Cover Page

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Chapter 7

A randomised controlled trial on erythropoietin and blood salvage as transfusion alternatives in orthopaedic surgery using a restrictive transfusion policy

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ABSTRACT

Objective: To investigate the combined and separate use of erythropoietin (Epo), cell saver and/or postoperative drain re-infusion devices (DRAIN) as red blood cell (RBC) sparing alternatives.

Design: A multi-centre randomised, controlled trial.

Setting: Four hospitals in the Netherlands using a restrictive transfusion policy.

Participants: 2442 elective knee- and hip-arthroplasty patients aged 18 years and older.

Interventions: Primary stratification by preoperative haemoglobin (Hb) level: stratum I, Hb 10 to 13 g/dL (low Hb), randomised for Epo or no Epo; stratum II, Hb above 13 g/dL (normal Hb), ineligible for Epo. Both strata were also randomised for cell saver, DRAIN or no blood salvage device.

Main outcome measure: Number of RBC transfusions.

Results: Mean RBC use was 0.3 (SD 1.2) units / patient (n=2442) and 11.6% were transfused. Transfusion protocol adherence was above 95%. In Intention-To-Treat analysis, Epo resulted in a significant 50% reduction in transfused patients (OR 0.5, 95% CI 0.35 to 0.75) and a 29% mean RBC reduction (ratio 0.71, 95% CI 0.42 to 1.13). Additional costs due to Epo were estimated at €785 per patient (95% CI 262 to 1309), i.e. €7300 per avoided transfusion (95% CI 1900 to 24000). In both strata, autologous blood re-infusion did not result in RBC reduction and increased costs by €378 per patient (95% CI 161 to 595). Because of significant heterogeneity of treatment effects, primary (n=2258) and revision (n=184) surgery patients were analysed separately. In stratum I the primary surgery group had a 55 % reduction in transfused patients (OR 0.45, 95% CI 0.28 to 0.69) and a 55 % mean RBC reduction (ratio 0.45, 95% CI 0.29 to 0.72) by Epo, whereas autologous blood re-infusion by cell saver or DRAIN did not result in a significant RBC reduction in either strata. No conclusions can be drawn for revision surgery patients.

Conclusions: Even with a restrictive transfusion trigger, Epo contributed significantly as a transfusion alternative for RBC use in knee- and hip-arthroplasty patients with a low Hb, but at unacceptably high costs per avoided transfusion. Possibly due to the restrictive transfusion policy, autologous blood salvage devices were not effective in RBC reduction and consequently only increased costs.

Trial registration: www.controlled-trials.com, number ISRCTN 96327523; Dutch Trial Register NTR303

INTRODUCTION

To achieve optimal blood management, the use of alternatives for red blood cell (RBC) transfusions in orthopaedic surgery is widely accepted. However, the effect on RBC reduction may vary considerably (from 20 to 80%) and is related to the use of a transfusion threshold [1-8]. As transfusion policies have recently become more restrictive, it is questionable whether the currently accepted transfusion alternatives can still effectively reduce RBC use. Over the years, the use of pre-operative au0tologous donation (PAD) has declined due to logistical problems and wastage [9,10]. On the other hand, the use of Erythropoietin (Epo) and peri-operative autologous blood salvage have become increasingly popular worldwide including the Netherlands [11]. In randomised controlled studies of elective hip and knee surgery patients, Epo resulted in a significant reduction in mean RBC use (referred to as "blood-sparing") and a significant reduction in the proportion of transfused patients (referred to as "transfusion-avoiding") for up to 75%, while using a restrictive transfusion threshold of 8 g/dL. These studies also showed that the optimal benefit from Epo can be reached in patients with preoperative Hb levels between 10 to 13 g/dL in order to decrease RBC use [12,7,13].

Using a cell saver intra-operatively, up to 70% of the shed blood can be recovered in orthopaedic surgery [14], which may significantly reduce RBC use [8]. Post-operative re-infusion of autologous shed blood may also result in allogeneic RBC reduction, although these study results are not reported consistently [1-4;15-19]. The evidence for RBC reduction by autologous salvaged blood re-infusion is mostly based on small and/or underpowered studies often not applying a restrictive transfusion threshold. Moreover, evidence is lacking on the effect of combined use of transfusion alternatives. To address this issue we performed a multi-centre study with adequate power (90%), to investigate whether the use of Epo, the intra- and postoperative use of cell saver or the use of a postoperative drainage and re-infusion device (DRAIN) as transfusion alternatives, resulted in allogeneic RBC reduction in patients undergoing elective knee- or hip-replacement surgery while applying a restrictive transfusion policy. Additionally, we compared cost-effectiveness of the use of Epo, cell saver and DRAIN.

METHODS

Patients

Patients were enrolled between May 1st, 2004 and October 1st, 2008 from four hospitals in the Netherlands with study closure after completed follow up on Oct 1st, 2009. The ethics committee at each institution approved the protocol and the amendments, and all patients provided written informed consent before enrolment. The study was undertaken

in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and local laws and regulations. Eligible patients were aged 18 years and older, being scheduled for a primary or revision hip or knee replacement. All patients received six weeks of postoperative anti-thrombotic prophylaxis with subcutaneous Low-Molecular Weight Heparin (LMWH) starting the day before surgery. Anti-platelet agents (NSAIDs, clopidogrel, acetyl salicylic acid) were discontinued 3 to 10 days before surgery according to the hospital protocol. Oral anticoagulants (acenocoumarol, phenprocoumon) were discontinued with monitoring of INR values, which was required to be 1.8 or lower before surgery.

Patients were excluded if they had: untreated hypertension (diastolic blood pressure >95 mm Hg); a serious disorder of the coronary, peripheral and/or carotid arteries; a recent myocardial infarction or CVA (within 6 months); sickle cell anaemia; a malignancy in the surgical area; a contra-indication for anticoagulation prophylaxis; a known allergy to Epo; an infected wound bed; a revision of an infected prosthesis which was being treated with local antibiotics (e.g. gentamycin bone cement beads); difficulty understanding the Dutch language (unable to give informed consent); or were pregnant or refused homologous blood transfusions.

Study design

We designed a double randomised, multi-centre trial in which the randomisation was stratified for hospital, type of surgery (primary/revision as well as hip/knee), and the preoperative haemoglobin (Hb) level in order to have a balanced randomisation. Double randomisation included randomisation for Epo and randomisation for autologous blood re-infusion by cell saver or DRAIN. By selecting this design, the three transfusion alternatives can be investigated in a combined setting as well as separately, and was intended to resemble daily practice in an optimal way. Randomisation took place in one run for all possible combinations using a computer generated allocation table, but is here described sequentially. Patients were first stratified according to the pre-operative Hb level: stratum I (low Hb) = Hb between 10 and 13 g/dL. These patients were randomised for Epo or no Epo. Stratum II (normal Hb) = Hb of 13 g/dL and higher was not eligible for Epo but continued as a separate non-Epo treatment group. Since knee replacement procedures were performed using a pneumatic tourniquet, which was deflated after wound closure, intra-operative use of cell saver was not applicable due to negligible intra-operative blood loss, and consequently knee replacement surgery patients were excluded from randomisation for cell saver. All patients in both strata were randomised for two (knee surgery) or three (hip surgery) treatment modalities: 1) an intra-and postoperative autologous re-infusion device (cell saver) that washed, filtered and re-infused the autologous shed blood (only in hip surgery), 2) a postoperative autologous re-infusion drainage system (DRAIN) that filtered and re-infused autologous unwashed shed blood (both knee and hip surgery) and 3) no blood salvage device, although a low vacuum wound drain was placed but the collected

blood discarded. The randomisation resulted in the following combinations of modalities: cell saver+DRAIN- (only hip surgery); cell saver-DRAIN+; cell saver-DRAIN- (this group represents the control group). Hence the entire trial consists of nine different treatment modalities: six in stratum I: 1) Epo+cell saver+DRAIN-; 2) Epo+cell saver-DRAIN+; 3) Epo+cell saver-DRAIN-; 4) Epo-cell saver+DRAIN-; 5) Epo-cell saver-DRAIN+; 6) Epo-cell saver-DRAIN- (=control group) and three in stratum II: 7) Epo-cell saver+DRAIN-; 8) Epo-cell saver-DRAIN+; 9) Epo-cell saver-DRAIN- (=control group). For each stratum a separate randomisation list was created, using blocks of random length to avoid predictability of the random treatment assignment towards the end of each block. All patients were transfused according to a restrictive transfusion policy as advised in the Dutch transfusion guidelines (see below) [20]. Preoperative anaemia was defined according to the WHO criteria [21] (for males: Hb <13 g/dL and for females: Hb <12 g/dL). Participating hospitals were free to choose the type of Epo (i.e. alpha-Epo or beta-Epo) and the post-operative drainage system, but were obligated to use the same type throughout the study. The type of cell saver was uniform for all patients.

The transfusion protocol considered age and normal or high risk patients as triggers for transfusion. High risk included: incapability to enlarge cardiac output to compensate for anaemia, serious pulmonary disease or symptomatic cerebro-vascular disease. The following transfusion thresholds were used: Hb=6.4 g/dL (=4.0 mmol/L) for age <60 years and normal risk; Hb=8.1 g/dL (=5.0 mmol/L) for age ≥60 years and normal risk; Hb=9.7 g/dL (=6.0 mmol/L) in case of high risk. Hb values were derived from mmol/L which is the standard unit to denote Hb values in the Netherlands. The protocol included a single-unit transfusion policy (RBC units transfused one by one to reach a target Hb level above the defined Hb thresholds). A check for transfusion protocol adherence was included in the CRF by verifying the Hb, age and cardiovascular history (for risk estimation) of the patient for every transfusion event. The RBC units were prepared from whole blood donations. After centrifugation, followed by plasma- and buffycoat depletion, SAG-M (Saline, Adenine, Glucose, Mannitol) was added, resulting in a RBC product with a Ht between 0.50 and 0.65 L/L (40-54 g Hb) and a total volume of 270-290 mL. A universal pre-storage leukocyte depletion policy was applied, resulting in a leukocyte concentration of less than 1 x 10E6 per unit.

