Chapter 1

General Introduction

Current transfusion alternatives in elective orthopaedic surgery

Total hip and knee prosthesis surgery is performed worldwide about two million times annually (approximately 50.000 in the Netherlands). These surgeries may result in significant intra- and postoperative blood loss (800 to1500mL) with a potential need for allogeneic Red Blood Cell (RBC) transfusions to compensate for the resulted anaemia. Although blood transfusions are relatively safe, transfusion reactions such as fever, haemolysis, antibody formation, Transfusion Associated Circulatory Overload (TACO), Transfusion Related Acute Lung Injury (TRALI), or transmission of infectious agents may occur. Furthermore, Natural Killer (NK) activity was found to be decreased in patients after an allogeneic RBC transfusion compared to no RBC transfusion or peri-operative autologous wound blood re-infusion [1]. It has been postulated that, immuno-modulatory effects of blood transfusions may result in an increased susceptibility for infections in the postoperative period [2-7]. In the field of orthopaedic surgery, there is an ongoing trend to aim for optimal Patient Blood Management (PBM). PBM is a new concept in Transfusion Medicine that is based on three approaches (pillars): 1. optimising the patient's own blood; 2. minimising surgical blood loss and bleeding; and 3. harnessing and optimising the patient-specific physiological reserve of anaemia (including restrictive transfusion thresholds) (http://www.health.wa.gov.au/bloodmanagement/home.health_professionals.cfm). This approach includes pre-operative, intra-operative and post-operative strategies for managing the patient, such as alternatives for RBC transfusions, but also surgical and anaesthesiological strategies. A comprehensive overview of blood conservation strategies in major orthopaedic surgery in the European setting is published in 2009 by Munoz et al [8]. In this overview, several of these strategies are discussed, such as correction of perioperative anaemia, pharmacological and non-pharmacological measures to reduce blood loss, preoperative autologous donation, and perioperative blood salvage. Based on the efficacy and safety of these strategies in literature, recommendations are offered. However, some recommendations are not supported by a high level of evidence due to a lack of appropriate data.

TRANSFUSION PRACTICE

A large variation in transfusion practice is present. Recently, in the Austrian benchmark study, Gombotz and colleagues found a transfusion rate varying from16 to 85% for patients undergoing primary total hip replacement (THR) and a 12 to 87% transfusion rate for patients undergoing primary total knee replacement (TKR) surgery [9]. The Orthopaedic Surgery Transfusion Haemoglobin European Overview (OSTHEO) study of Rosencher and co-workers assessed standard practice in blood management in six countries in Europe (225 centres, n=3996 patients) and found that, despite existing guidelines, a large percentage (21%) of the pre-transfusion Hb levels were greater than or equal to 10 g/dL and 10% even exceeded the level of 13.0 g/dL [10]. An additional problem is the implementation of

guidelines in daily practice, which is often difficult to achieve. This is not only relevant for implementing transfusion thresholds, but also for the number of transfusions at each event to reach a particular target Haemoglobin (Hb) level. Barr and co-workers investigated red blood cell transfusion practice in Northern Ireland in 2005 and still found a two-unit instead of single-unit transfusion practice in medical and surgery patients (n=1474) [11].

