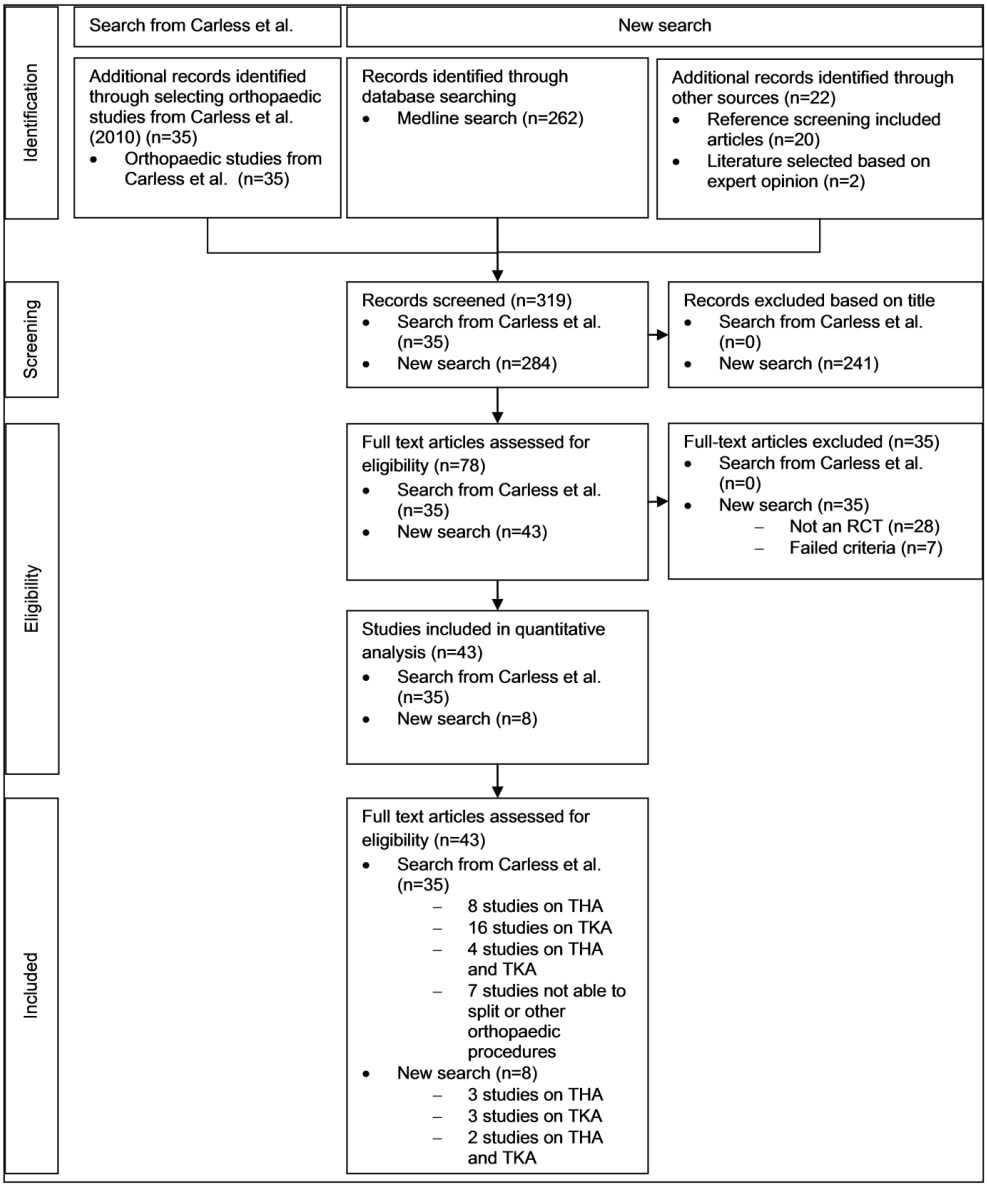

Figure 1: Literature search results

Results

We identified 284 titles in our search: 262 from MEDLINE and twenty-two after checking references and consulting experts (Figure 1). Review of these titles identified forty-three potentially eligible studies. Based on the full articles, eight studies fulfilled the inclusion criteria and were included in addition to the thirty-five studies identified by Carless et al.[1] Of these forty-three included studies (5631 patients), eleven included only THA,[4,12-21] nineteen included only TKA,[5,22-39] six included both THA and TKA,[6,40-44] and seven studies could not be split up or included other orthopaedic procedures.[45-51] Appendix 2 summarizes the characteristics and the risk-of-bias assessment of all included studies.

Risk-of-Bias Assessment

The risk of bias due to inadequate sequence generation was judged to be low in fifteen studies (Table 1). Five studies had adequate allocation concealment (that is, low risk of bias). Three studies were judged to be double-blinded. Recent studies more often seemed to have lower risk of bias (that is, higher quality) compared with studies published before 2010, particularly with respect to sequence generation and allocation concealment.

Table 1: Risk of bias of included studies

		Studies from Carless et al.		New search
	Total, N = 43	Published 1990-1999, n=22	Published 2000-2009, n=13	Published 2010-2012, n=8
Adequate sequence generation				
- Yes, i.e. low risk of bias	15	6	4	5
- No, i.e. high risk of bias	5	2	2	1
- Unclear, i.e. uncertain risk of bias	23	14	7	2
Adequate allocation concealment				
- Yes, i.e. low risk of bias	5	-	-	5
- No, i.e. high risk of bias	11	5	5	1
- Unclear, i.e. uncertain risk of bias	27	17	8	2
Adequate blinding				
- Yes, i.e. low risk of bias	3	1	-	2
- No, i.e. high risk of bias	39	21	13	5
- Unclear, i.e. uncertain risk of bias	1	-	-	1

Effects of Cell Salvage in Orthopaedic Surgery

Figure 2 shows the effect of cell salvage on the RBC exposure rate in orthopaedic surgery from Carless et al.[1]. In THA, cell salvage reduced the RBC exposure rate by 44% (RR, 0.56; 95% CI, 0.38 to 0.82; n = 11) and in TKA by 56% (RR, 0.44; 95% CI, 0.32 to 0.60; n = 18). Cell salvage did not significantly reduce the volume of RBCs transfused in either THA (WMD, −0.97; 95% CI, −1.94 to 0.00; n = 5) or TKA (WMD, −0.42; 95% CI, −0.92 to 0.09; n = 6).

Effects of Cell Salvage in THA

Overall, cell salvage still reduced the RBC exposure rate by 34% (RR, 0.66; 95% CI, 0.51 to 0.85) in THA when recent trials were included, without substantial heterogeneity among studies (I^2 = 50%). However, as shown in figure 3, the date of the study appeared to have an effect, with more recent studies (2010 to 2012) showing no significant effect of cell salvage (RR, 0.82; 95% CI, 0.66 to 1.02), without any heterogeneity (I^2 = 0%).

Overall, cell salvage in THA reduced the volume of RBCs transfused (WMD, −0.67; 95% CI, −1.08 to −0.27; I^2 = 91%). Again, an effect of the study date was observed, with recently published studies (2010 to 2012) showing a nonsignificant reduction in the volume of RBCs transfused (WMD, −0.13; 95% CI, −0.30 to 0.04; I^2 = 39%).

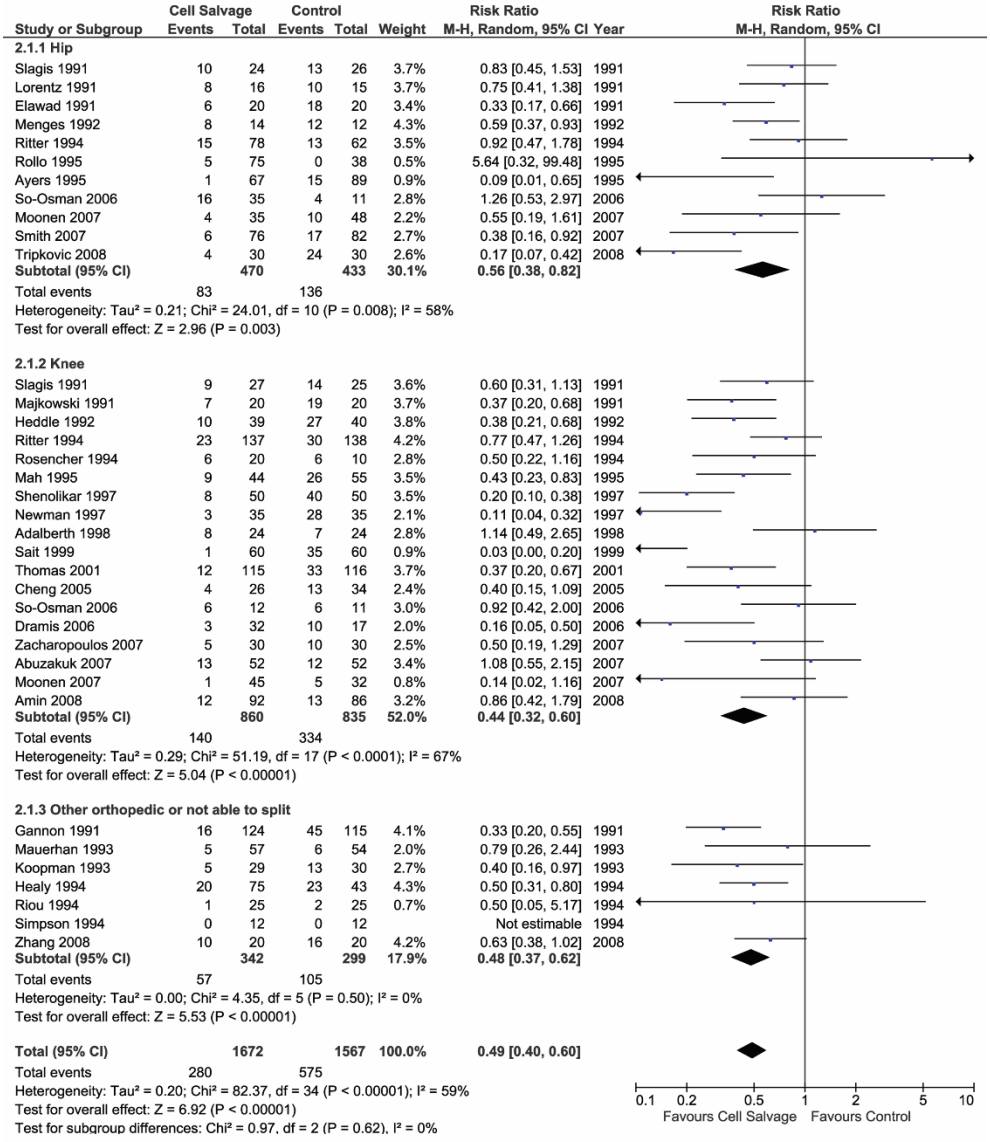

Figure 2: Effects of cell salvage in orthopaedic surgery in studies included in Carless et al: Hip versus Knee Arthroplasty

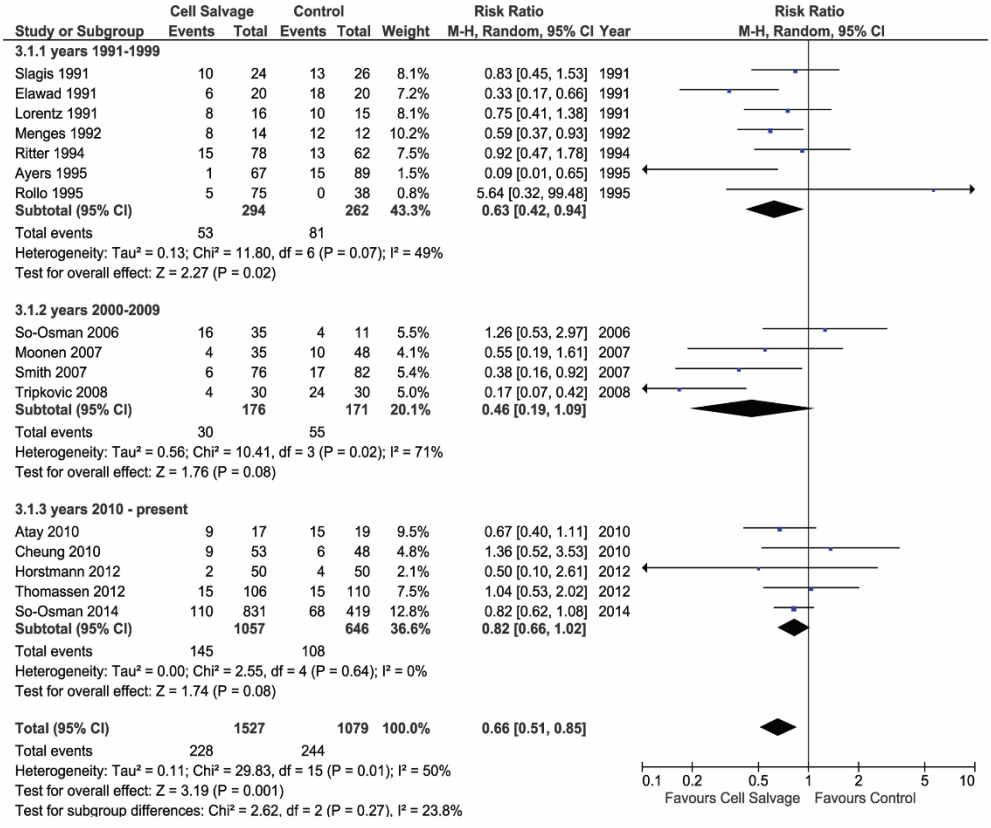

Figure 3: Effects of cell salvage in Hip Arthroplasty over time

Subgroup Analyses

To explain the time period effect described above, exploratory subgroup analyses were performed. Given the number of studies per time period, no further stratification was possible. Therefore, we included all studies from all time periods in the subgroup analyses and assessed 1) whether the effectiveness between subgroups was different, and 2) whether a possible explanatory variable (for example, a more strict transfusion threshold) was more frequently present in recent than in older studies. The variable was considered a possible explanation for a part of the observed change in effectiveness over time only if both criteria were true.

- In studies using a traditional transfusion threshold, cell salvage significantly reduced the RBC exposure rate (RR, 0.57; 95% CI, 0.36 to 0.89; I^2 = 67%; n = 6 [1 recent]) and

the volume of RBCs transfused (WMD, −1.56; 95% CI, −2.16 to −0.95; I^2 = 61%; n = 3 [none recent]). In studies with a more restrictive threshold, cell salvage resulted in a smaller reduction of the RBC exposure rate (RR, 0.72; 95% CI, 0.58 to 0.91; I^2 = 0%; n = 5 [3 recent]) and did not significantly reduce the volume of RBCs transfused (WMD, −0.13; 95% CI, −0.30 to 0.04; I^2 = 39%; n = 3 [all recent]).

- In studies using closed suction wound drainage in the control group, cell salvage significantly reduced the RBC exposure rate (RR, 0.78; 95% CI, 0.62 to 0.98, I^2 = 6%; n = 6 [3 recent]), but not the volume of RBCs transfused (WMD, −0.16; 95% CI, −0.45 to 0.13, I^2 = 61%; n = 4 [2 recent]). In studies using no drain in the control group, cell salvage did not significantly reduce the RBC exposure rate (RR, 0.69; 95% CI, 0.43 to 1.13, I^2 = 45%; n = 5 [2 recent]) or the volume of RBCs transfused (WMD, −1.04; 95% CI, −2.96 to 0.88; I^2 = 98%; n = 2 [1 recent]).
- Intraoperative cell salvage (only applied in one trial) reduced the RBC exposure rate (RR, 0.33; 95% CI, 0.17 to 0.66) and the volume of RBCs transfused (WMD, −2.04; 95% CI, −2.58 to −1.50). Postoperative cell salvage significantly reduced the RBC exposure rate (RR, 0.68; 95% CI, 0.49 to 0.93, I^2 = 55%; n = 13 [4 recent]) and the volume of RBCs transfused (WMD, −0.38; 95% CI, −0.72 to −0.04; I^2 = 86%; n = 6 [3 recent]). Perioperative cell salvage significantly reduced neither the RBC exposure rate (RR, 0.76; 95% CI, 0.58 to 1.00; I^2 = 0%; n = 4 [2 recent]) nor the volume of RBCs transfused (WMD, −0.28; 95% CI, −0.76 to 0.18; I^2 = 34%; n = 2 [1 recent]).

Effects of Cell Salvage in TKA

Overall, cell salvage still reduced the RBC exposure rate by 49% (RR, 0.51; 95% CI, 0.39 to 0.68) in TKA when recent trials were added (Figure 4), with substantial heterogeneity among studies (I^2 = 75%). Again, a time period effect was observed, with more recent studies (2010 to 2012) showing no significant effect of cell salvage (RR, 0.91; 95% CI, 0.63 to 1.31; I^2 = 54%).

Overall, cell salvage in total knee arthroplasty also reduced the volume of RBCs transfused (WMD, −0.33; 95% CI, −0.59 to −0.08; I^2 = 91%). Again, a time period effect was observed, with recently published studies (2010 to 2012) showing a nonsignificant reduction in the volume of RBCs transfused (WMD, −0.32; 95% CI, −0.63 to 0.00; I^2 = 95%).

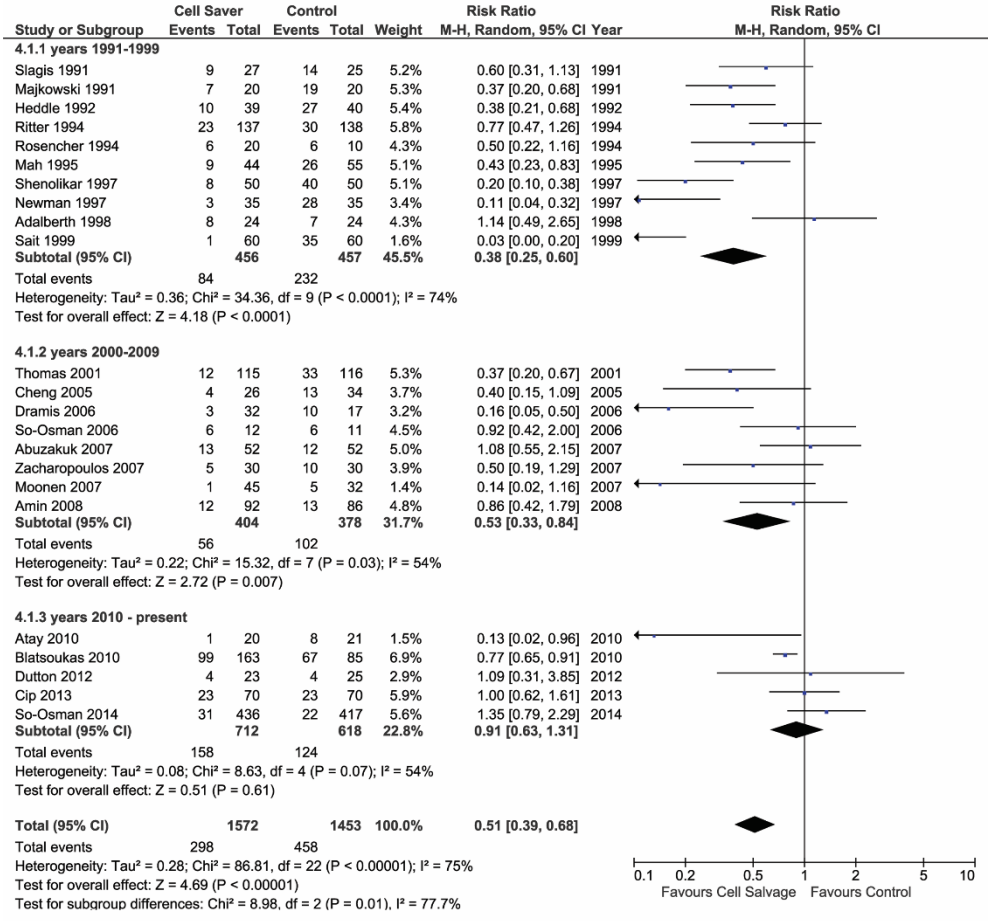

Figure 4: Effects of cell salvage in Knee Arthroplasty over time

Subgroup Analyses

To explain the time period effect described above, exploratory subgroup analyses similar to those for THA were performed.

- In studies using a traditional threshold, cell salvage significantly reduced the RBC exposure rate (RR, 0.54; 95% CI, 0.40 to 0.73; I^2 = 72%; n = 13 [2 recent]) and the volume of RBCs transfused (WMD, −0.60; 95% CI, −1.08 to −0.12; I^2 = 80%; n = 4 [1 recent]). In studies with a more restrictive threshold, cell salvage reduced neither the RBC exposure rate (RR, 0.54; 95% CI, 0.25 to 1.18, I^2 = 74%; n = 5 [2 recent]) nor the

volume of RBCs transfused (WMD, −0.45; 95% CI, −1.07 to 0.18; I^2 = 92%; n = 3 [2 recent]).

- In studies using closed suction wound drainage in the control group, cell salvage significantly reduced the RBC exposure rate (RR, 0.44; 95% CI, 0.27 to 0.72; I^2 = 78%; n = 13 [3 recent]), but not the volume of RBCs transfused (WMD, −0.38; 95% CI, −0.82 to 0.05; I^2 = 90%; n = 5 [1 recent]). In studies using no drain in the control group, cell salvage resulted in a smaller reduction of the RBC exposure rate (RR, 0.56; 95% CI, 0.37 to 0.85, I^2 = 75%; n = 8 [2 recent]), and did not significantly reduce the volume of RBCs transfused (WMD, −0.24; 95% CI, −0.92 to 0.45; I^2 = 96%; n = 3 [2 recent]).
- Postoperative cell salvage significantly reduced the RBC exposure rate (RR, 0.49; 95% CI, 0.37 to 0.66; I^2 = 73%; n = 22 [4 recent]) and the volume of RBCs transfused (WMD, −0.32; 95% CI, −0.55 to −0.08; I^2 = 92%; n = 10 [4 recent]). Perioperative cell salvage resulted in a smaller reduction of the RBC exposure rate (RR, 0.81; 95% CI, 0.68 to 0.97, I^2 = 0%; n = 2 [both recent]) and a reduction of the volume of RBCs transfused (WMD, −0.93; 95% CI, −1.21 to −0.65; n = 1 [recent]).
- In studies performing TKA under tourniquet control, cell salvage significantly reduced the RBC exposure rate (RR, 0.46; 95% CI, 0.33 to 0.65, I^2 = 71%; n = 20 [3 recent]), but did not reduce the volume of RBCs transfused (WMD, −0.22; 95% CI, −0.45 to 0.01; I^2 = 87%; n = 8 [3 recent]). In studies performing TKA without tourniquet control, cell salvage resulted in a smaller reduction of the RBC exposure (RR, 0.78; 95% CI, 0.67 to 0.91; I^2 = 0%; n = 3 [2 recent]) and a reduction in the volume of RBCs transfused (WMD, −0.85; 95% CI, −1.09 to −0.61; I^2 = 0%; n = 2 [1 recent]).

Discussion

Our meta-analysis showed that cell salvage significantly reduces the RBC exposure rate and the volume of RBCs transfused in both THA and TKA, with a larger effect in TKA than in THA based on group averages. However, in trials published more recently (2010 to 2012), cell salvage reduced neither the exposure rate nor the volume of RBCs transfused in both THA and TKA. We therefore conclude that, given changes in blood transfusion management, the effect of cell salvage may have changed over time and it may not be as effective as shown in previous meta-analyses.[1-3] This conclusion seems even stronger if the methodological quality of the studies is considered. Recent studies more often had a lower risk of bias and therefore higher quality of evidence.

Subgroup analyses showed that a more restrictive transfusion trigger (haemoglobin [Hb] ≤8.0 g/dL) was associated with a smaller effect of cell salvage. Cell salvage reduced the exposure rate only in THA and was not effective in TKA. Given that recent trials more

often used this restrictive transfusion threshold, this may partly explain the observed time period effect in effectiveness of cell salvage.

Similarly, using no drain as the standard treatment in the control group was also associated with smaller effects of cell salvage. Cell salvage was no longer effective in THA, and it reduced only the RBC exposure rate in TKA. These results are in line with the meta-analysis of Parker et al.,[9] who showed that routine use of closed suction drainage in THA and TKA was associated with higher transfusion rates and did not have any effect on the rate of wound infections or hematomas compared with no drain use. However, as recent studies did not use 'no drain' as the control treatment more frequently than studies published before 2010, it does not explain the observed time period effect.

Subgroup analyses regarding the timing of cell salvage and use of tourniquet control established no clear reasons for the observed time period effect. Only a few studies, although proportionally more recent studies, performed TKA without tourniquet control. This is in line with the results of the 2009 review by Smith and Hing[10] showing that the use of a tourniquet decreases intraoperative blood loss but could not influence postoperative blood loss in drains or affect transfusion rates.

Some relevant variables were not reported in a sufficient number of trials and could thus not be used in the meta-analysis: preoperative and postoperative haemoglobin levels, the exact timing of haemoglobin measurements resulting in the decision to transfuse or not, and the exact amount of blood given back to the patient, which differs among devices. Therefore, additional research is needed to be able to assess whether cell salvage may have benefit in raising haemoglobin levels for subgroups of patients and to interpret the effect of the timing of haemoglobin measurement and the volume of blood transfused on the effectiveness of cell salvage. Furthermore, we recommend that future studies report the utilized surgical techniques in more detail, enabling future meta-analyses to perform subgroup analyses to determine whether primary outcomes of cell salvage differ by surgical technique.

There are some important limitations of this meta-analysis. First, it included an insufficient number of high-quality studies to permit limiting our analyses to high-quality studies only. However, our risk-of-bias assessment showed that more recent studies seemed to have lower risk of bias compared with studies published before 2010, which strengthens our conclusion that cell salvage may no longer be effective in reducing the RBC exposure rate and the volume of RBCs transfused. Second, only three of the included studies were judged to be double-blinded. Although this is problematic for the quality of the studies, it is probably not possible to further improve blinding procedures given the nature of the intervention. However, as sequence generation and allocation concealment clearly

improved in recent studies, there is lower risk of bias and thus higher quality of evidence in recent studies. Third, the results of this meta-analysis only apply to cell salvage in THA and TKA. Cell salvage may still be effective for other surgical procedures (for example, during cardiac surgery), which could be a topic for further research. In addition, the results only allow us to draw conclusions about the effectiveness of perioperative collection and reinfusion of autologous blood (cell salvage) and not about preoperative autologous blood donation and reinfusion.

Given the results of this meta-analysis, the benefit of cell salvage in clinical practice in uncomplicated patients undergoing THA and TKA is questioned. Further research is needed to be able to definitely answer this question, as current trials have insufficient data on parameters such as haemoglobin levels. The current meta-analysis contributes to this debate by creating awareness among professionals that the effectiveness of cell salvage to reduce transfusion rates is minimized in recent studies, which have lower risk of bias and more often have used more restrictive transfusion triggers.

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References

1. Carless PA, Henry DA, Moxey AJ, O'Connell D, Brown T, Fergusson DA. Cell salvage for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2010;4(4):CD001888. Epub 2010 Apr 14.
1. Haien Z, Yong J, Baoan M, Mingjun G, Qingyu F. Post-operative auto-transfusion in total hip or knee arthroplasty: a meta-analysis of randomized controlled trials. PLoS One. 2013;8(1):e55073. Epub 2013 Jan 25.
2. Markar SR, Jones GG, Karthikesalingam A, Segaren N, Patel RV. Transfusion drains versus suction drains in total knee replacement: meta-analysis. Knee Surg Sports Traumatol Arthrosc. 2012 Sep;20(9):1766-72. Epub 2011 Nov 10.
3. Cheung G, Carmont MR, Bing AJ, Kuiper JH, Alcock RJ, Graham NM. No drain, autologous transfusion drain or suction drain? A randomised prospective study in total hip replacement surgery of 168 patients. Acta Orthop Belg. 2010 Oct;76(5):619-27.
4. Cip J, Widemschek M, Benesch T, Waibel R, Martin A. Does single use of an autologous transfusion system in TKA reduce the need for allogenic blood?: a prospective randomized trial. Clin Orthop Relat Res. 2013 Apr;471(4):1319-25. Epub 2012 Dec 11.
5. So-Osman C, Nelissen RG, Koopman-van Gemert AW, Kluyver E, Pöll RG, Onstenk R, Van Hilten JA, Jansen-Werkhoven TM, van den Hout WB, Brand R, Brand A. Patient blood management in elective total hip- and knee-replacement surgery (part 1): a randomized controlled trial on erythropoietin and blood salvage as transfusion alternatives using a restrictive transfusion policy in erythropoietin-eligible patients. Anesthesiology. 2014 Apr;120(4):839-51.
6. Adams RC, Lundy JS. Anesthesia in cases of poor surgical risk: some suggestions for decreasing the risk. Surg Gynecol Obstet. 1942;74:1011-9.
7. Young SW, Marsh DJ, Akhavani MA, Walker CG, Skinner JA. Attitudes to blood transfusion post arthroplasty surgery in the United Kingdom: a national survey. Int Orthop. 2008 Jun;32(3):325-9. Epub 2007 Mar 30.
8. Parker MJ, Livingstone V, Clifton R, McKee A. Closed suction surgical wound drainage after orthopaedic surgery. Cochrane Database Syst Rev. 2007;(3):CD001825. Epub 2007 Jul 18.
9. Smith TO, Hing CB. A meta-analysis of tourniquet assisted arthroscopic knee surgery. Knee. 2009 Oct;16(5):317-21. Epub 2009 Feb 23.
10. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. 2011.http://handbook.cochrane.org/. Accessed 2015 Jan 14.
11. Ayers DC, Murray DG, Duerr DM. Blood salvage after total hip arthroplasty. J Bone Joint Surg Am. 1995 Sep;77(9):1347-51.
12. Ekbäck G, Schött U, Axelsson K, Carlberg M. Perioperative autotransfusion and functional coagulation analysis in total hip replacement. Acta Anaesthesiol Scand. 1995 Apr;39(3):390-5.
13. Elawad AA, Ohlin AK, Berntorp E, Nilsson IM, Fredin H. Intraoperative autotransfusion in primary hip arthroplasty. A randomized comparison with homologous blood. Acta Orthop Scand. 1991 Dec;62(6):557-62.
14. Horstmann WG, Kuipers BM, Slappendel R, Castelein RM, Kollen BJ, Verheyen CC. Postoperative autologous blood transfusion drain or no drain in primary total hip arthroplasty? A randomised controlled trial. Int Orthop. 2012 Oct;36(10):2033-9. Epub 2012 Jul 13.
15. Lorentz A, Osswald PM, Schilling M, Jani L. [A comparison of autologous transfusion procedures in hip surgery]. Anaesthesist. 1991 Apr;40(4):205-13. German.
16. Menges T, Rupp D, van Lessen A, Hempelmann G. [Measures for reducing the use of homologous blood. Effects on blood coagulation during total endoprosthesis]. Anaesthesist. 1992 Jan;41(1):27-33. German.
17. Rollo VJ, Hozack WJ, Rothman RH, Chao W, Eng KO. Prospective randomized evaluation of blood salvage techniques for primary total hip arthroplasty. J Arthroplasty. 1995 Aug;10(4):532-9.
18. Smith LK, Williams DH, Langkamer VG. Post-operative blood salvage with autologous retransfusion in primary total hip replacement. J Bone Joint Surg Br. 2007 Aug;89(8):1092-7.
19. Thomassen BJ, Pilot P, Scholtes VA, Grohs JG, Holen K, Bisbe E, Poolman RW. Limit allogeneic blood use with routine re-use of patient's own blood: a prospective, randomized, controlled trial in total hip surgery. PLoS One. 2012;7(9):e44503. Epub 2012 Sep 13.
20. Tripković B, Buković D, Sakić K, Sakić S, Buković N, Radaković B. Quality of the blood sampled from surgical drainage after total hip arthroplasty. Coll Antropol. 2008 Mar;32(1):153-60.

21. Abuzakuk T, Senthil Kumar V, Shenava Y, Bulstrode C, Skinner JA, Cannon SR, Briggs TW. Autotransfusion drains in total knee replacement. Are they alternatives to homologous transfusion? Int Orthop. 2007 Apr;31(2):235-9. Epub 2006 Jun 8.
22. Adalberth G, Byström S, Kolstad K, Mallmin H, Milbrink J. Postoperative drainage of knee arthroplasty is not necessary: a randomized study of 90 patients. Acta Orthop Scand. 1998 Oct;69(5):475-8.
23. Altinel L, Kaya E, Kose KC, Fidan F, Ergan V, Fidan H. Effect of shed blood retransfusion on pulmonary perfusion after total knee arthroplasty: a prospective controlled study. Int Orthop. 2007 Dec;31(6):837-44. Epub 2006 Nov 4.
24. Amin A, Watson A, Mangwani J, Nawabi D, Ahluwalia R, Loeffler M. A prospective randomised controlled trial of autologous retransfusion in total knee replacement. J Bone Joint Surg Br. 2008 Apr;90(4):451-4.
25. Blatsoukas KS, Drosos GI, Kazakos K, Papaioakim M, Gioka T, Chloropoulou P, Verettas DA. Prospective comparative study of two different autotransfusion methods versus control group in total knee replacement. Arch Orthop Trauma Surg. 2010 Jun;130(6):733-7. Epub 2010 Feb 18.
26. Cheng SC, Hung TS, Tse PY. Investigation of the use of drained blood reinfusion after total knee arthroplasty: a prospective randomised controlled study. J Orthop Surg (Hong Kong). 2005 Aug;13(2):120-4.
27. Dramis A, Plewes J. Autologous blood transfusion after primary unilateral total knee replacement surgery. Acta Orthop Belg. 2006 Jan;72(1):15-7.
28. Dutton T, De-Souza R, Parsons N, Costa ML. The timing of tourniquet release and 'retransfusion' drains in total knee arthroplasty: a stratified randomised pilot investigation. Knee. 2012 Jun;19(3):190-2. Epub 2011 Mar 25.
29. Heddle NM, Brox WT, Klama LN, Dickson LL, Levine MN. A randomized trial on the efficacy of an autologous blood drainage and transfusion device in patients undergoing elective knee arthroplasty. Transfusion. 1992 Oct;32(8):742-6.
30. Kirkos JM, Krystallis CT, Konstantinidis PA, Papavasiliou KA, Kyrkos MJ, Ikonomidis LG. Postoperative re-perfusion of drained blood in patients undergoing total knee arthroplasty: is it effective and cost-efficient? Acta Orthop Belg. 2006 Jan;72(1):18-23.
31. Mah ET, Davis R, Seshadri P, Nyman TL, Seshadri R. The role of autologous blood transfusion in joint replacement surgery. Anaesth Intensive Care. 1995 Aug;23(4):472-7.
32. Majkowski RS, Currie IC, Newman JH. Postoperative collection and reinfusion of autologous blood in total knee arthroplasty. Ann R Coll Surg Engl. 1991 Nov;73(6):381-4.
33. Newman JH, Bowers M, Murphy J. The clinical advantages of autologous transfusion. A randomized, controlled study after knee replacement. J Bone Joint Surg Br. 1997 Jul;79(4):630-2.
34. Rosencher N, Vassilieff V, Tallet F, Toulon P, Leoni J, Tomeno B, Conseiller C. [Comparison of Orth-Evac and Solcotrans Plus devices for the autotransfusion of blood drained after total knee joint arthroplasty]. Ann Fr Anesth Reanim. 1994;13(3):318-25. French.
35. Sait MS, Earnshaw P. Autotransfusion in total knee arthroplasty - is it worth the effect? J Bone Joint Surg Br. 1999;81(Suppl 2):244.
36. Shenolikar A, Wareham K, Newington D, Thomas D, Hughes J, Downes M. Cell salvage auto transfusion in total knee replacement surgery. Transfus Med. 1997 Dec;7(4):277-80.
37. Thomas D, Wareham K, Cohen D, Hutchings H. Autologous blood transfusion in total knee replacement surgery. Br J Anaesth. 2001 May;86(5):669-73.
38. Zacharopoulos A, Apostolopoulos A, Kyriakidis A. The effectiveness of reinfusion after total knee replacement. A prospective randomised controlled study. Int Orthop. 2007 Jun;31(3):303-8. Epub 2006 Jun 30.
39. Atay EF, Güven M, Altıntaş F, Kadıoğlu B, Ceviz E, Ipek S. Allogeneic blood transfusion decreases with postoperative autotransfusion in hip and knee arthroplasty. Acta Orthop Traumatol Turc. 2010;44(4):306-12.
40. Moonen AF, Knoors NT, van Os JJ, Verburg AD, Pilot P. Retransfusion of filtered shed blood in primary total hip and knee arthroplasty: a prospective randomized clinical trial. Transfusion. 2007 Mar;47(3):379-84.
41. Ritter MA, Keating EM, Faris PM. Closed wound drainage in total hip or total knee replacement. A prospective, randomized study. J Bone Joint Surg Am. 1994 Jan;76(1):35-8.
42. So-Osman C, Nelissen RG, Eikenboom HC, Brand A. Efficacy, safety and user-friendliness of two devices for postoperative autologous shed red blood cell re-infusion in elective orthopaedic surgery patients: a randomized pilot study. Transfus Med. 2006 Oct;16(5):321-8.
43. Slagis SV, Benjamin JB, Volz RG, Giordano GF. Postoperative blood salvage in total hip and knee arthroplasty. A randomised controlled trial. J Bone Joint Surg Br. 1991 Jul;73(4):591-4.

44. Gannon DM, Lombardi AV Jr, Mallory TH, Vaughn BK, Finney CR, Niemcryk S. An evaluation of the efficacy of postoperative blood salvage after total joint arthroplasty. A prospective randomized trial. J Arthroplasty. 1991 Jun;6(2):109-14.
45. Healy WL, Pfeifer BA, Kurtz SR, Johnson C, Johnson W, Johnston R, Sanders D, Karpman R, Hallack GN, Valeri CR. Evaluation of autologous shed blood for autotransfusion after orthopaedic surgery. Clin Orthop Relat Res. 1994 Feb;299:53-9.
46. Koopman-van Gemert AWMM. Processed autotransfusion and homologous red cell requirement in elective cardiac and orthopaedic surgery: a randomised prospective study. In: Perioperative autotransfusion by means of a blood cell separator. Den Haag: Cip-Data Koninklijke Bibliotheek; 1993. p 105-26.
47. Mauerhan DR, Nussman D, Mokris JG, Beaver WB. Effect of postoperative reinfusion systems on hemoglobin levels in primary total hip and total knee arthroplasties. A prospective randomized study. J Arthroplasty. 1993 Oct;8(5):523-7.
48. Riou B, Arock M, Guerrero M, Ramos M, Thoreux P, Guillosson JJ, Roy-Camille R, Viars P. Haematological effects of postoperative autotransfusion in spinal surgery. Acta Anaesthesiol Scand. 1994 May;38(4):336-41.
49. Simpson MB, Murphy KP, Chambers HG, Bucknell AL. The effect of postoperative wound drainage reinfusion in reducing the need for blood transfusions in elective total joint arthroplasty: a prospective, randomized study. Orthopedics. 1994 Feb;17(2):133-7.
50. Zhang XF, Dong JM, Gong ML, Shen SM, Zhou Y, Pan YF, Mao JP. [Effectiveness of preoperative autologous plateletpheresis combined with intraoperative autotransfusion on the blood coagulation in orthopaedic patients]. Zhonghua Wai Ke Za Zhi. 2008 Jan 15;46(2):118-21. Chinese.