Treatment allocation was random using a uniform distribution and created a pre-generated list of sufficient length, based on the maximum expected sample size in each stratum. For each subject to be randomised, a sheet of paper with all relevant stratification and group-allocation information was produced and placed in a sealed opaque envelope. Batches were created according to the stratification factors. After receiving informed consent, the patient was preoperatively allocated by the research nurse to one of the groups by opening the first sealed envelope from the appropriate stratum. The exact moment of opening the envelope and its associated sequence number was verified against a centrally

stored randomisation list to check for selection bias. Hip surgery patients who were randomised for cell saver were automatically assigned to postoperative autologous blood re-infusion, as the used cell saver collected autologous blood intra- and postoperatively.

In order to avoid protocol violations, clinical-site staff members, clinicians, and patients were aware of study group assignments. The study investigators were blinded. The chart data were written on the Case Report Form (CRF) by the research nurses. All written information was transferred from the paper CRF to the secure on-line web based data management system (ProMISe) of the department of Medical Statistics & BioInformatics in Leiden. A built-in quality management system checked for irregularities, inconsistencies and coding errors and clarification was asked for whenever necessary.

The primary outcome measure was the number of allogeneic RBC transfusions. By comparing the mean RBC use we quantified the "blood-sparing" effect, and by comparing the proportion of transfused patients we quantified the "transfusion-avoiding" effect. Secondary outcomes (not all reported in this manuscript) were length of hospital stay (days), peri- and post-operative complications up to three months after surgery, transfusion reactions, rehabilitation time, quality of life and costs. All primary and secondary endpoints were scored until 3 months after surgery.

Procedures

A fixed weekly dose of 40.000 IU was given to patients randomised for Epo with simultaneous prescription of ferrofumarate 200 mg TID (=195 mg Fe^{2+} a day) during three weeks before surgery. A total of four Epo doses were administered by subcutaneous injection on days -21, -14, -7 and on the day of the operation (day 0), respectively. Hb levels were determined before administration of the fourth dose. If the Hb level exceeded the value of 15 g/dL, the final Epo dose was withheld. The Epo preparations were Neorecormon® (erythropoietin-beta, Roche Nederland BV, Woerden, Netherlands) (three hospitals) or Eprex® (erythropoietin-alpha, Janssen-Cilag BV, Tilburg, Netherlands) (one hospital). A protocol violation was scored if patient did not receive Epo therapy at all after being randomised for Epo. If at least one dose was given this was not regarded as violation and patients were included in the analysis as treated (AT) as having received Epo.

The OrthoPAT® cell saver (Haemonetics, Breda, Netherlands) was used for both intra- and post-operative collection and re-infusion of autologous blood. The collected shed blood was washed, centrifuged and concentrated to a hematocrit of 60-80% before being returned to the patient. Only hip surgery patients were randomised for the use of the cell saver. A protocol violation was scored if the cell saver was assigned but not used. When the cell saver device was truly used, the patient was included in the cell saver group in the AT-analysis whether or not autologous blood had been given to the patient.

Two different DRAIN devices were used: Bellovac-ABT® (Astra-Tech, Zoetermeer, the Netherlands) (two hospitals) and DONOR™ system (Van Straten Medical, Nieuwegein, The

Netherlands) (two hospitals). These systems differ slightly in filtration and vacuum pressure: the DONOR™ system uses a continuous suction at a vacuum pressure of 150 mm Hg and just prior to re-infusion a double shielded 40 micron filter (Pall Lipiguard VS filter) entrapping lipids larger than 10 micron and 2 log of leukocytes. The Bellovac-ABT® system uses intermittent suction pressure by a manually expandable bag at a maximum pressure of 90 mm Hg and three filters: a 200 micron filter, a secondary 80 micron filter and prior to re-infusion a third 40 micron filter. In a feasibility and efficacy study, we found both systems to be comparable [22]. A protocol violation was scored if the device was assigned but not used. When the DRAIN device was truly used, the patient was included in the DRAIN group in the AT- analysis whether or not autologous blood had been returned.

Intra-operative transfusions were prescribed by the anaesthesiologist and post-operative transfusions by the orthopaedic surgeon. Transfusion protocol violations and randomisation violations were recorded.

Serious Adverse Events (SAEs) were defined as events that occurred within one month after surgery, and were labelled as death, life threatening events, (prolongation of) hospitalization and/or events resulting in persistent disability, and categorised into prosthesis related (dislocation, wound infection or deep prosthetic infection, fractures or limitation in movement), thrombo-embolic (deep venous thrombosis diagnosed by ultrasound, pulmonary emboli, stroke or transient ischemic attack, myocardial infarction, cardiovascular other than myocardial infarction, allergic, infection/sepsis (not prosthesis related), malignancy and other events. All SAEs that were reported to the central coordinator during the three month-follow up, were scored.

Statistical methods

The study was designed to have statistical power of 90% with a type I error of 5% (two-sided test) to detect a difference of 75% in mean RBC use by Epo (the alternative to null-hypothesis 1) and a difference of 30% in mean RBC use by autologous blood re-infusion by either cell saver or DRAIN (alternative to null-hypothesis 2). The study design allowed to investigate the Epo versus no Epo effect (comparison 1), the combined autologous versus no autologous effect (comparison 2) and the cell saver versus DRAIN effect (comparison 3) (eFigure 1 and sample size calculation online material only). Various scenario's of literature based estimates of standard deviations were included as well as the possibility of severe treatment and stratum interactions. This required an inclusion of 2250 patients for analysis on an Intention-To-Treat (ITT) basis and included protection against a worst case scenario of high standard deviations and heterogeneity of treatment effects. Assuming a study dropout rate of 10%, our goal was to have 2500 patients eligible for randomisation. An interim analysis was carried out by an independent Data Safety Monitoring Committee (DSMC) at the half way mark (958 inclusions) using an alpha of 2.5% (instead of 5%). As pre-defined stopping criteria were not reached, neither for futility nor for efficacy, the DSMC advised to continue the study until its pre-specified number of patients was obtained.

Conforming to ICH-9 guidelines, the primary analyses were performed both as ITT and As Treated (AT). In case of the Epo (yes/no) covariate, AT is defined as the actual administration of at least one dose of Epo; in case of cell saver or DRAIN it is defined as the actual use of the device whether or not autologous blood had been re-infused to the patient.

Variables were described by frequencies, by mean and SD, and by median and inter-quartile range (IQR) in case of a non-normal distribution. Although RBC use can be severely non-normally distributed, we also report means (and standard deviations), since the power and sample size calculation was based on assumptions of these means. Ratio's (dividing the mean RBC values of two randomised groups to be compared) and 95% confidence intervals (CI) were reported to calculate the proportional reduction between the groups. Confidence intervals were obtained via bootstrapping methods for these highly non-normally distributed ratio's (software package R, using the standard package "boot"). For additional non-parametric testing we used the Mann-Whitney test. When comparing the proportion of patients receiving RBC transfusions, a Mantel-Haenszel procedure was applied, using the main risk factors and stratification variables as strata. This led to an overall, adjusted common Odds Ratio (OR) as a comparison of the probability of "receiving at least one RBC unit" between the randomisation arms. A linear mixed model was used for the primary outcome (RBC use) as a function of the interventions, the stratification factors (hip versus knee and primary versus revision surgery) and their interactions with the intervention. In case of significant interaction, the calculations were based on separate subpopulations (stratified by the interacting term) as pre-specified in the protocol. In case of non-significant interactions, the stratification factor was retained in the model as a main term for adjustment. The stratification factor "centre" was included as a random effect. Even though we were fully aware of the non-normal distribution of the RBC use among the various strata and intervention groups, we reported confidence intervals based on the mixed models for comparison with other literature; therefore significance of differences in this model needs to be interpreted with caution. Each analysis of intervention effect in this additive framework is accompanied by a robust estimate of the treatment effect as a ratio and its associated confidence interval.

After data checking the database was frozen. The conversion process transferred the data to a number of SPSS (version 17.0 for Windows (SPSS Inc, Chicago, IL, USA)) system files which were used for all analyses. The same files were used within the R software to obtain estimates and robust bootstrapped confidence intervals. The SPSS files were read using the library "foreign". A p- value of less than 0.05 was considered statistically significant.

Economic evaluation

Costs were estimated from a hospital perspective, with a three-months time horizon. Health care was valued at the 2011 price level, using market prices for Epo, cell saver and DRAIN (€1293 for four doses [23], €160, and €61, respectively) and using standard prices for

allogeneic RBC products, ICU care, and non-ICU care (€207 per unit, €2249 and €471 per day, respectively) [24]. The total price per unit of RBC use was estimated at four times the product price (i.e. €829 per unit), according to the paper of Shander and co-workers [25]. Average costs were compared according to intention-to-treat, using non-parametric bootstrapping (programmed in Stata/IC 11.0 for Windows). If a strategy resulted in transfusion avoidance but with higher costs, a cost-effectiveness analysis was performed comparing the difference in the proportion of transfused patients to the difference in costs. Confidence intervals for the cost-effectiveness ratio were calculated using net benefit analysis [26].

RESULTS

From May 2004 to October 2008, 3165 patients were screened for eligibility of which 586 patients were not enrolled (Figure 1). After completion of the study in October 2009, 2579 patients had been randomised, of which 2442 (95%) were evaluated. Of the 137 not evaluated patients, for the majority (82%) surgery was cancelled or performed elsewhere, six of whom had received at least one Epo dose. Baseline characteristics are shown in table 1. Mean preoperative Hb at first outpatient visit was 13.8 g/dL (SD 1.3) and mean Ht 0.42 L/L(SD 0.04). Sixty percent were hip procedures and 40% were knee procedures. Seventy percent was female. Revision surgery occurred in 7.5% (n=184), equally divided among the groups. 683 (28%) patients were eligible for Epo. In Table 2, peri-operative characteristics are shown. The median volumes of re-infused blood were 100 mL for cell saver [IQR 50-200 mL] with mean Ht: 0.70 [SD 0.11] and 350 mL for DRAIN [IQR 200-500 mL] with mean Ht:0.34 [SD 0.17]. Postoperative Hb values on day+1 were comparable in the groups with or without autologous blood re-infusion by cell saver or DRAIN. Revision surgery patients differed significantly for intra-operative blood loss, mean duration of surgery and total blood loss ($p<0.05$), but not for the mean and median re-infused volumes.