BLOOD TRANSFUSION PROTOCOLS

An important blood saving strategy is the use of a restrictive transfusion protocol. In 1988, the NIH published consensus guidelines for red blood cell transfusions [12]. Since then, several guidelines have been published, recommending that a range of Hb levels between 6 and 10 g/dL can be used, depending on the presence of serious co-morbidity [13-15]. These clinical practice guidelines, however, have based their recommendations on data from published reports on series of patients for whom red cell transfusions were withheld (for instance Jehovah's witnesses), and observational studies, rather than on the results of clinical trials. Since June 2004, the 4-5-6 Flexinorm transfusion trigger (Hb values in mmol/L), based on the NIH guidelines, in surgical setting was recommended in the Dutch national Consensus guideline for Blood Transfusion (CBO) [16]. This transfusion trigger policy is based on parameters as Hb level, age and condition of the patient (ASA criteria). In 2010, a Cochrane review of Carless and co-workers reported on seventeen Randomised Controlled Trials (RCTs) including surgical and medical patients, and concluded that a restrictive transfusion policy can reduce the need of receiving a RBC transfusion (further mentioned as *transfusion avoidance*) with 37% (RR 0.63 [95% CI 0.54 to 0.74]; however with a non-significant mean RBC reduction (further mentioned as *RBC sparing*) of 0.75 RBC unit [95% CI 0.20 to 1.3]). However, methodology was poor and significant heterogeneity between studies was present [17]. Only one study (Lotke 1999) reported on elective orthopaedic surgery patients who also donated pre-operatively 2 units of autologous blood (knee replacement surgery, n=152), which resulted in an increased allogeneic transfusion avoidance of 74% (RR 0.26 [95% CI 0.17 to 0.40]).

CURRENT ALTERNATIVES FOR RED BLOOD CELL TRANSFUSIONS

Many alternatives for an allogeneic RBC transfusion are available. Not all interventions are widely applied in the Netherlands. Next to efficacy, important factors that are of influence are costs and user friendliness. Based on recent randomised controlled studies, the efficacy of the different modalities will be discussed, first in general and in more detail for the elective

orthopaedic surgery patients. These alternatives for an allogeneic blood transfusion can be subdivided in two main groups:

A. Non-pharmacotherapeutical interventions:

1. *pre*-operative alternatives: Preoperative Autologous Donation (PAD)
2. *peri*-operative alternatives:
   a. Acute Normovolaemic Haemodilution (ANH), in which one or several units of whole blood is taken just before surgery and at the same time (=isovolaemic) the lost blood volume is replaced by normal saline or colloids. The retained whole blood is then transfused back to the patient during or after surgery;
   b. use of the cell saver, that collects autologous wound blood *during* (and sometimes *after*) surgery. The shed blood is washed, concentrated and then re-infused.
3. *post*-operative alternatives: devices that collect and re-infuse autologous wound blood *after* surgery (non-washed, filtered by several types of devices) by means of a wound-drainage and re-infusion system.

B. Pharmacotherapeutical interventions

This concerns the pre-operative use of Erythropoietin (Epo) and the peri-operative use of anti-fibrinolytics (e.g. aprotinin, tranexamic acid) and fibrin glue. The use of (intravenous) iron as a new modality will be discussed in chapter eight of this thesis.

CURRENT EVIDENCE ON TRANSFUSION ALTERNATIVES IN THE *GENERAL SURGICAL* POPULATION

Ad A Non-pharmacotherapeutical interventions

A Cochrane review by Henry and co-workers (2010) reported on 13 trials (n=1506) and concluded that **PAD** as a single intervention resulted in a significant transfusion avoidance of 68%. However, autologous donors were more likely to undergo transfusion with allogeneic and/or autologous blood (OR 1.24; 95% CI 1.02 to 1.51). The authors concluded, that overall transfusion rates were very high, raising the question of the true benefit of PAD.

In 2004, two systematic reviews reported on the use of **ANH** in elective surgery [18,19]. Carless and co-workers performed a systematic review on several autologous transfusion techniques (PAD, ANH and cell saver). Of 30 trials, ANH resulted in a significant transfusion avoidance of 31%. Mean RBC use was reported in 7 trials resulting in a significant mean RBC sparing of 1.9 units. However, studies were small, and methodology was judged as poor. Also, the blood sparing effect was less when a transfusion protocol (in 60%) was used. [18] Segal and co-workers compared 42 RCTs on ANH, but did not find a significant reduction in transfusion avoidance compared to controls, and a non-significant increase of 11%

compared to another blood conservation method (mostly PAD). They concluded that use of ANH can not be encouraged [19].

The effect of washed autologous salvaged blood (by means of cell saver) or non-washed salvaged blood (by means of post-operative re-infusion systems) on RBC use was investigated In a Cochrane review [20]: 75 randomised studies up to 1 June 2009 were analysed. The authors concluded a significant overall transfusion avoidance of 38% and mean RBC sparing of 0.68 RBC unit.