Appendix 1: Search Strategy

MEDLINE search strategy

1. cell$ sav$.mp.
2. cell$ salvage.mp.
3. blood transfusion, autologous/
4. autotransfusion$.mp.
5. auto-transfusion$.mp.
6. blood salvage.mp.
7. autovac.mp.
8. solcotrans system.mp.
9. constavac.mp.
10. solcotrans.mp.
11. hemovac.mp.
12. BRAT.mp.
13. fresenius.mp.
14. consta vac.mp.
15. cell saver.mp.
16. dideco.mp.
17. electromedic.mp.
18. electromedics.mp.
19. gish biomedical.mp.
20. haemonetics.mp.
21. orth-evac.mp.
22. pleur-evac.mp.
23. sorenson.mp.
24. reinfusion system.mp.
25. sorin biomedical.mp.
26. or/1-25
27. exp blood transfusion/
28. exp hemorrhage/
29. exp anesthesia/
30. transfusion$.mp.
31. bleed$.mp.
32. blood loss$.mp.
33. hemorrhag$.mp.
34. haemorrhag$.mp.
35. or/27-34
36. 26 and 35
37. randomized controlled trial.pt.
38. controlled clinical trial.pt.
39. randomized controlled trials.sh.
40. random allocation.sh.
41. double blind method.sh.
42. single blind method.sh.
43. or/37-42
44. clinical trial.pt.
45. exp Clinical trials/
46. (clin$ adj25 trial$).ti,ab.
47. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
48. placebos.sh.
49. placebo$.ti,ab.
50. random$.ti,ab.
51. research design.sh.
52. or/44-51
53. comparative study.sh.
54. exp Evaluation studies/
55. follow up studies.sh.
56. prospective studies.sh.
57. (control$ or prospectiv$ or volunteer$).ti,ab.
58. or/53-57
59. 43 or 52 or 58
60. 36 and 59
61. animal/ not human/
62. 60 not 6

Appendix 2: Study characteristics and risk of bias assessment of included studies

Author	Year	Summary of study characteristics									Assessment of risk of bias		
		Participants: Patients undergoing	Type[1]	Interventions		Transfusion trigger			Treatment policy in control group[4]	Tourniquet control	Random sequence generation	Allocation concealment	Blinding
				Description: Intervention (I) and Control (C)	Timing[2]	Yes/ No	Transfusion threshold	Subgroup[3]					
Abuzakuk	2007	Primary cemented total knee arthroplasty	Knee	I: autotransfusion (Bellovac ABT autotransfusion system), n=52; C: standard suction drain (Redivac), n=52	POST	Yes	Hb < 9.0 g/dl	Trigger 2	Control 1	Yes	Low risk	Unclear risk	High risk
Adalberth	1998	primary total knee arthroplasty	Knee	I: autotransfusion (Solcotrans - Solco Basle UK ltd.)), n=24; Control: no drain, n=24	POST	Yes	Hb < 9.0 g/dl	Trigger 2	Control 0	Yes	High risk	High risk	High risk
Altinel	2007	bi- or tri-compartmental total knee arthroplasties	Knee	I: autotransfusion (ConstaVac CBCII system), n=16; C: standard care (2 drains for shed blood drainage), n=16	POST	Yes	Hb < 9.0 g/dl	Trigger 2	Control 1	Yes	Unclear risk	Unclear risk	High risk
Amin	2008	total knee replacement	Knee	I: autotransfusion (Bellovac ABT autotransfusion system), n=92; C: standard vacuum drain, n=86	POST	Yes	Hb < 8.0 g/dl	Trigger 1	Control 1	Yes	High risk	High risk	High risk
Atay	2010	hip and knee arthroplasty	Hip and knee	I: autotransfusion (Transolog), n=17 (hip) and n=20 (knee); C: routine hemovac drain, n=19 (hip) and n=21 (knee)	POST	Yes	Hb < 8.0 g/dl or Hct < 25% and clinical symptoms of anaemia	Trigger 1	Control 1	Yes	Unclear risk	Unclear risk	High risk

Ayers 1995	primary total hip arthroplasty	Hip	I: autotransfusion (Autovac postoperative orthopaedic autotransfusion canister), n=67; C: closed suction drainage system, n=89	POST	No		None	Control 1	N.A.	High risk	High risk	High risk
Blatsoukas 2010	unilateral total knee replacement	Knee	I: 1. autotransfusion (Dideco Compact Advanced and ConstaVac CBCII), n=92; 2. Autotransfusion (ConstaVaC CBCII), n=71; C: no drain, n=85	PERI/ POST	Yes	Hb 9-10 g/dl: 1 unit; Hb 8-9 g/dl: 2 units; Hb 7-8 g/dl: 3 units	Trigger 2	Control 0	No	High risk	High risk	High risk
Cheng 2005	unilateral total knee arthroplasty	Knee	I: autotransfusion (DONOR system), n=26; C: no drain, n=34	POST	Yes	Hb < 9.0 g/dl	Trigger 2	Control 0	No	Unclear risk	High risk	High risk
Cheung 2010	primary total hip replacement	Hip	I: autotransfusion (Bellovac ABT autotransfusion systemt), n=53; C: no drain, n=48	POST	No		None	Control 0	N.A.	Low risk	Unclear risk	High risk
Cip 2012	total knee arthroplasty	Knee	I: autotransfusion (OrthoPAT), n= 70; C: no retransfusion system, n=70	PERI	Yes	Hb < 8.0 g/dl or signs of anaemia or tachycardia	Trigger 2	Control 1	No	Low risk	Low risk	High risk
Dramis 2006	primary unilateral total knee arthroplasty	Knee	I: autotransfusion (CellTrans system), n=32; C: Standard vacuum drain, n=17	POST	Yes	Hb < 9.0 g/dl or clinical symptoms of anaemia	Trigger 2	Control 1	Yes	Unclear risk	Unclear risk	High risk
Dutton 2012	total knee arthroplasty	Knee	I: autotransfusion (Bellovac ABT autotransfusion system), n=23; C: no drain, n=25)	POST	No		None	Control 0	Yes	Low risk	Low risk	Unclear risk
Ekback 1995	total hip arthroplasty	Hip	I: Autotransfusion (Haemonetics CellSaver 4, Althin model AT 1000 or Shiley/Dideco STAT), n=15; C: no autotransfusion, n=15	PERI	Yes	EVF < 27% (i.e. Hb < 9.2 g/dl)	Trigger 2	Control 1	N.A.	Unclear risk	Unclear risk	High risk

Elawad	1991	primary total hip arthroplasty	Hip	I: Autotransfusion (Electromedic Autotrans AT100) autotransfusion system), n=20; C: no drain, n=20	INTRA	Yes	Hb < 8.5 g/dl	Trigger 2	Control 0	N.A.	Unclear risk	High risk	High risk
Gannon	1991	total hip or total knee replacement	NAS	I: Autotransfusion (Solcotrans), n=124; C: standard suction canister, n=115	POST	Yes	Hb < 9.0 g/dl or by internist based on patients' condition	Trigger 2	Control 1	Yes	Low risk	Unclear risk	High risk
Healy	1994	hip arthroplasty, total knee arthroplasty or spine fusion	NAS	I: autotransfusion (Ortho-Evac system or Solcotrans), n=75; C: standard wound drainage system, n=43	POST	No		None	Control 1	Unknown	Unclear risk	Unclear risk	High risk
Heddle	1992	elective knee arthroplasty	Knee	I: autotransfusion (Solcotrans), n=39; C: standard care (drained blood collected by a Davol suction unit and discarded), n=40	POST	Yes	Hb 8.0-8.9 g/dl: 1 unit; Hb 7.0-7.9 g/dl: 2 units; Hb 6.0-6.9 g/dl: 3 units, Hb 5.0-5.9 g/dl: 4 units	Trigger 1	Control 1	Yes	Unclear risk	Unclear risk	High risk
Horstmann	2012	total hip arthroplasty	Hip	I: autotransfusion (Bellovac ABT autotransfusion system), n=50; C: no drainage, n=50)	POST	Yes	Hb < 6.4/ 8.0/ 9.6 g/dl dependent on ASA classification	Trigger 1	Control 0	N.A.	Unclear risk	Low risk	Low risk
Kirkos	2006	total knee arthroplasty	Knee	I: autotransfusion, n=78; C: standard vacuum drain, n=77	POST	Yes	Hb < 10.0 g/dl	Trigger 2	Control 1	Yes	High risk	Unclear risk	High risk
Koopman	1993	total hip arthroplasty or dorsal lumbo-sacral spinal fusion	NAS	I: autotransfusion (Haemonetics Haemolite-2 system), n=29; C: no autotransfusion, n=30	PERI	Yes	Hct at 30% (i.e. Hb <10.2 g/dl)	Trigger 2	Control 1	N.A.	Unclear risk	High risk	High risk

Lorentz	1991	total hip artrhoplasty	Hip	I: Autotransfusion, n=16; C: standard care, n=15	PERI	Yes	Hb < 9.0 g/dl (operating room, IC); Hb < 10.0 g/dl (other)	Trigger 2	Unknown	N.A.	Unclear risk	Unclear risk	High risk
Mah	1995	elective primary total knee replacement surgery	Knee	I: autotransfusion (Electromedics BT-795), n=44; C: standard care, n=55	POST	Yes	Hb < 10.0 g/dl	Trigger 2	Active	Yes	Low risk	Unclear risk	High risk
Majowski	1991	primary unilateral total knee arthroplasty	Knee	I: autotransfusion (Solcotrans), n=20; C: three standard Redivac drains	POST	Yes	Hb < 9.5 g/dl or if indicated hemodynamically	Trigger 2	Control 1	Yes	Unclear risk	Unclear risk	High risk
Mauerhan	1993	elective primary total hip arthroplasty and total knee arthroplasty	NAS	I: autotransfusion (CBC ConstaVac), n=57; C: standard post-operative collection system, n=54	POST	No		None	Control 1	Yes	Low risk	Unclear risk	High risk
Menges	1992	total hip surgery and pre-operative plasmapheresis	Hip	I: autotransfusion (Autotrans BT 795 P, Dideco system), n=14; C: No autotransfusion, n=12 (both groups also received crystalloids and colloids)	POST	Yes	Hb < 9.0 g/dl or Hct < 28% (i.e. Hb < 9.5)	Trigger 2	Active	N.A.	Unclear risk	Unclear risk	High risk
Moonen	2007	primary total knee arthroplasty or total hip arthroplasty	Hip and knee	I: autotransfusion (Bellovac ABT autotransfusion system), n=35 (hip) and n=45 (knee); C: regular post-operative low-vacuum drainage, n=48 (hip) and n=32 (knee)	POST	Yes	Hb < 8.1/ 8.9/ 9.7 g/dl dependent on ASA classification	Trigger 1	Control 1	Yes	Low risk	High risk	High risk
Newman	1997	unilateral total knee replacement	Knee	I: autotransfusion (Dideco 797 transfusion system), n=35; C: standard Hemovac suction drain, n=35	POST	No		None	Control 1	Yes	Low risk	Unclear risk	High risk

Riou	1994	elective, non-emergency spinal surgery	Other ortho paedic	I: autotransfusion (Solcotrans), n=25; C: postoperative drained blood collected into Solcotrans Orthopedic Plus system but salvaged blood was not considered for reinfusion, n=25	POST	Yes	Hct < 25% (i.e. Hb < 8.5 g/dl)	Trigger 2	Control 1	N.A.	Low risk	Unclear risk	Low risk
Ritter	1994	primary total hip or total knee replacement	Hip and knee	I: autotransfusion (Solcotrans), n=78 (hip) and n=137 (knee); C: no drainage system, n=62 (hip) and n=138 (knee)	POST	Yes	Hb < 9.0 g/dl	Trigger 2	Control 0	Yes	Unclear risk	Unclear risk	High risk
Rollo	1995	primary total hip arthroplasty	Hip	I: 1. autotransfusion (Haemonetics), n=35; 2. autotransfusion (Solcotrans), n=40; C: no drain, n=38	PERI/POST	No	Based on clinical condition of patient	None	Active	N.A.	Unclear risk	High risk	High risk
Rosencher	1994	knee replacement surgery	Knee	I: autotransfusion (Ortho-Evac system or Solcotrans), n=20; C: no drain, n=10	POST	Yes	Hct at 30% (i.e. Hb <10.2 g/dl)	Trigger 2	Control 0	Yes	Unclear risk	Unclear risk	High risk
Sait	1999	total knee arthroplasty	Knee	I: autotransfusion, n=60; C: standard care without autotransfusion, n=60	POST	No		None	Control 1	Yes	Unclear risk	Unclear risk	High risk
Shenolikar	1997	total knee replacement	Knee	I: autotransfusion (Haemonetics Cell Saver 3), n=50; C: no drain, n=50	POST	Yes	Hb < 9.0 g/dl	Trigger 2	Control 0	Yes	Low risk	Unclear risk	High risk
Simpson	1994	elective primary total joint arthroplasty	NAS	I: autotransfusion (Solcotrans), n=12; C: closede suction drain, n=12	POST	Yes	Hb < 10 g/dl or Hct < 30% (i.e. Hb < 10.2 g/dl)	Trigger 2	Control 1	Unknown	Unclear risk	Unclear risk	High risk

Slagis											
1991	total hip or knee replacement	Hip and knee	I: autotransfusion (Hemolite cell salver), n=24 (hip) and n=27 (knee); C: Hemovac standard drainage system, n=26 (hip) and n=25 (knee)	POST	No		None	Active	No	Unclear risk	Unclear risk	High risk
Smith											
2007	primary total hip replacement	Hip	I: autotransfusion (ABTrans autologous re-transfusion system), n=76; C: two standard Medinorm vacuum drains, n=82	POST	Yes	Hb < 8.0 g/dl and in symptomatic patients with Hb of 8.0-10.0 g/dl: 2 units	Trigger 1	Control 1	N.A.	Low risk	High risk	High risk
So-Osman											
2006	primary or revision total hip or knee replacement	Hip and knee	I: autotransfusion (DONOR or Bellovac ABT autotransfusion system), n=35 (hip) and n=12 (knee); C: standard closed suction wound drainage, n=11 (hip) and n=11 (knee)	POST	No		None	Control 1	Yes	Low risk	High risk	High risk
So-Osman											
2012	primary or revision total hip or knee replacement	Hip and knee	I: 1. autotransfusion (OrthoPat), n= 412 (hip); 2. Autotransfusion (Donor or Bellovac ABT autotransfusion system), n=419 (hip) and n=436 (knee); C: low vaccum wound drain, n=419 (hip) and n=417 (knee)	PERI/ POST	Yes	Hb < 6.4 for age < 60 years; Hb < 8.1 g/dl for age > 60 years; Hb < 9.6 g/dl in high risk	Trigger 1	Control 1	Yes	Low risk	Low risk	High risk
Thomas											
2001	total knee replacement	Knee	I: autotransfusion (Haemonetics Cell Saver 5), n=115, C: all drainaged blood was discarded, n=116	POST	Yes	Hb < 9.0 g/dl	Trigger 2	Control 1	Yes	Unclear risk	Unclear risk	High risk
Thomassen											
2012	primary or revision total hip arthroplasty	Hip	I: autotransfusion (Sangvia Blood Management System), n=106; C: regular postoperative low vacuum drain, n=110	PERI	Yes	Hb < 8.5 g/dl or clinical symptoms of anaemia	Trigger 2	Control 1	N.A.	Low risk	Low risk	Low risk

Tripkovic	2008	primary total hip replacement	Hip	I: autotransfusion (BIODREN system), n=30; C: no autotransfusion, n=30	POST	Yes	Hb < 10 g/dl or Hct < 30% (i.e. Hb < 10.2 g/dl)	Trigger 2	Active	N.A.	Unclear risk	Unclear risk	High risk
Zacharapoulos	2007	unilateral total knee replacement	Knee	I: autotransfusion (Gish Orthofuser system), n=30; C: standard wound suction drainage system, n=30	POST	Yes	Hb < 9.0 g/dl	Trigger 2	Control 1	Yes	Unclear risk	Unclear risk	High risk
Zhang	2008	orthopaedic procedures	NAS	I: autotransfusion (Haemonetics Cell Saver 5 system), n=20; C: standard care, n=20	INTRA	No		None	Control 1	N.A.	Unclear risk	Unclear risk	High risk

[1] Type: Hip, knee, hip and knee or not able to split (NAS).

[2] Timing Cell Salvage: POST = postoperative, INTRA = intraoperative, PERI = both intra- and postoperative.

[3] Subgroup: Trigger 1 Hb=<8.0 g/dl; Trigger 2 Hb> 8.0 g/dl

[4] Treatment policy in control group: Control 0 = in control groups no drain is used; Control 1 = in control group standard suction or vacuum drain is used; Active = in control group active treatment (active plus cell salvage versus active comparisons).

Chapter 3

Erythropoietin to reduce allogeneic red blood cell transfusion in patients undergoing total hip or knee arthroplasty

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Abstract

Background and Objectives: To determine the value of erythropoietin in reducing allogeneic transfusions, it is important to assess the effects, safety and costs for individual indications. Previous studies neither compared the effects of erythropoietin between total hip and total knee arthroplasty, nor evaluated the safety or costs. We performed a meta-analysis to assess the effects of erythropoietin in total hip and knee arthroplasty separately. Safety and costs were evaluated as secondary outcomes.

Materials and Methods: A systematic literature search was performed to identify randomized controlled trials evaluating the effect of erythropoietin in total hip and knee arthroplasty until April 2014. Study data were extracted using standardized forms and pooled using a random-effects model. Strength of the evidence was evaluated using Cochrane's Collaboration's tool for risk of bias assessment.

Results: Seven studies were included (2439 patients). Erythropoietin significantly reduced exposure to allogeneic transfusion in both hip (RR 0.45; 95%CI 0.33–0.61) and knee (RR 0.38; 95%CI 0.27–0.53) arthroplasty, without differences between indications ($P = 0.44$). Mean number of transfused red blood cell units was significantly decreased in erythropoietin-treated patients (mean difference −0.57; 95%CI −0.86 to −0.29)(unable to split). No differences in thromboembolic or adverse events were found. Only one study evaluated costs, so that no pooled cost-effectiveness estimates could be given.

Conclusion: Erythropoietin is effective in both hip and knee arthroplasty and can be considered as safe. However, the decision to use erythropoietin on a routine base should be balanced against its costs, which may be relatively high.

Introduction

Preoperative treatment with erythropoietin (EPO) is used in joint arthroplasty to correct preoperative anaemia, which is consequently a major risk factor for postoperative anaemia and allogeneic red blood cell (RBC) transfusion.[1] To determine the value of EPO in reducing allogeneic transfusions, it is important to assess the effects, safety and costs of EPO for individual indications. Previous reviews[1-3] and a recently published meta-analysis[4] showed that it is in general effective to use EPO to reduce allogeneic transfusion in orthopaedic procedures. However, neither of these studies compared the effect of EPO for individual indications such as total hip arthroplasty (THA) and total knee arthroplasty (TKA), nor evaluated the safety or cost involved in using EPO[4].

We hypothesized that the effects of preoperative EPO to reduce allogeneic transfusion might be larger in THA than in TKA due to a larger postoperative drop in haemoglobin (Hb) in THA than in TKA.[5] This hypothesis is supported by lower transfusion rates in TKA compared to THA,[6-9] with absolute differences up to 17%.[8] This might be due to differences in body mass index (BMI),[10,11] comorbidities,[10] anatomy of the surgical area and the extent of deep surgical dissection, leading to differences in blood loss.[10,12] These confounders necessitate a stratified analysis of patient blood management in TKA and THA, because a difference in the effect of EPO between TKA and THA could cause overtreatment.

In addition to the effects of EPO to reduce allogeneic transfusion, both the safety and costs of EPO need to be taken into account before implementation in daily practice. EPO increases the risk for thromboembolic and vascular adverse events and other non-thromboembolic adverse events.[3] On the other hand, treating patients with allogeneic transfusion might also be complicated by transfusion reactions.[13] Other concerns are the increased risks of wound or prosthesis infection after allogeneic transfusion, but the literature about this effect is ambiguous.[13-17]

Finally, also the costs of EPO treatment need to be considered. If EPO treatment is effective to reduce allogeneic transfusion, but the benefits of EPO do not outweigh the reduction in allogeneic transfusions which are relatively safe, there might be no advantage for routine use of EPO treatment in daily clinical practice.

Therefore, the aim of this meta-analysis was to assess the effect of EPO in reducing exposure to allogeneic transfusion and the mean number of RBC units transfused in both total hip and total knee arthroplasty. As secondary outcomes, the safety and costs of EPO were evaluated.

Materials and methods

Study selection

For this meta-analysis, Medline, Embase, Web of Science and the Cochrane library were systematically searched from inception through April 2014 without language restrictions (Appendix S1: Search strategy). Two reviewers independently performed the screening of titles, abstract and full-text articles. Consensus in the selection process was reached through discussion. If consensus was not reached, a third reviewer was consulted.

Articles were eligible for inclusion if they reported results of randomized controlled trials (RCT) that compared the effects of EPO and control in adult (age>18) patients undergoing elective THA or TKA. Studies had to report data on the number of patients exposed to allogeneic transfusion, or the mean number of allogeneic RBC units transfused. Administration of EPO should start prior to surgery. Excluded were studies in which the effect of EPO to augment preoperative autologous donation (PAD) was assessed. Studies with a combination of active comparisons were only included if both the intervention and control groups were equally exposed to the active treatment (active plus EPO compared to active only).

Data extraction

For each selected trial, the reviewers independently extracted study characteristics, primary (effect) and secondary (safety and cost) outcomes. When data could not be extracted separately for THA or TKA from the article, the authors of the study were contacted twice. When they did not respond, the article was excluded for the analyses. Study characteristics included type of surgery, description of the intervention (timing, dosage and frequency of EPO administration), description of the control group (placebo or no intervention), adjuvant usage of iron (oral or intravenous), usage of threshold for EPO eligibility, usage of threshold for allogeneic transfusion, concomitant interventions. Primary outcomes included the number of patients exposed to allogeneic transfusion and the mean number of RBC units transfused per patient. Secondary outcomes included the number of thromboembolic events, the number of adverse events and the costs per study arm (either EPO or control).

Statistical analysis

Data were analysed using Review Manager software (RevMan version 5.3 http://tech.cochrane.org/revman). Dichotomous and continuous data were pooled across trials using a random-effects model. For dichotomous data, a risk ratio was calculated using the Mantel–Haenszel method. For continuous data, a standardized mean

difference was calculated. If studies compared different EPO dosages or regimens with controls, these EPO arms were combined. Statistical heterogeneity was examined by the I^2 test. The I^2 test describes the percentage of the total variation across studies due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas values >50% indicate substantial heterogeneity[18].

The following *a priori* defined subgroup analyses with an explorative nature were performed to identify patient group(s) who might benefit from EPO use: 'Hb cut-off level for EPO treatment' including non-restricted use and restricted use; 'EPO dosage' including high dose (>1500 IU/kg bodyweight), low dose (<1500 IU/kg bodyweight) and fixed dose (fixed EPO dose irrespective to bodyweight); 'EPO timing' including short preoperative period (treatment starts 10–11 days preoperatively with daily injections) and long preoperative period (treatment starts 3–4 weeks preoperatively with a weekly injection regime); 'type of iron' including oral and intravenous; 'transfusion threshold' including restrictive (allogeneic transfusion if Hb </= 8.0 g/dl) and liberal (all others); and 'blinding' including blinded (placebo used in control group) and non-blinded (no placebo used). Differences were considered significant if the *P*-value was below 0.05.

Strength of the evidence

Included studies were assessed for methodological quality using the Cochrane Collaboration's tool for assessing the risk of bias by two independent reviewers. Overall quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach using the GRADEpro guideline development tool. By assessing the quality of the evidence, the confidence in the effect estimates can be determined.

Results

The literature search strategy resulted in a total of 799 potentially relevant articles (Figure 1). Seventy articles were selected for full-text screening. Finally, seven articles describing a total of 2497 patients met the inclusion criteria and were used in the meta-analysis.[19-25] Of the seven identified studies, two only included THA patients, two studies included both THA and TKA, two studies included several types of orthopaedic surgery (e.g. THA, TKA, spine, upper extremity, ankle) and one study included orthopaedic as well as non-orthopaedic patients (THA, TKA, cardiac surgery and 'other'). Five of seven studies included both primary and revision surgery of the hip and/or knee,[19-21-23-24] one study excluded patients undergoing revision surgery,[22] and one study did not specify if

revision surgery was included.[25] (Appendix 2: Study characteristics). Only one study reported costs of EPO use.[24]

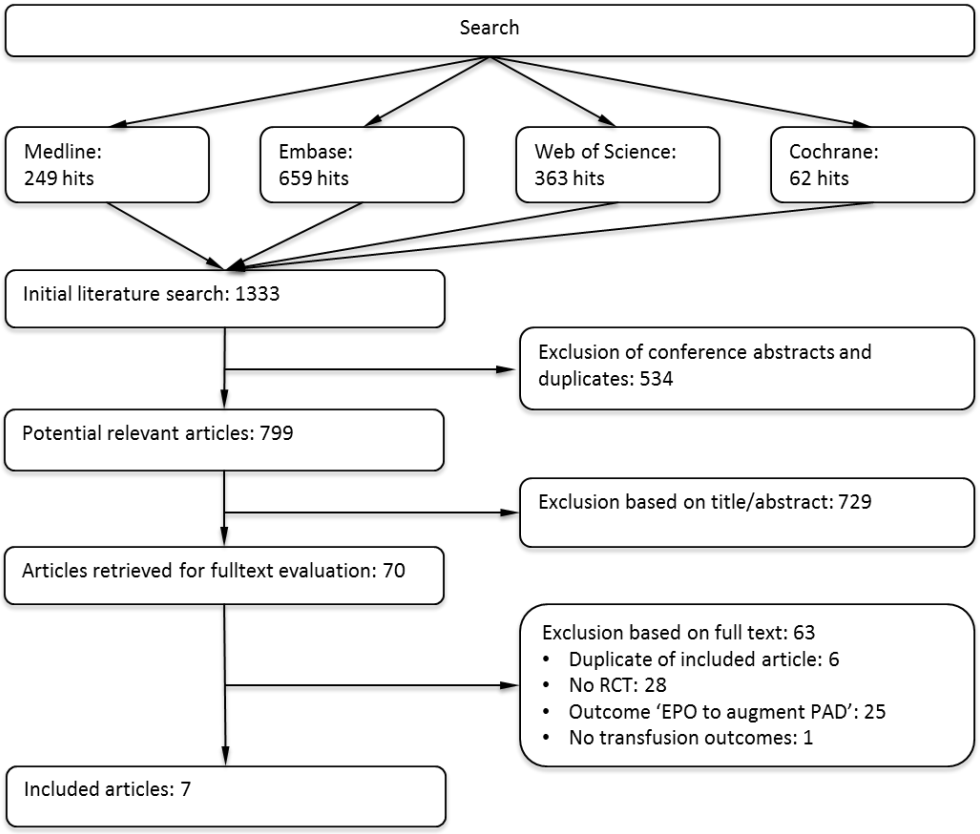

Figure 1: Flowchart

Effects of EPO

Overall EPO reduced the exposure rate by 54% compared with controls (RR 0.46; 95%CI 0.44–0.80) (Figure 2) in all included patients. However, various types of surgery were included in this analysis and the heterogeneity was substantial (I^2 = 71%). Subsequently, THA and TKA were analysed separately. In THA patients, EPO reduced the exposure rate by 55% (RR 0.45; 95%CI 0.33–0.61) (Figure 3). The heterogeneity between these studies was still substantial (I^2 = 67%). In TKA patients, EPO reduced the exposure rate by 62% (RR

0.38; 95%CI 0.27–0.53) (Figure 3), with no heterogeneity between studies (I^2 = 0%). There was no significant difference in the effect of EPO between THA and TKA (*P* = 0.44).

EPO significantly reduced the mean number of RBC units transfused (mean difference −0.57; 95%CI −0.86 to −0.29) (Figure 4), with substantial heterogeneity between the studies (I^2 = 84%). It was not possible to assess the effect of EPO on the mean number of RBC units transfused for THA and TKA separately.

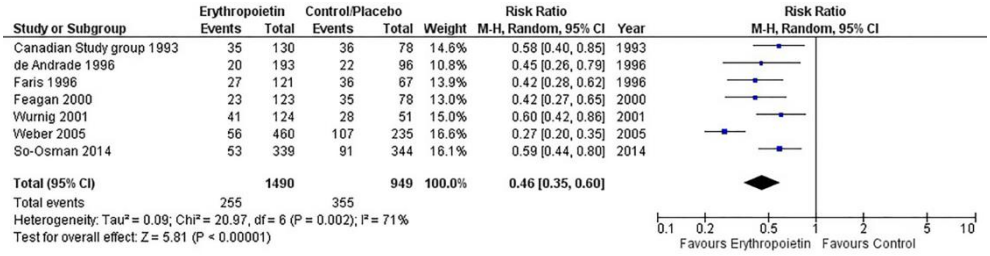

Figure 2: Patients exposed to allogeneic RBC transfusion

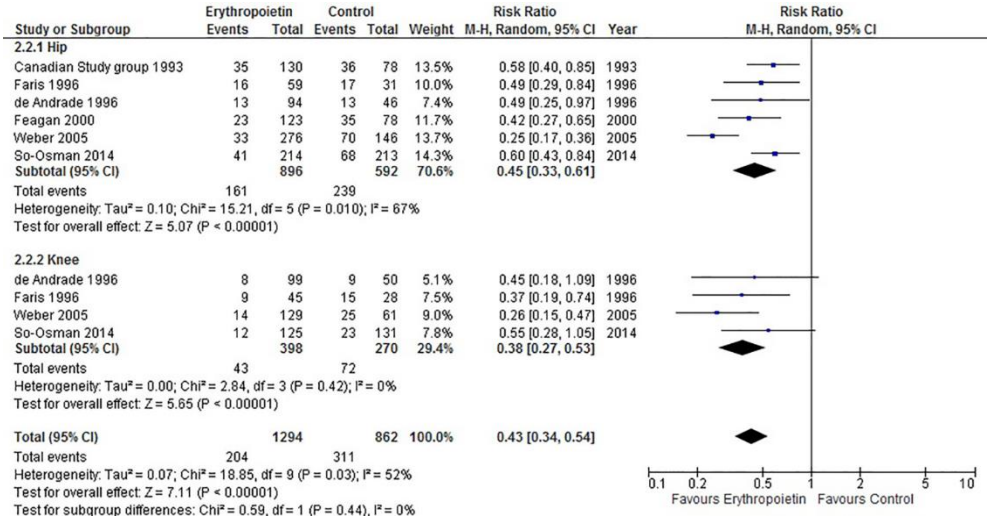

Figure 3: THA and TKA patients exposed to allogeneic RBC transfusion

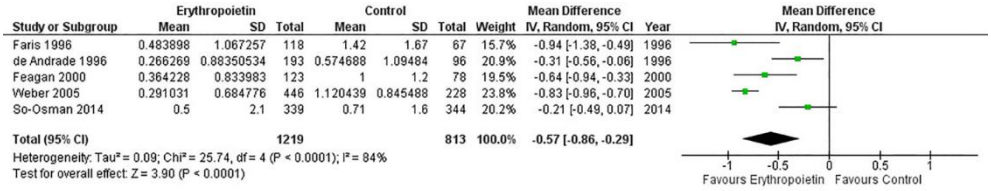

Figure 4: Mean number of RBC units transfused per patient

3

Safety and costs of EPO

Thromboembolic events were reported in different ways. Three studies actively searched for the presence of deep venous thrombosis (DVT) by ultrasonography or venography[19,21,22] whereas two others only reported symptomatic DVTs,[24,25] and two did not report how they assessed DVT.[20,23] Four studies reported thromboembolic events,[19,21-23] whereas the three other studies reported a combination of thromboembolic and vascular events.[20,24,25] Reporting of other adverse events also varied severely between studies. One study reported adverse events in patients that underwent surgery (excluding patients with adverse events after receiving study medication).[22] Four other studies reported adverse events of all patients that received at least one dose of study medication[20,21,24,25] or only stated 'there were no differences'.[19,23] Analysis of the thromboembolic and vascular adverse events showed that the use of EPO did not lead to an increase of events (RR 1.14; 95%CI 0.71–1.84). Heterogeneity between studies was negligible (I^2 = 3%) (Appendix 3: Thromboembolic events and adverse events, figure 1). Analysis of the other adverse events showed no significant differences between EPO and control (RR 1.01; 95%CI 0.94–1.01), again without any heterogeneity between studies (I^2 = 0%) (Appendix 3: Thromboembolic events and adverse events, figure 2).

Only one study evaluated the costs of EPO use.[24] In that study, costs were estimated from a hospital perspective, with a 3-month horizon. The EPO strategy increased costs with €785 per patient in comparison with no intervention. With an absolute reduction in exposure to transfusion from 26.4% to 15.6% in this study, EPO avoided transfusion in every nine patients, translating the cost estimate to €7300 per avoided transfusion.[24]

Subgroup analyses

No subgroups could be identified in which the effect of EPO to reduce allogeneic transfusions differs from the overall effect (Appendix 4: Subgroup analyses).

Strength of the evidence

The overall strength of the evidence using the GRADE approach is 'high'. A detailed description of the strength of the evidence is shown in Appendix 5: Strength of the evidence.

Discussion

This meta-analysis showed that the use of preoperative EPO reduces the exposure of patients to allogeneic transfusions in both THA and TKA, with no difference in its effect between THA and TKA. These results suggest that the differences between THA and TKA in the effect of EPO are either absent or too small to be detected given the number of studies and/or the number of patients. Furthermore, this meta-analysis shows that the use of EPO did not increase the number of thromboembolic events nor the number of other adverse events. Therefore, the use of EPO to prevent allogeneic transfusions in THA and TKA can be considered as safe. The costs of EPO treatment were derived from a single study and were estimated at an additional €785 per patient or €7300 per avoided allogeneic transfusion, but estimates may differ in other healthcare systems.

In addition to previous studies,[1-4] and the recently published meta-analysis on the effectiveness of EPO,[4] our study assessed the effects for hip and knee separately, and included safety and costs of erythropoietin. Furthermore, this meta-analysis included three more studies[21,24,25] and used more strict inclusion criteria as we believed that these more strict criteria increase the quality of the conclusion to whether or not to use EPO in hip and knee arthroplasty. The use of more strict inclusion criteria led to the exclusion of studies in which the effect of EPO to augment PAD was tested or in which the effect of EPO was compared with the effect of PAD,[4] a study that started EPO postoperatively[26] and a study in which the transfusion rate or mean number of RBC units was not reported[27] in comparison with the meta-analysis of Alsaleh *et al*.[4]

Some limitations of this meta-analysis should be mentioned. First, the studies included in this meta-analysis selectively reported their used methods for perioperative care (such as the use of venous thrombosis prophylaxis) and their outcomes. This made it impossible to analyse the mean number of transfused RBC units and safety outcomes for THA and TKA separately, to analyse postoperative Hb levels, and to compare the effect of EPO for primary or revision surgery separately. Despite several attempts, additional data could not be retrieved, except for the most recent study.[24]

A second limitation is that patient safety outcomes were not assessed nor reported in a uniform way in the included studies. Furthermore, studies may not be powered to find differences in safety as the adverse outcomes are more rare than allogeneic transfusions in the included studies. This heterogeneity in reporting and lack of power complicates the comparison between studies and limits the interpretability of the patient safety analyses for EPO. However, the non-uniform reporting of safety outcomes would be expected to result in heterogeneous estimates, which were not found so that we are confident that the results regarding the safety outcomes showing no effect are valid findings.

Third, the costs analysis of the use of EPO in both THA as well as TKA was only available in one study.[24] That study concluded that the EPO strategy costs were as high as €785 per patient or €7300 per avoided transfusion. Due to variation in dosage and frequency of administration of EPO and differences in costs of both EPO and allogeneic RBC units in countries,[28] the costs cannot be extrapolated to other studies or healthcare systems. However, the high costs of EPO treatment identified in this study[24] are confirmed by several non-randomized studies. Bedair *et al*. (2014) concluded that EPO was too expensive for routine use, especially because there are less expensive alternatives.[29] Coyle *et al*. (1999) concluded that the incremental costs of EPO compared with no intervention per life year gained were as high as $66 million.[30] This was substantiated further in a systematic review and economic model.[31] Only a single study concluded that EPO treatment was cost saving in orthopaedics, by assuming that in a population with a high-transfusion-rate EPO could prevent nearly all transfusions.[32] However, that assumption is not supported by our current findings.

In conclusion, this study shows that EPO reduces allogeneic transfusions in both hip and knee arthroplasty without any additional adverse outcomes. However, given that allogeneic transfusions are also relatively safe (Dutch data show that only 0.014% of the patients experience serious transfusion reactions[33]), in combination with the decreasing RBC use in THA and TKA (Figure 4) and the substantial costs for EPO treatment to avoid these allogeneic transfusions, it remains debatable whether routine use of EPO is justified in orthopaedic practice. Furthermore, less expensive alternatives can be considered as well. To decide on these issues, more well-designed studies, evaluating the costs relative to the effectiveness of individual elements in patient blood management, are needed. In addition, future research should be aimed at the identification of patients at risk for an allogeneic transfusion that benefit most from EPO treatment.

Acknowledgements

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References

1. Goodnough LT, Maniatis A, Earnshaw P, *et al*.: Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. *Br J Anaesth*2011; 106:13–22
2. Tran DHD, Wong GTC, Chee YE, *et al*.: Effectiveness and safety of erythropoiesis-stimulating agent use in the perioperative period. *Expert Opin Biol Ther* 2014; 14:51–61
3. Lin DM, Lin ES, Tran MH: Efficacy and safety of erythropoietin and intravenous iron in perioperative blood management: a systematic review. *Transfus Med Rev* 2013; 27(4):221–234
4. Alsaleh K, Alotaibi GS, Almodaimegh HS, *et al*.: The use of preoperative erythropoiesis-stimulating agents (ESAs) in patients who underwent knee or hip arthroplasty: a meta-analysis of randomized clinical trials. *J Arthroplasty* 2013; 28:1463–1472
5. Zhou Q, Zhou Y, Wu H, *et al*.: Changes of hemoglobin and hematocrit in elderly patients receiving lower joint arthroplasty without allogeneic blood transfusion. *Chin Med J (Engl)* 2015; 128:75–78
6. Theusinger OM, Kind SL, Seifert B, *et al*.: Patient blood management in orthopaedic surgery: a four-year follow-up of transfusion requirements and blood loss from 2008 to 2011 at the Balgrist University Hospital in Zurich, Switzerland. *Blood Transfus* 2014; 12:195–203
7. Yoshihara H, Yoneoka D: National trends in the utilization of blood transfusions in total hip and knee arthroplasty. *J Arthroplasty* 2014; 29:1932–1937
8. Frisch NB, Wessell NM, Charters MA, *et al*.: Predictors and complications of blood transfusion in total hip and knee arthroplasty. *J Arthroplasty* 2014; 29(9 Suppl):189–192
9. Marson BA, Shah J, Deglurkar M: Blood transfusion in hip and knee arthroplasties: the end of the pre-operative group and save? *Eur J Orthop Surg Traumatol* 2015; 25(5):871–875
10. Choi JK, Geller JA, Yoon RS, *et al*.: Comparison of total hip and knee arthroplasty cohorts and short-term outcomes from a single-center joint registry. *J Arthroplasty* 2012; 27:837–841
11. Sawalha S, Ralte P, Chan C, *et al*.: The effect of obesity on theatre utilisation time during primary hip and knee replacements. *Open Orthop J* 2015; 9:68–72
12. Pow RE, Vale PR: Thromboprophylaxis in patients undergoing total hip and knee arthroplasty: a review of current practices in an Australian teaching hospital. *Intern Med J* 2015; 45:293–299
13. Shah A, Stanworth SJ, McKechnie S: Evidence and triggers for the transfusion of blood and blood products. *Anaesthesia* 2015; 70(Suppl 1):10–15
14. Newman ET, Watters TS, Lewis JS, *et al*.: Impact of perioperative allogeneic and autologous blood transfusion on acute wound infection following total knee and total hip arthroplasty. *J Bone Joint Surg Am* 2014; 96:279–284
15. Friedman R, Homering M, Holberg G, *et al*.: Allogeneic blood transfusions and postoperative infections after total hip or knee arthroplasty. *J Bone Joint Surg Am* 2014; 96:272–278
16. Yates AJ Jr: The relative risk of infection from transfusions after arthroplasty: commentary on articles by Richard Friedman, MD, FRCSC, et al.: "Allogeneic blood transfusions and postoperative infections after total hip or knee arthroplasty" and Erik T. Newman, MD, et al.: "Impact of perioperative allogeneic and autologous blood transfusion on acute wound infection following total knee and total hip arthroplasty". *J Bone Joint Surg Am* 2014; 96:e33
17. Rohde JM, Dimcheff DE, Blumberg N, *et al*.: Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. *JAMA* 2014; 311:1317–1326
18. Higgins JPT, Green S (editors): *Cochrane Handbook for Systematic Reviews of Interventions*, version 5.1.0. The Cochrane Collaboration, 2009
19. Canadian Orthopedic Perioperative Erythropoietin Study Group Effectiveness of perioperative recombinant human erythropoietin in elective hip replacement. *Lancet* 1993; 341:1227–1232
20. Faris P: Use of recombinant human erythropoietin in the perioperative period of orthopedic surgery. *Am J Med* 1996; 101:28S–32S
21. de Andrade JR, Jove M, Landon G, *et al*.: Baseline hemoglobin as a predictor of risk of transfusion and response to Epoetin alfa in orthopedic surgery patients. *Am J Orthop (Belle Mead NJ)* 1996; 25:533–542
22. Feagan BG, Wong CJ, Kirkley A, *et al*.: Erythropoietin with iron supplementation to prevent allogeneic blood transfusion in total hip joint arthroplasty. A randomized, controlled trial. *Ann Intern Med* 2000; 133:845–854
23. Weber E, Slappendel R, Hemon Y, *et al*.: Effects of epoetin alfa on blood transfusions and postoperative recovery in orthopaedic surgery: the European Epoetin Alfa Surgery Trial (EEST). *Eur J Anaesthesiol* 2005; 22:249–257

24. So-Osman C, Nelissen RG, Koopman-van Gemert AW, *et al*.: patient blood management in elective total hip and knee-replacement surgery (part 1): a randomized controlled trial on erythropoietin and blood salvage as transfusion alternatives using a restrictive transfusion policy in erythropoietin-eligible patients. *Anesthesiology* 2014;120(4):839–51
25. Wurnig C, Schatz K, Noske H, *et al*.: Subcutaneous low-dose epoetin beta for the avoidance of transfusion in patients scheduled for elective surgery not eligible for autologous blood donation. *Eur Surg Res* 2001; 33:303–310
26. Na HS, Shin SY, Hwang JY, *et al*.: Effects of intravenous iron combined with low-dose recombinant human erythropoietin on transfusion requirements in iron-deficient patients undergoing bilateral total knee replacement arthroplasty. *Transfusion* 2011; 51:118–124
27. Olijhoek G, Megens JG, Musto P, *et al*.: Role of oral versus IV iron supplementation in the erythropoietic response to rHuEPO: a randomized, placebo-controlled trial. *Transfusion* 2001; 41:957–963
28. Baarsma B, Mutsaerts M: Costs of Blood (in Dutch). *ESB* 2012; 97:664–666
29. Bedair H, Yang J, Dwyer MK, *et al*.: Preoperative erythropoietin alpha reduces postoperative transfusions in THA and TKA but may not be cost-effective. *Clin Orthop Relat Res* 2014; 473(2):590–596
30. Coyle D, Lee KM, Fergusson DA, *et al*.: Economic analysis of erythropoietin use in orthopaedic surgery. *Transfus Med* 1999; 9:21–30
31. Davies L, Brown TJ, Haynes S, *et al*.: Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model. *Health Technol Assess* 2006; 10(44):iii-iv, ix-x, 1–210,
32. Green WS, Toy P, Bozic KJ: Cost minimization analysis of preoperative erythropoietin vs autologous and allogeneic blood donation in total joint arthroplasty. *J Arthroplasty* 2010; 25:93–96
33. Schipperus M.R: TRIP annual report 2012 Hemovigilance. Hemovigilance and biovigilance office the Netherlands 2012

Appendix 1: Search strategy performed on 2-4-2014

Pubmed: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?otool=leiden

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02-04-2014: 249 hits

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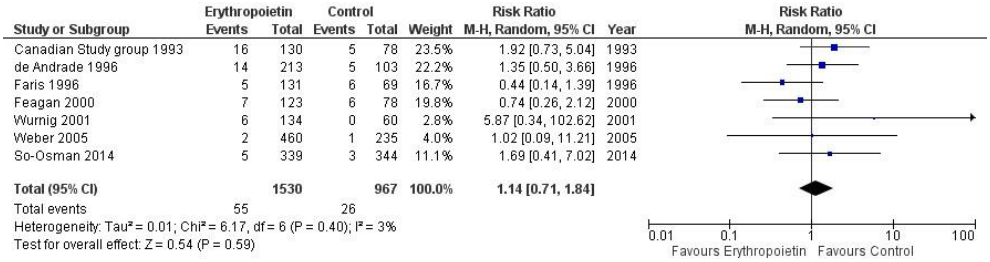
2-4-2014: 62 hits

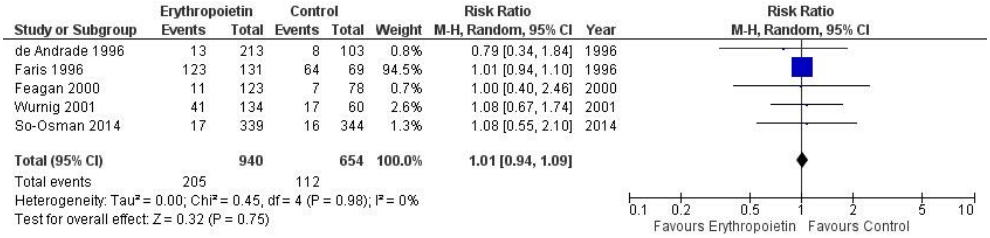
Appendix 2: Study characteristics

Author	No. of patients and mean age	Mean follow up-time	Type of surgery	Hb range to be eligible	Interventions	EPO dosage (total dosage)	Transfusion threshold
Canadian study group 1993	N=208 63 (SD 13)	3 weeks	THA	11-16 g/dl	Arm 1: EPO 14 days (started 11 days preoperative) + oral iron Arm 2: EPO 9 days, placebo 5 days (EPO started 11 days preoperative) + oral iron Arm 3: Placebo 14 days (started 11 days preoperative) + oral iron	14* 300IU/kg (4200 IU/kg) 9* 300 IU/kg (2700 IU/kg) -	Hb <9.0 g/dl
De Andrade 1996	N=316 67 (SD 12)	6 weeks	THA and TKA	≤15 g/dL	Arm 1: EPO 15 days (started 10 days preoperative) + oral iron Arm 2: EPO 15 days (started 10 days preoperative) + oral iron Arm 3: Placebo + oral iron	15* 300 IU/kg (4500 IU/kg) 15* 100 IU/kg (1500 IU/kg) -	Hb <9.0 g/dl
Faris 1996	N=200 66 (SD 13)	Until discharge	THA, TKA, spine, other orthopedic	not restricted	Arm 1: EPO 15 days (started 10 days preoperative) + oral iron Arm 2: EPO 15 days (started 10 days preoperative) + oral iron Arm 3: Placebo + oral iron	15* 300 IU/kg (4500 IU/kg) 15* 100 IU/kg (1500 IU/kg) -	Hb <9.0 g/dl
Feagan 2000	N=201 68 (SD 11)	Until discharge (at least 5 days)	THA	9.8-13.7 g/dl	Arm 1: EPO weekly (4 weeks preoperative) + oral iron Arm 2: EPO weekly (4 weeks preoperative) + oral iron Arm 3: Placebo + oral iron	4*40.000 U (160,000 U) 4*20.000U (80,000 U) -	None
Wurnig 2001	N=194 62-66 (SD N/A)	At least 6 days	Elective surgery (mainly orthopedic and cardiac)	10-14 g/dl	Arm 1: EPO weekly (3-4 weeks preoperative) + oral iron Arm 2: EPO weekly (3-4 weeks preoperative) + oral iron Arm 3: oral iron only	3-4*125 IU/kg (375-500 IU/kg) 3-4* 250 IU/kg (750-1000 IU/kg) -	Hb <8.5 g/dl
Weber 2005	N=695 67 (SD 11)	4-6 weeks	THA, TKA and spine	10-13 g/dl	Arm 1: EPO weekly (3 weeks preoperative) + oral iron Arm 2: 'usual care' (oral iron, IV iron or no iron)	4*40.000 U (160,000 U) -	Hb <8.0 g/dl
So-Osman 2014	N=683 71 (SD 12)	3 months	THA and TKA	10-13 g/dl	Arm 1: EPO weekly (3 weeks preoperative) + oral iron Arm 2: nothing	4*40.000 U (160,000 U) -	variable, Hb < 6.4 or 8.1 or 9.7 g/dl

Appendix 3: Thromboembolic events and adverse events



Appendix 3 Figure 1: Thromboembolic events



Appendix 3 Figure 2: Adverse events

Appendix 4: Subgroup analyses

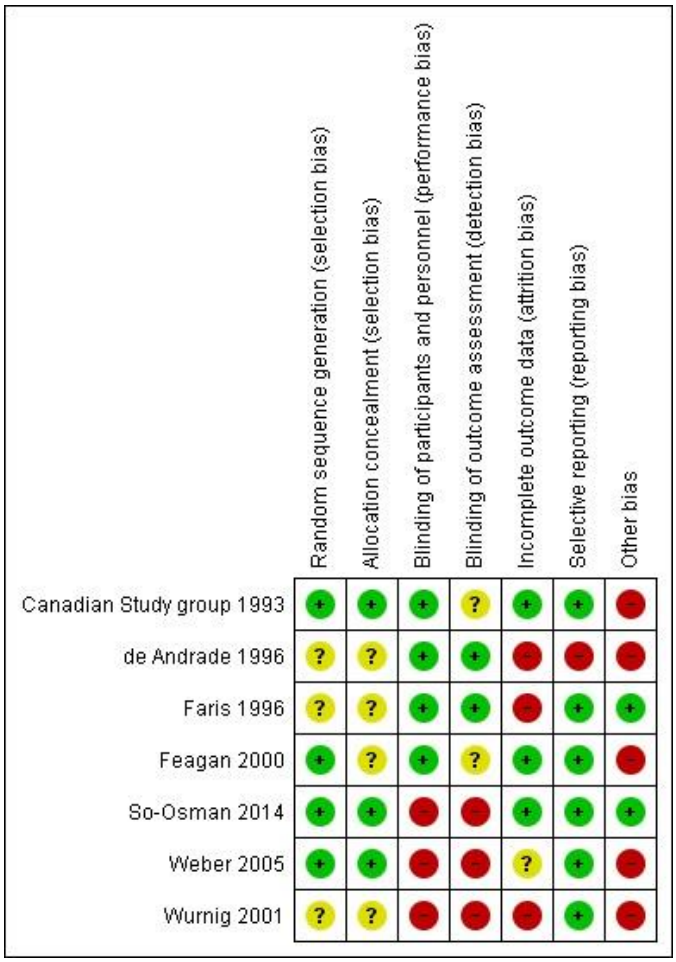
Two subgroup analyses, Hb cut-off level and type of iron used, could not be performed due to lack of variation between the studies on these variables

EPO was effective to reduce the percentage of patients exposed to allogeneic transfusion in all performed subgroups (EPO dosage, EPO timing, used transfusion threshold, and blinding). No differences in the effect of EPO between subgroups could be identified, with an I^2=0% in all subgroup analyses.