Primary endpoint

No heterogeneity was found among the four participating hospitals with respect to the effect-size in any comparison of the primary endpoint. Of 2442 evaluated patients, mean RBC use was 0.32 units (U) / patient [SD 1.2] and median use was 0 U/patient [range 0-27]. 11.6% (n=284) of patients received in total 775 RBC transfusions (median 2U [IQR 2-2]). The majority of patients (n=246) were transfused postoperatively up to 14 days after surgery (median of 2 U [IQR 2-2]). The median RBC units used and proportion transfused patients are outlined in Table 2. Overall, revision surgery patients were significantly transfused more often (19.6%) than primary surgery patients (11%) with more RBC transfusions. In addition, hip surgery patients were significantly more often transfused (15%) than knee surgery patients (6.6%), with more transfusions as well. Due to significant interaction between

primary or revision surgery and the allocated treatments (Epo and cell saver and DRAIN; p<0.001), we analysed these patient groups separately (2258 primary and 184 revision surgery).

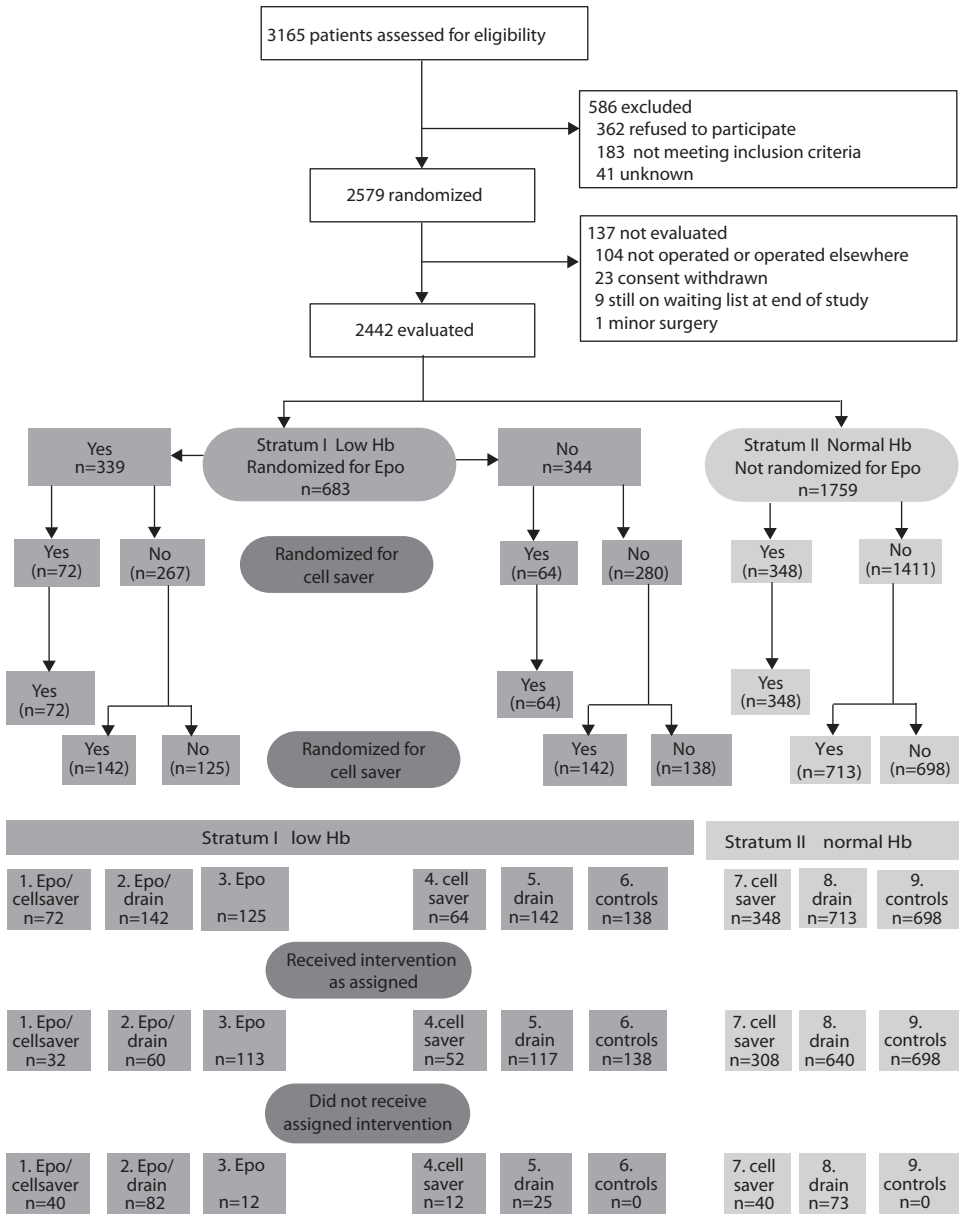

Figure 1. Patient flow diagram

Table 1. Baseline characteristics of the study population

Patient variables	All patients	STRATUM I (LOW HB)						STRATUM II (NORMAL HB)		
	Numbers (%) or mean (SD)	1. Epo/CS	2. Epo/DR	3. Epo	4. CS	5. DR	6.controls	7. CS	8. DR	9. controls
Evaluated	2442	72	142	125	64	142	138	348	713	698
Hip surgery	1464 (60%)[a]	72 (100)	78 (55)	64 (51)	64 (100)	72 (51)	77 (56)	348 (100)	347 (49)	342 (49)
Knee surgery	978 (40%)[b]	0 (0)	64 (45)	61 (49)	0 (0)	70 (49)	61 (44)	0 (0)	366 (51)	356 (51)
Primary hip	1332 (55%)	64 (89)	65 (46)	56 (45)	56 (87)	64 (45)	67 (49)	322 (93)	321 (45)	319 (46)
Primary knee	924 (38%)	0 (0)	61 (43)	56 (45)	0 (0)	64 (45)	60 (43)	0 (0)	344 (48)	339 (49)
Females (%)	1699 (70%)	63 (88)	121 (85)	113 (90)	55 (86)	122 (86)	121(88)	224 (66)	470 (66)	410 (59)
Mean age in years	69 (11)	70 (14)	70 (12)	71 (12)	70 (13)	72 (13)	70 (11)	68 (11)	69 (10)	68 (10)
Mean pre-operative Hb (g/dL) (outpatients; n=2426)	13.8 (1.3)	12.5 (1.2)	12.5 (1.2)	12.5 (1.2)	12.2 (0.9)	12.3 (0.9)	12.6 (0.8)	14.2 (1.0)	14.2 (0.9)	14.5 (1.0)
Pre-operative anaemia	210 (8.6%)	24 (33)	45 (32)	36 (29)	23 (36)	41 (29)	26 (19)	5[e] (1.4)	5[e] (0.7)	5[e] (0.7)
High risk[d]	92 (4%)	3 (4)	9 (6)	4 (3)	4 (6)	4 (3)	5 (4)	15 (4)	25 (4)	23 (3)
Co-morbidities:										
Cardiovascular	1225 (50%)	21 (29)	75 (53)	54 (43)	36 (56)	75 (53)	68 (49)	157 (45)	381 (53)	358 (51)
COPD	197 (8%)	7 (10)	16 (11)	10 (8)	6 (9)	8 (6)	16 (12)	26 (8)	55 (8)	53 (8)
Rheumatoid arthritis	287 (12%)	12 (17)	32 (23)	25 (20)	14 (22)	33 (23)	26 (19)	20 (6)	65 (9)	60 (9)
Diabetes	286 (12%)	4 (6)	29 (2)	20 (16)	10 (16)	16 (11)	25 (18)	33 (10)	83 (12)	66 (10)
Epo eligible	683 (28%)									

Abbreviations: Hb, haemoglobin; SD, standard deviation; Epo, erythropoietin; CS, cell saver; DR, postoperative drain re-infusion; COPD, chronic obstructive pulmonary disease.
For continuous variables mean (SD) is shown, for categorical variables numbers (percentages) are shown. Percentages are calculated within randomised group (columns). Pre-operative anaemia includes a Hb value <12 g/dL for women and a Hb value of <13 g/dL for men (WHO standards)
[a] 1 THP bilateral; [b] 14 TKP bilateral; [c] one TKP bilateral; [d] high risk denotes incapability to enlarge cardiac output to compensate for anaemia, serious pulmonary disease or symptomatic cerebrovascular disease; [e] wrongly randomised to normal Hb stratum

Table 2. Peri-operative patient characteristics by randomised group and transfused RBC units (means and proportion of patients transfused) by primary and revision surgery