Table 1. Transfusion avoidance and mean Red Blood Cell (RBC) reduction of transfusion alternatives in the general surgical population

Author (year)	Transfusion alternative	% transfusion avoidance	RR [95% CI]	Mean RBC reduction/patient [95% CI]
Henry (2010) [37]#	PAD	68%	0.32 [0.22 to 0.47]	NA
Carless (2004) [18]#	ANH	31%	0.69 [0.56 to 0.84]	1.9 [1.1 to 2.7]
Segal (2004) [19]	ANH	4% (NS)	0.90-1.01 [NA]	NA
Carless (2006) [20]#	Autologous blood salvage	38%	0.62 [0.55 to 0.70]	0.68 [0.49 to 0.88]
Laupacis (1998) [21]	Epo (cardiac surgery)	75%	0.25 [0.08 to 0.82]	NA

#=Cochrane review
Abbreviations: CI=Confidence Interval; PAD=Preoperative Autologous Donation; ANH=Acute Normovolaemic Haemodilution; NA=Not Available; NS=Not Significant; Epo=Erythropoietin.

Ad B Pharmacotherapeutical interventions

In a meta-analysis by Laupacis and co-workers [21] , Epo resulted in a significant transfusion avoidance (with or without the combination with PAD) with the largest effect (75% avoidance) in cardiac surgery patients (Table 1). A systematic review on the use of anti-fibrinolytics for minimising perioperative allogeneic blood transfusion and on their adverse events was published in 2007 and updated in 2011 by Henry and co-workers, comparing aprotinin, TraneXamic Acid (TXA) and Epsilon AminoCaproic Acid (EACA). [22] That review of over 250 clinical trials reported on the use of anti-fibrinolytic drugs in major surgery and found that these reduced bleeding, as well as the need for transfusions of red blood cells. Consequently, the need for revision surgery because of bleeding (in cardiac surgery) was reduced as well. This update was especially focussed on safety, since the results of the BART study (2008), a study in cardiac surgery patients comparing aprotinin to TXA and to EACA, showed that aprotinin was significantly associated with increased mortality compared to the lysine analogoues TXA and EACA. This resulted in abandoning the use of aprotinin in patients [23]. This finding suggests a potential bias of under-reporting adverse events, since

only 18 of 76 trials of aprotinin reported adverse events. Also, more studies with positive effects were published, resulting in asymmetric funnel plots, suggesting publication bias. The explanation for the increased mortality rates after aprotinin in comparison to lysine analogues might be due to a direct adverse effect by aprotinin or due to a protective effect of the lysine analogues. The lysine analogues TXA and EACA appeared to be safe.

Current evidence on transfusion alternatives in *elective hip-and knee replacement surgery* patients

Ad A Non-pharmacotherapeutical interventions:

Ad 1 Preoperative alternatives

Preoperative autologous donation (PAD)

Five trials reported on orthopaedic surgery patients (n=425) and showed a significant transfusion avoidance of 79%. However, autologous orthopaedic donors were more likely to have an increased overall transfusion rate with allogeneic and/or autologous blood (OR 1.78; 95% CI 0.61 to 5.20). In The Netherlands, PAD is predominantly collected at Sanquin Blood Supply (donor centres). Only one hospital, the Sint Maartenskliniek, a specialised orthopaedic centre in Nijmegen, has implemented this procedure as an in-house procedure within their own hospital setting.

The modality of PAD is relatively expensive and complex and needs a fixed surgery date (the patient needs to visit the centre several times to donate blood). In addition, the likelihood for mistakes by switching of blood products is high [24]. The British guidelines only advise PAD in exceptional cases if the normal donor stock is not sufficient as in cases of rare blood group typing and/or antibodies against public antigens etc [25]. The new CBO Guidelines (Richtlijn Bloedtransfusie) 2011 advises a limited use of PAD due to the complex logistics, the relative high costs, the lack of additional safety and the waste of plasma products (side product of PAD) and recommends for it's use for certain indications, like lack of compatible blood units in case of rare blood groups or antibodies to public or multiple red blood cell antigens and the occurrence of former haemolytic transfusion reactions with unknown cause.