The effect of EPO to reduce the mean number of transfused RBC units varied between the subgroups. For this outcome only five out of seven studies could be used due to a lack in the availability of data on the mean number of transfused RBC units. In the subgroups 'high EPO dosage', 'short preoperative period', 'restrictive transfusion threshold' and 'non-blinded' EPO did not significantly reduce the mean number of transfused RBC units. All these subgroups included 2 studies. In all other subgroups EPO did reduce the mean number of RBC units transfused. There were no subgroup differences, with I^2=0 in all subgroup analyses.

Appendix 5: Strength of the evidence

Figure 1 describes the author's judgments about the risk of bias for each included study. All studies had a high or unclear risk of bias on at least one domain. The highest risk of bias was found on the 'other bias' domain. All included studies were sponsored or supported by a pharmaceutical company. However, two studies reported that, although being sponsored, the funding did not have any influence in the design, data-collection, analysis or reporting of the study results and were therefore judged to have a low risk of 'other bias'. The other five studies were judged to have a high risk of bias. The overall strength of the evidence using the GRADE approach is 'high' (figure 2)



Appendix 5 Figure 1: Risk of bias assessment

EPO compared to control in total hip and knee arthroplasty

Patient or population: total hip and knee arthroplasty
Intervention: EPO
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (Studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	**Risk with EPO**				
Patients exposed to allogeneic transfusion	**Study population**		**RR 0.46** (0.35 to 0.6)	2439 (7 RCTs)	⨁⨁⨁⨁ HIGH[1,2,3]	
	374 per 1000	**172 per 1000 (131 to 224)**				
	Moderate					
	455 per 1000	**209 per 1000 (159 to 273)**				
Mean number transfused	The mean mean number transfused in the control group was **0**	The mean mean number transfused in the intervention group was 0.57 lower (0.86 lower to 0.29 lower)	-	(5 RCTs)	⨁⨁⨁⨁ HIGH[1,2,3]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. No explanation was provided
2. All studies have a high or unclear risk of bias on at least one domain
3. There was substantial heterogeneity among studies

Appendix 5 Figure 2: Summary of findings

Chapter 4

Designing a strategy to implement cost-effective blood transfusion management in elective hip and knee arthroplasties: A study protocol

Veronique MA Voorn, Perla J Marang-van de Mheen, Cynthia So-Osman, Thea PM Vliet Vlieland, Ankie WMM Koopman-van Gemert, Rob GHH Nelissen, Leti van Bodegom-Vos for the LISBOA study group

Implement Sci. 2012 Jun 30;7:58.

Abstract

Background: Total hip and knee arthroplasties are two of the most commonly performed procedures in orthopedic surgery. Different blood-saving measures (BSMs) are used to reduce the often-needed allogenic blood transfusions in these procedures. A recent large randomized controlled trial showed it is not cost-effective to use the BSMs of erythropoietin and perioperative autologous blood salvage in elective primary hip and knee arthroplasties. Despite dissemination of these study results, medical professionals keep using these BSMs. To actually change practice, an implementation strategy is needed that is based on a good understanding of target groups and settings and the psychological constructs that predict behavior of medical professionals. However, detailed insight into these issues is lacking. Therefore, this study aims to explore which groups of professionals should be targeted at which settings, as well as relevant barriers and facilitators that should be taken into account in the strategy to implement evidence-based, cost-effective blood transfusion management and to de-implement BSMs.

Methods: The study consists of three phases. First, a questionnaire survey among all Dutch orthopedic hospital departments and independent treatment centers (n = 99) will be conducted to analyze current blood management practice. Second, semi-structured interviews will be held among 10 orthopedic surgeons and 10 anesthesiologists to identify barriers and facilitators that are relevant for the uptake of cost-effective blood transfusion management. Interview questions will be based on the Theoretical Domains Interview framework. The interviews will be followed by a questionnaire survey among 800 medical professionals in orthopedics and anesthesiology (400 professionals per discipline) in which the identified barriers and facilitators will be ranked by frequency and importance. Finally, an implementation strategy will be developed based on the results from the previous phases, using principles of intervention mapping and an expert panel.

Discussion: The developed strategy for cost-effective blood transfusion management by de-implementing BSMs is likely to reduce costs for elective hip and knee arthroplasties. In addition, this study will lead to generalized knowledge regarding relevant factors for the de-implementation of non-cost-effective interventions and insight in the differences between implementation and de-implementation strategies.

Background

Total hip and knee arthroplasties are two of the most commonly performed procedures in orthopedic surgery.[1,2] It is expected that the number of these procedures within the Netherlands will increase to more than 100,000 by the year 2030.[3] During primary hip or knee arthroplasty, the calculated visible and invisible blood loss is 1500 ml on average, followed by a drop of hemoglobin of approximately 3 g/dl.[4] This leads to high rates of allogenic blood transfusions up to 69% depending on the transfusion threshold.[5] Even though blood transfusions may be necessary, they include the risk for infections and noninfectious transfusion reactions[6].

Many studies on blood-saving measures (BSMs) have therefore been performed, including erythropoietin (EPO) and perioperative autologous blood salvage (intra-operative use of Cell Saver (CS) and a postoperative drainage and reinfusion device (DR)). Reviews showed that these studies had several limitations, such as a retrospective design, small patient numbers and poor methodological quality.[5,7,8] A multicenter randomized controlled trial (RCT) with adequate power (n = 2442) was therefore performed recently to test the cost-effectiveness of using BSMs, including EPO, CS, and DR, in elective primary hip and knee arthroplasties.[9] It was shown that blood salvage (CS and DR) resulted in neither decreased mean red blood cell (RBC) use nor in a decrease in the proportion of transfused patients and was more expensive due to the costs of the devices used and a prolonged hospital stay. EPO showed a significant decrease in the proportion of transfused patients, but costs were considered too high. It was thus concluded that these BSMs were not cost-effective in primary hip and knee arthroplasties.[10]

Despite this evidence about BSMs not being cost-effective, medical professionals keep using these BSMs in daily practice. To decrease costs of care delivery to patients undergoing a hip or knee arthroplasty, cost-effective blood transfusion management needs to be implemented. However, little is known about how to effectively de-implement common practices. To actually change practice, a de-implementation strategy is needed that is based on a good understanding of target groups and settings and the barriers and facilitators that influence the behavior of medical professionals.[10,11] However, detailed insight into these factors is lacking. Psychological theories are used in understanding and predicting intentions and clinical behavior[12] and may help to outline an effective strategy to de-implement these non-cost-effective BSMs.

Objective

The Leiden Implementation Study of BlOod management in hip and knee Arthroplasties (LISBOA) aims to explore the target groups, settings, and relevant barriers and facilitators

that should be taken into account to develop a strategy directed at all involved medical professionals (target group) and their organizations to implement evidence-based, cost-effective transfusion management and to de-implement BSMs.

To reach the aim of this study, the following research questions were formulated:

A. How often and in what settings are BSMs applied in hip and knee arthroplasties?
B. Which barriers and facilitators influence the implementation of cost-effective blood transfusion management and de-implementation of non-cost-effective BSMs among the target group, including orthopedic surgeons and anesthesiologists?
C. What is a tailored implementation strategy for the uptake of cost-effective blood transfusion management given the results of the first two research questions?

Methods

The study will be subdivided in three study phases to be executed in one year:

A. Analysis of current blood transfusion management practice in elective primary hip and knee arthroplasties (months 1 to 3)
B. Analysis of barriers and facilitators relevant for the implementation of cost-effective blood transfusion management and de-implementation of non-cost-effective BSMs (months 4 to 8)
C. Development of an implementation strategy based on the results of phases A and B (months 9 to 12)

The study design, study population, analysis, and outcome measures are described per study phase.

Phase A: Analysis of current blood transfusion management

Study design

To analyze current blood transfusion management practice in hip and knee arthroplasties, a survey among all orthopedic departments of Dutch university, teaching, and general hospitals and independent treatment centers will be performed. A survey in the period 1995–1997 showed that EPO was used rarely in the Netherlands at that time, in only 2% of all hospitals, and that CS was used in 24% of hospitals[13]. A more recent survey in 2007 showed that approximately half of all Dutch orthopedic departments applied EPO and/or autologous blood salvage[14]. However, these surveys neither showed how frequent these BSMs were applied within hospitals nor in what type of setting (university, teaching, or

general hospital or independent treatment center). This information is needed to target the implementation strategy to the appropriate professionals and departments.

The current survey will thus include questions about the type and size of the department, the transfusion protocol used, and the frequency of application of BSMs in patients within the last 12 months. Furthermore, questions will be included about the policy of preoperative anticoagulant use. These last questions are added to assess whether these protocols are related to BSM use and should be taken into account in the implementation strategy. The content of the survey will be developed together with an orthopedic surgeon, anesthesiologist, and hematologist specialized in blood transfusions. Reminders to non-responders will be sent after two weeks and again by telephone after four weeks.

Study population

All heads of orthopedic departments of Dutch university, teaching, and general hospitals and independent treatment centers (n = 99) will be approached to participate in the survey. In case of non-response, a different orthopedic surgeon within the same department will be approached.

Analysis

Descriptive statistics will be used to describe current blood management practice. Independent *t* tests or Mann Whitney U tests for continuous variables and Chi-Square tests or Fisher's exact tests for proportions are used to analyze differences in frequency of use between the different settings, department sizes, or other conditions.

Outcome measures

The main outcome measures are the percentage of orthopedic departments applying BSMs per size and type of setting of the orthopedic department and the frequency of BSM use within a department. These results are used in phase C to address the implementation strategy to the appropriate (groups of) orthopedic departments. A secondary outcome measure is the number of days anticoagulants are stopped preoperatively. This is used to analyze whether this is associated with BSM use and should be taken into account in the implementation strategy.

Phase B: Analysis of barriers and facilitators for implementation of cost-effective blood transfusion management

Study design

Two steps will be taken to identify barriers and facilitators associated with the implementation of cost-effective blood transfusion management. First, semi-structured interviews will be performed to explore all relevant barriers and facilitators for the uptake of cost-effective blood transfusion management. The interview questions will be based on the Theoretical Domains Interview (TDI) framework,[15] complemented by the framework of Cabana, who subdivided largely similar constructs in three 'sequences of behavior change' to give a good overview of the used constructs.[16] The TDI framework includes 12 theoretical construct domains derived from 33 health psychology theories (covering 128 theoretical constructs) that help explain clinicians' behavior.[15,17]

Second, a survey will be held among a random sample of 400 Dutch orthopedic surgeons and 400 anesthesiologists to rank the barriers and facilitators identified in the interviews both on frequency and importance. The survey will include questions in which these barriers and facilitators of the identified theoretical domains can be related to specific clinical behavior.

Study population

Orthopedic surgeons and anesthesiologists are key stakeholders in deciding to use allogenic blood transfusions only or BSMs in patients that undergo hip and knee arthroplasty. Based on the analysis of current practice (phase A of this study), we will select a sample of departments that frequently apply BSMs to identify barriers, as well as departments with rare use of BSMs to identify facilitators. In this selection, the setting is taken into account (university, teaching, or general hospital or independent treatment center). In addition, departments with alternative answers (*e.g.*, the use of a different transfusion protocol) will be selected for interviews. In total, ten orthopedic surgeons and ten anesthesiologists will be interviewed to identify barriers and facilitators relevant for the uptake of a cost-effective blood transfusion policy and their motivations to apply BSMs. Data saturation for the interviews is defined as three consecutive interviews without new themes emerging. If there is no data saturation after 10 interviews per specialism, additional interviews will be conducted.[18] The total number of interviews will thus be determined by the number it takes to reach data saturation.

The interviews with orthopedic surgeons and anesthesiologists may reveal that other groups of stakeholders have an important role in deciding to use BSMs. In that case, additional interviews will be held with those stakeholders to elicit their views about relevant barriers and facilitators associated with the uptake of cost-effective transfusion management.

For the survey, a random sample (n = 400) of all Dutch orthopedic surgeons listed in the registry of the Dutch Orthopedic Association (NOV) (n = 595) and a random sample (n = 400) of anesthesiologists listed in the registry of the Netherlands Society of Anesthesiologists (NVA) (n ≈ 1200) will be approached for participation in the survey.

Analysis

The interviews will be audiotaped and transcribed in full for analysis. The interview transcripts will be analyzed by two researchers using the TDI framework as a base.[15] Important theoretical domains and the barriers and facilitators within these domains will be coded. This qualitative analysis will be executed using the software package ATLAS.ti (ATLAS.ti Scientific Software Development GmBH, Berlin, Germany).

The subsequent survey data will allow us to rank the importance of barriers and facilitators and their relationships with behavioral intention. These relationships will be assessed using regression analysis.

Outcome measures

The most important barriers and facilitators relevant for the uptake of cost-effective blood transfusion management by medical professionals will be the outcome measures from this phase.

Phase C: Development of an effective implementation strategy for cost-effective blood management

Study design

The results from the previous phases will be used to develop a tailored implementation strategy for cost-effective blood transfusion management for elective primary hip and knee arthroplasties. The results from phase A will show to which type of departments the strategy should be aimed. Phase B results will show the most important barriers and facilitators that should be taken into account in the development of the strategy.

From the literature, it is known that, in general, multifaceted strategies are more effective than single strategies.[19,20] Assuming this, and our expectation that several barriers on different theoretical domains will be found, it is very likely that the implementation strategy to be developed will include several components directed at different levels (*i.e.*, professional and organizational context). Furthermore, it is expected that the strategy components will include educational outreach or interactive educational strategy since these are known to be effective.[20,21]

In the development process, we will use a method based on the intervention mapping approach of Bartholomew et al.[22] This method begins with the creation of matrices in which the performance objectives are set against the top 10 ranking of factors that hinder or facilitate the implementation of a cost-effective transfusion policy. Subsequently, a brainstorming session will be held about the strategy components needed to achieve the performance objective, in the presence or absence of the hindering or facilitating factor mentioned in the matrix. The cells of the matrices will then gradually be filled with implementation strategy components.[23] Next, the formulated strategy components will be translated into practical strategies at each level (e.g., professional and organizational).

After the implementation strategy is developed, an expert meeting will be held with a panel of key opinion leaders in orthopedic surgery and anesthesiology, delegates of blood transfusion committees, and implementation experts (n = 10 to n = 20) to discuss the strategy's feasibility and to refine the developed implementation strategy. Their opinion about the strategy and their intention to use the strategy will be taken into account.

Analysis

The expert meeting will be audiotaped and transcribed. The panel members will receive a summary of the formulated implementation strategy and will be asked whether this summary is consistent with the conclusions reached in the meeting.

Outcome measures

The outcome from this phase will be a tailored implementation strategy likely to be effective for implementing cost-effective blood transfusion management and de-implementing BSMs in elective primary hip and knee arthroplasties.

Ethical approval

The study protocol has been presented to the Medical Ethical Committee of the Leiden University Medical Center. They declared ethical approval was not required under Dutch national law. (CME 11/104)

Discussion

The goal of this study is to develop an implementation strategy for cost-effective blood transfusion management in elective hip and knee arthroplasties in which BSMs are de-implemented. This study is the next step following a RCT on EPO and blood salvage as transfusion alternatives in orthopedic surgery using a restrictive transfusion policy that

showed that use of these BSMs is not cost-effective.[9] Given the number of hip and knee arthroplasties performed annually in the Netherlands and worldwide, and the accompanied blood loss and transfusion risks, implementing a cost-effective blood transfusion management may reduce costs.

Several studies have been performed to develop and test implementation strategies, including identification of barriers that prevent implementation.[10,16,19] They all conclude that a prior inventory of barriers to develop a tailored implementation strategy is useful and can confirm whether barriers differ in different settings. Prior inventory thereby reduces the number of costly trials evaluating different implementation strategies.[11,24,25] The present study, however, focuses on de-implementation of BSMs known to be non-cost-effective. Little is known about barriers and facilitators for de-implementation and whether these are similar to barriers and facilitators for implementation. The knowledge obtained by the present study may thus be further generalized to other practices that need to be de-implemented and contributes to general knowledge regarding differences between de-implementation and implementation strategies.

Strengths and limitations

Possible limitations of the study are biased results due to response bias in the phase A survey.[26] Non-response may cause an under- or overestimation of BSM use. The selection for the interviews in phase B is based on the results of phase A, so if non-responders have different intentions or experience different barriers and facilitators for the uptake of cost-effective blood transfusion management, this may influence the resulting barriers and facilitators.

We will try to overcome this by sending reminders by email and telephone, but this will not completely prevent response bias. In addition, response bias may also occur in the phase B survey if non-responders to this survey rank the selected barriers and facilitators in a different order; this may influence the likelihood of barriers and facilitators being included in the implementation strategy. Again, reminders will be sent to keep bias to a minimum, and we will compare respondents and non-respondents on demographic variables (*e.g.*, type of hospital) to estimate how likely it is that bias may be introduced.

A strength of this study is that it is one of the first studies to identify barriers and facilitators relevant for de-implementation. The study results will thus lead to generalized knowledge regarding factors that are important for the de-implementation of non-cost-effective interventions and how these differ from relevant factors for implementation.

Future work

The developed implementation strategy should be tested for effectiveness, feasibility, and costs within orthopedic practice in the Netherlands in a future study. As the current implementation strategy will be aimed at de-implementation of the use of EPO, CS, and DR, further research is needed to evaluate the cost-effectiveness of other BSMs in hip and knee arthroplasties. Cost-effective blood transfusion management implemented in this way is likely to improve efficiency of care.

Acknowledgments and competing interests

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The authors have no competing interests to declare.

References

1. Kurtz S, Mowat F, Ong K, Chan N, Lau E, Halpern M: Prevalence of primary and revision total hip and knee arthroplasty in the United States from 1990 through 2002. J Bone Joint Surg Am 2005, 87:1487–1497.
2. Manley M, Ong K, Lau E, Kurtz SM: Effect of volume on total hip arthroplasty revision rates in the United States Medicare population. J Bone Joint Surg Am 2008, 90:2446–2451.
3. Otten R, van Roermund PM, Picavet HS: Trends in the number of knee and hip arthroplasties: considerably more knee and hip prostheses due to osteoarthritis in 2030. Ned Tijdschr Geneeskd 2010, 154:A1534.
4. Sehat KR, Evans RL, Newman JH: Hidden blood loss following hip and knee arthroplasty. Correct management of blood loss should take hidden loss into account. J Bone Joint Surg Br 2004, 86:561–565.
5. Spahn DR: Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiology 2010, 113:482–495.
6. Squires JE: Risks of transfusion. South Med J 2011, 104:762–769.
7. Alshryda S, Sarda P, Sukeik M, Nargol A, Blenkinsopp J, Mason JM: Tranexamic acid in total knee replacement: a systematic review and meta-analysis. J Bone Joint Surg Br 2011, 93:1577–1585.
8. Sharma R, Farrokhyar F, McKnight LL, Bhandari M, Poolman RW, Adili A: Quality of assessment of randomized controlled trials in blood conservation after joint arthroplasty. J Arthroplasty 2011, 26:909–913.
9. So-Osman C, Nelissen RGHH, Koopman-van Gemert A, Kluyver E, Pöll R, Onstenk R, et al: A randomised controlled trial on erythropoietin and blood salvage as transfusion alternatives in orthopaedic surgery using a restrictive transfusion policy. Transfus Altern Transfus Med 2011, 3:25–26.
10. Baker R, Camosso-Stefinovic J, Gillies C, Shaw EJ, Cheater F, Flottorp S, et al: Tailored interventions to overcome identified barriers to change: effects on professional practice and health care outcomes. Cochrane Database Syst Rev 2010, 3: CD005470. DOI: 10.1002/14651858.CD005470.pub2.
11. Grol R: Personal paper. Beliefs and evidence in changing clinical practice. BMJ 1997, 315:418–421.
12. Godin G, Belanger-Gravel A, Eccles M, Grimshaw J: Healthcare professionals' intentions and behaviours: a systematic review of studies based on social cognitive theories. Implement Sci 2008, 3:36.
13. Fergusson D, Blair A, Henry D, Hisashige A, Huet C, Koopman-van GA, et al: Technologies to minimize blood transfusion in cardiac and orthopedic surgery. Results of a practice variation survey in nine countries. International Study of Peri-operative Transfusion (ISPOT) Investigators. Int J Technol Assess Health Care 1999, 15:717–728.
14. Horstmann WG, Ettema HB, Verheyen CC: Dutch orthopedic blood management surveys 2002 and 2007: an increasing use of blood-saving measures. Arch Orthop Trauma Surg 2010, 130:55–59.
15. Michie S, Johnston M, Abraham C, Lawton R, Parker D, Walker A: Making psychological theory useful for implementing evidence based practice: a consensus approach. Qual Saf Health Care 2005, 14:26–33.
16. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al: Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999, 282:1458–1465.
17. Francis JJ, Stockton C, Eccles MP, Johnston M, Cuthbertson BH, Grimshaw JM, et al: Evidence-based selection of theories for designing behaviour change interventions: using methods based on theoretical construct domains to understand clinicians' blood transfusion behaviour. Br J Health Psychol 2009, 14:625–646.
18. Francis JJ, Johnston M, Robertson C, Glidewell L, Entwistle V, Eccles MP, et al: What is an adequate sample size? Operationalising data saturation for theory-based interview studies. Psychol Health 2010, 25:1229–1245.
19. Grimshaw J, Eccles M, Thomas R, MacLennan G, Ramsay C, Fraser C, et al: Toward evidence-based quality improvement. Evidence (and its limitations) of the effectiveness of guideline dissemination and implementation strategies 1966–1998. J Gen Intern Med 2006, 21(Suppl 2):S14–S20.
20. Prior M, Guerin M, Grimmer-Somers K: The effectiveness of clinical guideline implementation strategies–a synthesis of systematic review findings. J Eval Clin Pract 2008, 14:888–897.
21. Legare F, Ratte S, Stacey D, Kryworuchko J, Gravel K, Graham ID, et al: Interventions for improving the adoption of shared decision making by healthcare professionals. Cochrane Database Syst Rev 2010, 5:CD006732. DOI: 10.1002/14651858.CD006732.pub2.
22. Bartholomew LK, Parcel GS, Kok G, Gottlieb NH: Planning health promotion programs: an intervention mapping approach. New York: John Wiley & Sons Inc; 2006.
23. van Bokhoven MA, Kok G, van der Weijden T: Designing a quality improvement intervention: a systematic approach. Qual Saf Health Care 2003, 12:215–220.

24. Francis JJ, Tinmouth A, Stanworth SJ, Grimshaw JM, Johnston M, Hyde C, et al: Using theories of behaviour to understand transfusion prescribing in three clinical contexts in two countries: development work for an implementation trial. Implement Sci 2009, 4:70.
25. Grol R, Grimshaw J: From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003, 362:1225–1230.
26. Braithwaite D, Emery J, De LS, Sutton S: Using the Internet to conduct surveys of health professionals: a valid alternative? Fam Pract 2003, 20:545–551.

Chapter 5

Frequent use of blood-saving measures in elective orthopaedic surgery: a 2012 Dutch blood management survey

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Abstract

Background: Blood loss in hip and knee arthroplasties may necessitate allogeneic blood transfusions. Different blood-saving measures (BSMs) were introduced to reduce these transfusions. Purpose of the present study was to assess the frequency of BSM use, stratified by type and hospital setting of orthopaedic departments in the Netherlands.

Methods: An internet-based questionnaire was sent to all heads of orthopaedic departments of Dutch hospitals and private clinics (n=99). Questions were asked on how often BSMs were used, reported on a 5-point Likert scale (never, almost never, regularly, almost always, always). In addition there were questions about discontinuation of anticoagulants preoperatively, the number of annually performed arthroplasties (size) and hospital setting.

Results: The survey was completed by 81 (82%) departments. BSMs used frequently (regularly, almost always, always) were erythropoietin (EPO), with 55 (68%) departments being frequent users; acute normovolemic haemodilution, used frequently in 26 (32%) departments; cell saver in 25 (31%) and postoperative drainage and re-infusion in 56 (69%) departments. When compared by size, frequent EPO use was more common in large departments (with 22 (88%) large departments being frequent users versus 13 (63%) small departments and 16 (55%) intermediate departments, p = 0.03). No differences by size or type were observed for other BSMs.

Conclusions: Compared with previous survey's there is a tremendous increase in use of BSMs. EPO and autologous blood salvage techniques are the most often used modalities. Costs might be saved if use of non-cost-effective BSMs is stopped.

Background

Blood loss in elective total hip and knee arthroplasties (THA and TKA) may necessitate allogeneic blood transfusions. Yet, allogeneic blood transfusions carry the risk of infections and non-infectious transfusion reactions.[1,2] Concerns about these risks have led to the development of blood-saving measures (BSMs) to reduce allogeneic blood transfusions. Many studies have been performed to assess the effectiveness and to a lesser extent the cost-effectiveness of various BSMs.[3-9] Results of reviews on this subject show that the effectiveness of the studied BSMs on allogeneic blood reduction and the accompanying costs vary largely among studies so that no firm conclusions on their use can be drawn.[3-9] Besides, the available reviews on BSMs show that the included studies had several limitations such as a retrospective design, small patient numbers and poor methodological quality.[3-10] In accordance with the latter in 2011 the Dutch transfusion guideline indicated that further research is needed to evaluate the cost-effectiveness of BSMs.[11]

A multi-centre randomized controlled trial with adequate power was therefore performed recently to investigate the cost-effectiveness of BSMs including preoperative erythropoietin (EPO), perioperative cell saver, and a postoperative drainage and re-infusion device (unwashed), in elective primary THA and TKA, using a restrictive transfusion trigger as described in the Dutch transfusion guideline.[11] It was shown that cell saver and postoperative drainage and re-infusion devices did neither result in a decreased mean red blood cell use, nor in a decrease in the proportion of transfused patients. Use of EPO showed a significant decrease in the proportion of transfused patients, but costs were considered too high. Adherence to a predefined uniform transfusion protocol was more than 95% in all participating hospitals. The conclusion of this study was thus that these three BSMs were not cost-effective in elective primary TKA and THA.[12] Annually, TKA are performed in about 20.000 patients and THA in about 26.000 patients,[13] so that cost savings might be considerable if BSMs are de-implemented.[14]

Previous surveys showed an increase in the use of BSMs between 1999 and 2007. A survey in 1999 showed that the proportion of Dutch hospitals using pharmacologic BSMs ranged from 0-2% and the use of non-pharmacologic BSMs ranged from 10-24%.[15] A more recent survey in 2007 showed that EPO and postoperative drainage and re-infusion were used in more than half of all Dutch orthopaedic departments.[16] However, these surveys did not distinguish between frequent and non-frequent use, nor in what hospital setting (university-, teaching-, general hospital or private clinic). This information is needed to focus on activities to abolish non cost-effective BSMs to those departments using BSMs frequently.

The aim of the present study was to assess the current frequency of BSM use, stratified by hospital setting and size of orthopaedic departments.

Methods

An internet-based questionnaire was sent in January 2012 to all heads of orthopaedic departments of hospitals and private clinics within the Netherlands performing THA and TKA (n=99). Hospitals with multiple locations were considered as a single hospital. Reminders were sent by email 2 weeks and 4 weeks after the first invitation, followed by a telephone call if necessary.

The study protocol has been presented to the Medical Ethical Committee of the Leiden University Medical Center. They declared ethical approval was not required under Dutch national law (CME 11/104).

Questionnaire

The primary outcome measures of the questionnaire were the frequency of use of the following 11 BSMs: preoperative autologous donation, acute normovolemic haemodilution, intraoperative cell saver, postoperative drainage and re-infusion, EPO, tranexamic acid, desmopressin, epsilon aminocaproic acid, fibrin glue, platelet gel, and controlled hypotension. The frequency of use was reported on a 5-point Likert scale (never, almost never, regularly, almost always, always). The secondary outcome measures were if, and how many days prior to surgery, Coumadin derivatives, anti-platelet drugs and NSAIDs were stopped. This was used to assess whether there are associations between BSM use and stopping anticoagulant drugs preoperatively, as this might be part of blood management as well.

In addition, the questionnaire included questions about department characteristics such as hospital setting (university-, teaching-, general hospital or private clinic), size of department (number of primary and revision THA and TKA performed annually), and use of a restrictive transfusion protocol as described in the national transfusion guideline (yes/no).[11]

Quality of care indicators

To test whether the transfusion rate in THA and TKA is associated with the frequency of BSM use, the results of this study were compared with self-reported allogeneic blood transfusion rates that are publicly available for all hospitals.[17] The number of patients with an ASA 1 or ASA2 classification[18] undergoing a total THA or TKA, and the number of these patients receiving an allogeneic blood transfusion are reported by all Dutch hospitals and private clinics.

Analysis

First, all responders were analysed together on frequency of BSM use to assess how often each BSM is used. Subsequently they were stratified into non-frequent users (never and almost never) and frequent users (regularly, almost always and always). It was tested whether frequent use varies among different hospital settings and size of departments

(number of arthroplasties divided into tertiles). Differences between groups as well as associations between frequent use of BSMs and the preoperative continuation or discontinuation of Coumadin derivatives, anti-platelet drugs and NSAIDs were tested by chi-square tests. In case of expected cell counts less than five, the Fisher-exact test was used. Unpaired t-tests were used to test differences in transfusion rates.

For the analysis of the data the statistical software of SPSS v17.0 was used. P-values ≤ 0.05 were considered statistically significant in all analyses.

Results

81 (82%) orthopaedic departments completed the questionnaire. The response rates did not differ between different hospital settings ($\chi 2=0.74$ with $p=0.86$)(Table 1). The median number of annually performed arthroplasties among responding departments was 320 for THA (range 0–900) and 285 for TKA (range 35–900). In one clinic only TKAs were performed.

Table 1: Characteristics of orthopaedic departments responding to the questionnaire on blood saving measures

	Total (n=99)	Responders (n=81)	% Responders of total
University medical centre	8	5	63
Teaching hospital	28	24	86
General hospital	54	46	85
Private clinic	9	6	67

Table 2 shows the frequency of BSM use among the orthopaedic departments. Frequent use of preoperative EPO was seen in 55 (68%) departments and frequent use of autologous blood salvage was also common; with acute normovolemic haemodilution used frequent by 26 (32%) departments, cell saver by 25 (31%) and postoperative drainage and re-infusion by 56 (69%) departments. A few departments were frequent users of pre-operative autologous donation (3 (4%)), pharmacologic techniques other than EPO (range 0–10 (0-12%)) or the local techniques fibrin glue (3 (4%)) and platelet gel (1 (1%)).

When the departments were stratified by size, it was shown that frequent EPO use was more common in hospitals with large numbers of arthroplasties (Table 3). No significant differences were observed for the other BSMs. When stratified by hospital setting no significant differences were observed, although there is a trend ($p=0.07$) that frequent EPO use was less common in university medical centres. Other observed trends were that frequent use of acute normovolemic haemodilution and controlled hypotension were more common in teaching hospitals and university medical centres (both $p=0.06$)(Table 4).

Table 2: Frequency of BSM use in Dutch orthopaedic departments of hospitals and private clinics (n=81)

	Non-frequent			*Frequent*			
	Never	Almost never	Total	Regularly	Almost always	Always	Total
Preoperative Autologous Donation (%)	64 (79)	14 (17)	78 (96)	1 (1)	2 (3)	0	3 (4)
Acute Normovolemic Haemodilution (%)	35 (43)	20 (25)	55 (68)	14 (17)	8 (10)	4 (5)	26 (32)
Perioperative cell saver (%)	30 (37)	26 (32)	56 (69)	20 (25)	1 (1)	4 (5)	25 (31)
Postoperative Drainage and Re-infusion (%)	17 (21)	8 (10)	25 (31)	16 (20)	15 (19)	25 (31)	56 (69)
Erythropoietin (%)	8 (10)	18 (22)	26 (32)	37 (46)	9 (11)	9(11)	55 (68)
Tranexamic acid (%)	58 (72)	13 (16)	71 (88)	4 (5)	3 (4)	3 (4)	10 (12)
Desmopressin (%)	70 (86)	11 (14)	81 (100)	0	0	0	0
Epsilon aminocaproic acid (%)	69 (85)	12 (15)	81 (100)	0	0	0	0
Fibrin glue (%)	67 (83)	11 (14)	78 (96)	3 (4)	0	0	3 (4)
Platelet gel (%)	74 (91)	6 (7)	80 (99)	0	0	1 (1)	1 (1)
Controlled hypotension (%)	32 (40)	22 (27)	54 (67)	17 (21)	6 (7)	4 (5)	27 (33)

Table 3: Differences in frequent BSM use by number of arthroplasties per year (hospital size)

	Small <439 (n=27)	Intermediate 439–720 (n=29)	Large >720 (n=25)	Total (n=81)	P-value
Preoperative Autologous Donation (%)	1 (4)	0	2 (8)	3 (4)	0.30
Acute Normovolemic Haemodilution (%)	8 (30)	8 (28)	10 (40)	26 (32)	0.59
Perioperative cell saver (%)	9 (33)	6 (21)	10 (40)	25 (31)	0.29
Postoperative Drainage and Re-infusion (%)	18 (67)	20 (69)	18 (72)	56 (69)	0.92
Erythropoietin (%)	17 (63)	16 (55)	22 (88)	55 (68)	0.03
Tranexamic acid (%)	4 (15)	1 (3)	5 (20)	10 (12)	0.16
Desmopressin (%)	0	0	0	0	-
Epsilon aminocaproic acid (%)	0	0	0	0	-
Fibrin glue (%)	0	2 (7)	1 (4)	3 (4)	0.39
Platelet gel (%)	0	1 (3)	0	1 (1)	0.40
Controlled hypotension (%)	12 (44)	5 (21)	9 (36)	27 (33)	0.16

Considering the effect of anticoagulant drugs on the frequency of BSM use, no effect was seen for the preoperative stopping of Coumadin derivatives and anti-platelet drugs (Data not shown). However, frequent EPO use was significantly more common in those hospitals that stopped NSAIDS before surgery (82% vs 60%, $\chi 2=3.98$ P =0.05).

Seventy-three (90%) of the respondents stated to use the national transfusion guideline.[11] Five departments use a different locally designed algorithm (extended version of the national transfusion guideline with advices for the use of BSMs),[19] the other 3 departments stated they do not have transfusions or they do not have a guideline. No associations were found between transfusion protocol and frequency of BSM use (data not shown).

Table 4: Differences in frequent BSM use by hospital setting

	Private (n=6)	General (n=46)	Teaching (n=24)	University (n=5)	Total (n=81)	P-value
Preoperative Autologous Donation (%)	0 (0)	2 (4)	1 (4)	0 (0)	3 (4)	0.92
Acute Normovolemic Hemodilution (%)	0 (0)	12 (26)	11 (46)	3 (60)	26 (32)	0.06
Perioperative cell saver (%)	2 (33)	13 (28)	9 (38)	1 (20)	25 (31)	0.82
Postoperative Drainage and Re-infusion (%)	3 (50)	34 (74)	17 (71)	2 (40)	56 (69)	0.32
Erythropoietin (%)	3 (50)	33 (72)	18 (75)	1 (20)	55 (68)	0.07
Tranexamic acid (%)	1 (17)	4 (9)	4 (17)	1 (20)	10 (12)	0.72
Desmopressin (%)	0	0	0	0	0	-
Epsilon aminocaproic acid (%)	0	0	0	0	0	-
Fibrin glue (%)	0	2 (4)	1 (4)	0	3 (4)	0.92
Platelet gel (%)	0	0	1 (4)	0	1 (1)	0.49
Controlled hypotension (%)	2 (33)	10 (22)	12 (50)	3 (60)	27 (33)	0.06

When self-reported transfusion rates were compared with the frequency of BSM use, no differences in transfusion rate between frequent or non-frequent BSM use were found (Table 5).

Table 5: Differences in percentage of transfused ASA 1 and ASA 2 patients in hospitals reporting frequent and non-frequent BSM use

	Non-frequent use	Frequent use	Confidence interval	P-value
Preoperative Autologous Donation (%)	5.6	4.3	−4.28 to 7.02	0.63
Acute Normovolemic Haemodilution (%)	6.3	4.2	−0.34 to 4.44	0.09
Perioperative cell saver (%)	5.4	6.0	−3.07 to 2.00	0.67
Postoperative Drainage and Re-infusion (%)	4.7	6.0	−3.75 to 1.16	0.30
Erythropoietin (%)	6.3	5.2	−1.34 to 3.46	0.38
Tranexamic acid (%)	5.4	7.6	−5.99 to 1.58	0.25
Desmopressin (%)	5.6	-	-	-
Epsilon aminocaproic acid (%)	5.6	-	-	-
Fibrin glue (%)	5.5	8.3	−8.41 to 2.83	0.33
Platelet gel (%)	5.7	0.0	−3.89 to 15.24	0.24
Controlled hypotension (%)	5.5	5.9	−2.81 to 2.02	0.74

Discussion

The present study showed that BSMs are frequently used in TKA and THA, especially preoperative EPO use and postoperative drainage and re-infusion. Frequent EPO use is more common in hospitals with large numbers of arthroplasties, and a trend is found that frequent EPO use is less common in university medical centres. Frequent EPO use is

significantly associated with stopping of NSAIDs before surgery. No differences were observed for the other BSMs.

A possible limitation of this study may be response bias if frequency of BSM use differs between responders and non-responders. Considering the high overall response rate (82%) and the fact that response did not differ per hospital setting, the effect of response bias is likely to be limited.

A second limitation of this study is the use of the subjective measure 'number of BSMs used'. The use of this measure assumes that the respondents in our survey, i.e. the heads of orthopaedic departments of hospitals and private clinics within the Netherlands performing THA and TKA, have an adequate insight in the frequency of BSM use. Within the scope of this study it was not possible to verify the reliability of their reporting. However, given the evidence from the recent multi-centre randomized controlled trial of So-Osman et al. on the effectiveness of EPO, perioperative cell saver and postoperative drainage and re-infusion,[12] the lack of an association between transfusion rates and BSM use seems plausible. Therefore the reported rates are likely to reflect actual practice.

Another limitation is the number of participating hospitals despite the high response rate in our survey (82%). Therefore, we were able to only detect large robust differences between frequent and non-frequent BSM users and we might have overlooked minor differences (i.e. type II error). However, it was not possible to further enlarge our study population, since we have approached all Dutch orthopaedic departments in The Netherlands for participation in our study.

A striking finding was that no association was found between frequent BSM use and the self-reported transfusion rates in ASA 1 and ASA 2 patients. This suggests that BSM use does not influence the transfusion rate so that these can be stopped without increasing this transfusion rate. As ASA 3 patients with more co-morbidity are more susceptible to receive allogeneic transfusions, it remains possible that these patients may benefit from BSMs. Given the restrictive transfusion policy used in the Netherlands, which has led to a significant drop in the number of blood transfusions [11,20], BSMs are probably used more frequently than strictly necessary on medical grounds.

The tremendous increase of BSM use over the past 13 years[7,8] in combination with the fact that EPO, cell saver, and postoperative drainage and re-infusion are not cost-effective[12] might give a huge cost reduction if these BSMs are abolished in clinical practice. The question remains why BSM use has increased so much over the past years, and whether barriers exist that prevent doctors to stop with these BSMs.

This survey is part of the 'Leiden implementation study of blood management in hip and knee arthroplasties' (LISBOA) which aims at designing an intervention to abolish non-cost-effective BSMs including EPO, perioperative cell saver and postoperative drainage and re-infusion from clinical practice. The present survey provides the target groups at which this intervention should be aimed. Frequent EPO use for instance is seen more commonly in departments with a large number of arthroplasties. The trend that frequent EPO use is

less common in university medical centres is likely to be due to the fact that university medical centre's do not perform large numbers of arthroplasties annually. A possible explanation for this finding might be that the logistics behind EPO administration are complicated and time consuming, which can make it difficult for departments with smaller numbers of arthroplasties to use EPO. The association between frequent EPO use and stopping NSAIDs before surgery may be explained by extra caution taken in these hospitals to avoid blood transfusions. Interviews with involved medical specialists in a later phase of the LISBOA study will provide information about why departments choose for BSMs and which barriers they experience to stop using these BSMs. These results will also be taken into account in designing an intervention to abandon non cost-effective BSM use in clinical practice.

Conclusions

In conclusion, this survey shows that BSMs are used frequently in TKA and THA in Dutch orthopaedic practice and its use has increased over the past years. The frequent use of EPO was observed particularly in large hospitals. Based on these findings, an intervention to abolish BSMs will be developed to arrive at a cost-effective blood transfusion policy. This will eventually lead to reduction of costs in perioperative orthopaedic care.

Abbreviations

LISBOA: Leiden implementation study of blood management in hip and knee arthroplasties, BSMs: Blood saving measures, EPO: Erythropoietin, THA and TKA: Total hip arthroplasty and total knee arthroplasty, NSAIDs: Non-steroidal anti-inflammatory drugs, ASA: American society of anaesthesiologists physical function score

Acknowledgments and competing interests

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All members of the LISBOA study group declare that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

References

1. Spahn DR: Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiology. 2010, 113: 482-495.
2. Squires JE: Risks of transfusion. South Med J. 2011, 104: 762-769.
3. Green WS, Toy P, Bozic KJ: Cost minimization analysis of preoperative erythropoietin vs autologous and allogeneic blood donation in total joint arthroplasty. J Arthroplasty. 2010, 25: 93-96.
4. Laupacis A, Fergusson D: Erythropoietin to minimize perioperative blood transfusion: a systematic review of randomized trials. The International Study of Peri-operative Transfusion (ISPOT) Investigators. Transfus Med. 1998, 8: 309-317.
5. Moonen AF, Neal TD, Pilot P: Peri-operative blood management in elective orthopaedic surgery. A critical review of the literature. Injury. 2006, 37: S11-S16. Suppl 5
6. Rao VK, Dyga R, Bartels C, Waters JH: A cost study of postoperative cell salvage in the setting of elective primary hip and knee arthroplasty. Transfusion. 2012, 52: 1750-1760.
7. Alshryda S, Sarda P, Sukeik M, Nargol A, Blenkinsopp J, Mason JM: Tranexamic acid in total knee replacement: a systematic review and meta-analysis. J Bone Joint Surg Br. 2011, 93: 1577-1585.
8. Carless PA, Henry DA, Moxey AJ, O'Connell D, Brown T, Fergusson DA: Cell salvage for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2010, 4: CD001888-
9. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2011, 3: CD001886-
10. Sharma R, Farrokhyar F, McKnight LL, Bhandari M, Poolman RW, Adili A: Quality of assessment of randomized controlled trials in blood conservation after joint arthroplasty. J Arthroplasty. 2011, 26: 909-913.
11. Dutch Institute for Healthcare Improvement (CBO): Guideline Bloodtransfusionpolicy (in Dutch). 2011, Available at: http://www.cbo.nl
12. So-Osman C, Nelissen RGHH, Koopman-van Gemert AWMM, Kluyver E, Pöll R, Onstenk R: A randomised controlled trial on erythropoietin and blood salvage as transfusion alternatives in orthopaedic surgery using restrictive transfusion policy. Patient Blood Management in Elective Orthopaedic Surgery. 2012, ISBN 9789461914569
13. 2007–2011 data on the Dutch Arthroplasty Register (LROI). 2013,http://www.lroi.nl,
14. Voorn VM, Marang-van de Mheen PJ, So-Osman C, Vliet Vlieland TP, Koopman-van Gemert AW, Nelissen RG: Designing a strategy to implement cost-effective blood transfusion management in elective hip and knee arthroplasties: A study protocol. Implement Sci. 2012, 7: 58-10.
15. Fergusson D, Blair A, Henry D, Hisashige A, Huet C, Koopman-van GA: Technologies to minimize blood transfusion in cardiac and orthopedic surgery. Results of a practice variation survey in nine countries. International Study of Peri-operative Transfusion (ISPOT) Investigators. Int J Technol Assess Health Care. 1999, 15: 717-728.
16. Horstmann WG, Ettema HB, Verheyen CC: Dutch orthopedic blood management surveys 2002 and 2007: an increasing use of blood-saving measures. Arch Orthop Trauma Surg. 2010, 130: 55-59.
17. Healthcare inspection: Transparent Care (in Dutch). 2012, Available at http://www.zichtbarezorg.nl
18. Bjorgul K, Novicoff WM, Saleh KJ: Evaluating comorbidities in total hip and knee arthroplasty: available instruments. J Orthop Traumatol. 2010, 11: 203-209.
19. Slappendel R, Dirksen R, Weber EW, Van der Schaaf DB: An algorithm to reduce allogenic red blood cell transfusions for major orthopedic surgery. Acta Orthop Scand. 2003, 74: 569-575.
20. So-Osman C, Nelissen R, Te Slaa R, Coene L, Brand R, Brand A: A randomized comparison of transfusion triggers in elective orthopaedic surgery using leucocyte-depleted red blood cells. Vox Sang. 2010, 98: 56-64.