Numbers (%) or mean (SD) or median (IQR)	STRATUM I (Low Hb) Randomisation groups 1- 6						STRATUM II (Normal Hb) Randomisation groups 7-9		
Intention-To-Treat analysis (numbers) Total patients n=2442	**1. Epo/CS N=72**	**2. Epo/drain N=142**	**3. Epo N=125**	**4. CS N=64**	**5. Drain N=142**	**6. Control N=138**	**7. CS N=348**	**8. Drain N=713**	**9. Control N=698**
Mean surgery duration (minutes) primary/ revisions	99 (55) 96/128	102 (45) 98/129	98 (44) 94/132	107 (86) 98/166	100 (46) 98/123	102 (40) 100/124	96 (40) 96/108	99 (43) 96/140	97 (40) 96/115
% of cemented prosthesis	34	47	47	39	47	47	25	43	43
Median blood loss (mL) during surgery (IQR)	300 (150-550)	200 (0-500)	200 (0-500)	300 (150-500)	240 (0-450)	200 (0-500)	325 (200-500) 375 (200-500)	200 (0-400)	200 (0-400)
Primary	300 (175-500)	200 (0-400)	200 (0-475)	300 (150-470)	200 (0-400)	160 (0-450)	300 (225-575)	200 (0-400)	200 (0-400)
Revisions	200 (135-660)	500 (200-925)	500 (0-880)	500 (200-1600)	500 (115-600)	500 (200-575)		350 (0-825)	275 (0-500)
Median total blood loss (mL) (IQR)	525 (350-900)	700 (350-1050)	650 (400-1000)	550 (300-800)	700 (400-1050)	650 (400-950)	550 (300-850)	700 (400-1000)	700 (400-1000)
Primary	525 (400-860)	690 (330-1050)	650 (400-1000)	500 (275-800)	665 (390-1015)	660 (350-980)	545 (310-850)	680 (400-990)	700 (400-1000)
Revisions	470 (250-1460)	900 (525-1570)	560 (300-915)	890 (470-1880)	860 (500-1200)	550 (400-870)	600 (410-1030)	820 (550-1375)	635 (360-975)
Median re-infused volume (mL) (IQR)	200 (100-415)	320 (200-500)	NA	100 (50-175)	320 (190-500)	NA	100 (40-200)	350 (150-500)	NA
g/dL Hb day+1 (SD)	10.3 (1.8)	10.5 (1.5)	10.8 (1.5)	9.5 (1.0)	9.5 (1.1)	9.5 (1.3)	10.8 (1.3)	11.1 (1.3)	11.0 (1.3)
Median units RBCs (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-2)	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Primary	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-2)	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Revisions	0 (0-1.5)	0 (0-2.8)	0 (0-0)	0 (0-1.5)	0 (0-2)	0 (0-2)	0 (0-0)	0 (0-0)	0 (0-0)
Proportion transfused (%) primary / revisions	21 20/25	18 15/44	10 9/15	30 30/25	28 28/29	23 23/27	7.7 7/15	7.7 7/17	8.3 8/10

Abbreviations: RBC=red blood cell; SD=standard deviation; IQR=inter-quartile range; Hb=haemoglobin;Epo=erythropoietin; CS=cell saver; Drain=postoperative drain re-infusion; mL=millilitre; NA, not applicable.

For continuous variables mean (SD) is shown, and median (IQ range) in case of a non- normal distribution. For categorical variables numbers (percentages) are shown. Percentages are calculated within randomised group (columns). Day+1 denotes one day postoperatively.

In Table 3 the intention-to-treat analysis of the effects of Epo and autologous blood re-infusion (combined cell saver and DRAIN effect) on mean RBC units used (mean difference and calculated ratio's with 95% CI) and proportion transfused patients (with OR and 95% CI) are outlined. To investigate the overall Epo effect in stratum I, regardless of the use of autologous blood, pooled estimates were calculated comparing the Epo+ and Epo- groups (a test for heterogeneity was not significant). The separate cell saver and DRAIN effect showed no difference (eTable 1).

In the low Hb stratum (stratum I) autologous blood re-infusion neither resulted in a decrease of mean RBC use nor in a decrease in proportion of transfused patients in either the total or primary surgery subgroup. Among those randomised to receive Epo, autologous blood use by cell saver or DRAIN even resulted in an increase in both mean RBC use (ratio 0.45, 95% CI 0.28 to 0.69; p<0.01) and the proportion of transfused patients (adjusted OR 2.2, 95% CI 1.1 to 4.4; p=0.02) compared to those without blood sparing devices. This effect mainly occurred in the revision surgery patients. The pooled Epo effect on RBC use in the total, primary and revision, group, showed a transfusion avoidance in 50% of patients (adjusted OR 0.50, 95% CI 0.35 to 0.75; p<0.001) from 26% to 16% (10% absolute difference), independent of assignment to autologous blood re-infusion and a non-significant 29% mean RBC reduction from 0.71 to 0.50 U/patient (ratio 0.71, 95% CI 0.42 to 1.13; p=0.15). Among the primary surgery patients, Epo was effective in both blood sparing (55% mean RBC reduction; ratio 0.45, 95% CI 0.28 to 0.69; p<0.01); and transfusion avoidance (55% reduction in transfused patients; adjusted OR 0.45, 95% CI 0.29 to 0.72; p<0.001) from 26% to 14% (12% absolute difference).

In the normal Hb stratum (II) of the total group, 8.3% of the control group was transfused with a mean RBC use of 0.22 U/patient. Autologous blood re-infusion using either DRAIN or cell saver resulted neither in a RBC sparing nor in transfusion avoidance in this stratum. This was similar in the primary surgery group. The revision surgery group was, however, too small and too heterogeneous to draw valid conclusions.

Economic evaluation

For this purpose, the total group of 2442 patients were analysed. When the operation was unexpectedly rescheduled to a date within three weeks after randomisation, no Epo was administered. As a result, 66% of the patients randomised to receive Epo actually received Epo, with average Epo costs of €851 per patient (table 4A, 95% CI 785 to 917). The change in costs for RBC use and hospital stay in stratum I was relatively small compared to the costs for Epo. The average total cost increase for the Epo strategy was estimated at €785 per patient (95% CI 262 to 1309). With a decrease in the proportion of transfused patients by 10.8% (from 26.4% to 15.6%), the cost difference translates to €7300 per avoided transfusion (95% CI 1900 to 24000).

Table 3A. ITT analysis of Epo and autologous blood re-infusion (=combined cell saver/ DRAIN) effect on RBC use of total group, and split by primary / revision surgery

Primary and revision surgery patients (total group)					
N=2442	**Mean RBC use (U)**	**Mean adjusted difference[a] (95% CI)**	**Ratio[b] (95% CI)**	**Proportion transfused (%)**	**Adjustedodds ratio[c] (95% CI)**
Stratum I no Epo					
Autologous blood (n=206)	0.76 (1.6)	0.10	1.2	29	1.3
No autologous blood (n=138)	**0.64 (1.6)**	(-0.25 to 0.45)	(0.7 to 2.0)	**23**	(0.8 to 2.1)
Stratum I with Epo					
Autologous blood (n=214)	0.65 (2.5)	0.34	2.6	19	2.2
No autologous blood (n=125)[d]	0.25 (0.9)	(-0.10 to 0.78) p=0.13	(1.2 to 6.5) p=0.02	10	(1.1 to 4.4) p=0.02
Pooled Epo effects					
With Epo (n=339)	0.50 (2.1)	-0.22	0.71	16	0.5
No Epo (n=344)	0.71 (1.6)	(-0.50 to 0.05) p=0.10	(0.42 to 1.13) p=0.15	26	(0.35 to 0.75) p< 0.001
Stratum II (n=1759)					
Autologous blood (n=1061)	0.19 (0.9)	-0.06	0.9	7.7	0.92
No autologous blood (n=698)	0.22 (0.9)	(-0.15 to 0.02) p=0.15	(0.6 to 1.3)	**8.3**	(0.65 to 1.3)
Primary surgery patients					
N=2258	**Mean RBC use (U) (SD)**	**Mean adjusted difference[e] (95% CI)**	**Ratio[b] (95% CI)**	**Proportion transfused (%)**	**Adjusted odds ratio[c] (95% CI)**
Stratum I no Epo (n=311)					
Autologous blood (n=184)	0.78 (1.7)	0.15	1.3	29	1.4
No autologous blood (n=127)	0.61 (1.6)	(-0.22 to 0.52)	(0.8 to 2.3)	23	(0.8 to 2.3)
Stratum I with Epo (n=302)					
Autologous blood (n=190)	0.36 (1.1)	0.09	1.5	17	2.1
No autologous blood (n=112)[d]	0.24 (0.9)	(-0.15 to 0.32)	(0.7 to 4.0)	9	(1.0 to 4.3) p=0.06
Pooled Epo effects					
With Epo (n=302)	0.32 (1.0)	-0.39	0.45	14	0.45
No Epo (n=311)	0.71 (1.6)	(-0.61 to -0.18) p<0.001	(0.28 to 0.69) p<0.01	26[f]	(0.29 to 0.72) p<0.001
Stratum II (n=1645)					
Autologous blood (n=987)	0.16 (0.7)	-0.08	0.73	7.1	0.86
No autologous blood (n=658)	**0.22 (0.9)**	(-0.16 to -0.01) p=0.04	(0.48 to 1.1) p=0.13	**8.2**	(0.6 to 1.2)

Table 3A. *(continued)*

Revision surgery patients					
N=184	**Mean RBC use (U) (SD)**	**Mean adjusted difference[e] (95% CI)**	**Ratio[b] (95% CI)**	**Proportion transfused (%)**	**Adjusted odds ratio[c] (95% CI)**
Stratum I no Epo (n=33)					
Autologous blood (n=22)	0.59 (1.0)	-0.48	0.54	27	
No autologous blood (n=11)	**1.1 (2.0)**	(-1.63 to 0.68)	(0.15 to 2.6)	**27**	(0.2 to 5.1)
Stratum I with Epo (n=37)					
Autologous blood (n=24)	3.0 (6.5)	2.0	9.6	38	3.3
No autologous blood (n=13)[d]	0.3 (0.8)	(-1.77 to 5.72)	(1.9 to 31.4)	15	(0.6 to 18)
Pooled Epo effects					
With Epo (n=37)	2.0 (5.3)	1.76	2.7	30	1.3
No Epo (n=33)	0.76 (1.4)	(-0.14 to 3.67) p=0.07	(0.7 to 8.0)	27	(0.5 to 3.7)
Stratum II (n=114)					
Autologous blood (n=74)	0.64 (2.2)	0.25	2.0	16	1.8
No autologous blood (n=40)	**0.33 (1.2)**	(-0.49 to 1.0)	(0.5 to 14.0)	**10**	(0.5 to 6.2)

Abbreviations: ITT=intention to treat; Epo=erythropoietin; RBC=red blood cell; U=units; CI, confidence interval; SD=standard deviation. Control groups are outlined in bold.