Ad 2a Acute Normovolaemic Haemodilution (ANH)

ANH is not often applied in the Netherlands, possibly due to its logistical difficulties. In the two systematic reviews of Carless and Segal, ANH was investigated in 6 and 13 orthopaedic trials, respectively. Both did not report a significant benefit of ANH on transfusion avoidance. Compared to another blood sparing modality (PAD or TXA), ANH was less effective in orthopaedic patients [19]. As a transfusion alternative, ANH is therefore not recommended in knee-and hip surgery.

Ad 2B en 3

Autologous re-infusion (cell saver and post-operative re-infusion systems)

In a Cochrane review [20] evaluating all randomised studies up to 1 June 2009, in which the effect on RBC use of washed shed blood (by means of cell saver) or non-washed shed blood by means of post-operative re-infusion systems was investigated, 36 studies reported on orthopaedic surgery (6 of which had been conducted in the Netherlands). The authors concluded a significant transfusion avoidance of 54% and a significant mean RBC sparing of 0.82 RBC unit per patient as well. The outcomes were similar using washed or non-washed blood. The authors also concluded that the methodological quality was poor and that the findings could have been influenced by bias. There was a lack of concealment, meaning that allocation of the randomisation was not centralised, but often on location by drawing an opaque envelope. This method can be susceptible to bias, because it can not be ruled out that the envelopes are drawn in the proper order [26].

Table 2. Transfusion avoidance and mean red blood cell (RBC) reduction of transfusion alternatives in the elective knee-and hip replacement surgical population

Author (year)	Transfusion alternative	% transfusion avoidance	RR [95% CI]	Mean RBC reduction / patient [95% CI]
Henry (2010) [37]#	PAD	79%	0.21 [0.11 to 0.43]	NA
Carless (2004) [18]#	ANH	21%	0.79 [0.60 to 1.06]	NA
Segal (2004) [19]	ANH	23% to none	0.77 to 1.06 [0.47 to 1.37]	NA
Carless (2006) [20]#	Autologous blood salvage	54%	0.46[0.37 to 0.57]	0.82 [-0.27 to -1.36]
Laupacis (1998) [21]	Epo with PAD	58%	0.42 [0.28 to 0.62]	NA
idem	Epo only	64%	0.36 [0.24 to 0.56]	0.14 [-0.04 to 0.31]
Fergusson (submitted)	Epo	56%	0.44 [0.31 to 0.64]	0.61 [0.22 to 1.01]
Henry (2011) [22]#	APR vs Co (n=1146)	32%	0.68 [0.5 to 0.89]	NA
idem	TXA vs Co (n=1381)	51%	0.49 [0.39-0.62]	NA
idem	EACA vs Co (n=304)	0%	1.00 [0.93 to 1.08]	NA

#=Cochrane review

Abbreviations: APR=APRotinin; PAD=Preoperative Autologous Donation; ANH=Acute Normovolaemic Haemodilution; NA=Not Available; NS=Not Significant; Epo=Erythropoietin; Co=Control group; TXA=TraneXamic Acid; EACA=Epsilon AminoCaproic Acid

Ad B. Pharmacotherapeutical interventions

Erythropoietin (Epo)