Chapter 6

Hospital variation in allogeneic transfusion and extended length of stay in primary elective hip and knee arthroplasty: a cross-sectional study

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Abstract

Objectives: Outcomes in total hip and knee arthroplasty (THA and TKA), such as allogeneic transfusions or extended length of stay (LoS), can be used to compare the performance of hospitals. However, there is much variation in these outcomes. This study aims to rank hospitals and to assess hospital differences of two outcomes in THA and TKA: allogeneic transfusions and extended LoS, and to additionally identify factors associated with these differences.

Design: Cross-sectional medical record review study.

Setting: Data were gathered in 23 Dutch hospitals.

Participants: 1163 THA and 986 TKA patient admissions.

Outcomes: Hospitals were ranked based on their observed/expected (O/E) ratios regarding allogeneic transfusion and extended LoS percentages (extended LoS was defined by postoperative stay>4 days). To assess the reliability of these rankings, we calculated which percentage of the existing variation was based on differences between hospitals as compared to random variation (after adjustment for variation in patient characteristics). Associations between hospital specific factors and O/E ratios were used to explore potential sources of differences.

Results: The variation in O/E ratios between hospitals ranged from 0 to 4.4 for allogeneic transfusion, and from 0.08 to 2.7 for extended LoS. Variation in transfusion could in 21% be explained by hospital differences in THA and 34% in TKA. For extended LoS this was 71% in THA and 78% in TKA. Better performance (low O/E ratios) in transfusion was associated with more frequent tranexamic acid (TXA) use in TKA (R=-0.43,P=0.04). Better performance in extended LoS was associated with more frequent TXA use in THA (R=-0.45,P=0.03) and TKA (R=-0.65,P<0.001) and local infiltration analgesia (LIA) in TKA (R=-0.60,P=0.002).

Conclusions: Ranking hospitals based on allogeneic transfusion is unreliable due to small percentages of variation explained by hospital differences. Ranking based on extended LoS is more reliable. Hospitals using TXA and LIA have relatively fewer patients with transfusions and extended LoS.

Introduction

In conditions such as osteoarthritis and rheumatoid arthritis, total hip arthroplasty (THA) and total knee arthroplasty (TKA) are widely accepted treatments and recommended in many guidelines.[1,2] In 2011, 160 per 100,000 persons received a THA and 119 per 100,000 persons received a TKA in high income countries.[3] From several studies it is known that there is a large variation in outcomes for THA and TKA between hospitals, such as allogeneic transfusions rates, length of stay (LoS), re-admission rates or revision rates.[4-8] This variation consists of three components: variation caused by the mix of patient characteristics present within a hospital, variation caused by differences between hospitals and random variation.

In order to gain insight into the differences between hospitals, rankings are used to compare hospitals on different outcome indicators.[9-12] However, such rankings are only reliable if they are based on true hospital differences and with little random variation.[9,12-15] Therefore the reliability of ranking hospitals on specific outcomes should be verified. Reliable rankings can be used as a starting point to look for explanatory factors and consequently to improve the performance of hospitals.[11,16]

In this study two short-term outcome indicators were used to rank hospitals on two frequently used short-term outcomes and to assess whether ranking on these outcomes is reliable. The outcome indicators were allogeneic red blood cell transfusion percentage and extended LoS, in patients undergoing primary elective THA or TKA.

Although allogeneic transfusions are relatively safe, transfusion reactions, transmission of diseases and immunomodulatory effects resulting in increased susceptibility of infections may occur.[17] In the Dutch transfusion guideline the following three thresholds were recommended for adult patients undergoing elective surgery: consider transfusion if the haemoglobin (Hb) level is <4 mmol/l (6,4g/dl) in healthy adults (American Society of Anesthesiologists physical status classification (ASA) 1), consider transfusion if the Hb level is <5 mmol/l (8g/dl) in ASA1 patients >60 years and in uncomplicated ASA 2 and ASA 3 patients, consider transfusion if the Hb level is <6 mmol/l (9.6g/dl) in ASA 4 patients, patients that are not able to increase their cardiac output to compensate for haemodilution, septic patients, patients with severe pulmonary disease or patients with symptomatic cerebrovascular disease.[18] Ninety percent of Dutch hospitals reported to use this guideline. The remaining ten percent reported to use the guideline with additional blood saving techniques or did not have any transfusions.[19] Consequently it seems unlikely that variability in allogeneic transfusions between hospitals is explained by variability in following the guidelines. Therefore, the allogeneic transfusion rate may be considered as a robust outcome indicator to judge hospital performance. A low percentage of allogeneic

transfusion is therefore pursued by both physicians, insurance companies and regulators.[20]

Another indicator for good quality of care is the absence of complications. Given that extended LoS may be caused by the occurrence of complications, it is thus often used as an indicator for quality of care.[9,21] Both outcome indicators are used frequently as short-term outcomes for studies regarding all kinds of interventions in the fields of patient blood management and joint replacement research,[22-24] and are used as quality indicators to assess hospital performance or for cost-calculations.[20,25-27]

To improve a hospitals' ranking, it is important to know which factors account for the differences between hospitals after adjustment for the mix of patients within a hospital. In the literature a number of patient characteristics were found to be associated with the outcomes allogeneic transfusion and LoS such as age, gender, body mass index (BMI), smoking status, diagnosis, preoperative Hb or ASA classification.[28,29] In addition to these patient characteristics a number of hospital specific factors such as the use of blood management techniques,[30-35] enhanced recovery programs,[36,37] the type of anesthesia,[38-40] the use of cement in THA,[41] the surgical approach in THA,[42] and the use of a tourniquet in TKA,[43,44] were identified from literature. Association between these factors and better performance of hospitals give starting points to improve quality of care.

The aim of this study is to rank hospitals based on 'allogeneic transfusions' and 'extended LoS', to assess which part of the variation in the outcomes 'allogeneic transfusions' and 'extended LoS' is due to true differences between hospitals and to identify hospital specific factors associated with these between-hospital differences in patients undergoing THA or TKA.

Materials and Methods

Study design and setting

In this retrospective study the medical records of patients undergoing a primary elective THA or TKA were reviewed. The used data was gathered for the baseline measurement of the 'Leiden Implementation Study of Blood management in hip and knee arthroplasty' (LISBOA) trial,[45] a cluster randomized trial in which a de-implementation strategy on blood management among THA and TKA patients was implemented and evaluated. The LISBOA trial is registered with the Dutch trial register www.trialregister.nl (ID: NTR4044). Data was gathered in 23 non-academic Dutch hospitals. A sample of approximately 100 patients in each hospital, undergoing surgery from May through October 2013, was selected (the first

20 THA/TKA procedures of a month in a 5-month period, as this was the timeframe of the baseline measurement of the LISBOA trial). Fifteen hospitals were located in the western urban part of the Netherlands, the other 8 hospitals were located in more rural areas. Included were 9 teaching hospitals, 13 general hospitals and 1 private clinic. A mean number of 6.2 orthopaedic surgeons were employed per hospital ranging from 3 to 10 orthopaedic surgeons. All participating hospitals reported to follow the Dutch transfusion guideline[18].

Population

Patients included in the LISBOA baseline measurement underwent primary elective THA or TKA and were ≥18 years. Exclusion criteria consisted of usual exclusion criteria for elective orthopaedic surgery (including patients with a serious disorder of the coronary, peripheral and/or carotid arteries, recent myocardial infarction or cerebrovascular accident (CVA) in the past six months, patients with untreated hypertension (diastolic >95 mmHg), patients with a pregnancy, patients with anaemia (Hb <10 g/dl) and exclusion criteria specifically used for this study, including bilateral surgery (within 6 weeks), patients with a malignancy (except skin cancer and cured cancer), patients with a coagulation disorder, patients refusing or with a contraindication for allogeneic blood transfusions.

Data collection

For each patient admission, the following characteristics were collected: age, gender, preoperative Hb (in g/dL), preoperative diagnosis (osteoarthritis, rheumatoid arthritis or other), BMI (in kg/m^2), smoking status (yes or no), and ASA classification (1, 2, 3-4). For each patient admission data was also collected on treatment factors determined by the hospital (hospital specific factors): type of anaesthesia (general or loco-regional), use of cement (yes or no), surgical approach in THA (anterior vs other), use of a tourniquet in TKA (yes or no), use of preoperative erythropoietin (EPO) (yes or no), intra- or postoperative use of cell salvage system (yes or no), use of tranexamic acid (TXA) (yes or no), use of local infiltration analgesia (LIA) (yes or no). These factors can be seen as patient specific, but the choice to use them is mainly included in hospital specific treatment protocols or selected for most patients within a hospital and were therefore included as hospital specific factors.

Finally the outcomes for each patient admission were assessed: allogeneic transfusion (yes or no) and postoperative LoS (in days, excluding the day of surgery). The outcome indicator 'extended LoS' was defined by the highest quartile of the LoS among all patients. In both THA and TKA patients this was >4 postoperative days.

Statistical analyses

The association of patient characteristics with the allogeneic transfusion and extended LoS were tested separately for THA and TKA. This was done using multivariate logistic regression models. The included patient characteristic variables were derived from the literature and included: age, gender, BMI, smoking status, diagnosis, preoperative Hb or ASA classification.[28,29]

Hospitals were ranked by using the O/E ratio for each hospital and for THA and TKA patients separately. For this calculation, the observed outcome was the number of THA or TKA patient admissions with a transfusion or an extended LoS within a hospital. The expected outcome was the sum of all patients' expected probabilities for either a transfusion or extended LoS, adjusted for patient characteristics calculated using a multivariate logistic regression model, fitted on the data of all included hospitals and including all patient characteristic variables.

The observed outcome was divided by the expected outcome resulting in an O/E ratio per hospital. For each hospital, the 95% confidence intervals of the O/E ratio was calculated with the Mid-P exact test for Poisson variates.[46] For an average performing hospital, the observed outcome will equal the expected outcome, resulting in an O/E ratio of 1. Hospitals with an O/E ratio significantly < 1 (including its 95% confidence interval) have significantly fewer events and are therefore performing better than average (positive outliers). Similarly, hospitals with an O/E ratio significantly > 1 are performing worse than average (negative outliers).

Second, we assessed which part of the variation in the outcomes 'allogeneic transfusion' and 'extended LoS' was due to true hospital differences and which part was due to random variation (after adjustment for patient characteristics). This was done by calculating the rankability as an indicator of the reliability of ranking.[15] This rankability is defined as the between-hospital variation divided by the sum of the between-hospital variation and the within-hospital variation. The between-hospital variation was estimated using the heterogeneity from the random effects logistic regression model in which hospitals were included as random factor and all patient characteristic variables mentioned above as fixed factors. The within-hospital variation was estimated using a fixed effects logistic regression model, including dummy variables for hospital and all patient characteristic variables as fixed factors. The median squared standard error of the coefficient for the hospital variable was used to estimate the within-hospital variation.[15]

The rankability for a particular outcome indicator is expressed as a percentage. High rankability means that a large percentage of the variation is explained by true hospital

differences. Rankability increases if the effect of being treated in a hospital can be estimated more precisely (less within-hospital variation) and if the differences between hospitals are larger (more between-hospital variation). Rankability in general will be lower for outcomes with lower event rates as this is usually estimated with lower precision. So within-hospital variation is likely to be larger thereby making it harder to detect between-hospital differences and resulting in lower rankability.

Finally, to explore which hospital factors may be associated with better performance of a hospital (lower O/E ratio) on the 2 outcome indicators, and thereby explain part of the true hospital differences, we calculated Pearson's pairwise correlation coefficients (R) between a hospital factor (percentage of patients exposed to the factor) and the hospital O/E ratio. Before calculating the correlation coefficients the data were visually checked for non-linearity by using scatter plots. The following factors were explored: type of anaesthesia, use of cement in THA, surgical approach in THA, use of a tourniquet in TKA, use of preoperative EPO, use of cell salvage, use of TXA, use of LIA.

P values <0.05 were considered significant in all analyses.

The Medical Ethical Committee of the Leiden University Medical Center decided that ethical approval was not required under Dutch National law (CME 13/132). The gathering of patient data is conducted in compliance with the Good Clinical Practices protocol.

Results

In total, the records of 1163 admissions of patients undergoing THA and 986 admissions of patients undergoing TKA were reviewed in 23 hospitals. Table 1 shows the distribution of patient characteristics and outcomes between hospitals. The number of total patient admissions per hospital ranged from 64 to 100 with a median of 97 (with a median of 51 THA and 42 TKA per hospital). The percentage of patient admissions requiring transfusion varied between hospitals from 1.9% to 26.1% in THA and from 0.0% to 29.2% in TKA (table 1). The percentage of patient admissions with extended hospital stay (> 4 postoperative days) ranged from 1.9% to 44.4% in THA and from 2.0% to 62.5% in patients with TKA between hospitals (table 1).

The impact of the different patient characteristic variables on the outcome indicators are shown separately for THA and TKA in appendix 1. Each patient characteristic was significantly associated with at least one of the outcome indicators in either THA or TKA except for smoking.

Table 1: Distribution of patient characteristics and outcomes in participating hospitals

	THA (n=23 hospitals)		TKA (n=23 hospitals)	
	Median	Range	Median	Range
Mean age (years)	69.2	64.9 - 74.6	69.5	66.5 - 73.7
Gender, Female	64.7%	56.1% - 76.9%	68.6%	54.8% - 81.8%
Mean BMI (kg/m^2)	27.4	25.9 - 28.7	30.0	28.6 - 31.3
Smoking	12.9%	8.1% - 21.3%	8.8%	6.3% - 8.0%
ASA classification				
- ASA 1	19.6%	10.5% - 38.2%	14.0%	5.4% - 29.2%
- ASA 2	64.8%	51.6% - 86.0%	65.3%	47.9% - 87.8%
- ASA 3	13.0%	0.0% - 29.0%	16.7%	2.4% - 29.7%
- ASA 4*	0%	-	0%	0.0% - 2.9%
Mean preoperative Hb (g/dl)	13.8	13.4 - 14.2	13.9	13.4 - 14.2
Diagnosis				
- OA/RA	93.6%	87.0% - 98.3%	97.6%	87.5% - 100%
- Other	6.4%	1.7% - 13.0%	0%	0.0% - 12.5%
Allogeneic blood transfusion	7.0%	1.9% - 26.1%	4.1%	0.0% - 29.2%
Mean LoS (days)	4.2	2.1 - 5.4	4.0	2.3 - 6.5
Extended LoS (>4 days)	24.5%	1.9% - 44.4%	22.0%	2.0% - 62.5%

*The value (either mean or percentage) of the median hospital and range between hospitals are shown. *In all further analyses ASA 3 and ASA 4 are combined due to the small number of ASA 4 patients (n= 2)*

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Variation between hospitals

All included hospitals were ranked based on their O/E ratios (figure 1 and 2 for allogeneic transfusion and figure 3 and 4 for extended LoS). Each hospital is represented by the same letter across figures. The O/E ratios between hospitals ranged from 0 to 4.4 for transfusions (figure 1 for THA and 2 for TKA) and from 0.08 to 2.7 for extended LoS (figure 3 for THA and 4 for TKA). Three hospitals were identified as negative outliers with significantly more transfusions than expected in both THA and TKA (hospitals V and W in THA, figure 1, and hospitals V,K and T in TKA, figure 2). For extended LoS after THA, three hospitals were positive outliers (hospitals A, C and O) and three hospitals were negative outliers (hospitals V, B and G) (figure 3). For extended LoS after TKA, five hospitals were positive outliers (hospitals N, A, C, J and R) and five hospitals were negative outliers (hospitals V, E, P, K, and T)(figure 4).

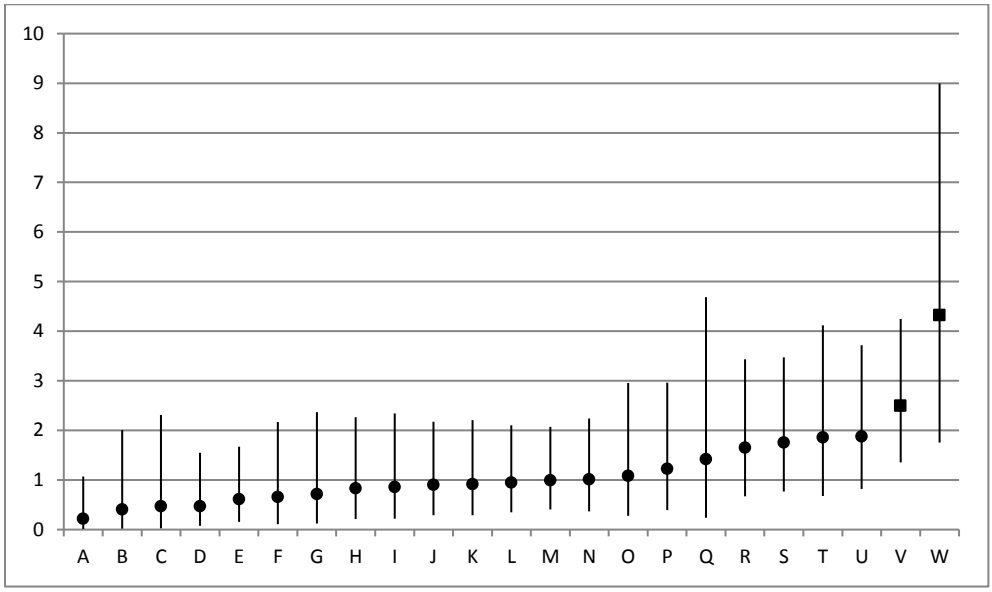

Figure 1: O/E-ranking of hospitals based on allogeneic transfusion in THA, adjusted for patient characteristics
Each hospital is marked by a letter corresponding to the same hospital across figures. Square dots indicate negative outlier hospitals.

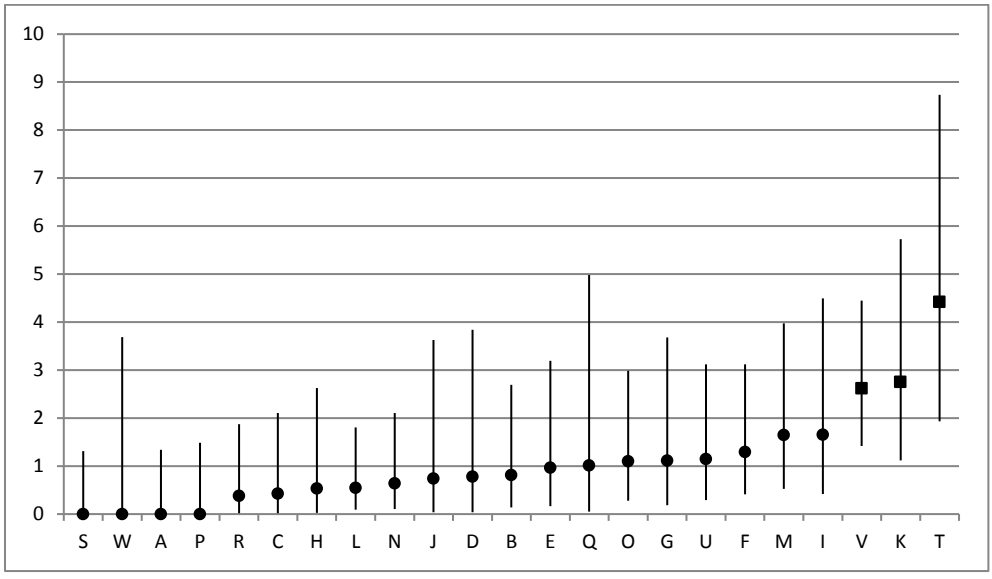

Figure 2: O/E-ranking of hospitals based on allogeneic transfusion in TKA, adjusted for patient characteristics
Each hospital is marked by a letter corresponding to the same hospital across figures. Square dots indicate negative outlier hospitals.

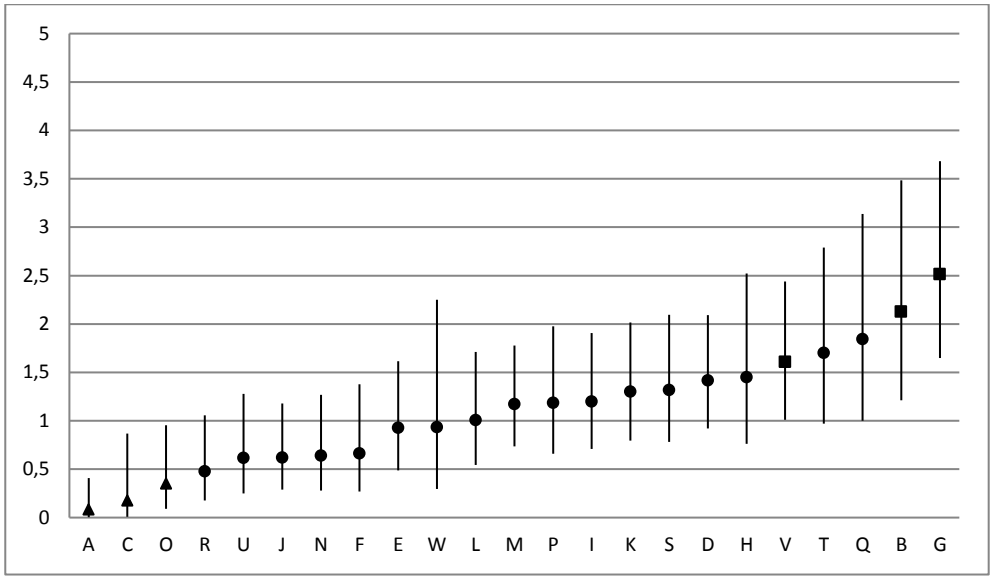

Figure 3: O/E-ranking of hospitals based on extended LoS in THA (>4 days) adjusted for patient characteristics
Each hospital is marked by a letter corresponding to the same hospital across figures. Triangle dots indicate positive outlier hospitals, square dots indicate negative outlier hospitals.

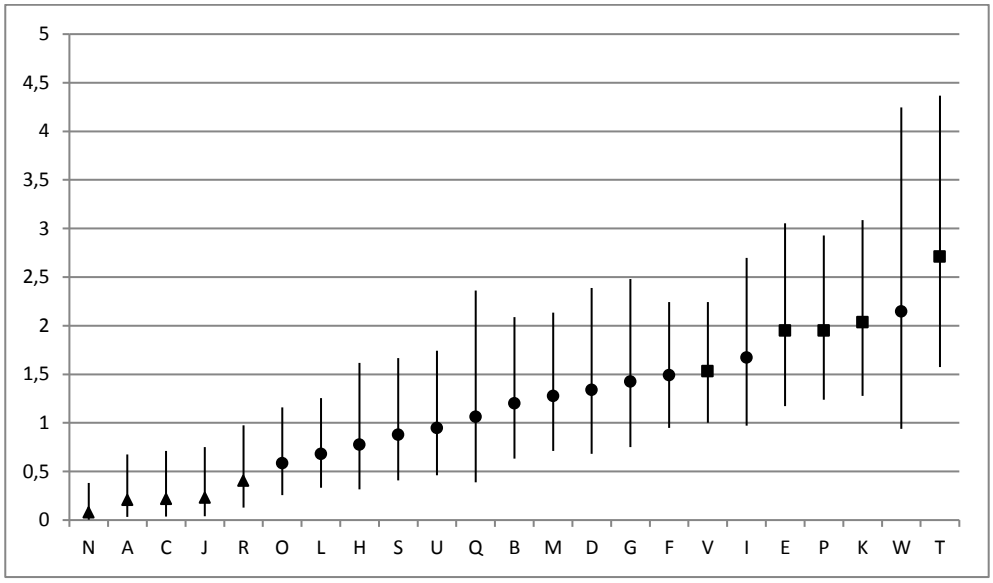

Figure 4: O/E-ranking of hospitals based on extended LoS in TKA (>4 days) adjusted for patient characteristics
Each hospital is marked by a letter corresponding to the same hospital across figures. Triangle dots indicate positive outlier hospitals, square dots indicate negative outlier hospitals.

Reliability of ranking

The rankability, to assess the reliability of ranking, is shown in appendix 2. The rankability allogeneic transfusion after THA was 21%, meaning that 21% of the observed differences in transfusions are true hospital differences and 79% is random variation (due to chance). Rankability of allogeneic transfusion after TKA is 34%. Rankability of percentage of patients with extended LoS is higher, 71% for THA and 78% for TKA so that the majority of the observed variation are true differences.

Possible explanatory factors for hospital performance

To explore which hospital factors could be associated with outcomes, we calculated the correlation coefficients (R) between hospital specific factors and O/E ratios (table 2). In THA patients, more frequent use of TXA within a hospital was associated with a lower O/E ratio (which might indicate better performance) for extended LoS (R=-0.45, P= 0.03). In TKA, more frequent TXA use was significantly associated with both a lower allogeneic transfusion percentage than expected (R= -0.43, P=0.04) and fewer patients with extended LoS (R= -0.65, P< 0.001). In addition, more frequent use of LIA in TKA patients was associated with fewer patients with extended LoS (R= -0.60, P=0.002). No other factors were identified to be associated with hospital performance.

Table 2: Correlation coefficients between hospital factor and outcomes in THA and TKA adjusted for patient characteristics

Hospital factor	R (p-value) allogeneic transfusion in THA	R (p-value) extended LoS in THA	R (p-value) allogeneic transfusion in TKA	R (p-value) extended LoS in TKA
- Preoperative EPO (if Hb <13.0g/dL)	-0.27 (0.21)	-0.10 (0.64)	-0.10 (0.66)	-0.10 (0.66)
- General anesthesia (vs regional))	-0.24 (0.24)	-0.01 (0.97)	0.22 (0.30)	-0.01 (0.95)
- Use of LIA	-0.12 (0.59)	-0.27 (0.21)	-0.30 (0.15)	-0.60 (0.002)
- Use of tranexamic acid	-0.14 (0.53)	-0.45 (0.03)	-0.43 (0.04)	-0.65 (<0.001)
- Use of a tourniquet	-	-	-0.21 (0.34)	-0.20 (0.36)
- Minimal invasive anterior approach (vs lateral/ posterolateral approach)	-0.04 (0.86)	-0.00 (1.0)	-	-
- Cemented acetabulum	-0.32 (0.14)	-0.22 (0.31)	-	-
- Cemented femur	-0.34 (0.11)	-0.23 (0.28)	-	-
- cell salvage system	-0.24 (0.28)	-0.18 (0.42)	-0.11 (0.61)	0.18 (0.42)

Discussion

This study has shown that the reliability of ranking hospitals on differences in their allogeneic transfusion percentage is low, especially for THA in which 21% of the variation between hospitals reflect true differences, but also for TKA (34%). The reliability of ranking hospitals based on differences in extended LoS is better (71% in THA and 78% in TKA) compared to allogeneic transfusion percentages. Thus, this indicator is more suitable for ranking hospitals. Hospitals using TXA more frequently, have fewer patients with extended LoS in both THA and TKA and fewer allogeneic transfusions in TKA patients. Furthermore, hospitals in which LIA is used more frequently, also have fewer patients with extended LoS in TKA.

Ranking seems to be a simple and pragmatic way to get insight into variation between hospitals. However, ranking on outcome indicators should be interpreted carefully as the ability to assess real hospital differences is limited in case of a low rankability. This study is the first that uses the rankability concept, as introduced by Van Houwelingen et al.[47] for a blood management indicator among orthopedic patients. A cut-off point for the rankability to indicate whether an indicator is reliable does not exist. Lingsma et al.[48] suggest that rankability >70% is fair to rank hospitals. Van Dishoeck,[15] uses the same categorization as the I^2 of heterogeneity in meta-analyses, which is similar in nature to the rankability measure. This categorization assigned low, moderate and high to the I^2 values 25%, 50% and 75%.[49] With the latter categorization the rankability of our outcome indicators is low for allogeneic transfusion and moderate to high for extended LoS. Following these suggestions, ranking hospitals based on allogeneic transfusion percentages should not be pursued as it is too unreliable, and this outcome indicator should therefore be preserved for individual monitoring and quality improvement purposes. Ranking based on percentage extended LoS is more reliable. However, any categorization of rankability is still considered arbitrary as already pointed out by others.[15,48]

Furthermore, caution is needed regarding the interpretation of O/E ranking and rankability. The O/E statistic will in theory show how much the number of events in a hospital differs from an idealized or fictive value based on the patient characteristics of that hospital. As such it expresses the magnitude of differences between hospitals and can be used to rank the hospitals. The rankability quantifies the reliability of ranking. However, the exact statistical properties and sensitivity for underlying between-hospital differences of both measures should be investigated in further research.

A possible limitation may be lack of power given the number of patients included per hospital in this study. However, given the observed average transfusion rate of 7% for THA

and median number of 51 patients per hospital, identifying a 14% transfusion rate with 80% power and 95% reliability would require 18 hospitals (assuming an intraclass correlation of 0.01). Such a difference is small in the total range that we report (from 1.9-26.1%, see table 1) and we have data from more hospitals, so that is likely that the number of THA patients has been sufficient. Similarly for TKA with a median number of 42 patients per hospital, we would be able to identify a difference between 4% and 10% with 20 hospitals. For length of stay the range between hospitals was even larger. Therefore we think it is not likely that a lack of power has been a major problem in identifying between-hospital differences.

The observed variation between hospitals may be determined by a different general perioperative policy between hospitals, different surgical techniques and treatment protocols and, in the case of allogeneic transfusion, by different blood management strategies. We tried to identify specific hospital factors that are associated with better or worse performance on allogeneic transfusion and extended LoS. A higher percentage of patients treated with TXA or LIA is associated with better performing hospitals on extended LoS and allogeneic transfusion. The use of TXA and LIA are frequently incorporated in broader programs such as 'enhanced recovery' or 'fast track',[39,50] which are developed to optimize care and reduce LoS, so this may be part of the explanation of the associations found.

A second limitation of this study is that we were not able to measure in which individual patients 'enhanced recovery' or 'fast track' protocols were used. However, we did measure the use of LIA and TXA, which are frequently part of these protocols. In addition, other factors that possibly contribute to the differences between hospitals, that are difficult to express in a number and couldn't be taken into account in this study. For instance: the discharge and rehab protocols of each hospital, regional differences, differences in the amount of complex cases, the use of risk assessment tools, the effect of resident participation or the use of dedicated operating rooms,[51-55] were not included.

In future research, other outcome indicators that are both relevant for clinical practice and reliable for rankings should be identified. Frequently used outcomes such as infection rate, 30-day readmission rate and revision rate should be tested whether these are reliable enough to make valid between-hospital rankings. Optionally outcome indicators could be combined to increase the rankability (e.g. extended LoS with readmission). In general, outcomes with low event rates will be estimated with larger imprecision and thus larger within- and between-hospital variation, mostly resulting in low rankability. Therefore it seems better to pursue outcome indicators with sufficient numbers of events. In addition, the identification and implementation of hospital specific factors associated

with better performance should be further expanded to improve performance of hospitals and to increase quality of care for the patients.

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References

1. Dutch Institute for Healthcare Improvement CBO. Guideline for diagnostis and treatment in hip- and knee arthritis (in Dutch). Utrecht: CBO, 2007.
2. Nelson AE, Allen KD, Golightly YM, et al. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. Semin Arthritis Rheum 2014;43(6):701-12.
3. OECD. Health at a Glance 2013: OECD indicators. www.oecd-ilibrary.org, 2015.
4. Siciliani L, Sivey P, Street A. Differences in length of stay for hip replacement between public hospitals, specialised treatment centres and private providers: selection or efficiency? Health economics 2013;22(2):234-42.
5. Menendez ME, Lu N, Huybrechts KF, et al. Variation in Use of Blood Transfusion in Primary Total Hip and Knee Arthroplasties. The Journal of arthroplasty 2016;31(12):2757-63.e2.
6. Bozic KJ, Grosso LM, Lin Z, et al. Variation in hospital-level risk-standardized complication rates following elective primary total hip and knee arthroplasty. J Bone Joint Surg Am 2014;96(8):640-47.
7. Solomon DH, Losina E, Baron JA, et al. Contribution of hospital characteristics to the volume-outcome relationship: dislocation and infection following total hip replacement surgery. Arthritis and rheumatism 2002;46(9):2436-44.
8. So-Osman C, Nelissen R, Te Slaa R, et al. A randomized comparison of transfusion triggers in elective orthopaedic surgery using leucocyte-depleted red blood cells. Vox Sang 2010;98(1):56-64.
9. Cram P, Cai X, Lu X, et al. Total knee arthroplasty outcomes in top-ranked and non-top-ranked orthopedic hospitals: an analysis of Medicare administrative data. Mayo Clin Proc 2012;87(4):341-48.
10. G.Olmsted M, Geisen E, Murphy J, et al. Methodology: U.S. News & World Report Best Hospitals 2014-15 2015 [updated 4/14/2015.
11. Robertsson O, Ranstam J, Lidgren L. Variation in outcome and ranking of hospitals: an analysis from the Swedish knee arthroplasty register. Acta Orthop 2006;77(3):487-93.
12. van Dishoeck AM, Koek MB, Steyerberg EW, et al. Use of surgical-site infection rates to rank hospital performance across several types of surgery. Br J Surg 2013;100(5):628-36.
13. Adab P, Rouse AM, Mohammed MA, et al. Performance league tables: the NHS deserves better. BMJ 2002;324(7329):95-98.
14. Goldman DA, Brender JD. Are standardized mortality ratios valid for public health data analysis? Stat Med 2000;19(8):1081-88.
15. van Dishoeck AM, Lingsma HF, Mackenbach JP, et al. Random variation and rankability of hospitals using outcome indicators. BMJ Qual Saf 2011;20(10):869-74.
16. Soohoo NF, Farng E, Lieberman JR, et al. Factors that predict short-term complication rates after total hip arthroplasty. Clin Orthop Relat Res 2010;468(9):2363-71.
17. So-Osman C. Red blood cell transfusion triggers and transfusion alternatives in elective orthopedic hip and knee replacement surgery - a review. . International Journal of Clinical Transfusion Medicine 2015;3:47-54.
18. (CBO) DIfHI. Guideline Bloodtransfusionpolicy (in Dutch). Available at: www cbo nl 2011.
19. Voorn VM, PJ M-vdM, Wentink MM, et al. Frequent use of blood-saving measures in elective orthopaedic surgery: a 2012 Dutch blood management survey. BMC Musculoskelet Disord 2013;14(1):230.
20. Dutch Healthcare Inspectorate. Transparant Care (in Dutch). The Hague: IGZ, 2012.
21. Soohoo NF, Tang EY, Krenek L, et al. Variations in the quality of care delivered to patients undergoing total knee replacement at 3 affiliated hospitals. Orthopedics 2011;34(5):356.
22. Goodnough LT, Maniatis A, Earnshaw P, et al. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. Br J Anaesth 2011;106(1):13-22.
23. Jans O, Kehlet H, Hussain Z, et al. Transfusion practice in hip arthroplasty--a nationwide study. Vox Sang 2011;100(4):374-80.
24. Yoshihara H, Yoneoka D. National trends in the utilization of blood transfusions in total hip and knee arthroplasty. J Arthroplasty 2014;29(10):1932-37.
25. de Bethune X, Ackaert K, Gillet P, et al. Total hip arthroplasty in Belgium: the contribution of a social health insurer to the debate. Acta OrthopBelg 2014;80(3):348-56.
26. de Vos M, Graafmans W, Kooistra M, et al. Using quality indicators to improve hospital care: a review of literature. Int J Qual Health Care 2009;21(2):119-29.
27. Van Leeuwen A. The best hospitals of 2011 (in Dutch). Elsevier, 2015.

28. Khanna MP, Hebert PC, Fergusson DA. Review of the clinical practice literature on patient characteristics associated with perioperative allogeneic red blood cell transfusion. Transfus Med Rev 2003;17(2):110-19.
29. Winemaker M, Petruccelli D, Kabali C, et al. Not all total joint replacement patients are created equal: preoperative factors and length of stay in hospital. Can J Surg 2015;58(3):160-66.
30. Alsaleh K, Alotaibi GS, Almodaimegh HS, et al. The use of preoperative erythropoiesis-stimulating agents (ESAs) in patients who underwent knee or hip arthroplasty: a meta-analysis of randomized clinical trials. JArthroplasty 2013;29(9):1463-72.
31. Alshryda S, Sarda P, Sukeik M, et al. Tranexamic acid in total knee replacement: a systematic review and meta-analysis. J Bone Joint Surg Br 2011;93(12):1577-85.
32. Bou MJ, Boettner F. Blood management may have an impact on length of stay after total hip arthroplasty. HSS J 2014;10(2):124-30.
33. Chimento GF, Huff T, Ochsner JL, Jr., et al. An evaluation of the use of topical tranexamic acid in total knee arthroplasty. J Arthroplasty 2013;28(8 Suppl):74-77.
34. Kotze A, Carter LA, Scally AJ. Effect of a patient blood management programme on preoperative anaemia, transfusion rate, and outcome after primary hip or knee arthroplasty: a quality improvement cycle. Br J Anaesth 2012;108(6):943-52.
35. van Bodegom-Vos L, Voorn VM, So-Osman C, et al. Cell Salvage in Hip and Knee Arthroplasty: A Meta-Analysis of Randomized Controlled Trials. J Bone Joint Surg Am 2015;97(12):1012-21.
36. Husted H, Jensen CM, Solgaard S, et al. Reduced length of stay following hip and knee arthroplasty in Denmark 2000-2009: from research to implementation. Arch Orthop Trauma Surg 2012;132(1):101-04.
37. White JJ, Houghton-Clemmey R, Marval P. Enhanced recovery after surgery (ERAS): an orthopaedic perspective. J Perioper Pract 2013;23(10):228-32.
38. Lirk P, Hollmann MW. Outcome after regional anesthesia: weighing risks and benefits. Minerva Anestesiol 2014;80(5):610-18.
39. Marques EM, Jones HE, Elvers KT, et al. Local anaesthetic infiltration for peri-operative pain control in total hip and knee replacement: systematic review and meta-analyses of short- and long-term effectiveness. BMC Musculoskelet Disord 2014;15:220.
40. Opperer M, Danninger T, Stundner O, et al. Perioperative outcomes and type of anesthesia in hip surgical patients: An evidence based review. World J Orthop 2014;5(3):336-43.
41. Kynaston-Pearson F, Ashmore AM, Malak TT, et al. Primary hip replacement prostheses and their evidence base: systematic review of literature. BMJ 2013;347:f6956.
42. Petis S, Howard JL, Lanting BL, et al. Surgical approach in primary total hip arthroplasty: anatomy, technique and clinical outcomes. Can J Surg 2015;58(2):128-39.
43. Yi S, Tan J, Chen C, et al. The use of pneumatic tourniquet in total knee arthroplasty: a meta-analysis. Arch Orthop Trauma Surg 2014;134(10):1469-76.
44. Zan PF, Yang Y, Fu D, et al. Releasing of tourniquet before wound closure or not in total knee arthroplasty: a meta-analysis of randomized controlled trials. J Arthroplasty 2015;30(1):31-37.
45. Voorn VM, PJ M-vdM, So-Osman C, et al. De-implementation of expensive blood saving measures in hip and knee arthroplasties: study protocol for the LISBOA-II cluster randomized trial. Implement Sci 2014;9:48.
46. Rothman KJ, Boice Jr. JD. Epidemiologic Analysis with a Programmable Calculator. NIH Pub No 79-1649. Bethesda, MD: National Institutes of Health, 1979:31-2.
47. Houwelingen Hv, Brand R, Louis T. Empirical bayes methods for monitoring health care quality Bulletin of the ISI2015 [updated 8/7/2015. 2004: Available from: http://stat.fi/isi99/proceedings/arkisto/varasto/vanh0228.pdf.
48. Lingsma HF, Eijkemans MJ, Steyerberg EW. Incorporating natural variation into IVF clinic league tables: The Expected Rank. BMC Med Res Methodol 2009;9:53.
49. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-60.
50. Kehlet H. Fast-track hip and knee arthroplasty. The Lancet 2013;381(9878):1600-02.
51. Cunic D, Lacombe S, Mohajer K, et al. Can the Blaylock Risk Assessment Screening Score (BRASS) predict length of hospital stay and need for comprehensive discharge planning for patients following hip and knee replacement surgery? Predicting arthroplasty planning and stay using the BRASS. Can J Surg 2014;57(6):391-97.
52. Pugely AJ, Gao Y, Martin CT, et al. The effect of resident participation on short-term outcomes after orthopaedic surgery. Clin Orthop Relat Res 2014;472(7):2290-300.

53. Roberts TT, Vanushkina M, Khasnavis S, et al. Dedicated orthopaedic operating rooms: beneficial to patients and providers alike. J Orthop Trauma 2015;29(1):e18-e23.
54. Tan C, Loo G, Pua YH, et al. Predicting discharge outcomes after total knee replacement using the Risk Assessment and Predictor Tool. Physiotherapy 2014;100(2):176-81.
55. Pitter FT, Jorgensen CC, Lindberg-Larsen M, et al. Postoperative Morbidity and Discharge Destinations After Fast-Track Hip and Knee Arthroplasty in Patients Older Than 85 Years. Anesth Analg 2016;122(6):1807-15.

Appendix 1: multivariate associations

Appendix 1 table 1: Multivariate associations between patient characteristics and allogeneic transfusion and extended LOS in THA

	Allogeneic transfusion		Extended Length of Stay	
	OR	**95% CI**	**OR**	**95% CI**
Age	1.05	1.02-1.08*	1.06	1.04-1.08*
Gender (Female relative to male)	1.18	0.66-2.10	0.95	0.67-1.35
BMI (kg/m^2)	0.95	0.90-1.01	1.06	1.03-1.10*
ASA (relative to ASA 1)				
ASA 2	0.96	0.45-2.03	2.49	1.44-4.31*
ASA 3-4	2.09	0.87-5.04	5.34	2.79-10.2*
ASA n/a	-	-	1.76	0.51-6.09
Preoperative hemoglobin (g/dl)	0.42	0.30-0.60*	0.94	0.76-1.16
Diagnosis (other relative to OA/RA)	1.70	0.70-4.17	2.57	1.41-4.69*
Smoking (yes relative to no)	1.2	0.56-2.59	1.14	0.71-1.84

*OR:Odds Ratio, CI:Confidence Interval, THA: Total hip arthroplasty, TKA: Total knee arthroplasty, BMI: Body mass index, ASA: American Society of Anesthesiologists, Hb: Hemoglobin, OA/RA: Osteoarthritis/Rheumatoid arthritis, LoS: Length of Stay, *P<0.05, Nagelkerke R^2 allogeneic transfusion model: 0.17, Nagelkerke R^2 extended length of stay model: 0.16*

Appendix 1 table 2: Multivariate association between patient characteristics and allogeneic transfusion and extended LOS in TKA

	Allogeneic transfusion		Extended Length of Stay	
	OR	**95% CI**	**OR**	**95% CI**
Age	1.06	1.01-1.10*	1.05	1.03-1.07*
Gender (Female relative to male)	0.40	0.20-0.81*	1.05	0.71-1.56
BMI (kg/m2)	0.91	0.85-0.98*	1.03	1.00-1.07
ASA (relative to ASA I)				
ASA 2	2.87	0.65-12.6	1.46	0.84-2.54
ASA 3-4	3.38	0.70-16.4	2.63	1.37-5.04*
ASA n/a	-	-	0.69	0.14-3.43
Preoperative hemoglobin (g/dl)	0.29	0.19-0.47*	0.75	0.59-0.94*
Diagnosis (other relative to OA/RA)	2.06	0.60-7.12	1.85	0.76-4.51
Smoking (yes relative to no)	0.48	0.10-2.16	1.25	0.71-2.22

*OR:Odds Ratio, CI:Confidence Interval, THA: Total hip arthroplasty, TKA: Total knee arthroplasty, BMI: Body mass index, ASA: American Society of Anesthesiologists, Hb: Hemoglobin, OA/RA: Osteoarthritis/Rheumatoid arthritis, LoS: Length of Stay, *P<0.05, Nagelkerke R^2 allogeneic transfusion model: 0.23, Nagelkerke R^2 extended length of stay model: 0.12*

Appendix 2: Rankability of outcome indicators

Appendix 2 Table 1: Rankability of outcome indicators

Outcome Indicator	Within-hospital variation	Between-hospital variation	Rankability
Allogeneic transfusion in THA	0.63	0.16	20.7%
Allogeneic transfusion in TKA	1.19	0.61	33.8%
Extended LoS in THA	0.26	0.64	70.9%
Extended LoS in TKA	0.34	1.17	77.7%

THA: Total hip arthroplasty, TKA: Total knee arthroplasty, LoS: Length of Stay

Chapter 7

Perceived barriers among physicians for stopping non–cost-effective blood-saving measures in total hip and total knee arthroplasties

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Abstract

Background: Despite evidence that the blood-saving measures (BSMs) erythropoietin (EPO) and intra- and postoperative blood salvage are not (cost-)effective in primary elective total hip and knee arthroplasties, they are used frequently in Dutch hospitals. This study aims to assess the impact of barriers associated with the intention of physicians to stop BSMs.