[a] adjusted for revision/non-revision surgery, hospital and knee/hip surgery; confidence intervals for reference purposes only (assuming normality)

[b] ratio was defined as the quotient of mean RBC values of two groups being compared; all estimates and robust standard errors were obtained via bootstrapping in R

[c] all estimates and standard errors were obtained using the Mantel-Haenszel procedure, stratifying by the pre-specified stratification factors hospital and knee/hip surgery

[d] denotes Epo alone group.

[e] adjusted for hospital and for knee/ hip surgery; confidence intervals for reference purposes only (assuming normality)

[f] 12% absolute difference in transfusion avoidance

Table 3B. AT analysis of primary surgery patients (truly received Epo and truly received device)

Primary surgery patients					
N=2258	**Mean RBC use (U) (SD)**	**Mean adjusted difference[a] (95% CI)**	**Ratio[b] (95% CI)**	**Proportion transfused (%)**	**Adjusted odds ratio[c] (95% CI)**
Stratum I no Epo (n=410)					
Autologous blood (n=240)	0.65 (1.6)	0.03	0.99	27	1.2
No autologous blood (n=170)	**0.65 (1.4)**	(-0.26 to 0.33)	(0.63 to 1.6)	**24**	(0.79 to 1.8)
Stratum I with Epo (n=202)					
Autologous blood (n=81)	0.17 (0.5)	-0.14	0.58	9.9	1.1
No autologous blood (n=121)[d]	0.30 (1.2)	(-0.43 to 0.15)	(0.19 to 1.7)	9.1	(0.42 to 2.9)
Pooled Epo effects					
With Epo (n=202)	0.25 (1.0)	-0.40	0.38	9.4	0.30
No Epo (n=410)	0.65 (1.5)	(-0.62 to -0.17) p=0.01	(0.19 to 0.66)	26	(0.18 to 0.51) P<0.001
Stratum II (n=1639)[e]					
Autologous blood (n=887)	0.14 (0.6)	-0.08	0.63	6.2	0.69
No autologous blood (n=752)	**0.22 (0.9)**	(-0.15 to 0.0) p=0.04	(0.42 to 0.95)	**8.8**[f]	(0.47 to 1.0) p=0.05

Abbreviations: ITT=intention to treat; Epo=erythropoietin; CS=cell saver; DR=postoperative drain re-infusion; RBC=red blood cell; U=units; CI=confidence interval; SD=standard deviation. Control groups are outlined in bold.

[a] adjusted for hospital and knee/hip surgery; confidence intervals for reference purposes only (assuming normality).

[b] ratio was defined as the quotient of mean RBC values of two groups being compared; all estimates and robust standard errors were obtained via bootstrapping in R.

[c] all estimates and standard errors were obtained using the Mantel-Haenszel procedure, stratifying by the pre-specified stratification factors hospital and knee/hip surgery.

[d] denotes Epo alone group.

[e] of 7 patients, it was not known whether the device was truly received.

[f] 2.6% absolute difference in transfusion avoidance.

Autologous blood re-infusion was associated with a significant decrease in the use of Epo by 4% (table 4B, 95% CI 2% to 7%) and increased the length of the non-ICU hospital stay by 0.56 days (95% CI 0.23 to 0.90, similar in both strata). The total cost increase for the autologous blood re-infusion strategy was estimated at €378 per patient (95% CI 161 to 595), without RBC reduction.

Study protocol adherence

A total of 284 patients did not receive the intended intervention. Of the 339 patients assigned to Epo, 114 received no Epo (34%), 225 patients assigned to Epo received at least one dose and of those 97% received at least three Epo doses. Sixty-two of 484 (13%) assigned patients did not receive cell saver (with or without Epo) and 110 of 997 (11%) assigned patients did not receive DRAIN (with or without Epo). Most common reasons for

not receiving the intended intervention were earlier rescheduling of surgery in case of Epo, technical problems with the machine (broken or incomplete device) for cell saver and not using the proper drain device or not placing a drain at all.

Table 4. Estimated costs by Epo among patients with low Hb (table 4A) and by autologous blood re-infusion among all patients (table 4B)

Table 4A

	Volumes of health care[a]		Costs (in €)			
	With Epo n=339	**No Epo n=344**	**With Epo n=339**	**No Epo n=344**	**Difference (95% CI)**	
Epo	66%	0.7%[b]	858	8	851	(785; 917)
Cell-saver and/or drain	63%	60%	56	52	4	(-4; 13)
RBC use	16%/0.50	26% / 0.71	418	591	-172	(-401; 57)
ICU care (days)	3.2%/0.04	2.3% / 0.04	100	98	1	(-99; 102)
Non-ICU care (days)	8.87	8.66	4182	4081	101	(-256; 459)
Total costs			5615	4829	785	(262; 1309)

[a] Volume = percentage of patients and/or mean usage
[b]Two patients received Epo while not randomised for Epo

Table 4B

	Volumes of health care[a]		Costs (in €)			
	Autologous blood n=1481	**No autologous blood n=961**	**Autologous blood n=1481**	**No autologous blood n=961**	**Difference (95% CI)**	
Epo	8%	12%	100	152	-53	(-84; -21)
Cell-saver and/or drain	100%	0.3%	89	0	89	(86; 91)
RBC use	12% / 0.34	11% / 0.29	279	238	41	(-38; 121)
ICU care (days)	2.0% / 0.03	1.0% / 0.02	73	37	35	(-9; 80)
Non-ICU care (days)	8.18	7.62	3857	3592	265	(107; 423)
Total costs			4399	4021	378	(161; 595)

[a] Volume=percentage of patients and/or mean usage

Transfusion protocol adherence

In over 95% of the patients, the transfusion protocol was correctly followed according to Hb, age and co-morbidity status (risk evaluation) of the patient before transfusion. Transfusion violations were equally found in all randomisation groups.

As Treated analysis

In table 3B the AT analysis, where the actual use of Epo and the actual use of the autologous blood re-infusion devices are analysed, shows the primary surgery group only. Patients who actually received Epo ("pooled effects with Epo" group) showed a larger reduction in mean RBC use of 62% (ratio 0.38, 95% CI 0.19 to 0.66) and a reduction in proportion transfused patients of 70% (adjusted OR 0.30, 95% CI 0.18 to 0.51). In this low Hb stratum, the actual use of the autologous blood re-infusion devices did not result in a mean RBC reduction or in a reduction in percentage transfused patients. In the patient group with normal pre-operative Hb levels (stratum II), a significant mean RBC reduction of 37% (ratio 0.63, 95% CI 0.42 to 0.95) and a reduction in transfused patients of 31% (adjusted OR 0.69, 95% CI 0.47 to 1.0) from 8.8% to 6.2% (2.6% absolute difference) was found. The AT analysis for the revision surgery patients, and the AT analysis for both separate cell saver and DRAIN are presented in eTables 2 and 3. No significant RBC reduction was found in the revision surgery group as well as no difference in effect of cell saver compared to DRAIN devices.

Serious adverse events (SAEs)

A total of 112 SAEs were reported in 103 patients (eight patients suffered 2 or more SAEs) (Table 5A and 5B). Eighty SAEs were registered within one month postoperatively and 32 SAEs were reported later within the three months of follow up. Categorisation according to intention-to-treat analysis (table 5A) and as treated analysis (table 5B), and occurrence (less or more than one month after surgery) is shown. One patient did not undergo surgery and was not further evaluated because of a stroke after one Epo dose (Hb value of 12.2 g/dL) and one patient was not further evaluated due to assignment of a wrong randomisation number. These patients were included in table 5. Total numbers of reported SAEs by group are outlined. A total of 31 thrombo-embolic (TE) events occurred: nine myocardial infarctions (MI), twelve strokes or TIA's, four deep venous thrombosis of the leg (diagnosed by ultrasound), five pulmonary emboli and one arterial occlusion of a bypass graft in the leg. Five TE events (three MIs and two strokes) occurred in the Epo-group (1.5%), all in patients with Hb levels of 12.2.g/dL or less, two of these events occurred after only one Epo dose. The proportion of TE events (1.5%) in the Epo-group was not significantly different from the non-Epo group (1.2%) (OR 1.2, 95% CI 0.46 to 3.1; p=0.72). In the as treated analysis, 1.8% in the Epo group suffered a TE event (table 5B) increasing the OR (not significantly) compared to the non-Epo group to 1.5 (95% CI 0.50 to 4.2; p=0.49). Non-TE related SAEs were: prosthesis related (n=33) (hip dislocation (n=10), prosthesis infections (n=4) or wound infections (n=7), limited knee flexion needing manipulation (n=5), fracture (n=3) or non-specified (n=4)), cardiovascular events (n=22) (arrhythmia, blood pressure instability etc), allergic events (n=3), non prosthesis related infections or sepsis (n=7), bleeding (n=3), malignancy (n=1) and other (n=12). Autologous blood re-infusion related complications were not specifically sepsis- or infection related. A relatively high proportion of SAEs were

Table 5. Reported numbers Serious Adverse Events (SAEs) by ITT (Table 5A) and by AT group (table 5B): thrombo-embolic (TE) complications[a], non-TE complications[b] and total numbers

Table 5A

ITT group (numbers)	TE complications (%)	Myocardialinfarction (<1 mo/ (1-3 mo)[c]	Stroke/TIA (<1 mo/ (1-3 mo)	DVT (<1 mo/ (1-3 mo)	Pulmonary emboli (<1 mo/ (1-3 mo)	Other (<1 mo/ (1-3 mo)	Non-TE complications	Total numbers of reported SAEs (%)
Epo/CS (n=72)	0 (0%)	0	0	0	0	0	3	3 (4.2%)
Epo/DR (n=142)	1 (2.4%)	1 (1/0)	0	0	0	0	8	9 (6.3%)
Epo (n=125)	4 (3.2 %)	2 (2/0)	2 (2/0)	0	0	0	1	5 (4.0%)
Epo groups (n=339)	**5 (1.5%)**						**12**	**17 (5.0%)[d]**
CS (n=412)	2 (0.5%)	0	2 (2/0)	0	0	0	14	16 (3.9%)
DR (n=855)	15 (0.2%)	4 (2/2)	5 (5/0)	1(0/1)	4 (2/2)	1(1/0)[e]	29	44 (5.1%)
Control group (n=836)	9 (1.1%)	2 (2/0)	3 (2/1)	3(0/3)	1 (0/1)	0	26	35 (4.2%)
Non Epo groups (n=2103)	**26 (1.2%)**						**69**	**95 (4.5%)[d]**
Totals (n=2442)	31 (1.3%)	9 (7/2)	12 (11/1)	4 (0/4)	5(2/3)	1 (1/0)	81	112 (5%)