Many randomised studies have been published in which the effect of Epo on RBC use has been investigated. Older studies report on the effect of Epo on the efficacy of donating PAD. In a meta-analysis by Laupacis et al [21] , in orthopaedic surgery, Epo resulted in a significant transfusion avoidance of 58% with or 64% without the combination with PAD (11 trials with PAD and 3 trials without PAD), but Epo did not significantly reduce the mean RBC use. The main reason for this finding was the low mean number of transfusions in the control group (0.46 RBC unit/patient), and a subsequent non-significant decrease of 0.14 RBC unit per patient after use of Epo. This finding was confirmed by a large European randomised study (n=695) (the EEST study) by Weber and colleagues [27], who found a proportion of 12% transfused patients in the Epo group which was significantly lower than the 46% transfused patients of the control group ($p<0.001$), but found a non-significant difference in mean RBC use (1.25 RBC/patiënt [SD 0.51] versus 1.42 RBC/patiënt [SD 0.70], respectively; $p=0.14$). A recent meta-analysis by Fergusson and co-workers performed on elective orthopaedic surgery studies until August 2007 (submitted) resulted in 36 evaluable RCTs of which Epo dose varied (>1800 UI/kg or <1800 UI/kg), as well as time of administration (pre-or postoperatively), use of PAD, route of Epo administration (subcutaneously or intravenously) and use of a transfusion threshold (in 15 trials not reported). Overall, compared to the control group, a significant RBC avoidance of 56% was found as well as a significant RBC sparing of 0.61 RBC unit. The aggregated risks of DVT was 3.5%, and 0.20% of myocardial infarction (MI), 0.29% of stroke, 0.15% of PE and 0.13% of death. It was concluded that Epo was a safe blood sparing modality in orthopaedic surgery, however, Epo exceeds the costs of an allogeneic blood transfusion [28,29].

Anti-fibrinolytics

Since trials on anti-fibrinolytics comprised mostly cardiac surgery patients, which are rather different from orthopaedic surgery patients, outcome on RBC use may be quite different between these study populations. The results of trials on orthopaedic surgery patients are discussed here, and when possible, separately reported:

1. Interventional drug versus control group

Of 108 trials of **aprotinin** compared with a control group, 15 were conducted in orthopaedic surgery with a total of 1146 patients. In these patients, the use of aprotinin resulted in a significant transfusion avoidance of 32%, however studies were heterogeneous ($p<0.001$). Total blood loss was also reduced by around 400 mL (Mean difference -399 mL [-563 to -235 mL]) (n=430; 10 studies), heterogeneity was again significant ($p<0.007$). Compared to controls, the use of aprotinin (pooled data) did not result in increased risk for mortality nor

in an increased risk for myocardial infarction or for thrombotic events (stroke, deep vein thrombosis or pulmonary embolus).

Of 65 reported trials on **TXA** compared with controls, 27 involved orthopaedic surgery (n=1381 patients), where a significant transfusion avoidance of 51% was found (RR 0.49, however heterogeneity between trials was present (p<0.0007). Total blood loss was significantly reduced by 446 mL [95% CI of mean difference 338 to 555 mL], also with heterogeneity between trials (p<0.00001).Compared to controls, the use of TXA (pooled data) did not result in increased mortality risk nor increased risk of myocardial infarction or thrombotic events (stroke, deep vein thrombosis or pulmonary embolus).

Of 16 reported trials of **EACA** compared with controls, four trials involved orthopaedic surgery (n=304 patients) of which the use of EACA did not reduce the need for allogeneic RBC transfusions. Two trials reported a marginally effective reduction in total blood loss of 300 mL [95% CI of mean difference 77 to 523 mL]. Mortality risk, risk of myocardial infarction, and thrombotic events were not increased.

2. Comparison between anti-fibrinolytics

A. Aprotinin versus TXA

Of 21 trials on aprotinin versus TXA that reported data on the number of patients exposed to allogeneic RBC transfusions, only one study [30] was performed in orthopaedic surgery patients (knee replacement surgery; n=36). The study consisted of three groups of 12 patients: controls versus TXA versus aprotinin, respectively) and showed no difference in the transfusion rate between all three groups. No adverse outcomes were reported other than deep venous thromboses (n=2 in TXA group, n=1 in aprotinin group and n=0 in control group).