Study Design and Methods: A survey among 400 orthopaedic surgeons and 400 anaesthesiologists within the Netherlands was performed. Multivariate logistic regression was used to identify barriers associated with intention to stop BSMs.

Results: A total of 153 (40%) orthopaedic surgeons and 100 (27%) anaesthesiologists responded. Of all responders 67% used EPO, perioperative blood salvage, or a combination. After reading the evidence on non–cost-effective BSMs, 50% of respondents intended to stop EPO and 53% to stop perioperative blood salvage. In general, barriers perceived most frequently were lack of attention for blood management (90% of respondents), department priority to prevent transfusions (88%), and patient characteristics such as comorbidity (81%). Barriers significantly associated with intention to stop EPO were lack of interest to save money and the impact of other involved parties. Barriers significantly associated with intention to stop perioperative blood salvage were concerns about patient safety, lack of alternatives, losing experience with the technique, and lack of interest to save money.

Conclusion: Physicians experience barriers to stop using BSMs, related to their own technical skills, patient safety, current blood management policy, and lack of interest to save money. These barriers should be targeted in strategies to make BSM use cost-effective.

Background

During total hip arthroplasty (THA) and total knee arthroplasty (TKA) the calculated visible and invisible blood loss is 1500 mL on average.[1] The ensuing drop of haemoglobin (Hb) of approximately 3 g/dL leads to high rates of allogeneic blood transfusions up to 69% in this patient group, depending on the transfusion threshold.[2,3] Concerns about the risk of (non)infectious transfusion reactions due to allogeneic transfusions have led to the development of blood-saving measures (BSMs) including preoperative erythropoietin (EPO) and intra- and postoperative autologous blood salvage and reinfusion (in short, perioperative blood salvage) to prevent these allogeneic blood transfusions. Many studies have been performed on the effectiveness of these BSMs, with varying results but mostly in favour of cell salvage. However, reviews showed that these studies had several limitations such as a retrospective design, small patient numbers, and poor methodologic quality. Trials were performed unblinded and lacked adequate concealment of treatment allocation, which may have influenced and biased the results in favour of perioperative blood salvage and EPO.[3-6]

A recent randomized controlled trial conducted by So-Osman and colleagues among approximately 2500 patients was performed to assess the effect of both EPO and perioperative blood salvage in patients receiving a THA or TKA. The results showed that, with a restrictive transfusion trigger, neither EPO nor perioperative blood salvage nor postoperative blood salvage alone were cost-effective in primary elective THA and TKA compared with no BSM use.[7,8] EPO is effective to prevent allogeneic blood transfusions, but at unacceptable high costs (€7300 or approx. $9500 per avoided transfusion) in patients with Hb range between 10 and 13 g/dL. Use of perioperative blood salvage did not avoid transfusion or had a blood-saving effect and consequently increased the costs per patient (€378 or approx. $500 per patient). Therefore, both techniques are considered non–cost-effective in primary elective THA and TKA.[7,8] For revision surgery no conclusions about the (cost-)effectiveness of EPO or perioperative blood salvage could be drawn.[7,8] Another study that advocates the financial benefits for selective use of intraoperative blood salvage was performed under the assumption that every unit of autologous blood replaces a unit of allogeneic blood transfusion. This assumption ignores the possibility that patients undergoing surgery without blood salvage might not need a transfusion and thereby overestimates the effectiveness and hence the cost-effectiveness.[9]

The study results of So-Osman and coworkers[7,8] are in line with recent literature. A number of recent trials that were not included in the currently available meta-analyses show that perioperative blood salvage is not superior to a regular drain or no drain.[10-14] With respect to EPO, other studies also show that EPO is effective but that the costs are

too high.[15,16] Despite the availability of this evidence, physicians keep using these BSMs in daily practice. A survey among orthopaedic departments in Dutch hospitals showed that approximately 85% of Dutch hospitals use at least one of these BSM types frequently in THA and TKA patients.[17]

To decrease costs of care delivery to patients undergoing primary elective THA or TKA, it is recommended that physicians stop routine use of non–(cost-)effective BSMs. However, little is known about effective interventions to stop current behaviour of physicians, that is, de-implementation of non–cost-effective BSMs. Overall, knowledge about barriers that hinder de-implementation of common practices is scarce,[18]whereas much more is known about barriers that hinder the implementation of new guidelines or techniques,[16,19-25] that is, that it requires knowledge, skills and time to adopt a new technique.

Improved insight into the barriers that are associated with the intention to stop using non–cost-effective BSMs is required to develop effective interventions and thereby to improve the efficiency of care delivery in THA and TKA. Therefore, this study aims to explore and quantify the impact of barriers that hinder physicians to stop the use of non–cost-effective BSMs in primary elective THA and TKA.

Materials and Methods

Study design and setting

The study had a cross-sectional design, using an Internet-based questionnaire. The development of this questionnaire was based on in-depth interviews with physicians involved in THA and TKA. Relevant for the setting of this study is that it was performed in the Netherlands where there is no shortage of allogeneic blood and elective surgery is basically never delayed or cancelled for this reason. However, costs of blood products are slightly higher when compared with other (European) countries.[26,27] The expenses of EPO are incurred by the outpatient pharmacy and reimbursed by the health care insurance company. The expenses of perioperative blood salvage are paid by the hospital. Physicians are either employed by the hospital or form a partnership of independent entrepreneurs and mostly do not bear the costs for BSMs. The Medical Ethical Committee of the Leiden University Medical Center declared that ethical approval was not required under the Dutch national law (CME 11/104).

Questionnaire development

To explore barriers, semi structured interviews were performed among 10 orthopaedic surgeons and 10 anaesthesiologists. Orthopaedic surgeons and anaesthesiologists were considered to be key stakeholders in the decision whether or not to use BSMs in THA and TKA. These physicians stated that it varies per hospital whether the orthopaedic surgeons or the anaesthesiologists make the decision to use EPO and perioperative blood salvage. Based on a previous survey[17] we selected physicians for the interviews from hospitals with both frequent and non-frequent use of BSMs, under the assumption that this would provide us with a broad spectrum of perceived barriers.

The interview topic guide was compared with the theoretical construct domains of the theoretical domains interview framework (TDF),[20,23] to ensure that no potentially relevant barriers would be excluded. The TDF includes 12 different domains derived from a large number of health psychology theories and their theoretical constructs. Previous studies already showed that the TDF is useful in identifying a broad spectrum of barriers and facilitators to change behaviour.[20,22-24] The interviews were transcribed in full, coded and analysed independently by two investigators (VV and MW). In case of disagreement, consensus was reached through discussion. There were 67 barriers reported that partially overlapped and were processed into 53 questionnaire items. To analyse the interviews a software package (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany) was used.

Study population

A random sample of 400 orthopaedic surgeons listed in the registry of the Netherlands Orthopaedic Association (n = 595) and a random sample of 400 anaesthesiologists listed in the registry of the Netherlands Society of Anaesthesiologists (n = 1200) were invited to fill out the questionnaire. We sampled by means of digital number allocation to the registry.

If the invited physician stated that he or she was not involved in THA and TKA, we invited another physician from the same region to fill out the questionnaire. Characteristics of invited physicians (sex and hospital type) were gathered using the Netherlands Orthopaedic Association and the Netherlands Society of Anaesthesiologists registries. Data of responders were saved anonymously.

Questionnaire

The Internet-based questionnaire started with two items concerning the current use of EPO and perioperative blood salvage on a 7-point Likert scale ranging from ‘none’ to ‘to a very large extent’. Next, the results of the blood management randomized controlled

trial[7,8] were presented (including the costs and limited benefits of EPO and perioperative blood salvage) followed by two items to assess the intention to stop the use of EPO and perioperative blood salvage after responders had read the study results. This was also measured on a 7-point Likert scale ranging from 'none' to 'to a very large extent.' The intention to stop with EPO and the intention to stop perioperative blood salvage were the outcome measures of this study. These outcome measures were used as a proxy for behaviour change because it is impossible to measure behaviour change in a cross-sectional study design and intention is known to be related to behaviour change[2,28]. The last part of the questionnaire consisted of 53 items covering the identified barriers. Physicians who did not use BSMs were asked to fill in these questions as if they used BSMs. Of these questions, 36 started with 'To what degree' and answers could be given on a 7-point Likert scale ranging from 'none' to 'to a very large extent.' Furthermore, 16 questions that could not be formulated in this way started with 'How important do you find', and answers could be given on a 7-point Likert scale ranging from 'not important' to 'very important', and there was one question with yes or no answering categories. All physicians were approached by e-mail in August 2012. Reminders were sent 2, 4, and 6 weeks after the first invitation.

Statistical analysis

To quantify the presence of barriers for de-implementation as perceived by the physicians, we dichotomized the 7-point Likert scale items (0-3 no barrier, 4-6 barrier). We described the characteristics of the physicians and the percentage of physicians that perceived the items as barrier.

To identify barriers associated with the intention to stop with either EPO or perioperative blood salvage, we used a multivariate logistic regression model. The outcome measures 'intention to stop EPO' and 'intention to stop perioperative blood salvage' were dichotomized into 'no intention to stop' (0-2) and 'intention to stop' (3-6). As the decision to stop or continue the use of BSMs is binary, logistic regression analysis was used, and we tried to be very sensitive by including all physicians who had some intention to stop BSMs so that we would capture the full range of possible barriers. To prevent overfitting of the logistic regression model by including too many variables and to determine the underlying concept of the 53 barriers (in their original 7-point scale), we first grouped coherent barriers. This was done by using an explorative factor analysis with an orthogonal rotation approach, using principal component analysis and varimax rotation.[29] For the interviews we used the TDF.[20,23] However, after analysing the interviews the identified barriers could fit within more than one domain. Exploratory factor analysis was therefore used, to analyse which factors clustered together into a single factor. The number of factors was determined based on Cattell's scree test.[30]

Barriers were assigned to a factor if their factor loading was greater than 0.30. Barriers with a factor loading of less than 0.30 were not used in subsequent analyses. In case of cross-loading, the barrier was assigned to the factor with the highest loading.[29] This resulted in a number of coherent barriers grouped in factors. We calculated the Cronbach's alpha for each factor to assess their internal consistency.

Within each factor we tested which barriers were significantly associated with the intention to stop EPO and with the intention to stop perioperative blood salvage. An ENTER selection method was applied in this logistic regression analysis including all barriers within a factor. Variables with p values of less than 0.05 were considered eligible for the following analysis.

Significant barriers within a factor were tested together in a multivariate logistic model. As individual barriers may be related to other barriers, we wanted to assess the independent contribution of each barrier on the intention to stop. In addition, we adjusted for professionals' characteristics (sex, type of hospital, current BSM use). This resulted in a number of barriers that are significantly and independently associated with the intention of physicians. The Nagelkerke R^2 was used to assess the variance explained by the model.[31] The analysis of questionnaire data was executed using a software package (SPSS, IBM SPSS Statistics, Version 20, IBM Corp., Armonk, NY).

Results

The questionnaire was completed by 100 (27%) anaesthesiologists and 153 (40%) orthopaedic surgeons with a total response of 253 completed questionnaires (34%; Figure 1). The reason for nonresponse was not verified. Eighty-nine percent of anaesthesiologists and 96% of the orthopaedic surgeons were male. None of the responding anaesthesiologists worked in a private clinic. Responding anaesthesiologists worked in 61 different hospitals, and orthopaedic surgeons in 76 different hospitals. In total, physicians in 89 of 99 hospitals in the Netherlands responded. EPO was used by 48% of the anaesthesiologists and by 41% of the orthopaedic surgeons. Perioperative blood salvage was used by 65% of the anaesthesiologists and by 50% of orthopaedic surgeons. In total 67% of respondents used EPO, perioperative blood salvage, or both. Further characteristics of the responders are shown in Table 1.

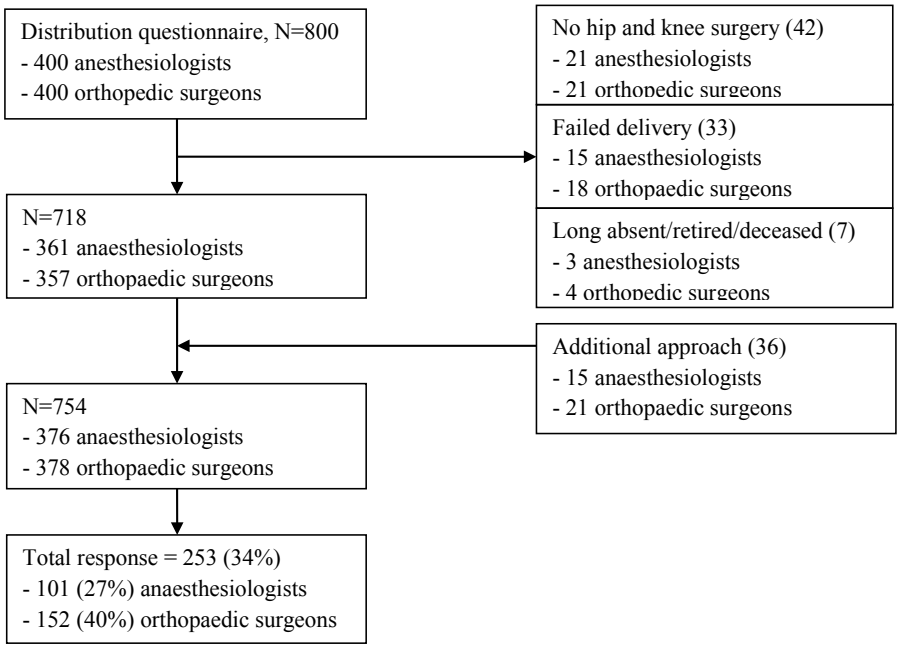

Figure 1: Flow diagram of questionnaire distribution and response.

Table 1: Characteristics of the participating physicians (n=253).

	Orthopaedic surgeons N= 153 (response 60%)	Anaesthesiologists N= 100 (response 40%)
Gender		
- Male	147 (96%)	89 (89%)
Type of hospital		
- University Medical Centre	16 (11%)	19 (19%)
- Teaching hospital	46 (30%)	33 (33%)
- General hospital	83 (54%)	48 (48%)
- Private clinic	8 (5%)	0 (0%)
Current use of BSMs		
- EPO	63 (41%)	48 (48%)
- Perioperative blood salvage	77 (50%)	64 (65%)

Quantification of barriers

Data of all respondents were analysed. Six factors were identified using the Cattell's scree-test, representing 42 items that were perceived as barriers. The remaining 11 items did not load sufficiently on the factors (<0.300). Examining the items represented within

the six factors, these seem to fit well with six of the TDF domains (Table 2). Each factor consisted of at least six items. The Cronbach's alpha values per factor varied between 0.60 and 0.86. The physicians perceived the items within the factors to varying degrees as barriers (Table 2). Barriers that were perceived most frequently were all in the domain labelled 'environmental context and resources': 'lack of attention for blood management' (90%), 'department priority to prevent blood transfusions' (88%), 'patient characteristics such as comorbidity' (81%), and 'importance to take experiences of colleagues within the hospital into account' (79%). Table 2 also shows that some potential barriers identified during the interviews were not considered important by the majority of respondents. These were 'lack of interest in new developments' (2%), 'lack of importance of recommendations of the physician associations' (1%), and 'lack of importance of national guidelines' (1%). These barriers were all in the domain labelled 'memory, attention, and decision processes.' Although orthopaedic surgeons and anaesthesiologists perceive the same barriers, there are differences in frequency. Anaesthesiologists perceived the following barriers more frequently than orthopaedic surgeons: 'difficulty of implementing changes within own department' (44% vs. 26%), 'importance to take patients' opinion into account' (63% vs. 45%), and 'convinced of effectiveness of perioperative blood salvage' (67% vs. 49%; Table 2).

Table 2: Number (%) of respondents that perceived an item as barrier (dichotomized)

	Total (n=253)	Orthopaedic surgeons (n=153)	Anaesthesiologists (n=100)
Memory, attention and decision processes (alpha =0.86)[†]			
- Lack of attention for an unequivocal blood management policy	19 (8%)	12 (8%)	7 (7%)
- Lack of attention for costs of BSMs and transfusions	7 (3%)	6 (4%)	1 (1%)
- Lack of attention for the number of blood transfusions	7 (3%)	5 (3%)	2 (2%)
- Lack of attention for literature about BSMs and transfusions	31 (12%)	23 (15%)	8 (8%)
- Lack of attention for study results compared with own clinical experience about effectiveness of BSMs	15 (6%)	10 (7%)	5 (5%)
- Lack of attention for new developments	4 (2%)	3 (2%)	1 (1%)
- Lack of importance of national guideline	4 (2%)	3 (2%)	1 (1%)
- Lack of importance of recommendations of the professional associations	2 (1%)	1 (1%)	1 (1%)
- Lack of importance of feedback about BSM use and transfusion rates	10 (4%)	8 (5%)	2 (2%)

Social influences (alpha =0.77)†			
- Lack of department priority for cost-effective blood management	48 (19%)	23 (15%)	25 (25%)
- Difficulty of implementing changes within own department	83 (33%)	39 (26%)	44 (44%)
- Difficulty of breaking established routines	95 (38%)	51 (34%)	44 (44%)
- Lack of discussion about blood management within in department	31 (12%)	12 (8%)	19 (19%)
- Lack of agreement within department about the blood management policy	10 (4%)	3 (2%)	7 (7%)
- Hindered by hospital management to adjust the blood management policy	21 (8%)	10 (7%)	11 (11%)
- Lack of influence of respondent on blood management policy	13 (5%)	5 (3%)	8 (8%)
- Lack of influence of department on stopping BSMs	14 (6%)	6 (4%)	8 (8%)
- Hindered by blood management policy of other medical specialties/blood transfusion committee	42 (17%)	25 (17%)	17 (17%)
Motivation and goals (alpha 0.72)†			
- Lack of reliability of TOMaat* study results	24 (10%)	14 (9%)	10 (11%)
- Lack of importance of RCTs in comparison to own clinical experience	14 (6%)	7 (5%)	7 (7%)
- Lack of benefit for delivery of care	52 (21%)	32 (21%)	20 (20%)
- Lack of benefit for organization of care delivery	36 (14%)	23 (15%)	13 (13%)
- Lack of interest to save money for the hospital by stopping blood salvage	94 (38%)	51 (34%)	43 (43%)
- Lack of interest to save money for the society by stopping EPO	79 (31%)	43 (28%)	36 (36%)
Beliefs about consequences (alpha 0.60)†			
- Concerns about losing experience with the use of BSMs	75 (30%)	37 (24%)	38 (38%)
- Difficulty of letting treatment team stop with EPO	44 (18%)	24 (16%)	20 (20%)
- Difficulty of letting treatment team stop with perioperative blood salvage	46 (18%)	21 (14%)	25 (25%)
- Pressure of suppliers to use BSMs	20 (8%)	10 (7%)	10 (10%)
- Concerns about safety of patients when BSMs are stopped	97 (39%)	56 (38%)	41 (41%)
- Importance to take patients' opinion into account	131 (52%)	68 (45%)	63 (62%)
Knowledge (alpha =0.65)†			
- Convinced of effectiveness of EPO	144 (58%)	84 (55%)	60 (61%)
- Convinced of effectiveness perioperative blood salvage	141 (56%)	75 (49%)	66 (67%)
- Lack of alternatives for EPO	116 (46%)	69 (45%)	47 (48%)
- Lack of alternatives perioperative blood salvage	145 (59%)	82 (55%)	63 (64%)
- Lack of interest to gain additional information about stopping EPO	114 (46%)	62 (41%)	52 (54%)
- Lack of interest to gain additional information about stopping perioperative blood salvage	120 (48%)	67 (44%)	53 (54%)

Environmental context and resources (alpha =0.65)†				
-	Department priority to prevent blood transfusions	221 (88%)	136 (89%)	85 (86%)
-	Importance to take experiences with BSMs of colleagues within the hospital into account	198 (79%)	124 (82%)	74 (74%)
-	Importance to take experience with BSMs of colleagues in other hospitals into account	139 (55%)	93 (61%)	46 (47%)
-	Patient characteristics such as co-morbidity	202 (81%)	120 (79%)	82 (83%)
-	Lack of attention for blood management	227 (90%)	139 (91%)	88 (88%)
-	Importance to prevent transfusions regardless of costs	127 (51%)	77 (51%)	50 (50%)

** TOMaat: Tranfusie Op Maat (tailored transfusion, study results of So-Osman et al.[7,8])*

† alpha: Cronbach's alpha coefficient to assess the internal consistency of items within a factor

Barriers associated with the physicians' intention to stop EPO

Among respondents, 50% had the intention to stop EPO, with comparable percentages between orthopaedic surgeons (50%) and anaesthesiologists (51%). When tested within each factor, five eligible barriers significantly associated with the intention to stop EPO use were identified (Table 3A). In multivariate analyses including all significantly associated barriers from all factors, three independent barriers remained significant in the domains labelled: 'social influences,' 'motivation and goals,' and 'beliefs about consequences.' The presence of the barriers 'the impact of blood management policy of other medical specialties/blood transfusion committee' ($p = 0.022$) and 'pressure of suppliers to use BSMs' ($p < 0.001$) made it more likely that physicians had the intention to stop with EPO. Perceiving the barrier 'lack of interest to save money for the society by stopping EPO' on the other hand, made it less likely that physicians had the intention to stop with EPO ($p < 0.001$; Table 3B). Together these three barriers explained 38% of the variance in intention to stop with EPO.

Table 3A: Barriers within each factor significantly associated with the intention to stop EPO

Domain	Barrier	OR*	CI
Memory, attention and decision process	- Lack of attention for costs of BSMs and transfusions	0.532	0.362-0.781
Social influences	- Hindered by blood management policy of other medical specialties/blood transfusion committee	1.278	1.063-1.537
Motivation and goals	- Lack of interest to save money for the society by stopping EPO	0.649	0.498-0.846
Beliefs about consequences	- Pressure of suppliers to use BSMs	1.595	1.251-2.032
	- Concerns about safety of patients when BSMs are stopped	0.770	0.638-0.929

** ORs adjusted for current EPO use: with a 1 step increase on the 7-point Likert scale the chance to have the intention to stop with EPO is multiplied by the OR.*

Table 3b. Barriers significantly associated with intention to stop EPO in multivariate analysis.

Domain	Barrier	OR*	CI
Social influences	- Impeded by blood management policy of other medical specialties/blood transfusion committee	1.263	1.034-1.544
Motivation and goals	- Lack of interest to save money for the society by stopping EPO	0.634	0.518-0.776
Beliefs about consequences	- Pressure of suppliers to use BSMs	1.583	1.225-2.046

** ORs adjusted for current EPO use: with a 1 step increase on the 7-point Likert scale the chance to have the intention to stop with EPO is multiplied by the OR*

Barriers associated with the physicians' intention to stop blood salvage

Among respondents, 53% had the intention to stop with blood salvage, with slightly more orthopaedic surgeons willing to stop when compared with anaesthesiologists (57% vs. 46%). When tested within each factor, eight eligible barriers significantly associated with the intention to stop with perioperative blood salvage were identified (Table 4A). In multivariate analyses including all significantly associated barriers from all factors, seven independent barriers remained significant in the domains labelled 'social influences,' 'motivation and goals,' 'beliefs about consequences,' and 'knowledge' (Table 4B). The barriers 'lack of interest to gain additional information about stopping perioperative blood salvage' ($p = 0.002$) and 'lack of influence of respondent on blood management policy' ($p = 0.034$) were, when perceived by physicians, associated with higher intention of physicians to stop perioperative blood salvage. The barriers 'lack of benefit for delivery of care' ($p = 0.039$), 'lack of alternatives for perioperative blood salvage' ($p = 0.001$), 'lack of interest to save money for the hospital by stopping perioperative blood salvage' ($p = 0.040$), 'concerns about losing experience with the use of BSMs' ($p = 0.027$), and 'concerns about safety of patients when BSMs are stopped' ($p = 0.020$) were, on the other hand, associated with significantly less intention to stop perioperative blood salvage (Table 4B). Overall, 44% of the variance in intention to stop with perioperative blood salvage was explained by these seven barriers.

Table 4A: Barriers within factors significantly associated with the intention to stop perioperative blood salvage

Domain	Barrier	OR*	CI
Social influences	- Lack of influence of respondent on blood management policy	1.399	1.002-1.954
Motivation and goals	- Lack of benefit for delivery of care	0.719	0.542-0.952
	- Lack of interest to save money for the hospital by stopping perioperative blood salvage	0.662	0.498-0.881
Beliefs about consequences	- Concerns about losing experience with the use of BSMs	0.815	0.680-0.976
	- Concerns about safety of patients when BSMs are stopped	0.745	0.618-0.896
Knowledge	- Convinced of effectiveness of perioperative blood salvage	0.682	0.542-0.858
	- Lack of alternatives for perioperative blood salvage	0.752	0.595-0.951
	- Lack of interest to gain additional information about stopping perioperative blood salvage	1.304	1.032-1.648

** OR adjusted for current perioperative blood salvage use: with a one-step increase on the 7-point Likert scale the chance to have the intention to stop with perioperative blood salvage is multiplied by the OR*

Table 4B. Barriers significantly associated with intention to stop perioperative blood salvage in multivariate analysis

Domain	Barrier	OR*	CI†
Social influences	- Lack of influence of respondent on blood management policy	1.396	1.027-1.899
Motivation and goals	- Lack of benefit for delivery of care	0.796	0.642-0.988
	- Lack of interest to save money for the hospital by stopping perioperative blood salvage	0.781	0.617-0.989
Beliefs about consequences	- Concerns about losing experience with the use of BSMs	0.794	0.647-0.974
	- Concerns about safety of patients when BSMs are stopped	0.765	0.611-0.958
Knowledge	- Lack of alternatives for perioperative blood salvage	0.648	0.499-0.842
	- Lack of interest to gain additional information about stopping perioperative blood salvage	1.336	1.115-1.601

** OR adjusted for current perioperative blood salvage use: with a one-step increase on the 7-point Likert scale the chance to have the intention to stop with perioperative blood salvage is multiplied by the OR.*

Discussion

The results of this study show that physicians perceive barriers for de-implementation of EPO and perioperative blood salvage in primary elective THA and TKA on the domains labelled 'memory, attention and decision processes,' 'social influences,' 'motivation and goals,' 'beliefs about consequences,' 'knowledge,' and 'environmental context and resources.' In general, barriers perceived most frequently were lack of attention for blood management (90% of respondents), department priority to prevent transfusions (88%), and patient characteristics such as comorbidity (81%). Although some barriers were perceived by many physicians, these barriers do not necessarily influence the behaviour of physicians. Therefore, we assessed which barriers were associated with the intention of physicians to stop with EPO and perioperative blood salvage. These barriers were related to their own technical skills, patient safety, current blood management policy, and the lack of interest to save money, explaining 38 and 44% of the variance in the intention to stop BSMs. This implies that a large proportion of a physician's intention is explained by the identified barriers.

It is notable that four of the identified barriers were associated with higher intention to stop with BSMs. This involves two barriers for EPO: 'the impact of blood management policy of other medical specialties/blood transfusion committee' and 'pressure of suppliers to use BSMs' and one barrier for perioperative blood salvage: 'lack of influence of respondent on blood management policy.' It is not likely that this is a causal effect relationship, so that these barriers result in higher intention to stop. Instead, we expect this effect to be the other way around, that it is due to the fact that physicians only perceive these barriers when they have the intention to stop with EPO or perioperative blood salvage and feel hindered by these factors. The last barrier associated with higher intention to stop: 'lack of interest to gain additional information' is not necessarily a barrier, as this item might indicate that physicians with enough knowledge about the subject 'blood management' have a high intention to stop.

The identified barriers for de-implementation in this study are partly in line with literature concerning implementation of guidelines or 'evidence-based practice.' In our study physicians experienced barriers through the impact of other medical specialties, transfusion committees, and BSM suppliers on their blood management policy. These environmental factors are also common when it involves implementation.[19,32,33] The same is true for lack of interest in (cost-)effectiveness.[34] However, there are differences. Implementing new techniques or behaviours is hindered by some specific barriers, for example, lack of knowledge (available evidence), skills, time, or resources that are necessary to perform the new behaviour or use a new technique,[20,22,34] whereas stopping current behaviour may lack an evident benefit and raises concerns in physicians about the

safety of patients and losing experience with a technique as found in this study. Therefore, this study provides a better understanding of barriers associated with de-implementation.

In changing blood management, there are some relevant issues that must be considered. For example, the awareness of transfusion triggers as well as infection risks of allogeneic transfusions may both be important issues with regard to BSM use. However, participating physicians in the interviews stated using a restrictive transfusion protocol as mentioned in the national guideline, with triggers as low as 6.4 g/dL.[35] These statements were in line with a previous survey among chairs of orthopaedic departments in the Netherlands, where 96% of orthopaedic departments reported using the national transfusion guideline or an extended version of this guideline.[17] The risks for infections due to allogeneic transfusions like hepatitis B and C or human immunodeficiency virus were not mentioned as relevant risks of transfusion in the interviews, when explicitly asked about these risks. This suggests that in the Netherlands, the physicians are aware of the safety of blood transfusions, having a low risk of transfusion related infections. So although these issues are both very relevant, they were not included in the questionnaire as potential barriers that may hinder the implementation of cost-effective blood management given current routine practice in the Netherlands.

Patients undergoing THA or TKA with preoperative anaemia form a distinct group in the consideration to stop using BSMs. This group is eligible for preoperative EPO treatment, which is known to be effective in preventing allogeneic transfusions. However, it has also been shown that the costs of this EPO treatment are too high when compared with an allogeneic transfusion.[7,8] Alternative techniques, for example, tranexamic acid or intravenous or oral iron, can be considered instead of EPO and may be more cost-effective.[3,15,16,36] Another distinct group to be aware of in changing blood management policy is the group of patients who refuse allogeneic transfusion (e.g., Jehovah witnesses) or patients who, for instance, due to the presence of alloantibodies, are not able to receive 'regular' allogeneic transfusions. These patients might benefit from EPO or perioperative blood salvage, despite the limited (cost-)effectiveness of these techniques.[37] However, it is beyond the scope of this article to produce a guideline or summary on which alternative techniques can be used and which cases might benefit from EPO or perioperative blood salvage.

The barriers that hinder the de-implementation of EPO and perioperative blood salvage are mostly similar, as de-implementation in both cases is hindered by social influences (other specialties, transfusion committee, suppliers) and for both techniques physicians do not have incentives to control costs. However, there are specific barriers that hinder physicians to stop with perioperative blood salvage. Concerns about patient safety and concerns to lose their own experience with the technique suggest that physicians strongly

believe in the effectiveness of perioperative blood salvage. This is striking, as there is convincing evidence that shows no overall reduction of transfused patients using this technique.[7,8,10-14] As this study is part of a de-implementation project, these results indicate that a different approach needs to be taken for de-implementation of perioperative blood salvage versus EPO.

A previous survey on the frequency of BSM use showed that more than 85% of Dutch hospitals frequently use either EPO, perioperative blood salvage, or a combination of these non–cost-effective BSMs in THA and TKA.[17]

Due to scientific development of new and better techniques many more current techniques that are applied in real life might become redundant or too expensive. Physicians do not stop with these techniques by themselves as there are numerous barriers that hinder them from doing so. De-implementation is a relatively new concept and physicians are not used to changing their current behaviour and stopping the use of techniques without it being replaced by a newer technique. A strong point of our study is that it is one of the first in the field of implementation that gives insight into barriers relevant for de-implementation. This makes it possible to compare these de-implementation barriers with barriers for implementation. More de-implementation studies are needed to broaden this insight and to identify barriers that can be addressed in specific situations.

Another strong point of this study is that the barriers in the questionnaire were based on previously identified factors during interviews with involved physicians. This ensures that the questionnaire does not test the authors' personal hypothesis but represents the complete set of possible barriers. Also the fact that we related the barriers to the intention to stop is a strong point. This ensures that the identified barriers are relevant to change behaviour.

A limitation of the study is the national setting. The recent trial showing that EPO and perioperative blood salvage were not cost-effective was performed in the Netherlands. The availability, price, and reimbursement of blood products and BSMs may vary per country and therefore study results cannot simply be extrapolated to other countries. The same is true for the identified barriers, which may also vary due to variance in the organization of health care (e.g., incentives to reduce costs).

A second limitation is the low response rate to the questionnaire of 34%. This can lead to response bias. We would expect that if an unequal ratio of users versus nonusers of BSMs would respond to our questionnaire, when compared with the total study population, this

would create bias. Therefore we asked physicians about their current use and adjusted for that in the analyses.

Another possible limitation may be the outcome measure. We used 'intention to stop' as outcome. However, having the intention to stop does not mean that a physician will actually stop. Although we asked about current use, we did not measure the actual frequency of use of EPO and perioperative blood salvage with our questionnaire. Therefore, future work includes testing a de-implementation intervention that is developed based on the barriers identified in this study, with actual BSM use before and after our intervention as primary outcomes.

In conclusion, this study has identified the main barriers associated with the intention to stop the use of EPO as well as perioperative blood salvage in primary elective THA and TKA among orthopaedic surgeons and anaesthesiologists. To effectively de-implement EPO and perioperative blood salvage in primary elective THA and TKA and to make health care more cost-effective, it is important to target the identified barriers and domains. This should be included in strategies to encourage physicians to stop using BSMs.

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References

1. Sehat KR, Evans RL, Newman JH. Hidden blood loss following hip and knee arthroplasty. Correct management of blood loss should take hidden loss into account. *J Bone Joint Surg Br*2004;**86**:561-565.
2. Eccles MP, Hrisos S, Francis J, et al. Do self-reported intentions predict clinicians' behaviour: a systematic review. *Implement Sci* 2006;**1**:28
3. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. *Anesthesiology* 2010;**113**:482-495.
4. Carless PA, Henry DA, Moxey AJ, et al. Cell salvage for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2010;(4):CD001888.
5. Moonen AF, Neal TD, Pilot P. Peri-operative blood management in elective orthopaedic surgery. A critical review of the literature. *Injury* 2006;**37**(Suppl 5):S11-S16.
6. Squires JE. Risks of transfusion. *South Med J* 2011;**104**:762-769.
7. So-Osman C, Nelissen RG, Koopman-van Gemert AW, et al. Patient blood management in elective total hip- and knee-replacement surgery (part 1): a randomized controlled trial on erythropoietin and blood salvage as transfusion alternatives using a restrictive transfusion policy in erythropoietin-eligible patients. *Anesthesiology* 2014;**120**:839-851.
8. So-Osman C, Nelissen RG, Koopman-van Gemert AW, et al. Patient blood management in elective total hip- and knee-replacement surgery (part 2): a randomized controlled trial on blood salvage as transfusion alternative using a restrictive transfusion policy in patients with a preoperative hemoglobin above 13 g/dL. *Anesthesiology* 2014;**120**:852-860.
9. Waters JR, Meier HH, Waters JH. An economic analysis of costs associated with development of a cell salvage program. *Anesth Analg* 2007;**104**:869-875.
10. Dutton T, De-Souza R, Parsons N, et al. The timing of tourniquet release and 'retransfusion' drains in total knee arthroplasty: a stratified randomised pilot investigation. *Knee* 2012;**19**:190-192.
11. Thomassen BJ, Pilot P, Scholtes VA, et al. Limit allogeneic blood use with routine re-use of patient's own blood: a prospective, randomized, controlled trial in total hip surgery. *PloS One*2012;**7**:e44503.
12. Cheung G, Carmont MR, Bing AJ, et al. No drain, autologous transfusion drain or suction drain? A randomised prospective study in total hip replacement surgery of 168 patients. *Acta Orthop Belg* 2010;**76**:619-627.
13. Cip J, Widemschek M, Benesch T, et al. Does single use of an autologous transfusion system in TKA reduce the need for allogenic blood?: A prospective randomized trial. *Clin Orthop Relat Res*2013;**471**:1319-1325.
14. Horstmann WG, Kuipers BM, Slappendel R, et al. Postoperative autologous blood transfusion drain or no drain in primary total hip arthroplasty? A randomised controlled trial. *Int Orthop*2012;**36**:2033-2039.
15. Kleinert K, Theusinger OM, Nuernberg J, et al. Alternative procedures for reducing allogeneic blood transfusion in elective orthopedic surgery. *HSS J* 2010;**6**:190-198.
16. Coyle D, Lee KM, Fergusson DA, et al. Economic analysis of erythropoietin use in orthopaedic surgery. *Transfus Med* 1999;**9**:21-30.
17. Voorn VM, Marang-van de Mheen PJ, Wentink MM, et al. Frequent use of blood-saving measures in elective orthopaedic surgery: a 2012 Dutch blood management survey. *BMC Musculoskelet Disord* 2013;**14**:230.
18. Voorn VM, Marang-van de Mheen PJ, So-Osman C, et al. Designing a strategy to implement cost-effective blood transfusion management in elective hip and knee arthroplasties: a study protocol. *Implement Sci* 2012;**7**:58.
19. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;**282**:1458-1465.
20. Francis JJ, Stockton C, Eccles MP, et al. Evidence-based selection of theories for designing behaviour change interventions: using methods based on theoretical construct domains to understand clinicians' blood transfusion behaviour. *Br J Health Psychol* 2009;**14**(Pt 4):625-646.
21. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *Lancet* 2003;**362**:1225-1230.
22. Islam R, Tinmouth AT, Francis JJ, et al. A cross-country comparison of intensive care physicians' beliefs about their transfusion behaviour: a qualitative study using the theoretical domains framework. *Implement Sci* 2012;**7**:93.

23. Michie S, Johnston M, Abraham C, et al. Making psychological theory useful for implementing evidence based practice: a consensus approach. *Qual Saf Health Care* 2005;**14**:26-33.
24. Michie S, Pilling S, Garety P, et al. Difficulties implementing a mental health guideline: an exploratory investigation using psychological theory. *Implement Sci* 2007;**2**:8.
25. Prior M, Guerin M, Grimmer-Somers K. The effectiveness of clinical guideline implementation strategies—a synthesis of systematic review findings. *J Eval Clin Pract* 2008;**14**:888-897.
26. Baarsma B, Mutsaerts M. Costs of blood (in Dutch). *ESB* 2012;**97**:664-666.
27. van Beek E, Lenssen M, van der Putten J, et al. European benchmark bloodproducts with limited preservation (in Dutch). Ministry of Health, Welfare and Sport: 2009 Aug 20.
28. Hrisos S, Eccles MP, Francis JJ, et al. Are there valid proxy measures of clinical behaviour? A systematic review. *Implement Sci* 2009;**4**:37.
29. Stevens JP. *Exploratory and confirmatory factor analysis. In: Stevens JP. Applied multivariate statistics for the social sciences*. 5th ed. New York: Routledge, Taylor & Francis Group; 2009. p. 325-394.
30. Catell RB. The scree test for numbers of factors. *Educ Psychol Meas* 1966;**20**:141-151.
31. Nagelkerke NJD. A note on a general definition of the coefficient of determination. *Biometrika*1999;**78**:691-692.
32. Ubbink DT, Guyatt GH, Vermeulen H. Framework of policy recommendations for implementation of evidence-based practice: a systematic scoping review. *BMJ Open*2013;**3**:e001881.
33. Francis JJ, Tinmouth A, Stanworth SJ, et al. Using theories of behaviour to understand transfusion prescribing in three clinical contexts in two countries: development work for an implementation trial. *Implement Sci* 2009;**4**:70.
34. Treloar CJ, Hewitson PJ, Henderson KM, et al. Factors influencing the uptake of technologies to minimize perioperative allogeneic blood transfusion: an interview study of national and institutional stakeholders. *Intern Med J* 2001;**31**:230-236.
35. Dutch Institute for Healthcare Improvement (CBO). Blood transfusion policy guideline (in Dutch). 2011 Oct 11. [cited 2013 May 20]. Available from: http://www.cbo.nl.
36. Bruce W, Campbell D, Daly D, et al. Practical recommendations for patient blood management and the reduction of perioperative transfusion in joint replacement surgery. *ANZ J Surg* 2013;**83**:222-229.
37. Waters JH, Dyga RM, Waters JF, et al. The volume of returned red blood cells in a large blood salvage program: where does it all go? *Transfusion* 2011;**51**:2126-2132.

Chapter 8

De-implementation of expensive blood saving measures in hip and knee arthroplasties: study protocol for the LISBOA-II cluster randomized trial

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Abstract

Background: Despite evidence that erythropoietin and intra- and postoperative blood salvage are expensive techniques considered to be non-cost-effective in primary elective total hip and knee arthroplasties in the Netherlands, Dutch medical professionals use them frequently to prevent the need for allogeneic transfusion. To actually change physicians' practice, a tailored strategy aimed at barriers that hinder physicians in abandoning the use of erythropoietin and perioperative blood salvage was systematically developed. The study aims to examine the effectiveness, feasibility and costs of this tailored de-implementation strategy compared to a control strategy.

Methods/Design: A cluster randomized controlled trial including an effect, process and economic evaluation will be conducted in a minimum of 20 Dutch hospitals. Randomisation takes place at hospital level. The hospitals in the intervention group will receive a tailored de-implementation strategy that consists of four components: interactive education, feedback in educational outreach visits, electronically sent reports on hospital performance (all aimed at orthopaedic surgeons and anaesthesiologists), and information letters or emails aimed at other involved professionals within the intervention hospital (transfusion committee, OR-personnel, pharmacists). The hospitals in the control group will receive a control strategy (*i.e.*, passive dissemination of available evidence). Outcomes will be measured at patient level, using retrospective medical record review. This will be done in all hospitals at baseline and after completion of the intervention period. The primary outcome of the effect evaluation is the percentage of patients undergoing primary elective total hip or knee arthroplasty in which erythropoietin or perioperative blood salvage is applied. The actual exposure to the tailored strategy and users' experiences will be assessed in the process evaluation. In the economic evaluation, the costs of the tailored strategy and the control strategy in relation to the difference in their effectiveness will be compared.

Discussion: This study will show whether a systematically developed tailored strategy is more effective for de-implementation of non-cost-effective blood saving measures than the control strategy. This knowledge can be used in national and international initiatives to make healthcare more efficient. It also provides more generalized knowledge regarding de-implementation strategies.