Table 5B

AT group (numbers)	TE complications (%)	Myocardial infarction (<1 mo/ (1-3 mo)[c]	stroke/TIA (<1 mo/ (1-3 mo)	DVT (<1 mo/ (1-3 mo)	Pulmonary emboli (<1 mo/ (1-3 mo)	Other (<1 mo/ (1-3 mo)	Non-TE complications	Total numbers of reported SAEs (%)
Epo/CS (n=24)	0 (0%)	0	0	0	0	0	2	2 (8.3%)
Epo/DR (n=50)	1 (2.0%)	1 (1/0)	0	0	0	0	8	9 (18%)
Epo (n=153)	3 (1.9 %)	2 (2/0)	1 (1/0)	0	0	0	1	4 (2.6%)
Epo groups (n=227)	**4 (1.8%)**						**11**	**15 (6.6)**[f]
CS (n=275)	0 (0%)	0	0	0	0	0	12	12 (4.4%)
DR (n=638)	15 (2.4%)	4 (2/2)	5 (5/0)	1(0/1)	4 (2/2)	1(1/0)[e]	29	44 (6.9%)
Control group (n=1302)	12 (0.9%)	2 (2/0)	6 (5/1)	3(0/3)	1 (0/1)	0	29	41 (3.1%)
Non Epo groups (n=2215)	**27 (1.2%)**						**70**	**97 (4.4%)**[f]
Totals (n=2442)	31 (1.3%)	9 (7/2)	12 (11/1)	4 (0/4)	5(2/3)	1 (1/0)	81	112 (5%)

Abbreviations: ITT, intention to treat; AT, as treated; mo, months; TIA, transient ischemic attack; DVT, deep venous thrombosis; Epo, erythropoietin; CS, cell saver; DR, postoperative drain re-infusion. Percentages are calculated within ITT or AT group (rows). Six SAE patients from the ITT analysis (Table 4A) did not actually receive the intervention. These patients were included in the control group in the AT analysis (Table 4B). Therefore, the control group comprised of 41 SAE patients in table 4B and 35 SAE patients in table 4A.

[a] TE complications were categorized in: myocardial infarction, stroke/TIA, DVT, pulmonary emboli or other

[b] non-TE complications were prosthesis related events (hip dislocations, prosthesis infections, wound infections, knee contractures, fractures), cardiovascular events (arrhythmia, blood pressure instability etc), allergic events, infection/sepsis not prosthesis related, bleeding etcetera

[c] categorized before and after one month (mo) post-operatively

[d] Chi2 test: p=0.69 (OR 1.1, 95% CI 0.66 to 1.9)

[e] denotes an arterial occlusion

[f] Chi2 test: p=0.13 (OR 1.5, 95% CI 0.88 to 1.9)

reported in the group that actually received Epo and DRAIN (table 5B: as treated group) (18%; n=9), but these were mostly non TE related. Six of them were due to cardiac failure in patients with a known cardiac history. One serious anaphylactic reaction occurred in the DR group after post-operative re-fusion of 50 mL, which was treated with adrenalin and fluid resuscitation, and resolved uneventfully.

DISCUSSION

In elective knee-and hip-arthroplasty patients, three widely used RBC transfusion alternatives were compared while using a baseline restrictive transfusion threshold. Only 11.6% of all patients were transfused. Within the control groups, 23% of patients with a low preoperative Hb (between 10 and 13 g/dL) and 8.3% in patients with a higher Hb level were transfused. In patients with the low preoperative Hb level (stratum I), Epo contributed significantly in avoiding RBC transfusions, but not in decreasing mean RBC reduction. In both strata I and II, the separate and combined use of cell saver and DRAIN did not result in a clinically significant decrease in RBC use. Since the revision surgery group was too small and effects were too heterogeneous, valid conclusions could only be made for the large primary surgery group (93% of the total cohort). Use of Epo in primary surgery patients resulted in a significant 12% absolute reduction and a 55% relative reduction in transfused patients irrespective of the use of cell saver or drain re-infusion. These results confirmed earlier reports that Epo has a significant benefit as a transfusion avoiding strategy (avoidance of exposure to allogeneic RBC transfusions) as well as a significant blood sparing effect (mean units RBC reduction). Our finding that neither cell saver nor DRAIN resulted in a clinically relevant RBC reduction may be explained by the low volume of recovered shed blood in combination with the applied restrictive transfusion threshold. This finding is consistent with a recent survey among 20 hospitals in the United States, in which the effect of blood salvage programs was investigated. The authors also observed that the volume of returned blood in orthopaedic joint surgery was small [27]. The development of better surgical techniques (i.e. less extensive incisions) to minimise blood loss may also have contributed to this effect.

Neither Epo nor blood salvage were cost-effective. From a hospital perspective, the additional costs for the Epo strategy in patients with low Hb levels were estimated at €785 per patient, mainly consisting of the additional Epo costs. Epo avoided a transfusion in about one in every nine patients, translating the cost estimate to €7300 per avoided transfusion. To justify such costs from a health economic perspective, transfusion would have to be associated with a considerable health risk. Specifically, at a cost-effectiveness acceptability threshold of €40.000 per quality adjusted life year, one in every hundred transfused patients would have to incur an average life expectancy loss of approximately

20 years (100 x 7300 / 40.000). According to haemovigilance registers, blood transfusion currently seems considerably safer than that [28]. In our trial, autologous blood re-infusion using cell saver or DRAIN did not reduce allogeneic RBC transfusions and from a health economic perspective the associated cost increase is not justified.

Strengths and limitations of the study

Our study has several strengths and limitations. Strengths were that the study was randomised, the study power was 90% and sufficient numbers of patients were included and evaluated. The design of the study was chosen to be optimally consistent with current clinical practice, allowing to evaluate the combined and separate effect of three types of transfusion alternatives. Despite this complex study design, patients were well balanced across the randomisation groups. Adherence to the restrictive transfusion protocol was over 95%. This high protocol adherence was in contrast to the non-adherence to the randomisation arms that occurred in all participating centres. Non-adherence to Epo randomisation in stratum I was high, namely 34% (n=114) and was mainly due to the surgery date being brought forward when surgery time became suddenly available. This resulted in lack of time to prescribe three weeks of Epo therapy with subsequent protocol violation in the assignment to Epo. This situation may be typical for the Netherlands: at the time of this study the waiting lists for elective orthopaedic surgery were short (less than two months). In the analysis of the effect of autologous re-infusion, we observed that patients randomised to receive autologous re-infusion showed an unexpected, statistically significant, 4% lower use of Epo than patients randomized not to receive autologous re-infusion (Table 4B: autologous versus no autologous: 8% versus 12%). This may have biased our analysis at the expense of autologous re-infusion. However, since the transfusion rate among patients with low Hb was 26%, the overall influence of this imbalance on the transfusion rate cannot have been more than 1% (i.e. 26% of 4%), which is insufficient to alter our negative conclusion on autologous re-infusion.

Non-adherence to the cell saver and to the DRAIN was present in 13% (n=62) and 11% (n=111) of patients, respectively. Despite use of these devices, some patients did not receive any autologous blood due to insufficient drainage and/or collection of shed blood. Of the patients who did receive the intended intervention (as treated analysis), use of Epo in primary surgery patients showed that RBC reduction was larger, but still did not reach the 75% reduction level as hypothesized. In this analysis, use of blood salvage devices did result in a significant decrease in RBC use in primary surgery patients, who had a normal preoperative Hb level. However, since the absolute reduction was only 0.08 RBC units, it is questionable whether this is clinically relevant.

Another limitation of the study may be that only the study investigators were blinded and not the clinical team, who was informed of the assigned randomisation arm in order to avoid protocol violations. The non-blinding of Epo may have resulted in transfusion

bias, however this was not likely, since clinicians adhered to the transfusion protocol and violations were equal in all randomisation groups.. Furthermore, since the study was not powered for safety evaluation, we are unable to draw valid conclusions on the incidence of complications. All patients in our study received thrombosis-prophylaxis, which may have an effect on the low proportion of thrombo-embolic complications in the Epo group. This finding is in contrast to a safety study in orthopaedic spine surgery patients not receiving thrombosis-prophylaxis that reported a higher incidence of post-operative thrombotic events (deep vein thrombosis in particular) in patients after Epo treatment compared to a control group [29]. Finally, all transfusion trials are flawed due to the fact that randomisation occurs prior to surgery, while the majority of included patients do not reach the trigger for transfusion. This however does not invalidate in any respect the intention-to-treat approach [30].

Implications for clinicians and other researchers

This study may serve as a valid estimate for the primary hip- and knee surgery population in the Netherlands (16.6 million inhabitants), where approximately 50.000 total hip and knee replacements are performed annually, which is expected to rise to over 100.000 in 2030 [31]. Considering the fact that use of autologous blood re-infusion devices are used in up to 80% of Dutch hospitals (year 2007) [11], and our findings that they have no blood sparing benefit, omission of these devices from blood management protocols may result in a considerable decrease in health care costs.

Our results confirm that patients with a low preoperative Hb were more likely to receive a RBC transfusion (23% of 138 control group patients in stratum I compared to 8.3% of 698 non-anaemic control group patients in stratum II) and the patients with overt pre-operative anaemia according to the WHO criteria even required a RBC transfusion in 32.4% [32-36]. For these anaemic patients, Epo is recommended in recently published guidelines, after excluding treatable causes of anaemia [33]. In our study, we did not investigate the cost-effectiveness of Epo in the anaemic subpopulation (210 patients in this study), nor corrected for anaemia, and propose to wait for more data to decide on the use of Epo in this subpopulation. Future research to aim for optimal blood management should rather focus on cheaper alternatives to Epo, such as iron supplements for the anaemic patient who is most at risk of being transfused.