B. Aprotinin versus EACA

Of 12 reported trials, three (Amar 2003;n=69 spine, Ray 2005; n=45 hip, Urban 2001; n=60 spine) were in orthopaedic surgery patients: no significant transfusion avoidance was found with aprotinin compared to EACA (RR 0.82; 95% CI 0.48 to 1.40) [31-33]. The relative risk, however, was comparable to the risk in cardiac surgery patients, in which a significant transfusion avoidance with aprotinin was found (RR 0.82; 95% CI 0.76 to 0.89). Ray and co-workers performed a study on 45 total hip arthroplasty patients and did not find a difference in blood loss between aprotinin and EACA (each 15 patients per group) or in mean RBC reduction or transfusion avoidance.

Pooled data on adverse events (myocardial infarction, thrombotic events) showed no difference between the study- and control groups. In the single hip surgery trial of Ray and co-workers [32] no thrombotic events as DVT or PE were found. Six cardiac adverse events were reported postoperatively in the intervention groups: two non-ST elevation MI, two atrial fibrillation (AF), and two patients with both MI and AF, however this did not reach statistical significance compared to the control group in these 45 patients (p=0.08).

C. TXA versus EACA

Of 8 reported trials (n=2003), only one orthopaedic study (knee replacement surgery; n=127) compared TXA (n=35) with EACA (n=32) and placebo (n=60) and found no difference in blood loss between TXA and EACA or in transfusion avoidance or mean RBC reduction or in adverse events [34].

Conclusions on the role of anti-fibrinolytics in orthopaedic blood management

Compared to controls, both aprotinin and TXA, but not EACA showed significant transfusion avoidance. Compared to one another, only three orthopaedic trials on knee- and hip replacement surgery, were available: no advantage of aprotinin compared to the lysine analogues could be found regarding blood loss and the need for RBC transfusions. None of these studies reported on mortality and only one study reported more cardiac adverse events [32]. Since data are lacking, and numbers were small, no valid conclusions can be drawn regarding the blood sparing effect or regarding adverse events in orthopaedic surgery due to the low numbers of study patients.

Fibrin glue

Carless and co-workers (2009) concluded in a Cochrane review that especially in orthopaedic surgery, where blood loss is often substantial, fibrin sealants appeared to demonstrate their greatest beneficial effects by significantly reducing blood loss and transfusion avoidance by 32% (RR 0.68; 95% CI 0.51 to 0.89), but large RCTs were lacking [35]. Therefore, the authors support initiating well-conducted large clinical trials on this matter.

SCOPE OF THIS THESIS

As discussed, several transfusion alternatives are available to reduce RBC use in elective orthopaedic surgery. Since the patient population eligible for knee-or hip replacement surgery is exponentially growing, expecting more than 100.000 of these type of surgeries in 2030 in the Netherlands [36], optimising peri-operative blood management is not only highly relevant with respect to patient risk and benefit, but also important in terms of cost effectiveness.

However, we found that insufficient evidence was published to provide a strategy for the optimal use these transfusion alternatives: most studies compared only one transfusion alternative with controls, which is inconsistent with daily practice; or studies were of older date, comparing transfusion alternatives as PAD with ANH, both are not widely applied anymore, especially not in the Netherlands; or studies did not use a transfusion protocol or used a liberal transfusion policy, which both may overestimate the blood sparing effect of the intervention.

To gain insight in the transfusion policy, we first evaluated RBC use during 6 months in the orthopaedic ward in the LUMC in 2000 (January to July). We found that a 68% reduction could be reached if a restrictive transfusion policy would be implemented. This was the reason to start a Randomised Controlled Trial (RCT), to investigate the effect of a restrictive transfusion trigger on mean RBC use and transfusion avoidance. To anticipate on a study to evaluate the use of postoperative autologous wound blood we compared the feasibility and effectiveness of different types of post-operative re-infusion devices, that were available in 2003, and to explore their possible use in a larger trial on the combined use of transfusion alternatives. Finally, we were fully prepared to study the effect of combinations of the mostly applied transfusion alternatives, while using a strict transfusion threshold, currently recommended in blood management protocols. The aim of this thesis is to optimise Patient Blood Management by providing evidence for cost-effective measures in elective orthopaedic surgery.