Background

Total joint replacement surgery such as total hip arthroplasty (THA) and total knee arthroplasty (TKA) is associated with intra- and postoperative blood loss leading to postoperative anaemia. This can be subsequently treated with allogeneic blood transfusion.[1,2] Yet, allogeneic blood transfusions carry the risk of infections and non-infectious transfusion reactions.[3] Therefore, different types of blood saving measures (BSMs) have been developed to reduce blood loss or to increase cell mass to avoid allogeneic transfusions.[4]

Many studies on the effectiveness of the frequently used BSMs erythropoietin (EPO) and intra- and postoperative drainage and re-infusion of autologous blood (in short: perioperative blood salvage) in orthopaedic surgery have been performed. Reviews and meta-analyses showed that EPO and perioperative blood salvage reduce transfusions. However, the included studies had several limitations such as a retrospective design, small patient numbers and poor methodologically quality leading to bias in favour of EPO and perioperative blood salvage.[1,5-10] When the costs of these techniques are considered, the use of EPO and perioperative blood salvage becomes controversial.[8,11-17] A large multicentre Randomized Controlled Trial (RCT) was recently performed to test the effectiveness and cost-effectiveness of EPO and perioperative blood salvage in elective THA and TKA.[18,19] It was shown that perioperative blood salvage in primary THA and TKA neither resulted in a decreased mean number of allogeneic blood units nor in a decrease in the proportion of transfused patients, and was more expensive due to the costs of the device and a prolonged hospital stay. EPO showed a significant decrease in the mean number of allogeneic blood units and proportion of transfused patients, but the costs of this technique were considered too high. It was thus concluded that EPO and perioperative blood salvage were not cost-effective in primary elective THA and TKA. For the use of EPO and perioperative blood salvage in revision THA and TKA no conclusions about the (cost-) effectiveness could be drawn.[18,19] These results are in line with recent literature. A number of trials that were not included in the currently available meta-analyses show that perioperative blood salvage is not superior to a regular drain or no drain in THA or TKA,[20-24] other studies concerning the costs of EPO also doubt the cost-effectiveness in orthopaedic surgery.[11,14]

Despite the evidence, medical professionals keep using these BSMs in daily practice. Over 85% of Dutch hospitals frequently use EPO, perioperative blood salvage, or a combination of these in elective orthopaedic surgery.[25] This leads to unnecessary healthcare costs. So, to improve the efficiency of care delivery, a strategy is needed aimed at barriers and facilitators to stop using these non-cost-effective BSMs (de-implementation strategy).[26-29] In the 'Leiden Implementation Study of BlOod management in hip and knee

Arthroplasties' (LISBOA I) problem analysis study,[30] such a strategy was developed in accordance with the implementation model of Grol.[31] This model, as with other theories of change, emphasizes that changes in current practice can only take place after the current barriers and facilitators for change have been identified and targeted. Therefore, prior inventory of barriers and facilitators incorporated in a tailored strategy can reduce the number of costly trials evaluating different implementation strategies.[31-33] The current study will test the hypothesis that the developed strategy is more effective for de-implementation of EPO and perioperative blood salvage in elective primary THA and TKA in comparison with a control strategy (i.e., passive dissemination of evidence).

Objective

The 'Leiden Implementation Study of BlOod management in hip and knee Arthroplasties, part two' (LISBOA-II) aims to assess the effectiveness, feasibility and costs of a systematically developed tailored strategy for de-implementation of EPO and perioperative blood salvage in primary elective THA and TKA compared to a control strategy in a cluster randomized trial.

Methods

Study design

A cluster randomized controlled trial including an effect-, process- and economic evaluation will be conducted in a minimum of 20 hospitals in the Netherlands using EPO and/or perioperative blood salvage in THA and TKA. Per hospital a representative orthopaedic surgeon will be invited to participate in the study (see Additional file 1 for CONSORT checklist); consent of hospitals willing to participate will be gathered according to local hospital regulations. To prevent contamination bias, randomisation will take place at the hospital level stratified by geographic location of the hospitals. Randomisation will be performed by an independent researcher using a computer generated randomisation table concealed in a sealed envelope. The randomisation result will be revealed to the investigators and participating hospitals after the baseline measurement on effect outcomes takes place. See Figure 1 for a flow-chart of the study design.

This trial compares:

1. The tailored strategy to de-implement use of EPO and perioperative blood salvage, and
2. A control strategy.

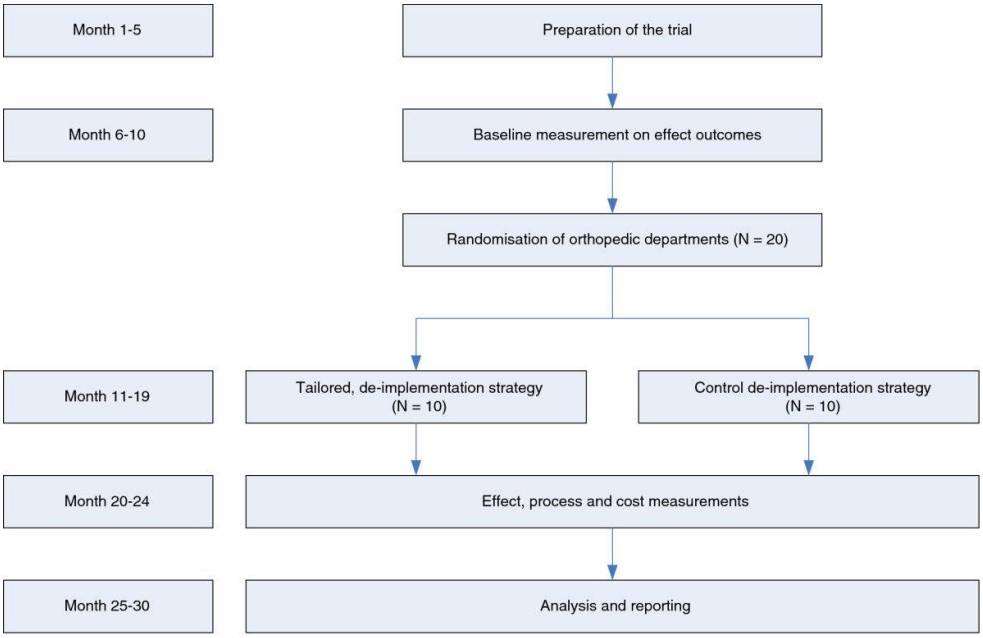

Figure 1: Flow-chart study design

Intervention: Tailored de-implementation strategy

The tailored de-implementation strategy in intervention hospitals is aimed at the barriers for de-implementation of non-cost-effective BSMs as identified in our problem analysis study, in which representative samples of orthopaedic surgeons and anaesthesiologists participated.[30,34] To ensure that we identified all relevant barriers, we used the Theoretical Domains Framework (TDF).[35-37] The TDF includes 12 different domains derived from a large number of health psychology theories and their theoretical constructs. The main barriers to stop using non-cost-effective BSMs in elective orthopaedic surgery were perceived by physicians within the following domains of the TDF:

1. Knowledge: lack of alternatives, lack of interest to gain additional information about stopping EPO and perioperative blood salvage.
2. Motivation & goals: lack of interest to save money for the society/ hospital, lack of benefit for the delivery of care.
3. Beliefs about consequences: pressure of suppliers to use BSMs, concerns about losing experience with the use of BSMs, concerns about the safety of patients when BSMs are stopped.
4. Social influences: the impact of blood management policy of other medical specialties/ blood transfusion committee, lack of influence of individual physician on blood management policy.

Barriers for EPO and perioperative blood salvage are largely similar and found within the same domains. Some barriers are more relevant for de-implementation of perioperative blood salvage (for example, concerns about losing experience with the use of BSMs) than for de-implementation of EPO. However, due to the large extent of overlap of barriers and the similar target groups, we developed a combined tailored strategy.

The developed tailored de-implementation strategy consists of four components carried out in a period of nine months. Every component targets one or more domains on which barriers have been identified.[35] For the complete de-implementation strategy, see Figure 2.

1. Interactive education for orthopaedic surgeons and anaesthesiologists with a single visit in intervention month 1 (to target the domain: motivation & goals).
2. Feedback in educational outreach visits for orthopaedic surgeons and anaesthesiologists with a single visit in intervention months 5/6 (to target the domain: beliefs about consequences).
3. Dissemination of reports on hospital performance (BSM use and transfusion percentage) and comparison with hospitals that do not use EPO or perioperative blood salvage, e.g. 'best practices,' to orthopaedic surgeons and anaesthesiologists with two electronic newsletters sent in intervention months 4 to 6 and 7 to 9 (to target the domain: social influences).
4. Email with available evidence to other involved professionals, e.g. transfusion committee, OR-personnel, pharmacists with a single newsletter sent in intervention months 1 or 2 (to target the domains: knowledge, motivation and goals, and beliefs about consequences).

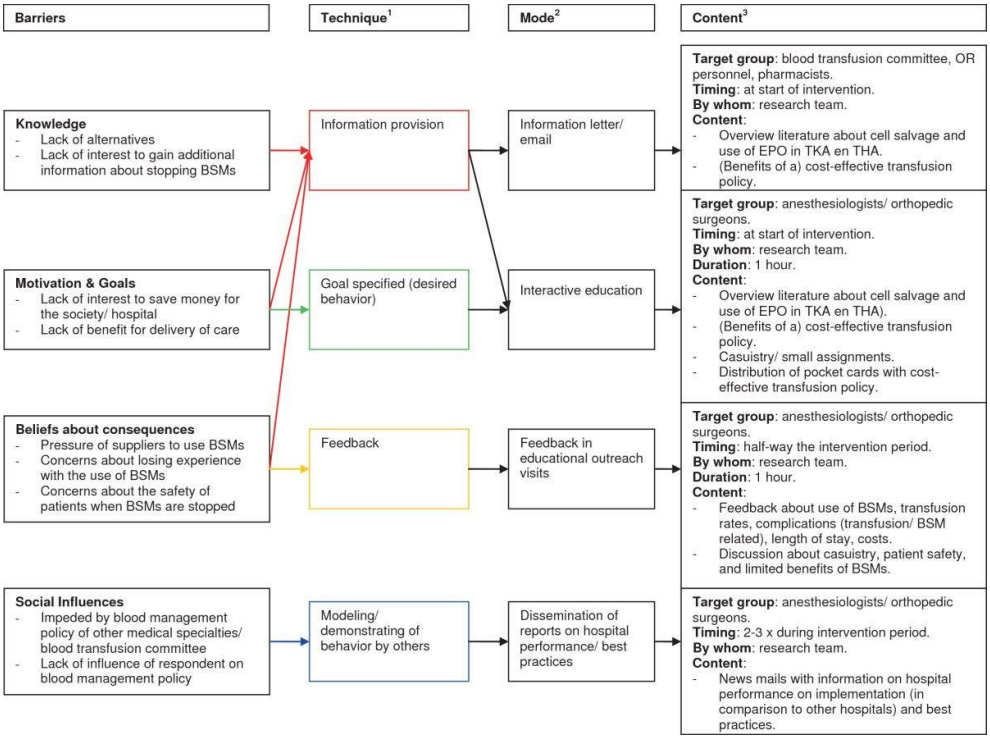

Figure 2: De-implementation strategy

[1]Technique: the behaviour change technique used to overcome the identified barrier. [2]Mode: the way the technique will be delivered. [3]Content: what will be delivered.

Control strategy

The control strategy consists of the passive dissemination of evidence via publication in scientific journals indexed for PubMed. No further actions to make the control hospitals aware of the published evidence will be undertaken. After the post-intervention measurement period, we will offer the control hospitals the possibility to have the interactive education as described for the intervention hospitals and a report on their hospital performance in comparison with best practices.

Study population

All types of hospitals (university hospitals, teaching hospitals, general hospitals and private clinics) that frequently use BSMs[25] will be invited to participate in this study. Further, we have previously shown that blood transfusion committees, hospital boards, patients, and other stakeholders are involved in blood management, but do not make decisions

regarding the use of BSMs in THA and TKA.[34] Therefore, the de-implementation strategy will primarily be focused at orthopaedic surgeons and anaesthesiologists in the participating hospitals, with one strategy-component aimed at other involved professionals. See Table 1 for in- and exclusion criteria for the participating hospitals and patients.

Table 1: In- and exclusion criteria for participating hospitals and patients

Inclusion criteria	Exclusion criteria
Participating hospitals	
- Hospitals using EPO and/or blood salvage in patients undergoing primary elective THA or TKA on a regular basis (more frequently than in exceptional cases) - Hospitals performing at least 50 THA and/or TKA on average per 5 months	- Hospitals considering abandoning the use of EPO or blood salvage on their own initiative - Hospitals participating in trials that interfere with the use or the discontinuation of EPO or blood salvage - Hospitals employing the same group of orthopaedic surgeons or anaesthesiologists as a previously included hospital
Patients	
- Patients scheduled for primary elective THA or TKA - Age >18 years	- Bilateral surgery - Patients with a malignancy (except skin cancer or cured cancers) - A serious disorder of the coronary, peripheral and/or carotid arteries, a recent myocardial infarction or CVA (past 6 months) - Untreated hypertension (diastolic BP >95 mmHg) - Patients with a pregnancy - Patients with a coagulation disorder - Patients refusing or with a contraindication for allogeneic blood transfusions - Patients with untreated anaemia Hb <10 g/dl

Effect evaluation

The effect of the tailored strategy will be compared with the control strategy before and after carrying out the strategy. Outcomes will be measured at patient level, using retrospective medical record review at least three weeks postoperative with standardized registration forms. Measurement periods last for five months. Within each month, medical records of at least 10 consecutively treated patients will be reviewed in each participating hospital, with a maximum of 20 patients per month (depending on the number of patients treated within that month).

Primary outcome

The primary outcome is the % of patients undergoing primary elective total THA or TKA in which EPO or perioperative blood salvage is applied.

Secondary outcomes

Secondary outcomes are the patient outcomes of the surgery including: Post-operative haemoglobin (Hb) level, length of hospital stay and number of allogeneic red blood cell transfusions. Adverse events will also be registered: reactions on EPO use, transfusion reactions due to the use of perioperative blood salvage, transfusion reactions due to allogeneic transfusions and complications registered in patients' medical records.

Other parameters measured in this study are patient characteristics (age, sex, BMI, ASA-classification, and pre-operative Hb), techniques used during the surgical procedure (type of anaesthesia, use of tourniquet in TKA, surgical approach, use of other BSMs, use of drains) and postoperative care (postoperative blood loss, re-infusion of salvaged blood, type and length of postoperative anticoagulation).

Process evaluation

A process evaluation will be performed to assess the feasibility of the de-implementation strategy in comparison with the control strategy. Such an evaluation gives insight into the mechanisms and processes responsible for the effect of the de-implementation strategy and the control strategy[38]. The actual 'exposure' of clinicians to the elements of the de-implementation strategy, together with their experience with these elements, may influence the final results. At the end of the study period, experiences of clinicians with the elements of the de-implementation strategy will be measured using questionnaires, to further improve the de-implementation strategy for future use (if necessary). In these questionnaires, we will also ask about the presence and their awareness of barriers for behaviour change. Table 2 provides an overview of all measurements.

Other local, non-study-related changes such as changes in staff, changes in blood management, changes in surgical techniques and local initiatives to optimize THA and TKA care will be registered in both study arms.

Table 2: Overview of measurements

	Baseline measurements		Intervention period		Post-intervention measurements	
	Intervention	Control	Intervention	Control	Intervention	Control
On physician level						
- Barrier questionnaire					x	x
- Process evaluation			x	x	x	
- Resource use					x	x
On patient level (through retrospective chart review)						
- Primary and secondary outcomes, complications and adverse events	x	x	x		x	x
- Patient characteristics	x	x	x		x	x
- Techniques during surgical procedure	x	x	x		x	x
- Postoperative care	x	x	x		x	x

Economic evaluation

The economic evaluation will compare the costs of both de-implementation strategies in relation to their difference in effects. The analyses will not be performed separately for the de-implementation of EPO and perioperative blood salvage since it is impossible to determine which costs of the de-implementation strategy are exclusively made for the de-implementation of EPO and for the de-implementation of perioperative blood salvage. The economic evaluation will be performed from a healthcare perspective. No discounting will be applied due to the short time frame of the study.

The implementation costs concern the cost of execution of the de-implementation strategy,[39] which consist of material costs (e.g. education material, information letter), and personnel cost (e.g. hours for the team of investigators conducting the strategy, hours of orthopaedic surgeons and anaesthesiologists attending the strategy-related activities). Resource use will be measured by questionnaires to the clinicians involved. For the valuation of the resource use, market prices (material) and wages including holiday allowance and social charges (personnel costs) are used.[40]

Statistical analysis

All data will be entered and stored in an electronic database. Descriptive statistics include frequencies, percentages, medians, means and SDs. Hospital and patient characteristics of study hospitals will be compared using t-tests and non-parametric tests (Mann-Whitney U

test) for continuous variables and χ^2-test for proportions. The overall effect of the intervention will be evaluated by comparing the average outcome in the control hospitals with the average outcome in the intervention hospitals. The effects on the percentage of patients receiving a THA or TKA in which BSMs (stratified to the % patients with EPO and % patients with perioperative blood salvage) are applied will be adjusted for clustering of patients in hospitals. Therefore, multilevel logistic regression analysis will be performed. Analyses will be based on the intention to treat principle, meaning that all participating hospitals will be included in the study arm (control or intervention) to which they are originally assigned, regardless of whether they participated in the components of the tailored strategy.

Sample size

We expect to detect an absolute difference of at least 20% in BSM use between the group receiving the de-implementation strategy and the control group. We assume that frequent BSM use, as assessed in the Dutch survey[25], means that BSMs are applied in 50% of the patients. To detect a difference of 20% (from 50% to 30%), with alpha 0.05, a two-sided testing and power of 80%, an intra-cluster-correlation coefficient of 0.08, 50 patients per hospital and 20 hospitals are needed (total of 1,000 patients). Given the 70% of hospitals in The Netherlands frequently applying BSMs[25], this means that 69 hospitals are eligible for the present study. Since the average hospital performs about 550 total hip and knee arthroplasties per year, it is feasible to include 20 hospitals and at least 50 patients per hospital in 5 months, before and after the intervention period.

Ethical approval

The Medical Ethical Committee of the Leiden University Medical Center decided that ethical approval was not required under Dutch National law for this type of study (CME 13/132). The gathering of patient data will be conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles[41].

Trial status

The LISBOA II study started in March 2013. The preparation of the study components and the recruitment of hospitals to participate in the study were completed in September 2013. The baseline data collection in all hospitals was performed from September 2013 until January 2014. Currently (March 2014), the intervention period is ongoing.

Discussion

The goal of this study is to test a tailored strategy to let physicians stop using EPO and perioperative blood salvage in primary elective THA and TKA, i.e., the de-implementation of non-cost-effective BSMs. This study is the next step following a RCT on EPO and perioperative blood salvage as transfusion alternatives in THA and TKA using a restrictive transfusion policy, showing that use of these BSMs is not cost-effective,[18,19] and a study in which a tailored de-implementation strategy was systematically developed.[25,30,34] Given the large number of THA and TKA performed annually in the Netherlands and worldwide, de-implementation of non-cost effective BSMs contributes to more efficient healthcare.

A strength of this study is that it is one of the first studies that assesses the effect of a de-implementation strategy. The study results will thus lead to generalizable knowledge regarding de-implementation strategies of non-cost-effective interventions and how this differs from strategies for implementation. This knowledge is useful to contain healthcare spending and optimize outcomes.[26,27]

A possible limitation of the study is the awareness of the study purpose among physicians within the control group. During the recruitment of hospitals for participation in our study, hospitals cannot be blinded to the aim of this study. Physicians want to know the study goal before giving approval for participation in a study. As a consequence, physicians of control hospitals are actively made aware of the fact that they deliver non-efficient care and thereby can make changes in their blood management policy. This does not resemble 'standard practice' in hospitals not participating in a study and may lead to a smaller difference in the effect between the intervention and control hospitals. We will try to limit this awareness by asking the study coordinators of each participating hospital not to inform their staff members (orthopaedic surgeons and anaesthesiologists) about the study.

A second limitation is bias as a result of local initiatives to optimize care for THA and TKA during the intervention period. For example, the implementation of 'fast track' or 'joint care' programs for THA and TKA may lead to abandoning perioperative blood salvage because of logistic reasons. Therefore, information on local, non-study related changes will be additionally inquired during the process evaluation.

Our study will not only demonstrate whether a tailored strategy to de-implement BSMs is effective, feasible and cost-effective compared to the control strategy, but will also contribute to general knowledge regarding differences between de-implementation and implementation strategies. Little is known about strategies to effectively de-implement common practices, for instance, whether de-implementation strategies should also be

constructed following the same theoretical models and frameworks as implementation. It is likely that it is far more attractive for clinicians to implement something new than to de-implement something expensive or ineffective.[26,27] Our study will thus not only assess whether a tailored strategy to de-implement BSMs is effective, feasible and cost-effective compared to the control strategy, but will also contribute to general knowledge regarding differences between de-implementation and implementation strategies.

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References

1. Spahn DR: Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiology. 2010, 113: 482-495. 10.1097/ALN.0b013e3181e08e97.
2. Treloar CJ, Hewitson PJ, Henderson KM, Harris G, Henry DA, McGrath KM: Factors influencing the uptake of technologies to minimize perioperative allogeneic blood transfusion: an interview study of national and institutional stakeholders. Intern Med J. 2001, 31: 230-236. 10.1046/j.1445-5994.2001.00047.x.
3. Squires JE: Risks of transfusion. South Med J. 2011, 104: 762-769. 10.1097/SMJ.0b013e31823213b6.
4. Munoz M, Garcia-Erce JA, Villar I, Thomas D: Blood conservation strategies in major orthopaedic surgery: efficacy, safety and European regulations. Vox Sang. 2009, 96: 1-13.
5. Alsaleh K, Alotaibi GS, Almodaimegh HS, Aleem AA, Kouroukis CT: The use of preoperative erythropoiesis-stimulating agents (ESAs) in patients who underwent knee or hip arthroplasty: a meta-analysis of randomized clinical trials. J Arthroplasty. 2013, 28: 1463-1472. 10.1016/j.arth.2013.01.024.
6. Sharma R, Farrokhyar F, McKnight LL, Bhandari M, Poolman RW, Adili A: Quality of assessment of randomized controlled trials in blood conservation after joint arthroplasty. J Arthroplasty. 2011, 26: 909-913. 10.1016/j.arth.2010.08.014.
7. Alshryda S, Sarda P, Sukeik M, Nargol A, Blenkinsopp J, Mason JM: Tranexamic acid in total knee replacement: a systematic review and meta-analysis. J Bone Joint Surg Br. 2011, 93: 1577-1585.
8. Carless PA, Henry DA, Moxey AJ, O'Connell D, Brown T, Fergusson DA: Cell salvage for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2010, 4: CD001888-
9. Haien Z, Yong J, Baoan M, Mingjun G, Qingyu F: Post-operative auto-transfusion in total hip or knee arthroplasty: a meta-analysis of randomized controlled trials. PLoS One. 2013, 8: e55073-10.1371/journal.pone.0055073.
10. Markar SR, Jones GG, Karthikesalingam A, Segaren N, Patel RV: Transfusion drains versus suction drains in total knee replacement: meta-analysis. Knee Surg Sports Traumatol Arthrosc. 2012, 20: 1766-1772. 10.1007/s00167-011-1761-0.
11. Otten N: Economic Evaluation of Erythropoietin Use in Surgery. 1998. 1998, Ottawa: Canadian coordinating office for health technology assessment (CCOHTA)
12. Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C: Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model. Health Technol Assess. 2006, 10: iii-iv. ix-x, 1-210
13. Coyle D, Lee KM, Fergusson DA, Laupacis A: Economic analysis of erythropoietin use in orthopaedic surgery. Transfus Med. 1999, 9: 21-30. 10.1046/j.1365-3148.1999.009001021.x.
14. Green WS, Toy P, Bozic KJ: Cost minimization analysis of preoperative erythropoietin vs autologous and allogeneic blood donation in total joint arthroplasty. J Arthroplasty. 2010, 25: 93-96. 10.1016/j.arth.2008.10.005.
15. Fergusson DA, Hebert P: The health(y) cost of erythropoietin in orthopedic surgery. Can J Anaesth. 2005, 52: 347-351. 10.1007/BF03016274.
16. Waters JH, Dyga RM, Waters JF, Yazer MH: The volume of returned red blood cells in a large blood salvage program: where does it all go?. Transfusion. 2011, 51: 2126-2132. 10.1111/j.1537-2995.2011.03111.x.
17. Waters JR, Meier HH, Waters JH: An economic analysis of costs associated with development of a cell salvage program. Anesth Analg. 2007, 104: 869-875. 10.1213/01.ane.0000258039.79028.7c.
18. So-Osman C, Nelissen RG, Koopman-van Gemert AW, Kluyver E, Poll RG, Onstenk R, van Hilten JA, Jansen-Werkhoven TM, van den Hout WB, Brand R, Brand A: Patient blood management in elective total hip- and knee-replacement surgery (part 1): a randomized controlled trial on erythropoietin and blood salvage as transfusion alternatives using a restrictive transfusion policy in erythropoietin-eligible patients. Anesthesiology. 2014, 120 (4): 839-851. 10.1097/ALN.0000000000000134.
19. So-Osman C, Nelissen RG, Koopman-van Gemert AW, Kluyver E, Poll RG, Onstenk R, van Hilten JA, Jansen-Werkhoven TM, van den Hout WB, Brand R, Brand A: Patient blood management in elective total hip- and knee-replacement surgery (part 2): a randomized controlled trial on blood salvage as transfusion alternative using a restrictive transfusion policy in patients with a preoperative hemoglobin above 13 g/dl. Anesthesiology. 2014, 120 (4): 852-860. 10.1097/ALN.0000000000000135.
20. Dutton T, De-Souza R, Parsons N, Costa ML: The timing of tourniquet release and 'retransfusion' drains in total knee arthroplasty: a stratified randomised pilot investigation. Knee. 2012, 19: 190-192. 10.1016/j.knee.2011.02.013.

21. Thomassen BJ, Pilot P, Scholtes VA, Grohs JG, Holen K, Bisbe E, Poolman RW: Limit allogeneic blood use with routine re-use of patient's own blood: a prospective, randomized, controlled trial in total hip surgery. PLoS One. 2012, 7: e44503-10.1371/journal.pone.0044503.
22. Cheung G, Carmont MR, Bing AJ, Kuiper JH, Alcock RJ, Graham NM: No drain, autologous transfusion drain or suction drain? A randomised prospective study in total hip replacement surgery of 168 patients. Acta Orthop Belg. 2010, 76: 619-627.
23. Cip J, Widemschek M, Benesch T, Waibel R, Martin A: Does single use of an autologous transfusion system in TKA reduce the need for allogenic blood?: a prospective randomized trial. Clin Orthop Relat Res. 2013, 471: 1319-1325. 10.1007/s11999-012-2729-1.
24. Horstmann WG, Kuipers BM, Slappendel R, Castelein RM, Kollen BJ, Verheyen CC: Postoperative autologous blood transfusion drain or no drain in primary total hip arthroplasty? A randomised controlled trial. Int Orthop. 2012, 36: 2033-2039. 10.1007/s00264-012-1613-7.
25. Voorn VM, de Mheen PJ M-v, Wentink MM, So-Osman C, Vliet Vlieland TP, Koopman-van Gemert AW, Nelissen RG, van Bodegom-Vos L, for the LISBOA study group: Frequent use of blood-saving measures in elective orthopaedic surgery: a 2012 Dutch blood management survey. BMC Musculoskelet Disord. 2013, 14: 230-10.1186/1471-2474-14-230.
26. Prasad V, Cifu A, Ioannidis JP: Reversals of established medical practices: evidence to abandon ship. JAMA. 2012, 307: 37-38. 10.1001/jama.2011.1960.
27. Prasad V, Ioannidis JP: Evidence-based de-implementation for contradicted, unproven, and aspiring healthcare practices. Implement Sci. 2014, 9: 1-10.1186/1748-5908-9-1.
28. Baker R, Camosso-Stefinovic J, Gillies C, Shaw EJ, Cheater F, Flottorp S, Robertson N: Tailored interventions to overcome identified barriers to change: effects on professional practice and health care outcomes. Cochrane Database Syst Rev. 2010, 3: CD005470-
29. Grol R: Personal paper. Beliefs and evidence in changing clinical practice. BMJ. 1997, 315: 418-421. 10.1136/bmj.315.7105.418.
30. Voorn VMA, de Mheen PJ M-v, So-Osman C, Vliet Vlieland TPM, Koopman-van Gemert AWMM, Nelissen RGHH, van Bodegom-Vos L, for the LISBOA study group: Designing a strategy to implement cost-effective blood transfusion management in elective hip and knee artroplasties: a study protocol. Implement Sci. 2012, 7: 58-10.1186/1748-5908-7-58.
31. Grol R, Grimshaw J: From best evidence to best practice: effective implementation of change in patients' care. Lancet. 2003, 362: 1225-1230. 10.1016/S0140-6736(03)14546-1.
32. Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, Whitty P, Eccles MP, Matowe L, Shirran L, Wensing M, Dijkstra R, Donaldson C: Effectiveness and efficiency of guideline dissemination and implementation strategies. Health Technol Assess. 2004, 8: 1-72.
33. Prior M, Guerin M, Grimmer-Somers K: The effectiveness of clinical guideline implementation strategies–a synthesis of systematic review findings. J Eval Clin Pract. 2008, 14: 888-897. 10.1111/j.1365-2753.2008.01014.x.
34. Voorn VMA, de Mheen PJ M-v, Wentink MW, Kaptein AA, Koopman-van Gemert AWMM, So-Osman C, Vliet Vlieland TPM, Nelissen RGHH, van Bodegom-Vos L, for the LISBOA study group: Perceived barriers among physicians for stopping non cost-effective blood saving measures in total hip and total knee arthroplasties. Transfusion. 2014, Oct;54(10 Pt 2):2598-607.
35. Michie S, Johnston M, Abraham C, Lawton R, Parker D, Walker A: Making psychological theory useful for implementing evidence based practice: a consensus approach. Qual Saf Health Care. 2005, 14: 26-33. 10.1136/qshc.2004.011155.
36. Francis JJ, Tinmouth A, Stanworth SJ, Grimshaw JM, Johnston M, Hyde C, Stockton C, Brehaut JC, Fergusson D, Eccles MP: Using theories of behaviour to understand transfusion prescribing in three clinical contexts in two countries: development work for an implementation trial. Implement Sci. 2009, 4: 70-10.1186/1748-5908-4-70.
37. Michie S, Johnston M, Francis JJ, Hardeman W, Eccles M: From theory to intervention: mapping theoretically derived behavioural determinants to behaviour change techniques. Appl Psychol Int Rev. 2008, 57: 660-680. 10.1111/j.1464-0597.2008.00341.x.
38. Hulscher ME, Laurant MG, Grol RP: Process evaluation on quality improvement interventions. Qual Saf Health Care. 2003, 12: 40-46. 10.1136/qhc.12.1.40
39. Severens JL: Value for money of changing healthcare services? Economic evaluation of quality improvement. Qual Saf Health Care. 2003, 12 (5): 366-371. 10.1136/qhc.12.5.366.

40. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM: Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. College voor zorgverzekeringen. 2010.
41. WMA general Assembly: WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 2013, Fortaleza.

Chapter 9

The effectiveness of a de-implementation strategy to reduce low-value blood management techniques in primary hip and knee arthroplasty: a pragmatic cluster-randomized controlled trial

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Abstract

Background: Perioperative autologous blood salvage and preoperative erythropoietin are not (cost) effective to reduce allogeneic transfusion in primary hip and knee arthroplasty, but are still used. This study aimed to evaluate the effectiveness of a theoretically informed multifaceted strategy to de-implement these low-value blood management techniques.

Methods: Twenty-one Dutch hospitals participated in this pragmatic cluster-randomized trial. At baseline, data were gathered for 924 patients from 10 intervention and 1040 patients from 11 control hospitals undergoing hip or knee arthroplasty. The intervention included a multifaceted de-implementation strategy which consisted of interactive education, feedback on blood management performance, and a comparison with benchmark hospitals, aimed at orthopaedic surgeons and anaesthesiologists. After the intervention, data were gathered for 997 patients from the intervention and 1096 patients from the control hospitals. The randomization outcome was revealed after the baseline measurement. Primary outcomes were use of blood salvage and erythropoietin. Secondary outcomes included postoperative haemoglobin, length of stay, allogeneic transfusions, and use of local infiltration analgesia (LIA) and tranexamic acid (TXA).

Results: The use of blood salvage (OR 0.08, 95% CI 0.02 to 0.30) and erythropoietin (OR 0.30, 95% CI 0.09 to 0.97) reduced significantly over time, but did not differ between intervention and control hospitals (blood salvage OR 1.74 95% CI 0.27 to 11.39, erythropoietin OR 1.33, 95% CI 0.26 to 6.84). Postoperative haemoglobin levels were significantly higher (β 0.21, 95% CI 0.08 to 0.34) and length of stay shorter (β −0.36, 95% CI −0.64 to −0.09) in hospitals receiving the multifaceted strategy, compared with control hospitals and after adjustment for baseline. Transfusions did not differ between the intervention and control hospitals (OR 1.06, 95% CI 0.63 to 1.78). Both LIA (OR 0.0, 95% CI 0.0 to 0.0) and TXA (OR 0.3, 95% CI 0.2 to 0.5) were significantly associated with the reduction in blood salvage over time.

Conclusions: Blood salvage and erythropoietin use reduced over time, but not differently between intervention and control hospitals. The reduction in blood salvage was associated with increased use of local infiltration analgesia and tranexamic acid, suggesting that de-implementation is assisted by the substitution of techniques. The reduction in blood salvage and erythropoietin did not lead to a deterioration in patient-related secondary outcomes.

Trial registration: www.trialregister.nl, NTR4044

Background

In the last decades, abandonment of low-value care has become more important in many countries. Evidence shows that, e.g. in the USA, an estimated 30% of all medical spending is unnecessary and does not add value in care.[1,2] Elimination or reduction of this low-value care (de-implementation) may lead to improved quality of care while reducing expenditures.[3] The importance of abandoning low-value care is underscored by the Choosing Wisely campaign which was launched in the USA in 2012 to encourage physicians and patients to engage in conversations about unnecessary tests, treatments, and procedures; the campaign is now being adopted in many other countries.[1,2] A key element of Choosing Wisely is that medical societies create 'better not to do' lists of tests, treatments, and procedures in their discipline for which there is strong evidence of overuse, potential harm, or significant and unjustifiable costs.

The next step is to translate these 'better not to do' lists into action.[4] However, although there is extensive literature on how to adopt new practices (implementation) and change human behaviour,[5-12] the understanding of the abandonment of long-established existing techniques or practices that might have become redundant or cause overtreatment is limited.[1] It is suggested that there are fundamental differences between de-implementation and implementation, as it is harder to give up low-value care, particularly when not substituted with something else, than to adopt new and promising techniques.[13,14] But theory or empirical evidence on how to effectively de-implement is sparse, and only limited knowledge is available about the specific agents involved in de-implementation, the relevant barriers and facilitators, and the effective interventions for successful de-implementation of low-value care.[13-21]

An example of low-value care can be found in perioperative blood management. Perioperative blood loss may necessitate allogeneic red blood cell (RBC) transfusion. Therefore, to prevent allogeneic transfusions, various blood-saving techniques are used.[22-26] In total hip arthroplasty (THA) and total knee arthroplasty (TKA), blood salvage and erythropoietin (EPO) are frequently used.[23,27-29] Blood salvage includes the collection of shed blood during and after surgery and the reinfusion of this blood intravenously. EPO is given in the preoperative stage to patients with anaemia to increase the haemoglobin (Hb) level. Both techniques are used to avoid the postoperative Hb level to drop below the threshold for allogeneic transfusion. The indication to use the technique is determined by an orthopaedic surgeon or anaesthesiologist. However, a recent meta-analysis showed that, based on RCTs published between 2010 and 2012, blood salvage did not lead to a reduction in transfused patients or in the volume of transfused blood in THA and TKA.[30] Other literature showed that EPO was effective to reduce the number of transfused patients and the volume of transfused blood,[31,32] but the costs of EPO were so high that it

was considered not cost-effective in THA and TKA.[29,31-35] Despite this evidence, both techniques are still used in clinical practice.[27,36,37] Additional effort is needed to reduce the use of this low-value care in patients in which the use of blood salvage and EPO is not cost-effective, taking into account the existing barriers and facilitators for de-implementation as recommended by Lorencatto et al. who calls for more theoretically informed behaviour change research in transfusion.[38,39]

The aim of this study therefore was to evaluate the effectiveness of a multifaceted strategy to de-implement blood salvage and EPO in patients undergoing primary THA and TKA.

Methods

A pragmatic cluster-randomized controlled trial was performed to assess the effectiveness of a multifaceted de-implementation strategy. The Medical Ethical Committee of the Leiden University Medical Center declared that ethical approval was not required (CME 13/132) and waived the need for written consent from patients. The trial was registered at www.trialregister.nl (ID: NTR4044) on 25 June 2013. The study protocol has been published.[40]

The Dutch Orthopaedic Association and the Dutch Association of Anaesthesiology were involved only in the design of the intervention. They were not involved in the execution phase. There were no incentives or (financial) reimbursements either to participate in the study or to actively change during the study.

An invitation to participate was sent to all 70 Dutch hospitals and private clinics who had indicated to use either blood salvage or EPO in our preceding survey.[37] A single contact person per hospital was contacted to avoid awareness of the study goal among all participants. Exclusion criteria for both patients and hospitals are shown in Table 1. In each hospital, orthopaedic surgeons were participants, except if they stated that they did not perform THA or TKA, and anaesthesiologists were participants if they were involved in orthopaedic blood management.

Table 1: Exclusion criteria for participation of hospitals and patients

Hospitals	Patients
- Hospitals considering to abandon the use of EPO or blood salvage on their own initiative - Hospitals participating in trials that interfere with the use or the discontinuation of EPO or blood salvage - Hospitals in which orthopedic surgeons or anesthesiologists are employed who are also employed at another participating hospital or hospitals with partnerships with another participating hospital - Hospitals that perform less than 50 THA or TKA within 5 months	- Bilateral surgery - Revision surgery - Patients with a malignancy (except skin cancer or cured cancers) - A serious disorder of the coronary, peripheral and/or carotid arteries, a recent myocardial infarction or CVA (past 6 months) - Untreated hypertension (diastolic BP >95 mmHg) - Patients with a pregnancy - Patients with a coagulation disorder - Patients refusing or with a contraindication for allogeneic blood transfusions - Patients with untreated anemia, Hb < 10 g/dl

Design

Hospitals were randomly assigned to the intervention or control group in a 1:1 ratio using a computer-generated randomization table. Prior to randomization, hospitals were stratified by geographic location (western part versus the rest of the Netherlands) to prevent influence of regional preferences. The randomization outcome was revealed to the researchers and the hospitals' contact person after the baseline measurement was completed. In the baseline measurement, data of individual patients, clustered within the randomized hospitals, was gathered. In figure 1, a timeline is shown.

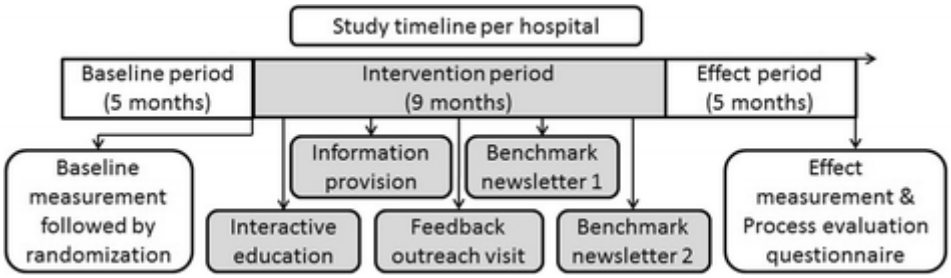

Figure 1: Study timeline
Components marked in *white* were applicable to all the hospitals. *Grey* components are applicable to the intervention hospitals only. Control hospitals were not contacted during the *grey* intervention period

Intervention

In intervention hospitals, the participants were exposed to a multifaceted de-implementation strategy during a 9-month intervention period. The strategy was tailored to address barriers identified in our problem analysis study.[38,40] The Theoretical Domains Framework (TDF) was used to identify relevant barriers. This framework includes 12 different domains derived from a large number of health psychology theories and their theoretical constructs.[9,41,42] Barriers were identified on four domains and were targeted by the four components of the de-implementation strategy.

1. Information letter/email aimed at professionals involved in blood management, other than the study participants (orthopaedic surgeons and anaesthesiologists), e.g. blood transfusion committee members, operating room personnel, pharmacists. A single email sent at the start of the intervention, to give an overview of literature about blood salvage and EPO use in TKA and THA, and information on the benefits of a cost-effective transfusion policy.
2. An interactive education for participants (orthopaedic surgeons and anaesthesiologists) with a single visit per hospital at the start of the intervention. A researcher (and also orthopaedic resident) (VV) presented an overview of literature about blood salvage and EPO use in TKA and THA and information on the benefits of a cost-effective transfusion policy. Thereafter, data on the current use of blood salvage and EPO, postoperative Hb levels, transfusion rates, and length of stay (LoS) within the visited hospital were presented to specify where improvement could be achieved. During the visit, there was opportunity to openly discuss the presented information. Additionally pocket cards summarizing the literature and criteria for the use of blood salvage and EPO were handed to the participants
3. An educational outreach visit (second visit to each intervention hospital) for participants to give feedback on the use of blood salvage and EPO planned halfway the intervention period (month 5/6). The same researcher/orthopaedic resident (VV) presented data on the use of blood salvage and EPO, postoperative Hb levels, transfusion rates, and length of stay (LoS) of the visited hospital from the period after the interactive education to report and promote change in transfusion policy.
4. Dissemination of two newsletters with reports on hospital performance in which own hospital data were compared to data of other intervention hospitals (anonymized) and 'best practice' hospitals (two Dutch hospitals that do not use blood salvage or EPO) by email to all participants (orthopaedic surgeons and anaesthesiologists). The data of the 'best practice' hospitals were included to emphasize the safety of not using blood salvage or EPO. The first newsletter was sent following the educational outreach visit (month 5/6), and the second newsletter was sent at least 3 months thereafter (month 8/9).

Control hospitals were not contacted during the 9-month intervention period and only received evidence by e.g. publication of evidence in scientific journals. Likewise, there were no data gathered during the intervention period as this might create awareness and contamination of the control group. After completion of data collection for the effect measurement, the control hospitals were offered a modified intervention including the interactive education, feedback, and benchmark.

Effect evaluation

The effect of the de-implementation strategy in intervention hospitals was compared with the usual care strategy in control hospitals. Individual patient data were gathered using a medical record review; in each hospital, two measurements took place: a baseline measurement prior to the intervention period and an effect measurement afterwards to compare the use of blood management techniques and patient outcomes between the intervention and control group, corrected for baseline. A sample size calculation was performed based on the use of blood salvage and EPO estimated in our preceding survey[37]. We assumed that if hospitals answered to frequently use these techniques, it is applied in 50% of patients. To detect a difference of 20% (from 50 to 30%) with an alpha of 0.05, a two-sided testing and power of 80%, and an intra-cluster correlation coefficient of 0.08, 50 patients per hospital and 20 hospitals were needed. Per measurement, a sample of 50–100 patients was retrospectively taken from the preceding 5 months by selecting the first 10–20 eligible patients of each month. Patients undergoing primary elective THA or TKA and aged ≥18 years were eligible. Exclusion criteria are shown in Table 1. With this, patients were excluded that are ineligible for elective surgery as well as patients in which blood salvage and EPO are potentially (cost)-effective.

The primary outcomes were blood salvage use (yes/no) and EPO use (yes/no). All patients were deemed eligible for blood salvage, patients with a preoperative Hb <13 g/dL were deemed eligible for EPO. Blood salvage included both intra-operative cell-saver and postoperative drainage and reinfusion; although, cell-saver was used only once. EPO-treatment was defined as a weekly dose of 600 IE/kg epoetin alfa subcutaneously starting 4 weeks before surgery, supplemented with oral iron.

Secondary outcomes evaluated patient outcomes to ensure their safety: postoperative Hb level (measured 1 day postoperatively in g/dl, continuous outcome), LoS (postoperative days, continuous outcome), and allogeneic transfusions (yes/no). The following data on patient characteristics were collected: age (years), sex (female/male), joint (hip/knee), American Society of Anaesthesiologists Classification (ASA 1, 2, 3, and 4), body mass index (BMI; kg/m^2), and preoperative Hb (g/dl).

Process evaluation

To evaluate the de-implementation process, we gathered the following data:

1. Data about perioperative management of THA and TKA patients at patient level (alongside the data gathering for the primary and secondary outcomes at baseline and at the effect measurement) including the use of anticoagulants and antiplatelet agents, type of anaesthesia (general vs. loco-regional), use of local infiltration analgesia (LIA), use of tranexamic acid (TXA), surgical approach and cementation in THA, use of tourniquet and patella prostheses in TKA, number of RBC units given, adverse events, and transfusion reactions. These data were gathered to identify changes in perioperative management of THA and TKA patients which potentially could affect the de-implementation process.
2. Information about changes in perioperative management of THA and TKA patients by field notes during all visits (including the interactive education and educational outreach visit in intervention hospitals, and data gathering in both intervention and control hospitals). During the interactive education and the educational outreach visit, a research assistant (AvdH) was present to take notes about the questions and remarks made during these meetings. During the data gathering, the person who gathered the data (the researcher VV or research assistant AvdH) made field notes about changes in perioperative management of THA and TKA patients.
3. Exposure of participants (orthopaedic surgeons, anaesthesiologists, and other professionals involved blood management) to the different components of the de-implementation strategy and the appreciation of the individual components by the participants[43]. For the first intervention component, the information letter aimed at professionals involved in blood management other than orthopaedic surgeons and anaesthesiologists, and it was reported by the research team (VV, AvdH) whether this information letter was sent and to whom. For the second (interactive education) and third (educational outreach visit) intervention component, the research assistant (avdH) that attended these meetings, reported who were attending the meetings. For the fourth component (the newsletters with reports on hospital performance/best practice), it was reported by the research team (VV, AvdH), whether and when these newsletters were sent and to whom. In addition, all participants in the intervention hospitals were asked to fill in a questionnaire (sent after completion of the intervention) including questions that evaluated the extent to which the intervention components (interactive education, educational outreach visit, and newsletters including reports on hospital performance/best practice) provided new knowledge, caused behaviour change, and were appreciated on a four-point scale. For the analyses, these answer categories were dichotomized.