CONCLUSIONS

In elective knee-and hip-arthroplasty patients with preoperative Hb levels between 10 and 13 g/dL, even with a restrictive transfusion policy, Epo contributed as a significant transfusion alternative, but at unacceptably high costs. No clinically relevant decrease in RBC

use was found using autologous blood salvage by cell saver or DRAIN, which consequently only increased costs. These findings may have a substantial impact for current blood management protocols in which Epo usage and autologous blood re-infusion devices are frequently embedded.

What is already known on this topic:

- In elective hip- and knee- replacement surgery, the use of Erythropoietin (Epo) and autologous blood re-infusion as red blood cell alternatives are widely accepted and embedded in daily practice.
- However, the effect sizes differ in literature and are smaller when a transfusion protocol is present.
- Since transfusion protocols have become more restrictive, it is questionable whether these alternatives are still in place in blood management protocols.

What this study adds:

Even with a restrictive transfusion policy, Epo significantly decreased red blood cell use in elective knee-and hip-arthroplasty patients with a preoperative Hb value of 13 g/dL or less, but at unacceptably high costs. The use of cell saver or postoperative drain re-infusion device did not result in a red blood cell reduction and consequently only increased costs.

Based on costs without apparent clinical benefit, the findings of this study do not support the use of Epo or autologous blood re-infusion by cell saver or post-operative drain re-infusion device as transfusion alternatives and support the use of a restrictive transfusion policy in this study population.

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Contributors

AB was principal investigator. CS, AK and RN were lead clinical investigators. CS was study coordinator. RB was lead investigator for statistics, study design and management. CS, RN, JH and AB obtained ethical approval of the study and obtained funding. AB and RN supervised the study. All authors were members of the project management team. RN, EK, RO, RP, CS

and AK participated in recruitment of centres or patients, or both. TJ was responsible for the design of the data base and the data (quality) management as well as basic reporting of data to the investigators. WH was responsible for the economic evaluation. All authors participated in data interpretation and in reporting of results. All authors have seen and approved the final version.

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Data sharing: Dataset is available from the corresponding author at C.So@sanquin.nl

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ONLINE-ONLY MATERIAL

Includes:

- Sample size calculation (text)
- eFigure 1 Statistical design of the study
- Legend to eFigure 1
- eTable 1 ITT analysis of separate cell saver and DRAIN effect by surgery group (primary or revision)
- eTable 2 AT analysis of revision surgery patients
- eTable 3 AT analysis of separate cell saver and DRAIN effect by surgery group (primary or revision)

SAMPLE SIZE CALCULATION

The actual design is made keeping in mind that theoretically there could be an interaction between the Epo, the cell saver and the DRAIN effect on the outcome. If such an interaction is clinically irrelevant (and statistically absent) power can be gained without introducing any bias, by making the univariate comparisons as indicated in the design chart (eFigure 1), through pooling the unbiased effects within two or more stratification categories, leading to a smaller sample size. However, we have designed the trial to have sufficient power even in the case of (severe) interaction, i.e. the situation in which for example the effect of "DRAIN with or without cell saver" versus "Neither DRAIN nor cell saver" would in itself depend on the Epo-stratum. If that were the case, we would have to report this effect in the three strata separately. It should be noted that only in our statistical design (eFigure 1) the cell saver device is denoted as cell saver+DRAIN+ for statistical convenience, but for convenience of the reader the cell saver group is denoted in the print article as cell saver+DRAIN-. Likewise, the Epo versus no-Epo effect is an "intention-to-treat" estimate so one could argue that it is only necessary to compare both arms without regard for the other randomisation consequences (DRAIN and cell saver). However, the randomisation of the three components takes place at the same time, i.e. it is actually a randomisation into 6 different treatment modalities (depending on the stratification variables). Hence it would be prudent to anticipate a possible interaction between the Epo effect and the cell saver/DRAIN effect. In a worst case scenario the "pure" Epo effect could then only be estimated by comparing the Epo versus non-Epo in the no-DRAIN, no-cell saver situation, thus reducing the sample size for this comparison.

To accommodate all these scenario's and realizing that this clinical design should answer the various comparisons in one study and also if assumptions of no-interaction will turn out not to be met, we decided to safeguard the power of the trial such that at the end a decision among all scenario's can be made with 90% power. The following assumptions are made:

1. 1/3 is eligible for Epo, randomisation for EPO is 1:1
2. Mean transfusion rate is 1.0 RBC Unit, with SD=1.4 (medium risk scenario SD=1.6, worst case scenario SD=1.8)
3. Power of the trial =90%
4. Hypothesis 1: Epo versus no Epo, Hypothesis 2: DRAIN with or without cell saver versus none (any autologous blood re-infusion device versus no autologous re-infusion). Hypothesis 3: cell saver versus no cell saver in case of autologous re-infusion (intra-and postoperative re-infusion by cell saver versus postoperative re-infusion by DRAIN).

In case of hypothesis 1: for a 75% reduction in blood use (from 1,0 to 0,25 U RBC) 125 patients are needed per group. Therefore, 2 times 125 patients are needed. In a worst case scenario (SD= 1.8) 3 times 2 times 125=750 patients are needed.

Please note that we do not compare percentages but average amounts of blood used.

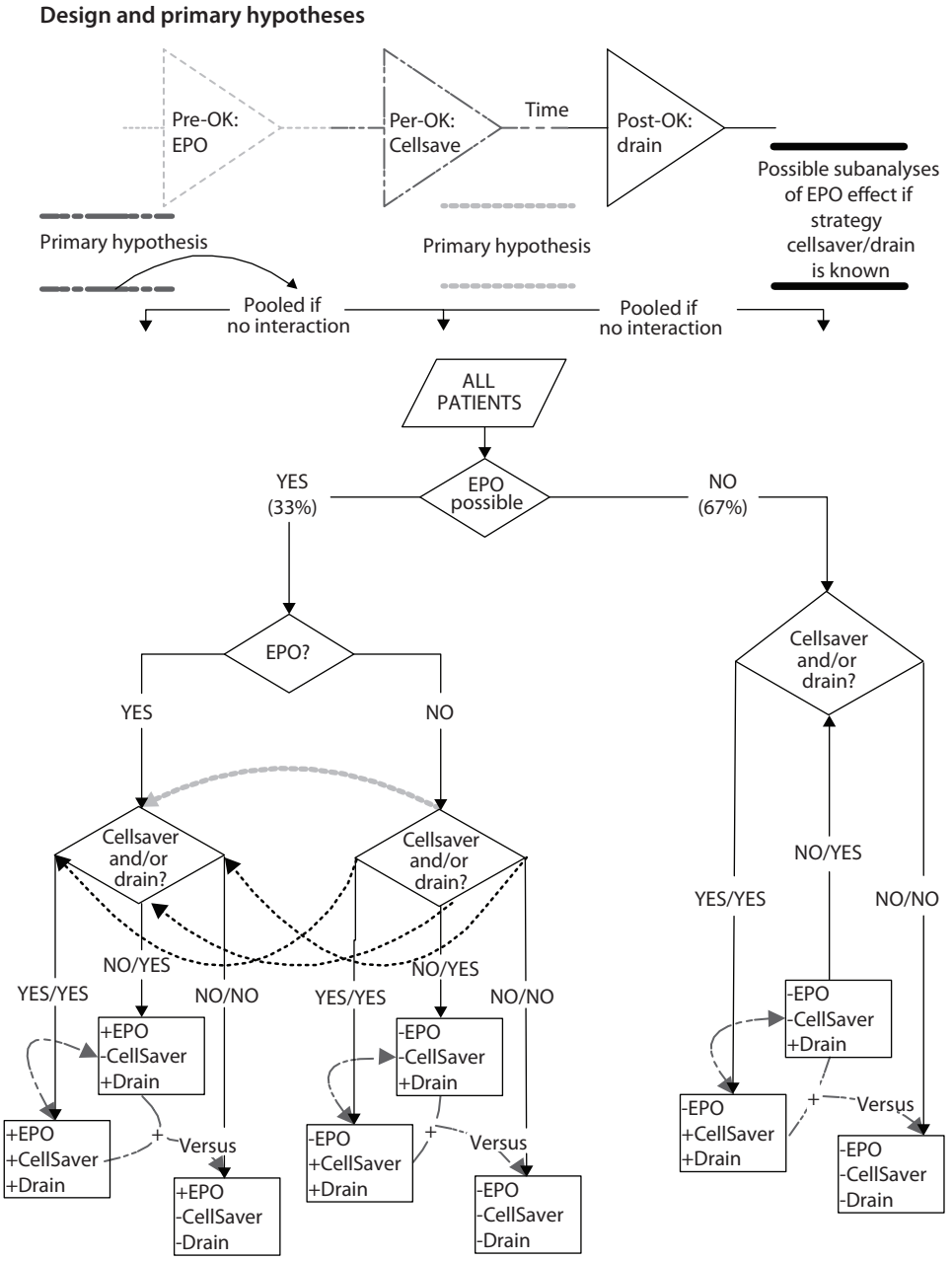
In case of hypothesis 2 and hypothesis 3: this involves 2/3 of all patients included (sum of "DRAIN with cell saver" and "DRAIN without cell saver"). For a reduction of 30% in blood use (from 1,0 to 0,7 U RBC) we need 1000 patients in a worst-case scenario, so for this group it will be 3/2 times1000=1500 patients. We then protect the trial against severe clinical interactions between the various components of the distinguished scenario's:

However, in case of interaction between Epo and DRAIN/cell saver the analysis must be performed within the no Epo group (this consists of 5/6 of the total number of patients), so 6/5 times 1500=1800 patient inclusions are needed. In the worst case, analysis can only be performed in ''no Epo not eligible for Epo group"=2/3 of total inclusions, that is: 3/2 times 1500=2250 patients.