OUTLINE OF THIS THESIS

Chapter 2 describes the results of a RCT on the effect of a restrictive trigger on RBC sparing. In three hospitals, a restrictive transfusion policy was compared with standard care transfusion policy. A randomised comparison of transfusion triggers in elective orthopaedic surgery using leucocyte-depleted red blood cells was performed. The clinical consequences of this restrictive transfusion policy on post-operative complications and well-being are discussed in **Chapter 3.** Quality of Life and fatigue scores in relation to postoperative haemoglobin levels were analysed in **Chapter 4.**

In **Chapter 5** we investigated the efficacy and feasibility of two types of postoperative drainage and re-infusion systems and compared these to a control group. To evaluate the immuno-modulatory effects of salvaged blood in the post-operative patient, we analysed the effect of autologous salvaged blood re-infusion on the patients' cytokine gene expression profiles compared to the effect of surgery itself (**Chapter 6**).

Chapter 7 reports the combined strategies of Epo and autologous salvaged blood on RBC use compared to a control group under a restrictive transfusion policy (TOMaat study). In **Chapter 8,** future trends and ongoing studies are discussed in order to aim for an optimal and Tailor Made Patient Blood Management Program for elective orthopaedic surgery patients. In the final chapter, **Chapter 9**, an implementation protocol is described to investigate the barriers and facilitators for implementation of the TOMaat study results in daily practice.

REFERENCES

1. Gharehbaghian A, Haque KM, Truman C, Evans R, Morse R, Newman J, Bannister G, Rogers C, Bradley BA: Effect of autologous salvaged blood on postoperative natural killer cell precursor frequency. Lancet 2004; 363(9414):1025-1030.
2. Duffy G, Neal KR: Differences in post-operative infection rates between patients receiving autologous and allogeneic blood transfusion: a meta-analysis of published randomized and nonrandomized studies. Transfus Med 1996; 6(4):325-328.
3. Fernandez MC, Gottlieb M, Menitove JE: Blood transfusion and postoperative infection in orthopedic patients. Transfusion 1992; 32(4):318-322.
4. Jensen LS, Andersen AJ, Christiansen PM, Hokland P, Juhl CO, Madsen G, Mortensen J, Moller-Nielsen C, Hanberg-Sorensen F, Hokland M: Postoperative infection and natural killer cell function following blood transfusion in patients undergoing elective colorectal surgery. Br J Surg 1992; 79(6):513-516.
5. Murphy P, Heal JM, Blumberg N: Infection or suspected infection after hip replacement surgery with autologous or homologous blood transfusions. Transfusion 1991; 31(3):212-217.
6. Vignali A, Braga M, Gianotti L, Radaelli G, Gentilini O, Russo A, Di C, V: A single unit of transfused allogeneic blood increases postoperative infections. Vox Sang 1996; 71(3):170-175.
7. Triulzi DJ, Vanek K, Ryan DH, Blumberg N: A clinical and immunologic study of blood transfusion and postoperative bacterial infection in spinal surgery. Transfusion 1992; 32(6):517-524.
8. 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):1-13.
9. Gombotz H, Rehak PH, Shander A, Hofmann A: Blood use in elective surgery: the Austrian benchmark study. Transfusion 2007; 47(8):1468-1480.
10. Rosencher N, Kerkkamp HE, Macheras G, Munuera LM, Menichella G, Barton DM, Cremers S, Abraham IL: Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) study: blood management in elective knee and hip arthroplasty in Europe. Transfusion 2003; 43(4):459-469.
11. Barr PJ, Donnelly M, Morris K, Parker M, Cardwell C, Bailie KE: The epidemiology of red cell transfusion. Vox Sang 2010; 99(3):239-250.
12. Consensus conference. Perioperative red blood cell transfusion: JAMA 1988; 260(18):2700-2703.
13. Consensus statement on red cell transfusion. Royal College of Physicians of Edinburgh: Transfus Med 1994; 4(3):177-178.
14. Practice Guidelines for blood component therapy: A report by the American Society of Anesthesiologists Task Force on Blood Component Therapy: Anesthesiology 1996; 84(3):732-747.
15. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies: Anesthesiology 2006; 105(1):198-208.
16. Richtlijn Bloedtransfusie. Alphen aan den Rijn, Van Zuiden Communications BV, 2004, p. 107-10.
17. Carless PA, Henry DA, Carson JL, Hebert PP, McClelland B, Ker K: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 2010;(10):CD002042.
18. Carless P, Moxey A, O'Connell D, Henry D: Autologous transfusion techniques: a systematic review of their efficacy. Transfus Med 2004; 14(2):123-144.
19. Segal JB, Blasco-Colmenares E, Norris EJ, Guallar E: Preoperative acute normovolemic hemodilution: a meta-analysis. Transfusion 2004; 44(5):632-644.
20. Carless PA, Henry DA, Moxey AJ, O'connell DL, Brown T, Fergusson DA: Cell salvage for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2006;(4):CD001888.
21. 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(4):309-317.

22. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, Ker K: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2011; 3:CD001886.
23. Fergusson DA, Hebert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussieres JS, Cote D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R: A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 2008; 358(22):2319-2331.
24. Wiersum-Osselton JC, Schipperus MR: [Transfusion reactions in patients: haemovigilance reports to the Dutch National Haemovigilance Office in 2003]. Ned Tijdschr Geneeskd 2005; 149(47):2622-2627.
25. Boulton FE, James V: Guidelines for policies on alternatives to allogeneic blood transfusion. 1. Predeposit autologous blood donation and transfusion. Transfus Med 2007; 17(5):354-365.
26. Torgerson DJ, Roberts C: Understanding controlled trials. Randomisation methods: concealment. BMJ 1999; 319(7206):375-376.
27. Weber EW, Slappendel R, Hemon Y, Mahler S, Dalen T, Rouwet E, van OJ, Vosmaer A, van der Ark P: 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(4):249-257.
28. Coyle D, Lee KM, Fergusson DA, Laupacis A: Economic analysis of erythropoietin use in orthopaedic surgery. Transfus Med 1999; 9(1):21-30.
29. Fergusson DA, Hebert P: The health(y) cost of erythropoietin in orthopedic surgery. Can J Anaesth 2005; 52(4):347-351.
30. Engel JM, Hohaus T, Ruwoldt R, Menges T, Jurgensen I, Hempelmann G: Regional hemostatic status and blood requirements after total knee arthroplasty with and without tranexamic acid or aprotinin. Anesth Analg 2001; 92(3):775-780.
31. Amar D, Grant FM, Zhang H, Boland PJ, Leung DH, Healey JA: Antifibrinolytic therapy and perioperative blood loss in cancer patients undergoing major orthopedic surgery. Anesthesiology 2003; 98(2):337-342.
32. Ray M, Hatcher S, Whitehouse SL, Crawford S, Crawford R: Aprotinin and epsilon aminocaproic acid are effective in reducing blood loss after primary total hip arthroplasty--a prospective randomized double-blind placebo-controlled study. J Thromb Haemost 2005; 3(7):1421-1427.
33. Urban MK, Beckman J, Gordon M, Urquhart B, Boachie-Adjei O: The efficacy of antifibrinolytics in the reduction of blood loss during complex adult reconstructive spine surgery. Spine (Phila Pa 1976) 2001; 26(10):1152-1156.
34. Camarasa MA, Olle G, Serra-Prat M, Martin A, Sanchez M, Ricos P, Perez A, Opisso L: Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: a randomized clinical trial. Br J Anaesth 2006; 96(5):576-582.
35. Carless PA, Henry DA, Anthony DM: Fibrin sealant use for minimising peri-operative allogeneic blood transfusion. Cochrane Database Syst Rev 2003;(2):CD004171.
36. 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.
37. Henry DA, Carless PA, Moxey AJ, O'Connell D, Forgie MA, Wells PS, Fergusson D: Pre-operative autologous donation for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2010;(3):CD003602.