Statistical analysis - Effect evaluation

The software package IBM SPSS 20 was used. In all analyses, a p value <0.05 was considered statistically significant. Differences in case mix and outcomes at baseline were compared with unpaired t-tests for continuous variables and χ^2 tests for proportions.

To analyse the effects of the intervention on dichotomous outcomes, a generalized linear mixed model was used (i.e., logistic regression with a hospital included as a random effect) and for continuous outcomes, a linear mixed model was fitted. Both models compare the differences in outcomes in the intervention group with the control group in the effect measurement, corrected for differences at baseline and taking into account the clustering of patients within hospitals. The specified covariates included were sex, ASA classification, BMI, preoperative Hb, age, and joint. In the analyses for the primary outcomes, individual hospitals and measurement (baseline vs. effect) were added as random effects with covariance structure 'unstructured.' For the secondary outcomes, individual hospitals were added as random effect with covariance structure 'unstructured.' The subject-specific adjusted estimates per hospital of both measurements and effect of the intervention were presented as odds ratios (OR) for dichotomous outcomes and β's for continuous outcomes.

Analyses were performed using the intention-to-treat principle. An as-treated analysis was performed in case of cross-over of hospitals. Cross-over took place if, e.g. control hospitals merged with intervention hospitals, causing participants from the control hospitals being exposed to the intervention.

Statistical analysis - process evaluation

To analyse patient, the data gathered for the process evaluation were first compared between the baseline and the effect measurement using unpaired t tests for continuous variables and χ^2 tests for proportions. In case of significant changes between measurements, these variables were added to the previously described analyses. The qualitative data gathered for the process evaluation (field notes about changes in perioperative management of THA and TKA patients) were only used to observe trends and not formally analysed.

The data on the exposure of participants (orthopaedic surgeons, anaesthesiologists, and other professionals involved blood management) to the different components of the de-implementation strategy and the appreciation of the individual components by the participants in the intervention hospitals were analysed by using descriptive statistics.

Results

Study population

Twenty-one hospitals were included and randomized into 10 intervention (9 non-academic hospitals and 1 private clinic) and 11 control hospitals (all non-academic hospitals). At baseline, 924 patients were evaluated from the intervention hospitals (median 97 patients/hospital, range 75–100) and 1040 patients from the control hospitals (median 98 patients/hospital, range 64–100). In the effect measurement, data from 997 patients in the intervention hospitals were evaluated (median 100 patients/hospital, range 97–101) and 1096 patients from the control hospitals (median 100 patients/hospital, range 96–100).

At baseline, both blood salvage and EPO were more frequently used in patients from the control hospitals compared with those in the intervention hospitals (Table 2). Postoperative Hb did not differ, LoS was longer, and transfusion percentage was higher in intervention hospitals (Table 2). The distribution of patient characteristics and outcomes at the effect measurement are shown in eTable 1.

Table 2: Patient characteristics and outcomes in intervention and control groups at baseline (unadjusted)

Characteristic	Intervention (n=924)	Control (n=1040)	p-value
Joint, % Knee	417 (45%)	485 (47%)	0.50
Age, years	69.3 (SD 10.0)	70.1 (SD 9.5)	0.053
Gender, % Female	616 (67%)	708 (68%)	0.51
BMI, kg/m^2	28.6 (SD 4.8)	28.7 (SD 4.9)	0.68
Smoking, %	128 (10%)	90 (13%)	0.047
Physical status classification[(a)]			0.001
- % ASA 1	164 (18%)	201 (20%)	
- % ASA 2	631 (71%)	653 (64%)	
- % ASA 3-4	97 (11%)	170 (17%)	
Preoperative Hb, g/dl	13.8 (SD 1.2)	13.8 (SD 1.2)	0.30
Use of LIA, %	184 (20%)	221 (21%)	0.54
Use of TXA, %	213 (24%)	190 (18%)	0.001
Type of anesthesia, % general anesthesia	302 (33%)	295 (28%)	0.038
Use of blood salvage	275 (30%)	556 (54%)	<0.001
Use of EPO (in EPO eligible patients)	62 (29%)	132 (51%)	<0.001
Postoperative Hb, g/dl	11.2 (SD 1.4)	11.2 (SD 1.4)	0.40
Length of Stay	4.2 (SD 2.9)	3.8 (SD 1.8)	<0.001
Allogeneic transfusion, %	79 (8.5%)	62 (6.0%)	0.027
Number of RBC units transfused (in transfused patients)	2.5 (SD 1.44)	2.2 (SD 0.87)	0.093

(a) Due to the small number of ASA 4 patients (n=1), ASA 3 and 4 are combined.

Primary outcomes

A significant reduction in blood salvage over time was found when comparing the effect measurement with the baseline of all 21 hospitals (OR 0.1, 95% CI 0.0 to 0.3). The use of blood salvage at the effect measurement, adjusted for baseline, did not differ significantly between the intervention and the control group (OR 1.7, 95% CI 0.3 to 11.4) (Table 3). A significant reduction in EPO use over time was also found (OR 0.3, 95% CI 0.1 to 1.0), again without significant differences between the intervention and control hospitals (OR 1.3, 95% CI 0.26 to 6.84), after adjustment for baseline (Table 4). The effects of the intervention varied per hospital. In intervention hospitals, the median difference between the baseline and effect measurement, based on unadjusted data, in the use of blood salvage was −11% (IQR −18 to +1%) and in the use of EPO −12% (IQR −24 to +10%). In control hospitals, the median difference, based on unadjusted data, in the use of blood salvage was −28% (IQR −45 to −3%) and in the use of EPO −17% (IQR −37 to −1%).

During the study, 4 control hospitals merged with intervention hospitals and crossed over, resulting in an as-treated analysis with 14 intervention and 7 control hospitals. The as-treated analyses did not lead to new insights regarding differences between the intervention and control group (etable 2a and 2b).

Table 3: Effects of the de-implementation strategy, measurement, and covariates on the outcome 'use of blood salvage'

	OR	95% CI	P-value
Intervention group, relative to control group	1.7	0.3 to 11.4	0.57
Time effect, effect-measurement relative to baseline	0.1	0.02 to 0.3	**<0.001**
Joint, knee relative to hip	4.6	3.7 to 5.7	**<0.001**
Sex, female relative to male	0.8	0.6 to 1.0	**0.042**
ASA classification, relative to 1			
ASA 2	1.1	0.8 to 1.4	0.62
ASA 3-4	0.8	0.5 to 1.2	0.23
BMI	1.0	1.0 to 1.0	0.27
Preoperative Hb	1.0	0.9 to 1.1	0.30
Age	1.0	1.0 to 1.0	0.58

Table 4: Effects of the de-implementation strategy, measurement, and covariates on the outcome 'use of EPO' in EPO eligible patients (Hb <13 g/dL)

	OR	95% CI	P-value
Intervention group, relative to control group	1.3	0.3 to 6.8	0.73
Time effect, effect-measurement relative to baseline	0.3	0.1 to 0.9	**0.043**
Joint, knee relative to hip	0.9	0.6 to 1.3	0.60
Sex, female relative to male	1.2	0.7 to 2.1	0.50
ASA classification, relative to 1			
ASA 2	1.0	0.5 to 1.7	0.88
ASA 3-4	0.5	0.3 to 1.1	0.07
BMI	1.0	1.0 to 1.0	0.42
Preoperative Hb	0.3	0.2 to 0.4	**<0.001**
Age	1.0	1.0 to 1.0	0.97

Secondary outcomes

Postoperative Hb was significantly higher after the intervention in the intervention hospitals compared with that in controls, after adjustment for baseline (*β* 0.21, 95% CI 0.08 to 0.34). No trend over time was observed (*β* 0.02, 95% CI −0.07 to 0.11). LoS significantly reduced over time (*β* −0.40, 95% CI −0.60 to −0.02) and was, in the intervention group, significantly shorter compared with the control group, adjusted for baseline, (*β* −0.36, 95% CI −0.64 to −0.09). Allogeneic transfusions did not differ over time (OR 0.74, 95% CI 0.50 to 1.09), nor between the intervention and control hospitals (OR 1.06, 95% CI 0.63 to 1.78).

As-treated analyses on secondary outcomes showed only slight differences: Postoperative Hb was higher over time, but the significant effect of the intervention on postoperative Hb and LoS compared with those in control hospitals is no longer present (data not shown).

The reporting of adverse events and transfusion reactions was complicated by varying availability of patient records during data collections and was considered too heterogeneous to be included.

Process evaluation

Changes were observed in perioperative management of THA and TKA patients. From the patient data, it appeared that the proportion of patients treated with LIA (a drug locally injected to reduce postoperative pain and to accelerate recovery)[44-46] increased in control hospitals from 21.3 to 40.8% and in intervention hospitals from 20.1 to 32.9%. Several physicians in the intervention hospitals mentioned during the interactive education and educational outreach visit that they hesitate to use both LIA and postoperative blood

salvage to avoid drainage of the LIA and to avoid systemic effects by reinfusion of the LIA. The proportion of patients treated with TXA (a drug given to reduce perioperative blood loss)[47] increased in the control hospitals from 18.3 to 41.5% and even more in the intervention hospitals from 24.3 to 69.2%. Both techniques are frequently used as elements within multimodal rehabilitation programs.[48,49] Eight out of ten intervention and eight out of eleven control hospitals used such a program.

Whether the observed reduction in blood salvage and EPO might be explained by the increased use of LIA and TXA was tested by adding these two variables to the previously specified models. The results are shown in eTable 3a and 3b. Both LIA (OR 0.0, 95% C 0.0 to 0.0) and TXA (OR 0.3, 95% CI 0.2 to 0.5) were significantly associated with the reduction in blood salvage over time, and adding these to the statistical models rendered the reduction of blood salvage over time as non-significant (OR 0.2, 95% CI 0.1 to 1.0). The addition of LIA and TXA to the EPO model did not change the results. Increased use of LIA and TXA was also significantly associated with all secondary outcomes (data not shown).

No other changes in perioperative management of THA and TKA patients are observed as potential explanatory factors for the effect of the de-implementation strategy.

Further, exposure of participants in the intervention hospitals to the de-implementation strategy components was assessed and the different components were evaluated. One component was not executed: 'information provision by mail to other involved professionals' was deemed unnecessary by the participants. Exposure to the other components is shown in eTable 4. Evaluation of the executed components by participants in the intervention hospitals showed that all components had contributed to a large extent (eTable 5).

Discussion

The use of blood salvage and EPO significantly reduced over time in patients undergoing THA and TKA, but similarly in the intervention and control hospitals, without an effect of the de-implementation strategy. Reduction in blood salvage was associated with increased use of LIA and TXA. A significant effect of the strategy on secondary outcomes was seen: a higher postoperative Hb and a reduced length of stay in the intervention group, suggesting improved quality of care; although, the clinical relevance of these findings can be questioned.

Findings in context of existing research

In this study, a theoretically informed de-implementation strategy to change blood management practice, tailored to previously identified barriers was tested. The rationale behind this study was that this de-implementation strategy would lead to a reduction in the use of blood salvage and EPO. We expected that the control group would continue their current practice. However, the results showed that there was a reduction in the use of blood salvage and EPO in both intervention and control groups over time. Additionally, we observed an interaction of the use of LIA and TXA with the outcomes. In a recently published review of Niven et al.,[15] all studies on the de-implementation of low-value care (*n* = 38) except for one were studies without a control group. In our study, the lack of a control group would have resulted in the conclusion that use of blood salvage and EPO was reduced due to the de-implementation strategy and the observed trend in increased LIA and TXA use could have been seen as an intervention effect. This underlines the importance of including a control group in (de-)implementation studies and is thus a strength of the present study.

This study is the first study that promotes the de-implementation of blood salvage and EPO in patients undergoing THA or TKA in daily practice. It is therefore a pioneering study in a new field. Previously, studies on the implementation of transfusion guidelines, and its associated difficulties, have been published.[39,50-52] However, this study focuses on a new phenomenon within the field of transfusion medicine, the de-implementation of low-value practices. The reduction in blood salvage over time in this study could be explained by the increased use of LIA and TXA, while the decreased use of EPO remains unclear. When considering blood salvage, this substitution of one practice by something else seemed to be an important factor. From the literature, it is known that, once established, it can be very difficult to abandon low-value clinical practices. De-implementation is not the opposite of implementation of new clinical practices and may need a different approach.[13,15] This study is the first to suggest that substitution of low-value care may encourage de-implementation. In this study the substitutes were TXA, a simple, safe, and inexpensive blood-sparing technique[47] and LIA, a technique aimed at pain relief, which is found difficult to combine with blood salvage, as the blood salvage drain directly drains the analgesic fluid.[44-46]

Although the de-implementation strategy was not effective, the result of the study is a reduction in blood salvage and EPO without deterioration of secondary outcomes related to quality of care. This substantiates that blood salvage and EPO are low-value care. Regarding blood salvage, this is in line with the literature, on which the current study is based.[30,33,53] Regarding the use of EPO it is striking to see that, although effective (but not cost-effective), the EPO reduction did not lead to more transfusions, lower postoperative

Hb, or increased LoS. The ongoing trend that allogeneic transfusions occur less frequent in the past years, as is shown for instance in the meta-analysis of van Bodegom et al.,[30] might be an explanation for this, as the benefit of EPO becomes smaller if the number of transfusions decreases.

In addition, the results of this study showed that in the intervention group the LoS of patients was significantly reduced and the postoperative Hb significantly improved as compared with that in the control hospitals. Both outcomes were used in the de-implementation strategy components to give feedback on hospitals' performance and for benchmarking. Insight into this information may have caused awareness among participants leading to improvement on these outcomes or, for example, triggered participants to introduce LIA or TXA.

Strengths and weaknesses of the study

A study limitation is that participants in both the intervention and control hospitals were aware of their participation in a study about blood management. We tried to avoid this by informing a single person per hospital. However, contact-persons wanted or needed to discuss participation with their colleagues. This potentially resulted in two problems: participants with intrinsic motivation to change are more willing to participate in a study that stimulates change and awareness of the study goal could be the reason that participants changed their behaviour. We could not objectify this as we do not have data about non-participating hospitals.

A second limitation of the study is the data gathering. Retrospective data gathering from patient records is dependent on the availability and quality of data. The reporting of adverse events and transfusion reactions varied too much to produce reliable outcomes. On the other hand, prospective data collection would have increased the awareness among participants.

A strength of this study is that it was preceded by a problem analysis study[37,38,54]. In this preceding study, we identified the extent of the problem (frequency of use of blood salvage and EPO) and which barriers play a role in this specific situation of low-value care. Hence, the TDF was used to identify relevant barriers and to develop a strategy which tailored the relevant barriers.

Another strength is the addition of a process evaluation. Instead of retrospectively looking at possible explanations for results, changes in hospital policies were observed. We observed an increased use of LIA and TXA and found associations with the reduction in blood salvage. The use of LIA and TXA in a multimodal rehabilitation program may have

contributed to the observed reduction in LoS (both LIA and TXA) and the increased postoperative Hb (TXA).

In addition, we could not objectify whether other factors played a role in the observed time trends in the primary outcomes and the lack of influence of the intervention, e.g. that a decrease in the waiting time for surgery makes it undesirable to treat patients with EPO or the publication of several (Dutch) studies about blood salvage convinced the control group to abandon it.[33,53,55] These unforeseen changes were possibly stronger facilitators than the strategy components and thereby explain the lack of effect of the intervention.

Unanswered questions and future research

In the process evaluation, we tried to identify factors that explain the observed time effect in the reduction of blood salvage and EPO and the lack of influence of the de-implementation strategy. However, we could not objectify whether other processes played a role to the findings in this study. For instance, it is a possibility that a decrease in waiting time for surgery makes it undesirable to treat patients with EPO as this normally starts 4 weeks in advance of the surgery, or the publication of several (Dutch) studies concluding that blood salvage does not decrease allogeneic transfusion may have convinced the control group hospitals to stop the use of blood salvage.[33,53,55] These developments over time were possibly far stronger facilitators than any of the strategy components and thereby explain the lack of effect of the de-implementation strategy, which could not have been foreseen in the earlier problem analysis study.

Finally, a room for improvement remains, as a considerable number of patients was still treated with blood salvage and EPO. Future research should be aimed at the identification of (more) effective strategies to de-implement the use of low-value care practices to eventually improve the quality of care and lower health care costs. In this identification, a comprehensive analysis of psychological phenomena such as sticking to routines, resistance to change, peer pressure, the influence of marketing strategies of companies that supply products, and possible financial incentives should be included.

Conclusions

This study is the first study that actively promoted to stop blood salvage and EPO in patients undergoing THA or TKA in daily practice. Although the de-implementation strategy was not effective, the result of the study is a reduction in blood salvage and EPO without deterioration of secondary outcomes related to quality of care. This substantiates

that blood salvage and EPO are low-value care. Another important finding from the study is that the reduction in blood salvage was associated with the increased use of local infiltration analgesia and tranexamic acid. This suggests that that de-implementation is assisted by the substitution of techniques. Future research must reveal whether substitution is indeed an effective strategy to de-implement low-value care.

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Ethical approval and consent to participate

The Medical Ethical Committee of the Leiden University Medical Center declared that ethical approval was not required (CME 13/132) and waived the need for written consent from patients.

References

1. Levinson W, Kallewaard M, Bhatia RS, Wolfson D, Shortt S, Kerr EA. 'Choosing Wisely': a growing international campaign. BMJ Qual Saf. 2015;24:167–74.
2. Smith M, Saunders R, Stuckhardt L, McGinnis JM. Best Care at Lower Cost: The Path to Continuously Learning Health Care in America. National Academies Press (US). 2013. doi:10.17226/13444.
3. Colla CH, Morden NE, Sequist TD, Schpero WL, Rosenthal MB. Choosing wisely: prevalence and correlates of low-value health care services in the United States. J Gen Intern Med. 2015;30:221–8.
4. van Bodegom-Vos L, Davidoff F, Marang-van de Mheen PJ. Implementation and de-implementation: two sides of the same coin? BMJ Qual Saf. 2016;26:495–501. May C. Towards a general theory of implementation. Implement Sci. 2013;8:18.
5. Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. Health Technol Assess. 2004;8(6):iii–iv, 1–72.
6. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet. 2003;362:1225–30.
7. Grol R, Personal paper. Beliefs and evidence in changing clinical practice. BMJ. 1997;315:418–21.
8. Michie S, Johnston M, Abraham C, Lawton R, Parker D, Walker A. Making psychological theory useful for implementing evidence based practice: a consensus approach. Qual Saf Health Care. 2005;14:26–33.
9. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA. 1999;282:1458–65.
10. Baker R, Camosso-Stefinovic J, Gillies C, Shaw EJ, Cheater F, Flottorp S et al. Tailored interventions to overcome identified barriers to change: effects on professional practice and health care outcomes. Cochrane Database Syst Rev. 2010;17(3):CD005470. Prior M, Guerin M, Grimmer-Somers K. The effectiveness of clinical guideline implementation strategies—a synthesis of systematic review findings. J Eval Clin Pract. 2008;14:888–97.
11. Davidoff F. On the undiffusion of established practices. JAMA Intern Med. 2015;175:809–11.
12. Ubel PA, Asch DA. Creating value in health by understanding and overcoming resistance to de-innovation. Health Aff (Millwood). 2015;34:239–44.
13. Niven DJ, Mrklas KJ, Holodinsky JK, Straus SE, Hemmelgarn BR, Jeffs LP, et al. Towards understanding the de-adoption of low-value clinical practices: a scoping review. BMC Med. 2015;13:255.
14. Prasad V, Ioannidis JP. Evidence-based de-implementation for contradicted, unproven, and aspiring healthcare practices. Implement Sci. 2014;9:1.
15. Elshaug AG, Hiller JE, Tunis SR, Moss JR. Challenges in Australian policy processes for disinvestment from existing, ineffective health care practices. Aust New Zealand Health Policy. 2007;4:23.
16. Montini T, Graham ID. "Entrenched practices and other biases": unpacking the historical, economic, professional, and social resistance to de-implementation. Implement Sci. 2015;10:24.
17. Polisena J, Clifford T, Elshaug AG, Mitton C, Russell E, Skidmore B. Case studies that illustrate disinvestment and resource allocation decision-making processes in health care: a systematic review. Int J Technol Assess Health Care. 2013;29:174–84.
18. Roman BR, Asch DA. Faded promises: the challenge of deadopting low-value care. Ann Intern Med. 2014;161:149–50.
19. Willson A. The problem with eliminating 'low-value care'. BMJ Qual Saf. 2015;24:611–4.
20. Munoz M, Garcia-Erce JA, Villar I, Thomas D. Blood conservation strategies in major orthopaedic surgery: efficacy, safety and European regulations. Vox Sang. 2009;96:1–13.
21. Spahn DR, Goodnough LT. Alternatives to blood transfusion. Lancet. 2013;381:1855–65.
22. So-Osman C. Red blood cell transfusion triggers and transfusion alternatives in elective orthopedic hip and knee replacement surgery—a review. Int J Clin Transfus Med. 2015;3:47–54.
23. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiology. 2010;113:482–95.
24. Treloar CJ, Hewitson PJ, Henderson KM, Harris G, Henry DA, McGrath KM. Factors influencing the uptake of technologies to minimize perioperative allogeneic blood transfusion: an interview study of national and institutional stakeholders. Intern Med J. 2001;31:230–6.
25. Fergusson D, Blair A, Henry D, Hisashige A, Huet C, Koopman-van GA, et al. Technologies to minimize blood transfusion in cardiac and orthopedic surgery. Results of a practice variation survey in nine countries. International study of Peri-operative transfusion (ISPOT) investigators. Int J Technol Assess Health Care. 1999;15:717–28.

26. Henry DA, Henderson KM, Fryer JL, Treloar CJ, McGrath KM, Deveridge SF. Use of interventions to minimise perioperative allogeneic blood transfusion in Australia. A survey by the International Study of Perioperative Transfusion (ISPOT) Study Group. Med J Aust. 2000;172:365–9.
27. Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C. Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model. Health Technol Assess. 2006;10:1–114.
28. van Bodegom-Vos L, Voorn VM, So-Osman C, Vliet Vlieland TP, Dahan A, Koopman-van Gemert AW, et al. Cell salvage in hip and knee arthroplasty: a meta-analysis of randomized controlled trials. J Bone Joint Surg Am. 2015;97:1012–21.
29. Voorn VM, van der Hout A, So-Osman C, Vliet Vlieland TP, Nelissen RG, van den Akker-van Marle ME et al. Erythropoietin to reduce allogeneic red blood cell transfusion in patients undergoing total hip or knee arthroplasty. Vox Sang. 2016;111:219–25.
30. Alsaleh K, Alotaibi GS, Almodaimegh HS, Aleem AA, Kouroukis CT. The use of preoperative erythropoiesis-stimulating agents (ESAs) in patients who underwent knee or hip arthroplasty: a meta-analysis of randomized clinical trials. J Arthroplasty. 2013;28:1463–72.
31. So-Osman C, Nelissen RG, Koopman-van Gemert AW, Kluyver E, Poll RG, Onstenk R et al. Patient Blood Management in Elective Total Hip- and Knee-replacement Surgery (Part 1): A Randomized Controlled Trial on Erythropoietin and Blood Salvage as Transfusion Alternatives Using a Restrictive Transfusion Policy in Erythropoietin-eligible Patients. Anesthesiology. 2014;120:839–51.
32. Bedair H, Yang J, Dwyer MK, McCarthy JC. Preoperative Erythropoietin Alpha Reduces Postoperative Transfusions in THA and TKA but May Not Be Cost-effective. Clin Orthop Relat Res. 2014;473:590–6.
33. Coyle D, Lee KM, Fergusson DA, Laupacis A. Economic analysis of erythropoietin use in orthopaedic surgery. Transfus Med. 1999;9:21–30.
34. Struijk-Mulder MC, Horstmann WG, Verheyen CC, Ettema HB. Ten-year follow-up on Dutch orthopaedic blood management (DATA III survey). Arch Orthop Trauma Surg. 2014;134:15–20.
35. Voorn VM, de Mheen PJ M-v, Wentink MM, So-Osman C, Vliet Vlieland TP, Koopman-van Gemert AW, et al. Frequent use of blood-saving measures in elective orthopaedic surgery: a 2012 Dutch blood management survey. BMC Musculoskelet Disord. 2013;14:230.
36. Voorn VM, de Mheen PJ M-v, Wentink MM, Kaptein AA, Koopman-van Gemert AW, So-Osman C, et al. Perceived barriers among physicians for stopping non-cost-effective blood-saving measures in total hip and total knee arthroplasties. Transfusion. 2014;54:2598–607.
37. Lorencatto F, Stanworth SJ, Gould NJ. Bridging the research to practice gap in transfusion: the need for a multidisciplinary and evidence-based approach. Transfusion. 2014;54:2588–92.
38. Voorn VM, de Mheen PJ M-v, So-Osman C, Kaptein AA, van der Hout A, van den Akker-van Marle ME, et al. De-implementation of expensive blood saving measures in hip and knee arthroplasties: study protocol for the LISBOA-II cluster randomized trial. Implement Sci. 2014;9:48.
39. Michie S, Johnston M, Francis JJ, Hardeman W, Eccles M. From theory to intervention: mapping theoretically derived behavioural determinants to behaviour change techniques. Appl Psychol:An Inter Rev. 2008;57:660–80.
40. Francis JJ, Stockton C, Eccles MP, Johnston M, Cuthbertson BH, Grimshaw JM, et al. Evidence-based selection of theories for designing behaviour change interventions: using methods based on theoretical construct domains to understand clinicians' blood transfusion behaviour. Br J Health Psychol. 2009;14:625–46.
41. Hulscher ME, Laurant MG, Grol RP. Process evaluation on quality improvement interventions. Qual Saf Health Care. 2003;12:40–6.
42. Andersen LO, Kehlet H. Analgesic efficacy of local infiltration analgesia in hip and knee arthroplasty: a systematic review. Br J Anaesth. 2014;113:360–74.
43. Thomassen BJ, Touw D, van der Woude P, van der Flier RE, Veld BA I't. Safety of blood reinfusion after local infiltration analgesia with ropivacaine in total knee arthroplasty. Int J Clin Pharmacol Ther. 2014;52:135–42.
44. Thomassen BJ, Pool L, Van Der Flier R, Stienstra R, Veld BA I't. Safety of retransfusing shed blood after local infiltration analgesia in total knee arthroplasty. Acta Orthop Belg. 2012;78:506–11.
45. Melvin JS, Stryker LS, Sierra RJ. Tranexamic acid in hip and knee arthroplasty. J Am Acad Orthop Surg. 2015;23:732–40.
46. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg. 2008;248:189–98.

47. Kehlet H, Thienpont E. Fast-track knee arthroplasty—status and future challenges. Knee. 2013;20 Suppl 1:S29–33.
48. Tinmouth A, Macdougall L, Fergusson D, Amin M, Graham ID, Hebert PC, et al. Reducing the amount of blood transfused: a systematic review of behavioral interventions to change physicians' transfusion practices. Arch Intern Med. 2005;165:845–52.
49. Gould NJ, Lorencatto F, Stanworth SJ, Michie S, Prior ME, Glidewell L, et al. Application of theory to enhance audit and feedback interventions to increase the uptake of evidence-based transfusion practice: an intervention development protocol. Implement Sci. 2014;9:92.
50. Lorencatto F, Gould NJ, McIntyre SA, During C, Bird J, Walwyn R, et al. A multidimensional approach to assessing intervention fidelity in a process evaluation of audit and feedback interventions to reduce unnecessary blood transfusions: a study protocol. Implement Sci. 2016;11:163.
51. So-Osman C, Nelissen RG, Koopman-van Gemert AW, Kluyver E, Poll RG, Onstenk R et al. Patient Blood Management in Elective Total Hip- and Knee-replacement Surgery (Part 2): A Randomized Controlled Trial on Blood Salvage as Transfusion Alternative Using a Restrictive Transfusion Policy in Patients with a Preoperative Hemoglobin above 13 g/dl. Anesthesiology. 2014;120:852–60.
52. Voorn VM, de Mheen PJ, So-Osman C, Vlieland TP, Gemert AW, Nelissen RG, et al. Designing a strategy to implement cost-effective blood transfusion management in elective hip and knee arthroplasties: a study protocol. Implement Sci. 2012;7:58.
53. Thomassen BJ, den Hollander PH, Kaptijn HH, Nelissen RG, Pilot P. Autologous wound drains have no effect on allogeneic blood transfusions in primary total hip and knee replacement: a three-arm randomised trial. Bone Joint J. 2014;96-B:765–71.

eTable 1: Patient characteristics and outcomes in intervention and control group at the effect measurement (unadjusted)

Characteristic	Intervention	Control
Joint, % Knee	465 (47%)	549 (50%)
Mean age, years	69.7 (SD 9.7)	69.8 (SD 9.5)
Gender, % Female	625 (63%)	708 (65%)
Mean BMI, kg/m^2	28.8 (SD 4.8)	28.5 (SD 4.8)
Smoking, %	96 (10%)	124 (14%)
Physical status classification*		
- % ASA 1	191 (19%)	203 (19%)
- % ASA 2	677 (68%)	690 (63%)
- % ASA 3-4	120 (12%)	195 (18%)
Mean preoperative Hb, g/dl	13.9 (SD 1.2)	13.9 (SD 1.2)
Use of LIA, %	328 (33%)	446 (41%)
Use of TXA, %	690 (69%)	454 (41%)
Type of anaesthesia, % general anaesthesia	237 (24%)	287 (26%)
Use of blood salvage	170 (17%)	292 (27%)
Use of EPO (in EPO eligible patients)	46 (23%)	84 (32%)
Postoperative Hb	11.5 (SD 1.4)	11.3 (SD 1.4)
Length of Stay	3.4 (SD 3.0)	3.4 (SD 2.0)
Allogeneic transfusion, %	59 (6%)	51 (5%)
Number of RBC units transfused (in transfused patients)	2.4 (SD 1.7)	2.3 (SD 1.2)

***** *Due to the small number of ASA 4 patients (n=1), ASA 3 and 4 are combined.*

eTable 2a: Effects of the de-implementation strategy, time and covariates on the outcome 'use of blood salvage' in an as-treated analysis

	OR	95% CI	P-Value
Intervention group, relative to control group	0.6	0.1 to 4.4	0.61
Time effect, effect measurement relative baseline	0.2	0.0 to 0.8	**0.03**
Joint, knee relative to hip	4.6	3.7 to 5.7	**<0.001**
Sex, female relative to male	0.8	0.6 to 1.0	**0.04**
ASA classification relative to 1			
- ASA 2	1.1	0.8 to 1.4	0.68
- ASA 3	0.8	0.5 to 1.2	0.22
BMI	1.0	1.0 to 1.0	0.27
Preoperative Hb (g/dl)	1.0	0.9 to 1.0	0.30
Age	1.0	1.0 to 1.0	0.58

eTable 2b: Effects of the de-implementation strategy, time and covariates on the outcome 'use of EPO' in EPO eligible patients (Hb<13 g/dL) in an as-treated analysis

	OR	95% CI	P-Value
Intervention group, relative to control group	0.4	0.1 to 2.2	0.30
Time effect, effect measurement relative baseline	0.6	0.2 to 2.5	0.51
Joint, knee relative to hip	0.9	0.6 to 1.3	0.57
Sex, female relative to male	1.2	0.7 to 2.0	0.52
ASA classification relative to 1			
- ASA 2	1.0	0.5 to 1.7	0.89
- ASA 3	0.5	0.2 to 1.1	0.07
BMI	1.0	0.9 to 1.0	0.43
Preoperative Hb (g/dl)	0.3	0.2 to 0.4	<0.001
Age	1.0	1.0 to 1.0	0.95

eTable 3a: Effects of the de-implementation strategy, measurement and covariates on the outcome 'use of blood salvage', after the addition of LIA and TXA to the model

	OR	95% CI	P-value
Intervention group, relative to control group	1.1	0.1 to 8.7	0.9
Time effect, effect measurement relative baseline	0.2	0.1 to 1.0	0.053
Local infiltration analgesia	0.0	0.0 to 0.0	**<0.001**
Tranexamic acid	0.3	0.2 to 0.5	**<0.001**
Joint, knee relative to hip	26.0	18.8 to 35.9	**<0.001**
Sex, female relative to male	0.8	0.6 to 1.0	**0.049**
ASA classification, relative to 1			
ASA 2	0.9	0.9 to 1.7	0.27
ASA 3-4	1.2	0.6 to 1.5	0.69
BMI	1.0	1.0 to 1.0	0.47
Preoperative Hb	0.9	0.8 to 1.0	0.20
Age	1.0	1.0 to 1.0	0.71

eTable 3b: Effects of the de-implementation strategy, measurement and covariates on the outcome 'use of EPO', after the addition of LIA and TXA to the model

	OR	95% CI	P-value
Intervention group, relative to control group	1.2	0.3 to 6.4	0.80
Time effect, effect measurement relative baseline	0.3	0.1 to 1.0	**0.044**
Local infiltration analgesia	0.9	0.5 to 1.8	0.85
Tranexamic acid	1.2	0.6 to 2.4	0.54
Joint, knee relative to hip	0.9	0.6 to 1.4	0.66
Sex, female relative to male	1.2	0.7 to 2.0	0.56
ASA classification, relative to 1			
ASA 2	1.0	0.5 to 1.8	0.93
ASA 3-4	0.5	0.3 to 1.1	0.09
BMI	1.0	0.9 to 1.0	0.44
Preoperative Hb	0.3	0.2 to 0.4	**<0.001**
Age	1.0	1.0 to 1.0	0.93

eTable 4: Exposure to de-implementation strategy components

	Interactive Education	Educational outreach visits	Reports on hospital performance/best practices
Exposure to the component			
Orthopaedic surgeons	27/63 attended	14/63* attended	63/63 received report
Anaesthesiologists	19/37 attended	1/37** attended	37/37 received report

** In 3 hospitals it was unknown how many orthopaedic surgeons attended the feedback meeting*
*** In 1 hospital it was unknown how many anaesthesiologists attended the feedback meeting*

eTable 5: Evaluation of de-implementation strategy components (questionnaire response n=50/100)

	Interactive Education	Educational outreach visits	Reports on hospital performance/ best practices
To what extent did individual components provide new knowledge (n=50)			
Limited extent	16 (32%)	12 (24%)	24 (48%)
Great extent	24 (48%)	27 (54%)	14 (28%)
No opinion/component not received	10 (20%)	11 (22%)	12 (24%)
To what extent did individual components caused behaviour change (n=50)			
Limited extent	21 (42%)	24 (48%)	24 (48%)
Great extent	20 (40%)	16 (32%)	14 (28%)
No opinion/ component not received	9 (18%)	10 (20%)	12 (24%)
To what extent where individual components appreciated by participants (n=50)			
Limited extent	13 (26%)	10 (20%)	12 (24%)
Great extent	26 (52%)	28 (56%)	25 (50%)
No opinion/ component not received	11 (22%)	12 (24%)	13 (26%)

Chapter 10

Summary and General discussion

This thesis aimed to evaluate the effectiveness of a de-implementation strategy to reduce the use of blood salvage techniques (blood salvage) and preoperative treatment with erythropoietin (EPO) in primary elective hip and knee arthroplasty (THA and TKA).

Blood salvage and EPO are used to reduce the need for allogeneic red blood cell transfusion in patients undergoing elective orthopaedic surgery. However, it is considered to be low-value care, as previous research demonstrated that their use led to increased costs and had limited beneficial effects. This thesis described the stepwise de-implementation (i.e. the abandoning of low-value care) of these techniques according to the implementation model of Grol.[1] The first step described in this thesis was the development of concrete targets for the de-implementation of blood salvage and EPO in THA and TKA. For this purpose, the evidence that is currently available on the effectiveness of blood salvage and EPO was evaluated by means of two meta-analyses. It was followed by an analysis of current performance, target group and setting. Based on this information we developed a comprehensive strategy for de-implementation of low-value patient blood management (PBM) techniques which was followed by the execution and evaluation of this strategy using a cluster-randomized controlled trial.

This chapter starts with a summary of the main findings of the previous chapters. Subsequently these findings and relevant methodological issues are discussed in the light of available literature and finally recommendations for future practice and research are given.

Main Findings

The structure of this thesis is related to the model of Grol including: 1) the development of concrete targets for de-implementation of blood salvage and EPO in THA and TKA, 2) an analysis of current performance, targets group and setting in a problem analysis study, 3) the development of a de-implementation strategy, 4 and 5) the execution and evaluation of the developed de-implementation strategy.

Concrete targets for de-implementation (step 1)

The starting point for de-implementation is the development of concrete targets for de-implementation of blood salvage and EPO in THA and TKA. For this purpose, evidence is needed that proves that blood salvage and preoperative treatment with EPO in patients undergoing orthopaedic surgery is low-value care.

A systematic review including a meta-analysis on blood salvage in THA and TKA patients was presented in **Chapter 2**. The main aim of the systematic review was to assess the effectiveness of blood salvage on the reduction of allogeneic red blood cell transfusion, separately in THA and TKA patients, and to examine whether the results of recent trials would change the conclusions from previous meta-analyses. Forty-three trials (5631 patients) were included. Overall, blood salvage was found to reduce allogeneic transfusion in THA and TKA patients. However, trials with a low risk of bias published from 2010 to 2012 showed no significant effect of blood salvage on the rate of allogeneic blood transfusion nor the volume of transfused blood in neither THA nor TKA patients. These results suggest that other factors have changed over time such as the introduction of more restrictive transfusion thresholds, awareness of intra-operative blood loss, improved surgical techniques and the introduction of new modalities to reduce blood loss while the blood salvage product and the indication to use blood salvage remained unchanged.

A systematic review including a meta-analysis on EPO in THA and TKA was presented in **Chapter 3**. The primary aim was to assess the effectiveness of EPO on the reduction of allogeneic red blood cell transfusion in THA and TKA separately, secondary aims were to evaluate safety and costs. Seven trials (2439 patients) were included. EPO was found to reduce the exposure rate to blood transfusion in both THA and TKA and the volume of transfused blood (unable to split for hip/knee). No differences in thrombo-embolic or adverse events were found. Only one study evaluated costs, whereby no pooled estimates could be given for cost-effectiveness. The costs in this study were estimated at an additional €785 per patient or €7300 per avoided allogeneic transfusion (estimates may differ in other healthcare systems). Overall, the use of EPO was found to be effective and safe. However, the decision to use EPO on a routine base should be balanced against the costs, which are high.

Based on the results of the meta-analyses, we consider blood salvage and EPO as low-value care.

Analysis of current performance, target groups and setting (step 2).

The second step for the de-implementation of low-value care, with reference to the model of Grol, was a problem analysis study in which current performance, target group and setting for the use of blood salvage and EPO are explored. The protocol for this problem analysis is described in **Chapter 4**.

In **Chapter 5** a survey among Dutch orthopaedic departments was performed to assess the current use of low-value PBM techniques. The survey evaluated the frequency of use of various types of PBM of Dutch orthopaedic departments. Responders reported on a 5-

point Likert scale (never, almost never, regularly, almost always, always) how frequent a technique was used. The answers were divided into non-frequent use (never and almost never) and frequent use (regularly, almost always and always). The survey, completed by 81 Dutch orthopaedic departments (response rate 82%), showed that in 2012 intra-operative cell-savers were frequently used in 25 departments (31%), post-operative drainage and reinfusion of salvaged blood was used in 56 departments (69%) and EPO was frequently used at 55 departments (68%). When departments were compared on the basis of size, frequent EPO use was more common in large departments, with 22 (88%) large departments being frequent users versus 13 (63%) small departments and 16 (55%) intermediate departments, p = 0.03. No differences by size or type of department were observed for other techniques. Based on this survey, a target group of frequent users was identified. These frequent users were then invited to participate in the cluster-RCT.

In **Chapter 6** we evaluated whether specific outcome measures regarding PBM are suitable to compare the quality of care for THA and TKA patients between hospitals to be used by e.g. the health care inspection. In other words, we evaluated whether it is reliable to rank hospitals on the outcome measures 'allogeneic transfusion' and 'extended length of stay' (defined as postoperative stay >4 days) in patients undergoing THA and TKA. We did this by assessing which part of the observed variation between hospitals is due to true differences and which part is noise. Furthermore, we evaluated which factors are associated with the true hospital differences. To perform this evaluation, we first ranked hospitals based on Observed/Expected (O/E) ratios for the outcome measures 'allogeneic transfusion' and 'extended length of stay'. Observed variation between hospitals was assessed by calculating the rankability, a measure that expresses the reliability of ranking. Medical records from 1163 THA patients and 986 TKA patients from 23 hospitals were analysed. Rankability, expressed in a percentage of the existing variation based on differences between hospitals as compared to random variation, was low for the outcome allogeneic transfusion (21% in THA and 34% in TKA). The variation explained by hospital differences for the outcome extended length of stay was higher (71 % in THA and 78% in TKA), and therefore ranking based on extended length of stay is more reliable. Hospitals using local infiltration analgesia (LIA) and tranexamic acid (TXA) had relatively fewer patients with transfusions and extended length of stay, therefore they were associated with better performance of hospitals.

In **Chapter 7** a combined qualitative-quantitative study on barriers for de-implementation of low-value PBM techniques in THA and TKA was done. This study aimed to identify barriers associated with the intention of physicians to stop using blood salvage and EPO. Semi-structured interviews with 10 orthopaedic surgeons and 10 anaesthesiologists were conducted, followed by a questionnaire completed by 153 orthopaedic surgeons (response rate 40%) and 100 anaesthesiologists (response rate 27%). Identified barriers

corresponding with domains of the Theoretical Domains Framework (TDF)[2,3] were linked to the intention to stop either blood salvage or EPO. This resulted in a number of barriers within the domains 'social influences', 'motivation and goals' and 'beliefs about consequences' related to the intention to stop EPO and barriers within the domains 'social influences', 'motivation and goals', 'beliefs about consequences' and 'knowledge' related to the intention to stop blood salvage.

Development of a de-implementation strategy (step 3)

Following the analysis of current performance, target groups and setting, a strategy to reduce the use of blood salvage techniques and preoperative treatment with EPO in patients undergoing primary elective THA and TKA was developed which was geared at the barriers identified in **chapter 7**. This corresponds to the third step of the model of Grol.

Chapter 8 describes the developed de-implementation strategy. In the development process we selected behavioural change-techniques that are deemed to be effective in targeting the identified barriers[4] This resulted in a de-implementation strategy with four separate components:

1) the provision of information with a letter sent by email to all involved parties in the use of blood salvage and EPO, with an overview of the current literature.

2) Interactive education for the study participants (orthopaedic surgeons and anaesthesiologists) with an overview of the literature about blood salvage and EPO in THA and TKA. A summary is printed on a pocket card. Data on their blood management use and patient outcomes are presented and discussed.

3) Feedback during educational outreach visits aimed at study participants. A comparison is made over time between their current practice and their practice at baseline towards blood salvage, EPO, allogeneic transfusions and length of stay (LoS).

4) Electronic newsletter for study participants, sent twice. A comparison is made between participants' current practice and 'best practice' Benchmark hospitals (Dutch hospitals that do not use blood salvage or EPO) to emphasize safety.

Execution and evaluation of the developed de-implementation strategy (step 4 and 5)

The fourth and fifth step in the model of Grol were to execute and evaluate the developed de-implementation strategy. In **Chapter 9** the effectiveness of this theoretically-informed multifaceted strategy to de-implement low-value PBM techniques was evaluated by means of a multicentre cluster-randomized controlled trial. The exposure rate of patients

to blood salvage and EPO was measured before and after the strategy was carried out. By randomisation it was determined which hospitals received the intervention and were exposed to the strategy and which hospitals were controls. 21 hospitals were included. Before the intervention at baseline data of 924 patients in intervention hospitals and 1040 patients in control hospitals were analysed. After the intervention the data of 997 patients in the intervention hospitals and 1096 in control hospitals were analysed. The use of blood salvage and EPO reduced significantly over time, but it did not differ between intervention and control hospitals. The intervention hospitals had significantly higher postoperative haemoglobin levels compared with control hospitals and a greater reduction in length of stay. Allogeneic transfusions were comparable. In the process evaluation we noticed that the increased use of LIA and TXA was strongly associated with the reduction in blood salvage over time. This latter suggests that the de-implementation was assisted by the substitution of PBM techniques.