Since we have more than one test involved in reaching a final recommendation for a scenario, multiple testing should be taken into account: to protect against multiple testing a Bonferroni correction is used and in case of a SD of 1.4 and 30% mean RBC reduction we need 1800 patient inclusions. When analysis has to be restricted to the non-Epo group we need 6/5 times 1800=2200 inclusions.

In conclusion when 2250 patients are included we expect sufficient power for all hypotheses 1 to 3, even in a worst case scenario. When interaction is not found, then pooling is allowed and much less than 2250 patients are needed.

An interim analysis will be performed at 1000 patients by an independent Data Safety and Monitoring Committee. Study-stop criteria are: 1. p smaller than 0.025 for the primary endpoint; 2. p smaller than 0.025 for less than 30% reduction by Epo and less than 15% by transfusions by shed blood (cell saver/DRAIN).



eFigure 1. Statistical design of the study

Since the cell saver device (OrthoPAT®) collected and re-infused both intra-and postoperative wound blood, the DRAIN notation in combination of cell saver (cell saver+DRAIN+) denotes the use of the cell saver device only. This notation is used only in this figure and has been used for statistical purposes only to calculate sample sizes and to construct the hypotheses. The light gray arrow denotes hypothesis 1 (Epo versus no Epo). The dark gray arrows denote hypothesis 2 (autologous blood versus no autologous blood) and hypothesis 3 (cell saver device versus DRAIN device within the autologous blood re-infusion groups). In case of no interaction, groups were pooled.

eTable 1. ITT analysis of separate cell saver (CS) and DRAIN (DR) effect by surgery group (primary or revision)

Primary surgery patients					
N=2258	**Mean RBC use (U) (SD)**	**Mean adjusted difference[a] (95% CI)**	**Ratio[b] (95% CI)**	**Proportion transfused (%)**	**Adjusted odds ratio[c] DR versus CS (95% CI)**
Stratum I no Epo (n=311)					
Autologous blood (n=184)	0.78 (1.7)				
CS (n=56)	0.93 (1.8)	0.13	1.3	30	1.1 (0.6 to 2.2)
DR (n=128)	0.71 (1.6)	(-0.46 to 0.73)	(0.64 to 2.4)	28	
Stratum I with Epo (n=302)					
Autologous blood (n=190)	0.36 (1.1)				
CS (n=64)	0.36 (0.7)	-0.12	0.98	20	1.4 (0.7 to 3.1)
DR (n=126)	0.37 (1.2)	(-0.49 to 0.25)	(0.44 to 2.2)	15	
Stratum II (Normal Hb) (n=1645)					
Autologous blood (n=987)	0.16 (0.7)				
CS (n=322)	0.13 (0.5)	-0.12	0.74	7.1	1.0 (0.6 to1.7)
DR (n=665)	0.17 (0.7)	(-0.22 to -0.02) p=0.02	(0.41 to 1.2)	7.1	
Revision surgery patients					
N=184	**Mean RBC use (U) (SD)**	**Mean adjusted difference[a] (95% CI)**	**Ratio[b] (95% CI)**	**Proportion transfused (%)**	**Adjusted odds ratio[d] (95% CI)**
Stratum I no Epo					
Autologous blood (n=22)	0.59 (1.0)				
CS (n=8)	0.63 (1.2)	-0.20	1.1	25	0.83 (0.12 to 6.0)
DR (n=14)	0.57 (0.9)	(-1.63 to 1.22)	(0.0 to 4.8)	29	
Stratum I with Epo					
Autologous blood (n=24)	3.0 (6.5)				
CS (n=8)	1.3 (2.8)	-3.14	0.33	25	0.43 (0.07 to 2.8)
DR (n=16)	3.8[4] (7.6)	(-9.4 to 3.1)	(0.0 to 2.2)	44	
Stratum II (Normal Hb)					
Autologous blood (n=74)	0.64 (2.2)				
CS (n=26)	0.46 (1.3)	-0.81	0.63	15	0.91 (0.25 to 3.4)
DR (n=48)[e]	0.73 (2.5)	(-2.0 to 0.40) p=0.18	(0.05 to 3.0)	17	

Abbreviations: ITT=intention to treat; CS=cell saver; DR=postoperative drain re-infusion; Epo=erythropoietin; RBC=red blood cell; U=units; CI=confidence interval; SD=standard deviation.

[a] adjusted for hospital and for knee/ hip surgery; confidence intervals for reference purposes only (assuming normality)

[b] ratio was defined as the quotient of mean RBC values of two groups being compared; all estimates and robust standard errors were obtained via bootstrapping in R

[c] all estimates and standard errors were obtained using the Mantel-Haenszel procedure, stratifying by the pre-specified stratification factors hospital and knee/hip surgery

[d] included 2 hip surgery patients with respectively 17 and 27 RBC transfusions; when analysed as treated, these patients did not receive the drain device and ended in the epo only group. (see eTable 3)

[e] mean of hip surgery group (n=26) was 1.27 (3.3) and mean of knee surgery group (n=22) was 0.09 (0.4)

eTable 2. AT analysis of revision surgery patients (combined effect of cell saver and DRAIN denoted as autologous blood)

Revision surgery patients					
N=184	**Mean RBC use (U) (SD)**	**Mean adjusted difference[a] (95% CI)**	**Ratio[b] (95% CI)**	**Proportion transfused (%)**	**Adjusted odds ratio[c] (95% CI)**
Stratum I no Epo (n=45)					
Autologous blood (n=26)	1.62 (3.6)	0.91	1.92	39	1.8
No autologous blood (n=19)	**0.84 (1.6)**	(-0.99 to 2.8)	(0.53 to 8.8)	**26**	(0.48 to 6.4)
Stratum I with Epo (n=25)					
Autologous blood (n=11)	1.0 (2.5)	-0.92	0.45	18	0.82
No autologous blood (n=14)[d]	2.2 (7.2)	(-5.8 to 3.9)	(0.0 to 9.0)	21	(0.11 to 6.0)
Pooled Epo effects					
With Epo (n=25)	1.7 (5.6)	0.88	1.3	20	0.60
No Epo (n=45)	1.3 (2.9)	(-1.12 to 2.88)	(0.11 to 4.6)	33	(0.20 to 1.8)
Stratum II (n=113)[e]					
Autologous blood (n=62)	0.56 (2.2)	0.04	1.2	13	0.80
No autologous blood (n=51)	**0.49 (1.4)**	(-0.68 to 0.75)	(0.25 to 4.5)	**16**	(0.28 to 2.3)

Abbreviations: AT=as treated; RBC=red blood cell; U=units; CI=confidence interval; SD=standard deviation; Epo=erythropoietin. Control groups are outlined in bold

[a] adjusted for hospital and for knee/ hip surgery; confidence intervals for reference purposes only (assuming normality)

[b] ratio was defined as the quotient of mean RBC values of two groups being compared; all estimates and robust standard errors were obtained via bootstrapping in R

[c] all estimates and standard errors were obtained using the Mantel-Haenszel procedure, stratifying by the pre-specified stratification factors hospital and knee/hip surgery

[d] denotes Epo alone group.

[e] in one patient it was unknown whether the device was truly received

eTable 3. AT analysis of separate cell saver (CS) and DRAIN (DR) effect by surgery group (primary or revision)

Primary surgery patients					
N=2258	**Mean RBC use (U) (SD)**	**Mean adjusted difference[a] (95% CI)**	**Ratio[b] (95% CI)**	**Proportion transfused (%)**	**Adjusted odds ratio[c] DR versus CS (95% CI)**
Stratum I no Epo (n=410)					
Autologous blood (n=240)					
CS (n=70)	0.79 (1.5)	0.09	1.34	31	1.4
DR (n=170)	0.59 (1.4)	(-0.35 to 0.54)	(0.72 to 2.3)	25	(0.73 to 2.5)
Stratum I with Epo (n=202)					
Autologous blood (n=81)					
CS (n=27)	0.19 (0.6)	0.01	1.11	11	1.2
DR (n=54)	0.17 (0.5)	(-0.30 to 0.31)	(0.0 to 5.1)	9.3	(0.27 to 5.6)
Stratum II (n=1645)					
Autologous blood (n=888)[d]					
CS (n=282)	0.13 (0.5)	-0.15	0.83	6.4	0.94
DR (n=606)	0.15 (0.7)	(-0.26 to -0.04) p=0.01	(0.42 to 1.5)	6.3	(0.3 to 1.7)
Revision surgery patients					
N=184	**Mean RBC use (U) (SD)**	**Mean adjusted difference[a] (95% CI)**	**Ratio[b] (95% CI)**	**Proportion transfused (%)**	**Adjusted odds ratio[c] (95% CI)**
Stratum I no Epo (n=45)					
Autologous blood (n=26)					
CS (n=12)	2.5 (5.1)	0.94	2.92	33	0.67
DR (n=14)	0.86 (1.0)	(-2.68 to 4.56)	(0.26 to 9.6)	43	(0.14 to 3.3)
Stratum I with Epo (n=25)					
Autologous blood (n=11)					
CS (n=5)	1.6 (3.6)	0.01	3.2	20	1.3
DR (n=6)	0.50 (1.2)	(-5.5 to 5.5)	(0.0 to 9.6)	17	(0.06 to 26.9)
Stratum II (n=113)					
Autologous blood (n=62)					
CS (n=26)	0.58 (1.4)	-0.24	1.0	19	2.4
DR (n=36)	0.56 (2.7)	(-1.66 to 1.19)	(0.16 to 13.3)	8.3	(0.54 to 11.1)

Abbreviations: AT=as treated; CS=cell saver; DR=postoperative drain re-infusion; RBC=red blood cell; U=units; CI=confidence interval; SD=standard deviation; Epo=erythropoietin.

[a] adjusted for hospital and for knee/ hip surgery; confidence intervals for reference purposes only (assuming normality)

[b] ratio was defined as the quotient of mean RBC values of two groups being compared; all estimates and robust standard errors were obtained via bootstrapping in R

[c] all estimates and standard errors were obtained using the Mantel-Haenszel procedure, stratifying by the pre-specified stratification factors hospital and knee/hip surgery

[d] one patient received CS (intra-operatively) AND drain (postoperatively)