Discussion of the main findings

This thesis focused on the de-implementation of low-value PBM care. It is the first study that promotes the specific de-implementation of blood salvage and EPO in orthopaedic practice. It is therefore a pioneering study in a new field. The strengths of this thesis are the stepwise approach of de-implementation and the testing of the developed de-implementation strategy in a cluster-randomised trial that included a control group.

Theoretical underpinning of de-implementation strategies

For the stepwise approach the 5-step implementation model of Grol[1] was used. This led to a tailored strategy for de-implementing two low-value care topics, the use of blood salvage and EPO in primary elective orthopaedic surgery. De-implementation studies in general are not always preceded by a problem analysis study that gives insight into the relevant barriers and facilitators for the specific case, nor substantiated by a theoretical model. This is illustrated by the 39 de-implementation efforts that are described in the scoping review of Niven.[5] Of these studies, 26 do not describe a specific intervention to facilitate de-implementation. Of the 13 studies that did describe an intervention, 9 concerned market withdrawal of specific medications, which is in fact a very effective way of de-implementation, but not widely applicable (in these 9 studies a drug was withdrawn because patient safety was at stake). In the remaining 4 de-implementation studies, 3 did not describe a preceding problem analysis[6-8] and one used a problem analysis only to identify frequent users of low-value care.[9] Of these 4 studies only one reported why their used interventions were chosen.[6]

If we regard the literature on de-implementation efforts that are more closely related to the topic of this thesis, the de-implementation of inappropriate allogeneic transfusions, there is extensive literature available. Modern (international) transfusion guidelines advise a restrictive transfusion trigger with a threshold of 7-8 g/dL (4.3-5.0 mmol/l) for hemodynamic stable patients, as opposed to the fairly liberal threshold of 10 g/dL (6.2 mmol/l) by Adams and Lundy in 1942.[10-12] Several studies from all over the world report overuse or inappropriate use of transfusions.[13-19] Additionally, inappropriate use of transfusion is addressed by 'Choosing wisely', a campaign that supports de-implementation of low-value care in the USA[20] and it is addressed in the UK where appropriate use of transfusions has been audited by the National Comparative Audit of Blood Transfusion (NCABT) programme.[21] As de-implementation often does not happen by itself, the awareness of inappropriate use should be translated into action to change this.[22-24] A systematic review published in 2002 by Wilson et al. described which interventions were effective to change transfusion practice. Nine studies published between 1988 and 2000 were included. It was concluded that interventions identified as being generally effective to change behaviour included educational outreach visits, interactive educational meetings, reminders and multifaceted strategies[25] (corresponding to the strategy used in this thesis). A systematic review of interventions to change physicians' transfusion behaviour published by Tinmouth et al. in 2005[26], included 19 studies published between 1974 and 2004, concluding that multifaceted strategies did not lead to greater reductions in transfusions than studies with single interventions. It was additionally concluded that interventions with immediate feedback did not result in greater reductions than indirect feedback. In short, both reviews suggest which type of interventions can be effective, however they do not reach the same conclusions as to which interventions are most effective. This may suggest that the effects do not only depend on the type of intervention, but also on the presence of barriers and facilitators relevant to the topic and whether the chosen interventions are tailored to the present barriers and facilitators.

Several new studies have been published on strategies to reduce (inappropriate) allogeneic transfusions since the above mentioned reviews. We searched for 'reduction of inappropriate transfusions' using PubMed and selected 15 articles that were published in the period 2005-2017[27] In 7 studies the (de-)implementation strategies or interventions were chosen based on literature.[28-35] However, the other 8 out of 15 studies did not describe why the specific implementation strategy was chosen.[36-42] Of the selected 15 studies, only 3 described some type of problem analysis prior to the implementation to identify a target group or relevant barriers and facilitators.[28, 34, 37]

In comparison with this literature we attempted to improve the quality and thereby the effectiveness of our intervention by using a systematic approach with the 5-step model of

Grol.[1] The included problem analysis identified the relevant barriers (chapter 7). Barriers for de-implementation were identified on different domains relevant in behavioural change. Interventions tailored to the identified barriers that were deemed effective, based on literature, were chosen in the development of the de-implementation strategy (chapter 8). Implementation strategies tailored to previously identified determinants are frequently recommended to approach (de-)implementation, as behaviour change might be impeded by a variety of barriers. Nevertheless, the conclusion of the Cochrane review on tailored interventions to address determinants of practice by Baker et al[43] is that tailored implementation can be effective, but the effect is variable and tends to be small to moderate. A more recently published article by Wensing[44] raises concerns about tailoring as a recommended approach to implementation of innovations, due to the limited effects of tailored intervention strategies. In particular ongoing monitoring of factors during the delivery of the interventions seems required to adapt to contextual and political changes. Additionally it is not yet clear how best to select effective interventions tailored to address determinants, as there is limited insight into the linkages of determinants and interventions.[43,44] In this thesis we used the method described by Michie[4] to link interventions to previously identified barriers. However, here the linkage between determinants and interventions was based on expert opinion and was not substantiated with empirically evidence.

With this knowledge, the lack of effectiveness of our de-implementation strategy is not completely surprising, as the effect of tailored de-implementation strategies in general is found to be limited and highly variable. In executing the de-implementation strategy in chapter 9, we did (deliberately) not adapt the strategy during the execution, because adding new components to the strategy during the execution would have been a violation of our study protocol. Therefore, as is suggested by Wensing,[44] we might have missed out on developments influencing the uptake op cost-effective blood management.

Study design of de-implementation studies

In addition to this, in de-implementation research a control group is relatively often lacking. In Niven's review[5] the market withdrawal studies logically do not include a control group, in the other 4 intervention studies, 2 do not have a control group,[7,9] one study was a quasi-experimental study with interrupted time series[6] and only one was a controlled trial.[8] The reviews from Wilson and Tinmouth on the change of transfusion practice[25,26] included mainly before-after studies where no control group was included. In the more recent inappropriate transfusion studies 14 out of 15 lacked a control group.[29-42] The only study with a control group was a study protocol.[28] In this thesis the de-implementation strategy was tested in a cluster-randomized controlled trial. The results showed that in both the intervention group exposed to the de-implementation strategy and the control

group the use of EPO and blood salvage reduced (chapter 9). In other words, the de-implementation strategy was not more effective compared to the control strategy. This underlines the value of a control group, as in this study the lack of a control group would have resulted in the conclusion that the strategy was effective to reduce low-value blood management.

Methodological issues

Some limitations could be identified, which were related to the methodology. First, in our cluster randomized controlled trial (chapter 8), participants of both the intervention and control group hospitals were aware of their participation in a study, and they were aware of the study goal. We tried to avoid this during the inclusion of hospitals by involving a single person per hospital. However, contact persons wanted or needed to discuss participation in our trial with their colleagues. It is possible that the results, a decrease of blood salvage use and EPO use in both the intervention and control group, were influenced by the awareness of participants to be participating in a study. A different design, such as a stepped wedge model, could have prevented this bias. However, within a stepped wedge design the effect of the intervention might be confounded with any underlying temporal trends. Additionally, a more practical issue, with a stepped wedge design the study duration would have been doubled.

Secondly, the model of Grol used in this thesis was originally intended for implementation efforts. The use of an implementation model in de-implementation research may not have been the right choice, as different factors may be involved.[45] It is suggested that there are fundamental differences between implementation and de-implementation, as the perception of people regarding gains and losses is not symmetrical and it is harder to give up old (low-value) clinical practices that they have come to believe in, than to adopt new and promising innovations.[45-49] However, when starting the LISBOA de-implementation project, there were no de-implementation models available and we chose a model with a systematic approach to change behaviour. Other models for the implementation of behaviour change were available, such as the innovation process framework by Fleuren et al.,[50] a model that takes socio-political, organisational, personal characteristics and the characteristics of the topic and the change strategy into account in the implementation process; or the 'Knowledge to action process' by Graham et al.,[51] which describes a circular process on how available knowledge can be implemented. Meanwhile Niven et al. [5] suggested a model for the process of de-adoption largely similar to the implementation model of Graham. These models and the model of Grol that we have used resemble each other in their stepwise approach of implementation: assessment of the topic that needs implementation, a context analysis, selection and execution of a strategy for

implementation tailored to identified barriers and facilitators, and an evaluation of the results.

New developments and insights on de-implementation research have evolved during the research process of this thesis. For example in the article of Helfrich[52] medical overuse and its de-implementation is explained by the dual process model of cognition. In this model clinical decision-making is based on reflective cognition, a conscious process of evaluating option and automatic cognition, an unconscious process in response to environmental or emotive cues. De-implementation strategies may be conceptualized as corresponding to cognition: unlearning, based on reflective cognition; and substitution, based on automatic cognition. Unlearning may cause a reaction in clinicians with anger and negative cognition because they feel restricted in their decision-making. In substitution an alternative is promoted, in which the substitute replaces or displaces the low-value care. This model introduces the idea of substitution as a strategy to address overuse. This closely matches the findings in this thesis, where the de-implementation of low-value blood management techniques is accompanied by substituting the low-value techniques with a cheap and effective alternative, TXA, and by the increased use of LIA as local analgesic. Although it was not promoted in the de-implementation strategy, in both intervention and control groups the substitution was significantly associated with the reduction of low-value blood management techniques.

Implications for practice

In this thesis it was found that substitution of low-value care might contribute to de-implementation of this low-value care. In the development of de-implementation strategies this can be used to improve the results. Additionally, this thesis followed the stepwise model of Grol, including the identification of barriers to tailor the de-implementation strategy. The use of this model did not lead to the intended results in this thesis. More recent literature suggests that the tailoring of strategy components to the previously identified barriers may not be sufficient and continuous adaption to the factors and barriers might be needed. However, more factors may have played a role, such as awareness of participation in a study in the control arm of the cRCT or an overarching time trend of abandoning the selected blood management techniques. Therefore we cannot say whether the use of the Grol model should be stimulated or slowed down in further de-implementation efforts.

Recommendations for future research

This thesis gives insight into the process of de-implementation. However, the complicated matter of de-implementation research still needs to be further unravelled. More

knowledge on the determinants that hinder or facilitate de-implementation is needed. In particular knowledge is needed on how to tailor interventions to determinants (barriers or facilitators) and whether continuously adapting the interventions within a de-implementation strategy is of added value. Regarding future studies evaluating new de-implementation strategies we would like to emphasize the importance of a control group. In this thesis the lack of a control group would have led to reversed results. Instead of concluding that the de-implementation strategy was not effective in reducing low-value care compared to the control group, a great reduction in low-value care would have been observed in the intervention group.

Furthermore, we observed that de-implementation of a low-value technique is facilitated by the introduction of a substitute, a new or different technique, such as the use of TXA and LIA in this thesis. From literature it is known that, once established, it can be very difficult to discontinue low-value clinical practices.[5,46,48] As de-implementation of low-value care is essential to improve the quality of care for patients and reduce the ever increasing healthcare costs, it is very important to identify more relevant factors, such as substitution, that facilitate de-implementation. In addition to this, more knowledge is needed on the differences and similarities of implementation vs. de-implementation on the specific personal and contextual factors involved.[5,45] The development of systematic approaches or models for de-implementation would be very useful.

References

1. Grol R, Wensing M, Eccles M. Improving Patient Care: The Implementation of Change in Clinical Practice. Oxford: Elsevier 2005.
2. Francis JJ, Stockton C, Eccles MP, et al. Evidence-based selection of theories for designing behaviour change interventions: using methods based on theoretical construct domains to understand clinicians' blood transfusion behaviour. Br J Health Psychol. 2009;14(Pt 4):625-646.
3. Michie S, Johnston M, Abraham C, et al. Making psychological theory useful for implementing evidence based practice: a consensus approach. Qual Saf Health Care. 2005;14(1):26-33.
4. Michie S, Johnston M, Francis JJ, et al. From Theory to Intervention: Mapping Theoretically Derived Behavioural Determinants to Behaviour Change Techniques. Applied Psychology:An International Review. 2008;57(4):660-680.
5. Niven DJ, Mrklas KJ, Holodinsky JK, et al. Towards understanding the de-adoption of low-value clinical practices: a scoping review. BMC Med. 2015;13:255.
6. Roumie CL, Grogan EL, Falbe W, et al. A three-part intervention to change the use of hormone replacement therapy in response to new evidence. Ann Intern Med. 2004;141(2):118-125.
7. Andreasen JJ, Sindby JE, Brocki BC, et al. Efforts to change transfusion practice and reduce transfusion rates are effective in coronary artery bypass surgery. J Cardiothorac Vasc Anesth. 2012;26(4):545-549.
8. Krol N, Wensing M, Haaijer-Ruskamp F, et al. Patient-directed strategy to reduce prescribing for patients with dyspepsia in general practice: a randomized trial. Alimentary pharmacology & therapeutics. 2004;19(8):917-922.
9. Kulawik D, Sands JJ, Mayo K, et al. Focused vascular access education to reduce the use of chronic tunneled hemodialysis catheters: results of a network quality improvement initiative. Seminars in dialysis. 2009;22(6):692-697.
10. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2012;4:CD002042.
11. Salpeter SR, Buckley JS, Chatterjee S. Impact of More Restrictive Blood Transfusion Strategies on Clinical Outcomes: A Meta-analysis and Systematic Review. The American Journal of Medicine. 2014;127(2):124-131.
12. Adams RC, Lundy JS. Anesthesia in cases of poor surgical risks. Some suggestions for decreasing the risk. Surg Gynecol Obstet. 1942;74:1011-1019.
13. Tsuno NH, Nagura Y, Kawabata M, et al. The current status of autologous blood transfusion in Japan--the importance of pre-deposit autologous blood donation program and the needs to achieve patient blood management. Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis. 2013;49(3):673-680.
14. Tinmouth A, Thompson T, Arnold DM, et al. Utilization of frozen plasma in Ontario: a provincewide audit reveals a high rate of inappropriate transfusions. Transfusion. 2013;53(10):2222-2229.
15. Oddason KE, Gudbjartsson T, Gudmundsson S, et al. [Inappropriate use of blood components in critical care?]. Laeknabladid. 2014;100(1):11-17.
16. Abbas K, Askari R, Umer M, et al. Transfusion practice in orthopedic patients: do we really need it? JPMA The Journal of the Pakistan Medical Association. 2014;64(12 Suppl 2):S144-150.
17. Zhu C, Gao Y, Li Z, et al. A Systematic Review and Meta-Analysis of the Clinical Appropriateness of Blood Transfusion in China. Medicine (Baltimore). 2015;94(50):e2164.
18. Alcorn K, Ramsey G, Souers R, et al. Appropriateness of Plasma Transfusion: A College of American Pathologists Q-Probes Study of Guidelines, Waste, and Serious Adverse Events. Arch Pathol Lab Med. 2017;141(3):396-401.
19. Sadeghi A, Belali S, Ali Asgari A, et al. Inappropriate Packed RBC Transfusion in a Tertiary Care Center. Archives of Iranian medicine. 2017;20(2):83-85.
20. Banks AAoB. Choosing Wisely - Five Things Physicians and Patients Should Question Available: http://www.choosingwisely.org/societies/american-association-of-blood-banks/. Accessed August 2017.
21. National comparative audit of blood transfusion Available: http://hospital.blood.co.uk/audits/national-comparative-audit/. Accessed August 2017.
22. Murphy MF. The Choosing Wisely campaign to reduce harmful medical overuse: its close association with Patient Blood Management initiatives. Transfus Med. 2015;25(5):287-292.

23. Clement F, Charlton B. Challenges in choosing wisely's international future: support, evidence, and burnout. JAMA Intern Med. 2015;175(4):644-645.
24. Rosenberg A, Agiro A, Gottlieb M, et al. Early Trends Among Seven Recommendations From the Choosing Wisely Campaign. JAMA Intern Med. 2015;175(12):1913-1920.
25. Wilson K, Macdougall L, Fergusson D, et al. The effectiveness of interventions to reduce physician's levels of inappropriate transfusion: what can be learned from a systematic review of the literature. Transfusion. 2002;42(9):1224-1229.
26. Tinmouth A, Macdougall L, Fergusson D, et al. Reducing the amount of blood transfused: a systematic review of behavioral interventions to change physicians' transfusion practices. Arch Intern Med. 2005;165(8):845-852.
27. Voorn VMA, van Bodegom-Vos L, So-Osman C. Towards a systematic approach for (de)implementation of patient blood management strategies. Transfus Med. 2018 Apr;28(2):158-167.
28. Hartley S, Foy R, Walwyn REA, et al. The evaluation of enhanced feedback interventions to reduce unnecessary blood transfusions (AFFINITIE): protocol for two linked cluster randomised factorial controlled trials. Implementation science : IS. 2017;12(1):84.
29. Goodnough LT, Shah N. The next chapter in patient blood management: real-time clinical decision support. Am J Clin Pathol. 2014;142(6):741-747.
30. Butler CE, Noel S, Hibbs SP, et al. Implementation of a clinical decision support system improves compliance with restrictive transfusion policies in hematology patients. Transfusion. 2015;55(8):1964-1971.
31. Borgert M, Binnekade J, Paulus F, et al. Implementation of a transfusion bundle reduces inappropriate red blood cell transfusions in intensive care - a before and after study. Transfusion medicine (Oxford, England). 2016;26(6):432-439.
32. Smith M, Triulzi DJ, Yazer MH, et al. Implementation of a simple electronic transfusion alert system decreases inappropriate ordering of packed red blood cells and plasma in a multi-hospital health care system. Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis. 2014;51(3):53-58.
33. Yerrabothala S, Desrosiers KP, Szczepiorkowski ZM, et al. Significant reduction in red blood cell transfusions in a general hospital after successful implementation of a restrictive transfusion policy supported by prospective computerized order auditing. Transfusion. 2014;54(10 Pt 2):2640-2645.
34. Norgaard A, Stensballe J, de Lichtenberg TH, et al. Three-year follow-up of implementation of evidence-based transfusion practice in a tertiary hospital. Vox Sang. 2017;112(3):229-239.
35. Freedman J, Luke K, Escobar M, et al. Experience of a network of transfusion coordinators for blood conservation (Ontario Transfusion Coordinators [ONTraC]). Transfusion. 2008;48(2):237-250.
36. King R, Michelman M, Curran V, et al. Patient-centered approach to ensuring appropriateness of care through blood management. Southern medical journal. 2013;106(6):362-368.
37. Watson S, Kendrick K. Management of anaemia and blood transfusion in critical care - implementing national guidelines in ICU. BMJ quality improvement reports. 2014;3(1).
38. Tavares MM, Diquattro PJ, Sweeney JD. Reduction in red blood cell transfusion associated with engagement of the ordering physician. Transfusion. 2014;54(10 Pt 2):2625-2630.
39. Hicks CW, Liu J, Yang WW, et al. A comprehensive Choosing Wisely quality improvement initiative reduces unnecessary transfusions in an Academic Department of Surgery. Am J Surg. 2017 Oct;214(4):571-576.
40. Patel VM, Rains AW, Clark CT. Effectiveness of Provider Education Followed by Computerized Provider Order Entry Alerts in Reducing Inappropriate Red Blood Cell Transfusion. Journal of blood transfusion. 2016;2016:2859720.
41. Boral LI, Bernard A, Hjorth T, et al. How do I implement a more restrictive transfusion trigger of hemoglobin level of 7 g/dL at my hospital? Transfusion. 2015;55(5):937-945.
42. Yazer MH, Waters JH. How do I implement a hospital-based blood management program? Transfusion. 2012;52(8):1640-1645.
43. Baker R, Camosso-Stefinovic J, Gillies C, et al. Tailored interventions to address determinants of practice. The Cochrane database of systematic reviews. 2015(4):Cd005470.
44. Wensing M. The Tailored Implementation in Chronic Diseases (TICD) project: introduction and main findings. Implementation science : IS. 2017;12(1):5.
45. van Bodegom-Vos L, Davidoff F, Marang-van de Mheen PJ. Implementation and de-implementation: two sides of the same coin? BMJ Qual Saf. 2017 Jun;26(6):495-501.
46. Ubel PA, Asch DA. Creating value in health by understanding and overcoming resistance to de-innovation. Health Aff (Millwood). 2015;34(2):239-244.

47. Roman BR, Asch DA. Faded promises: the challenge of deadopting low-value care. Ann Intern Med. 2014;161(2):149-150.
48. Davidoff F. On the undiffusion of established practices. JAMA Intern Med. 2015;175(5):809-811.
49. Willson A. The problem with eliminating 'low-value care'. BMJ Qual Saf. 2015;24(10):611-614.
50. Fleuren M, Wiefferink K, Paulussen T. Determinants of innovation within health care organizations: literature review and Delphi study. International journal for quality in health care : journal of the International Society for Quality in Health Care. 2004;16(2):107-123.
51. Graham ID, Logan J, Harrison MB, et al. Lost in knowledge translation: time for a map? The Journal of continuing education in the health professions. 2006;26(1):13-24.
52. Helfrich CD, Rose AJ, Hartmann CW, et al. How the dual process model of human cognition can inform efforts to de-implement ineffective and harmful clinical practices: A preliminary model of unlearning and substitution. Journal of evaluation in clinical practice. 2018;24(1):198-205.

Nederlandse samenvatting

Bij het plaatsen van een primaire totale heup- of knieprothese (THP en TKP) bestaat er risico op groot bloedverlies. Om de kans op een bloedtransfusie te verkleinen, worden bij deze ingrepen diverse bloed besparende maatregelen ingezet, waaronder het gebruik van re-infusie systemen of het preoperatief toedienen van erytropoëtine (EPO). Bij het gebruik van een re-infusie systeem wordt tijdens (intra-operatief) en/of na de operatie (post-operatief) bloed van de patiënt uit de operatiewond met een drain opgevangen en teruggegeven. Het preoperatief toedienen van EPO heeft als doel om voorafgaand aan een operatie het hemoglobine gehalte in het bloed van de patiënt te optimaliseren. Uit onderzoek is echter gebleken dat deze twee maatregelen beschouwd kunnen worden als 'low-value care'. Het gebruik van re-infusie systemen draagt namelijk niet bij aan het verkleinen van de kans op een transfusie met donorbloed (homologe transfusie), en de voordelen van het gebruik van EPO wegen niet op tegen de hoge kosten die het gebruik met zich mee brengen.

Dit proefschrift beschrijft de stapsgewijze de-implementatie (stoppen of verminderen van low-value care) van re-infusie systemen en EPO bij patiënten die een THP of TKP krijgen volgens de stappen uit het implementatiemodel van Grol:

1. Ontwikkeling van concrete doelen voor de-implementatie.
2. Analyse van het huidige gebruik van bloed besparende maatregelen in Nederland en barrières voor de-implementatie.
3. Ontwikkeling van een strategie voor de de-implementatie van bloed besparende maatregelen.
4. Uitvoering ontwikkelde de-implementatie strategie.
5. Evaluatie ontwikkelde de-implementatie strategie.

De ontwikkeling van concrete doelen voor de-implementatie (stap 1)

In de eerste stap zijn concrete doelen ontwikkeld voor de de-implementatie van re-infusie-systemen en EPO bij patiënten die een THP of TKP operatie zullen ondergaan. Om deze doelen vast te stellen, is eerst het wetenschappelijke bewijs over de effectiviteit van het gebruik van re-infusie systemen en EPO bij THP en TKP systematisch verzameld en geëvalueerd.

Hoofdstuk 2 beschrijft een systematisch literatuuronderzoek met een meta-analyse over re-infusie systemen bij THP en TKP patiënten. Het doel van dit literatuuronderzoek was het vaststellen van de effectiviteit van re-infusiesystemen op de vermindering van homologe bloedtransfusies, met een aparte analyse voor THP en TKP patiënten. Daarnaast werd ook onderzocht of resultaten van recente onderzoeken de conclusies van eerder uitgevoerde meta-analyses veranderen. We includeerden 43 gerandomiseerde onderzoeken (5631

patiënten). De resultaten lieten zien dat re-infusiesystemen zorgen voor een vermindering van patiënten blootgesteld aan homologe transfusies bij THP en TKP patiënten. Echter, onderzoeken met een laag risico op bias die werden gepubliceerd tussen 2010 en 2012 lieten geen effect zien van het gebruik van re-infusie systemen op het aantal THP en TKP patiënten met transfusie of het volume van bloed dat patiënten toegediend kregen. Deze resultaten suggereren dat er veranderingen in de zorg hebben plaatsgevonden, zoals de introductie van meer restrictieve transfusiegrenzen, het bewustzijn t.a.v. perioperatief bloedverlies, verbeterde chirurgische technieken en de introductie van nieuwe maatregelen om bloedverlies te beperken, terwijl de indicatie om een re-infusie systeem te gebruiken niet veranderd is.

Hoofdstuk 3 geeft een overzicht van de resultaten van een systematisch literatuuronderzoek met een meta-analyse over EPO bij THP en TKP patiënten. Het doel van dit literatuuronderzoek was het vaststellen van de effectiviteit van EPO op het verminderen van homologe bloedtransfusies, apart voor THP en TKP patiënten. Daarnaast evalueerden we de veiligheid en kosten. We includeerden zeven gerandomiseerde onderzoeken (2439 patiënten). Het bleek dat EPO de blootstelling aan transfusies bij zowel THP als TKP patiënten verminderde en ook het volume bloed dat patiënten toegediend kregen afnam. We vonden geen verschillen in het aantal trombo-embolische complicaties of andere nadelige effecten. Slechts één onderzoek evalueerde de kosten waardoor geen gepoolde schattingen gemaakt konden worden. In dit onderzoek waren de additionele kosten bij gebruik van EPO €785 per patiënt of €7300 per voorkomen transfusie (waarbij de kosten in andere zorgsystemen kunnen verschillen). Uiteindelijk bleek EPO effectief en veilig. Echter, de keuze om EPO routinematig te gebruiken moet worden afgewogen tegen de kosten, die erg hoog zijn.

Op basis van de resultaten van hoofdstuk 2 en 3 beschouwen we re-infusiesystemen en EPO als laagwaardige zorg bij patiënten die een primaire THP of TKP krijgen.

Vaststellen van huidig gebruik en barrières voor de-implementatie (stap 2)

In de tweede stap is een probleemanalyse studie uitgevoerd waarin het huidige gebruik van de re-infusie systemen en EPO is vastgesteld en de barrières voor de-implementatie zijn geëxploreerd. Het protocol van deze probleemanalyse beschreven we in **hoofdstuk 4**.

In **hoofdstuk 5** zijn de resultaten beschreven van een survey naar het huidige gebruik van re-infusie systemen en EPO onder de orthopedische afdelingen van alle Nederlandse ziekenhuizen en privé klinieken. Respondenten rapporteerden op een 5-punts schaal (nooit, bijna nooit, regelmatig, bijna altijd, altijd) hoe vaak een techniek op hun afdeling gebruikt

werd. De antwoorden werden opgesplitst in niet-frequent (nooit en bijna nooit) en frequent gebruik (regelmatig, bijna altijd en altijd). De enquête, die door 81 orthopedische afdelingen in Nederland werd ingevuld (responsepercentage 82%), liet zien dat in 2012 25 orthopedische afdelingen (31%) intra-operatieve re-infusie frequent gebruikten, 56 orthopedische afdelingen (69%) postoperatieve re-infusie frequent gebruikten, en 55 afdelingen (68%) EPO nog frequent preoperatief voorschreven. Wanneer de afdelingen vergeleken werden op basis van grootte, werd EPO frequenter gebruikt door grote orthopedische afdelingen ten opzichte van kleine en gemiddeld grote afdelingen. Er werden geen andere verschillen gevonden op basis van de grootte of het type orthopedische afdeling. Op basis van deze enquête werd de doelgroep van frequente gebruikers geïdentificeerd. Deze frequente gebruikers werden uitgenodigd voor deelname aan de cluster-gerandomiseerde studie.

In **hoofdstuk 6** evalueerden we of specifieke uitkomstmaten met betrekking tot bloedmanagement bij THP en TKP geschikt zijn om de kwaliteit van zorg te vergelijken tussen ziekenhuizen. Met andere woorden, we evalueerden of het betrouwbaar is om ziekenhuizen te rangschikken op de uitkomstmaten: 'homologe bloed transfusies' en 'verlengde opnameduur' (gedefinieerd als een postoperatief verblijf >4 dagen) bij THP en TKP patiënten. Hiervoor beoordeelden we welk deel van de geobserveerde variatie tussen ziekenhuizen verklaard wordt door 'echte' ziekenhuisverschillen en welk deel door ruis. Verder evalueerden we welke factoren geassocieerd zijn met de gevonden ziekenhuisverschillen. Om deze evaluaties uit te voeren werden eerst de ziekenhuizen gerangschikt op basis van de Observed/Expected (O/E) ratio voor de uitkomstmaten 'homologe transfusies' en 'verlengde opnameduur'. De geobserveerde variatie tussen ziekenhuizen werd geëvalueerd door het berekenen van de 'rankability', een maat die de betrouwbaarheid van rangschikken aangeeft. Patiëntendossiers van 1163 THP en 986 TKP patiënten uit 23 ziekenhuizen werden geanalyseerd. De rankability, uitgedrukt in een percentage van de variatie verklaard door ziekenhuis verschillen ten opzichte van random variatie, was laag voor de uitkomst homologe transfusie (21% in THP en 34% in TKP). De variatie verklaard door ziekenhuisverschillen voor de uitkomst verlengde opnameduur was hoger (71% in THP en 78% in TKP). De betrouwbaarheid van rangschikken op basis van verlengde opnameduur was daarom groter dan bij homologe transfusies. Ziekenhuizen die gebruik maken van lokale infiltratie analgesie en tranexaminezuur hadden relatief minder patiënten met transfusies en verlengde opnameduur. Het gebruik van lokale infiltratie analgesie en tranexaminezuur werden daarom geassocieerd met betere prestaties van ziekenhuizen.

In **hoofdstuk 7** werd een gecombineerde kwalitatieve-kwantitatieve studie uitgevoerd om relevante barrières voor de-implementatie van re-infusie systemen en EPO in kaart te brengen. We voerden semigestructureerde interviews uit onder 10 orthopedisch chirurgen

en 10 anesthesiologen om op grond van de bevindingen een vragenlijst op te kunnen stellen. Deze vragenlijst werd vervolgens door 153 orthopedisch chirurgen (responspercentage 40%) en 100 anesthesiologen (responspercentage 27%) ingevuld. De resultaten van dit vragenlijstonderzoek lieten zien dat de intentie om met het gebruik van re-infusie drains te stoppen samenhing met barrières op het gebied van 'sociale invloeden', 'motivatie en doelen', 'overtuigingen over de gevolgen' en 'kennis'. De intentie om te stoppen met voorschrijven van EPO hing samen met barrières op het gebied van 'sociale invloeden', 'motivatie en doelen' en 'overtuigingen over de gevolgen'.

Ontwikkeling van een de-implementatie strategie om de praktijk te veranderen (stap 3)

Volgend op de analyse van het huidige gebruik en de barrières voor de-implementatie is een strategie ontwikkeld om het gebruik van re-infusie systemen en EPO bij primaire electieve THP en TKP te verminderen.

Hoofdstuk 8 beschrijft de ontwikkelde strategie, welke uit de volgende 4 onderdelen bestond:

1) Verspreiding van de bewijslast t.a.v. het gebruik van re-infusiesystemen en EPO aan alle partijen die betrokken zijn bij het gebruik van re-infusie systemen en EPO (vb. ziekenhuisapothekers, inkopers).

2) Een interactieve educatie voor orthopedisch chirurgen en anesthesiologen. Tijdens deze educatie werd een overzicht gegeven van de literatuur over het gebruik van re-infusie systemen en EPO bij THP en TKP. Daarnaast ontvingen de deelnemers van de educatie een zakkaartje met daarop de belangrijkste conclusies t.a.v. gebruik van re-infusie systemen en EPO bij THP en TKP.

3) Feedback over het gebruik van re-infusie systemen en EPO en bijbehorende uitkomsten op patiëntniveau (tweemaal aan het begin van het de-implementatie project, en nog een keer halverwege).

4) Een benchmark van de resultaten tussen deelnemende ziekenhuizen en twee 'best practice' ziekenhuizen (Nederlandse ziekenhuizen waar geen re-infusie systeem of EPO gebruikt werd). Met deze benchmark werd beoogd de deelnemers te laten zien dat het veilig is om geen re-infusie systemen en EPO te gebruiken, omdat patiënten uitkomsten vergelijkbaar waren met betrekking tot het aantal homologe bloed transfusies, de opnameduur en het postoperatieve hemoglobine gehalte.

De uitvoering en evaluatie van de ontwikkelde de-implementatie strategie (Stap 4 en 5)

De ontwikkelde de-implementatie strategie werd door middel van een effect- en procesevaluatie geëvalueerd in een multicenter cluster-gerandomiseerde gecontroleerde studie. Deze studie is beschreven in **Hoofdstuk 9.** Voor de effectevaluatie werd de blootstelling aan re-infusie systemen en EPO vooraf en nadat de de-implementatie strategie was uitgevoerd gemeten. Door randomisatie werd bepaald welke ziekenhuizen werden blootgesteld aan de strategie en welke ziekenhuizen de controle groep vormden, waar geen interventie plaats vond. We includeerden 21 ziekenhuizen. Voorafgaand aan het uitvoeren van de de-implementatie strategie werden de gegevens van 924 patiënten interventie ziekenhuizen en 1040 patiënten in controle ziekenhuizen geanalyseerd. Na de de-implementatie strategie werden de gegevens van 997 patiënten in interventie ziekenhuizen en 1096 in controle ziekenhuizen geanalyseerd. Het gebruik van re-infusie systemen en EPO daalde significant over tijd, echter er was geen verschil tussen de interventie en controle ziekenhuizen. Na afloop van de de-implementatie strategie hadden patiënten in de interventie ziekenhuizen gemiddeld een hoger postoperatief hemoglobine gehalte en een kortere opname duur vergeleken met de controle ziekenhuizen. Blootstelling aan homologe transfusie bleef gelijk. In de proces evaluatie viel op dat het gebruik van lokale infiltratie analgesie en tranexaminezuur sterk geassocieerd was met de vermindering van het gebruik van een re-infusiesysteem. Dit laatste suggereert dat de de-implementatie werd bevorderd door gebruik te maken van een vervangende techniek.

Conclusies en discussie

Het onderzoek beschreven in dit proefschrift is één van de eerste studies waarin getracht is om (1) systematisch 'low-value care' te de-implementeren met een 'op-maat' ontwikkelde strategie en (2) de resultaten hiervan door middel van gedegen onderzoek te evalueren. Het onderzoek liet zien dat een 'op-maat' gemaakte strategie niet zonder meer succesvol is. Er werd over de tijd zowel in de ziekenhuizen die blootgesteld werden aan de de-implementatie strategie als in de ziekenhuizen in de controle groep een afname gevonden in het gebruik van re-infusie systemen en EPO. Daarnaast bleek dat de-implementatie van re-infusie systemen samenging met een toename in het gebruik van een substituut, zoals lokale infiltratie analgesie en tranexaminezuur. Deze bevinding kan een ingang zijn voor toekomstig onderzoek dat zal moeten uitwijzen of en in welke gevallen substitutie een effectieve strategie voor de-implementatie kan zijn. Omdat de-implementatie essentieel is om de kwaliteit van zorg te verbeteren en de kosten in de zorg te drukken is het erg belangrijk dat er nieuwe studies komen om onder meer de verschillen tussen implementatie en de-implementatie verder in kaart te brengen, om essentiële factoren die de-

implementatie belemmeren te identificeren en meer inzicht te krijgen in effectieve strategieën voor de reductie van 'low-value care'. Bij dit toekomstige onderzoek zijn sterke studie designs, met een controle groep, van groot belang. Hierbij ligt wel het risico van contaminatie van de controle groep op de loer, echter andere ontwikkelingen die niet gemeten worden tijdens de uitvoering van een de-implementatie strategie en het voorbijgaan van tijd kunnen een belangrijke invloed hebben op de resultaten. In dit proefschrift zou het ontbreken van een controlegroep immers geresulteerd hebben in de onterechte conclusie dat de de-implementatie strategie geleid had tot een significante afname van het gebruik van re-infusie drains en EPO in THA en TKA.

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Curriculum Vitae

Veronique Maria Anna Voorn werd geboren op 26 februari 1987 te Zevenhoven. Zij groeide hier op en behaalde in 2005 haar VWO diploma aan het Alkwin Kollege te Uithoorn. Vanaf 2005 startte zij met de studie geneeskunde aan de Universiteit Leiden die zij in december 2011 afsloot. Tijdens haar studie deed ze haar wetenschapsstage onder supervisie van Prof. dr T.P.M. Vliet Vlieland en dr. H.M.J. van der Linden. Deze wetenschapsstage was de opstap naar dit proefschrift.

Na haar afstuderen startte Veronique als onderzoeker op de afdeling medische besliskunde in het Leids Universitair Medisch Centrum (LUMC). Het onderzoek concentreerde zich op de de-implementatie van kosteneffectief bloedmanagement bij heup en knieprotheses en werd uitgevoerd onder supervisie van Prof. dr. R.G.H.H. Nelissen, Prof. dr. T.P.M. Vliet Vlieland en dr. L. van Bodegom – Vos. Tijdens deze periode was zij ook een dagdeel per week actief als arts-assistent op de poli orthopedie van het LUMC.

Na een periode van fulltime promotieonderzoek vervolgde Veronique haar loopbaan als arts. Dit deed zij als arts-assistent niet in opleiding op de afdeling orthopedie in het Groene Hart Ziekenhuis te Gouda en in het Medisch Centrum Leeuwarden. Vanaf januari 2019 is Veronique gestart met haar opleiding tot orthopedisch chirurg. Dit doet zij in het Ikazia Ziekenhuis te Rotterdam op de afdeling chirurgie onder supervisie van dr. P.T. den Hoed. Zij zal haar opleiding vervolgen in het Elisabeth-TweeSteden Ziekenhuis te Tilburg onder supervisie van dr. T. Gosens en in het Erasmus Medisch Centrum te Rotterdam onder supervisie van dr. P.K. Bos.

Bibliography

Publications

• **V.M.A. Voorn**, L. van Bodegom-Vos, C. So-Osman, 'Towards a systematic approach for (de)implementation of patient blood management strategies' Transfus Med. 2018 Apr;28(2):158-167

• **V.M.A. Voorn**, P.J. Marang-van de Mheen, A. van der Hout, S.N. Hofstede, C. So-Osman, M.E. van den Akker-van Marle, A.A. Kaptein, T. Stijnen, A.W.M.M. Koopman-van Gemert, T.P.M.M. Vliet Vlieland, R.G.H.H. Nelissen, L. van Bodegom-Vos, 'The effectiveness of a de-implementation strategy to reduce low-value blood management techniques in primary hip- and knee arthroplasty: a pragmatic cluster randomized controlled trial' Implement Sci. 2017 May 30;12(1):72

• **V.M.A. Voorn**, P.J. Marang-van de Mheen, A. van der Hout, C. So-Osman, M. E. van den Akker-van Marle, A.W.M.M. Koopman-van Gemert, A. Dahan, T.P.M. Vliet Vlieland, R.G.H.H. Nelissen, L. van Bodegom-Vos 'Hospital variation in allogeneic transfusion and extended length of stay in primary elective hip and knee arthroplasty' BMJ Open. 2017 Jul 20;7(7):e014143

• **V.M.A. Voorn**, A. van der Hout, C. So-Osman, T.P.M. Vliet Vlieland, R.G.H.H. Nelissen, M. E. van den Akker-van Marle, A. Dahan, P.J. Marang-van de Mheen, L. van Bodegom-Vos 'Erythropoietin to reduce allogeneic red blood cell transfusion in patients undergoing total hip or knee arthroplasty' Vox Sang. 2016 Oct;111(3):219-225

• L.M. Kok, B.M.A. Huisstede, **V.M.A. Voorn**, J.W. Schoones, R.G.H.H. Nelissen 'The occurrence of musculoskeletal complaints among professional musicians, a systematic review' Int Arch Occup Environ Health. 2016 Apr;89(3):373-96

• L. van Bodegom-Vos, **V.M.A. Voorn**, C. So-Osman, T.P.M. Vliet Vlieland, A. Dahan, A.W.M.M. Koopman-van Gemert, S.B. Vehmeijer, R.G.H.H. Nelissen, P.J. Marang-van de Mheen 'Cell Salvage in Hip and Knee Arthroplasty: A Meta-Analysis of Randomized Controlled Trials' J Bone Joint Surg Am. 2015 Jun 17;97(12):1012-21

• **V.M.A. Voorn**, P.J. Marang van de Mheen, C. So - Osman, A.A. Kaptein, A. van der Hout, M.E. van den Akker - van Marle, A.W.M.M. Koopman - van Gemert, A. Dahan, R.G.H.H. Nelissen, T.P.M. Vliet Vlieland, L. van Bodegom - Vos 'De-implementation of expensive blood saving measures in hip and knee arthroplasties: study protocol for the LISBOA-II cluster randomized trial' Implement Sci 2014, 9:48

• **V.M.A. Voorn**, P.J. Marang - van de Mheen, M.M. Wentink, A.A. Kaptein, A.M.M. Koopman - van Gemert, C. So - Osman, T.P.M. Vliet Vlieland, R.G.H.H. Nelissen, L. van Bodegom - Vos 'Perceived barriers among physicians for stopping non–cost-effective blood-saving measures in total hip and total knee arthroplasties' TRANSFUSION 2014;54:2598-2607.

• **V.M.A. Voorn**, P.J.M. Marang - van de Mheen, M.M. Wentink, C. So - Osman, T.P.M. Vliet Vlieland, A.W.M.M. Koopman - van Gemert, R.G.H.H. Nelissen, L. Van Bodegom - Vos and the LISBOA study group 'Frequent use of blood-saving measures in elective orthopaedic surgery: a 2012 Dutch blood management survey' BMC Musculoskelet Disord. 2013 Aug 5;14:230.

• **V.M.A. Voorn**, H.M. Vermeulen, R.G.H.H. Nelissen, M. Kloppenburg, T.W.J. Huizinga, N.A.C. Leijerzapf, H.M. Kroon, T.P.M. Vliet Vlieland, H.M.J. van der Linden 'An innovative care model coordinated by a physical therapist and nurse practitioner for osteoarthritis of the hip and knee in specialist care: a prospective study' Rheumatol Int. 2013 Jul;33(7):1821-8

• **V.M.A. Voorn**, P.J. Marang - van de Mheen, C. So - Osman, T.P.M. Vliet Vlieland, A.W.M.M. Koopman - van Gemert, R.G.H.H. Nelissen, L. van Bodegom - Vos 'Designing a strategy to implement cost-effective blood transfusion management in elective hip and knee arthroplasties: A study protocol.' Implement Sci 2012; 7(1): 58.

Presentations

• **V.M.A. Voorn**, P.J. Marang-van de Mheen, A. van der Hout, C. So-Osman, M. E. van den Akker-van Marle, A.W.M.M. Koopman-van Gemert, A. Dahan, T.P.M. Vliet Vlieland, R.G.H.H. Nelissen, L. van Bodegom-Vos, 'Hospital variation in allogeneic transfusion and length of stay in primary elective hip and knee arthroplasty' European Orthopaedic Research Society (EORS) Annual meeting, Bristol, United Kingdom, 2015 (Oral presentation)

• **V.M.A. Voorn**, C. So-Osman, M.M. Wentink, T.P.M. Vliet Vlieland, R.G.H.H. Nelissen, A.W. Koopman-van Gemert, P.J. Marang-van de Mheen, L. van Bodegom-Vos, 'De-implementation of non-cost-effective blood saving measures in orthopedic practice' European Federation of National Associations of Orthopaedics and Traumatology (EFORT) annual congress, Istanbul, Turkey, 2013 (Oral presentation)

• **V.M.A. Voorn**, C. So-Osman, T.P.M. Vliet Vlieland, R.G.H.H. Nelissen, A.W. Koopman-van Gemert, P.J. Marang-van de Mheen, L. van Bodegom-Vos, 'De-implementation of non-cost-effective blood saving measures in orthopedic practice' International Society of Blood Transfusion (ISBT) bi-annual congress, Cancun, Mexico, 2012 (Oral presentation)

• **V.M.A. Voorn**, H.M. Vermeulen, N. Leyerzapf, T.P.M. Vliet Vlieland, G. Kloppenburg, H.M.J. van der Linden, R.G.H.H. Nelissen, Advies Behandel Centrum (ABC) Artrose: een prospectieve studie naar resultaten en tevredenheid. NOV najaarsdagen, Noordwijk, 2011 (Oral presentation)

• **V.M.A Voorn**, H.M. Vermeulen, N.A.C. Leyerzapf, R.G.H.H. Nelissen, M. Kloppenburg, T.W.J. Huizinga, T.P.M. Vliet Vlieland, H.M.J. van der Linden 'An innovative care model executed by a physical therapist and clinical nurse specialist for osteoarthritis of hip and knee in specialist care, a prospective study' European League Against Rheumatism (EULAR) annual European congress, London, United Kingdom, 2011 (Poster presentation)