Patient Blood Management in Elective Total Hip- and Knee-replacement Surgery (Part 1)

A Randomized Controlled Trial on Erythropoietin and Blood Salvage as Transfusion Alternatives Using a Restrictive Transfusion Policy in Erythropoietin-eligible Patients

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ABSTRACT

Background: Patient blood management combines the use of several transfusion alternatives. Integrated use of erythropoietin, cell saver, and/or postoperative drain reinfusion devices on allogeneic erythrocyte use was evaluated using a restrictive transfusion threshold.

Methods: In a factorial design, adult elective hip- and knee-surgery patients with hemoglobin levels 10 to 13 g/dl (n = 683) were randomized for erythropoietin or not, and subsequently for autologous reinfusion by cell saver or postoperative drain reinfusion devices or for no blood salvage device. Primary outcomes were mean allogeneic intra- and postoperative erythrocyte use and proportion of transfused patients (transfusion rate). Secondary outcome was cost-effectiveness.

Results: With erythropoietin (n = 339), mean erythrocyte use was 0.50 units (U)/patient and transfusion rate 16% while without (n = 344), these were 0.71 U/patient and 26%, respectively. Consequently, erythropoietin resulted in a nonsignificant 29% mean erythrocyte reduction (ratio, 0.71; 95% CI, 0.42 to 1.13) and 50% reduction of transfused patients (odds ratio, 0.5; 95% CI, 0.35 to 0.75). Erythropoietin increased costs by €785 per patient (95% CI, 262 to 1,309), that is, €7,300 per avoided transfusion (95% CI, 1,900 to 24,000). With autologous reinfusion, mean erythrocyte use was 0.65 U/patient and transfusion rate was 19% *with* erythropoietin (n = 214) and 0.76 U/patient and 29% *without* (n = 206). Compared with controls, autologous blood reinfusion did not result in erythrocyte reduction and increased costs by €537 per patient (95% CI, 45 to 1,030).

Conclusions: In hip- and knee-replacement patients (hemoglobin level, 10 to 13 g/dl), even with a restrictive transfusion trigger, erythropoietin significantly avoids transfusion, however, at unacceptably high costs. Autologous blood salvage devices were not effective. **(Anesthesiology 2014; 120:839-51)**

PATIENT blood management promotes the combined use of erythrocyte transfusion alternatives as a multimodel strategy.[1] The effect on erythrocyte use of the separate alternatives may vary considerably (from none to 80%) and is strongly related to the use of a transfusion threshold.[2–9] Because transfusion policies have become more restrictive, it is questionable whether the currently accepted transfusion alternatives can still effectively reduce erythrocyte use. Moreover, evidence is lacking on the combined use of these alternatives. Over the years, the use of preoperative autologous donation has declined due to logistical problems and wastage.[10,11] However, the use of erythropoietin and perioperative autologous blood salvage have become increasingly popular worldwide, including The Netherlands.[12] In a number of randomized, controlled trials involving elective total hip– and knee–replacement surgery patients, erythropoietin resulted in a significant reduction in mean erythrocyte use (referred to as "blood-sparing") and a significant reduction in the proportion of transfused patients (referred to as "transfusion-avoiding") of up to 75%, when using a

What We Already Know about This Topic

- Erythrocyte transfusion is associated with a significant impact on postoperative morbidity, making transfusion policies more restrictive
- Whether the currently accepted transfusion alternatives can still effectively reduce erythrocyte use is uncertain

What This Article Tells Us That Is New

- In this prospective, randomized, controlled trial including 683 patients with a preoperative hemoglobin level between 10 and 13 g/dl undergoing hip and/or knee arthroplasty, erythropoietin was found to significantly reduce the number of patients requiring the use of erythrocyte transfusion, but not the amount of erythrocytes transfused
- Costs due to erythropoietin were €7,300 per avoided transfusion.
- Autologous blood salvage devices were not effective in sparing erythrocyte transfusion

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restrictive transfusion threshold of 8 g/dl. In addition, these studies showed that an optimal benefit from erythropoietin is obtained in patients with preoperative hemoglobin levels between 10 and 13 g/dl to decrease erythrocyte use.[8,13,14]

Intraoperative use of a cell saver may recover up to 70% of the shed blood in orthopedic surgery,[15] which may significantly reduce erythrocyte use.[9] Postoperative reinfusion of autologous shed blood may also result in allogeneic erythrocyte reduction, although reported results are not consistent.[2–5,16–20] The evidence for erythrocyte reduction by autologous salvaged blood reinfusion is generally based on small and/or underpowered studies often not applying a restrictive transfusion threshold. To address this issue, we performed a multicenter study with adequate power, to investigate whether the combined and separate use of erythropoietin, the intra- and postoperative use of cell saver or the use of a postoperative drainage and reinfusion device (further mentioned as DRAIN) as transfusion alternatives, resulted in an allogeneic erythrocyte reduction in patients undergoing elective total hip– or knee–replacement surgery while applying a restrictive transfusion policy to all patients. We hypothesized that a 75% reduction in both mean erythrocyte use and proportion transfused patients can be achieved by use of erythropoietin and that a 30% reduction in both mean erythrocyte use and proportion of transfused patients can be reached by use of autologous blood salvage devices. In addition, we compared cost-effectiveness of the use of erythropoietin, cell saver, and DRAIN. In this study, we report on the erythropoietin-eligible patients with preoperative hemoglobin values between 10 and 13 g/dl.

Materials and Methods

This randomized, multicenter, controlled study was registered in the public registry: controlled-trials.com, (No. ISRCTN 96327523) and the Dutch Trial Register (No. NTR303). Approval was obtained from the ethics committee at each participating center 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. Included were adult patients (18 yr or older), scheduled for primary or revision total hip– or knee–replacement surgery. These patients were enrolled between May 1, 2004 and October 1, 2008 from four hospitals in The Netherlands (one university hospital and three medium-sized to large general hospitals) with study closure after completed follow-up on October 1, 2009.

Patients were excluded if they had untreated hypertension (diastolic blood pressure >95 mmHg); a serious disorder of the coronary, peripheral and/or carotid arteries; a recent myocardial infarction or stroke (within 6 months); sickle cell anemia; a malignancy in the surgical area; a contraindication for anticoagulation prophylaxis; a known allergy to erythropoietin; 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-randomized, multicenter trial in which the patients were stratified for the preoperative hemoglobin level, the hospital, and type of surgery (primary/revision as well as hip/knee). Within each combination of these stratification factors, a balanced randomization for the treatment arms was achieved. Double randomization included randomization for erythropoietin and randomization for autologous blood reinfusion by cell saver or DRAIN. By selecting this factorial design, the three transfusion alternatives can be analyzed in a combined setting as well as separately, to resemble current clinical practice in an optimal way. Randomization took place in one run for all possible combinations using a computer-generated allocation table, but is here described sequentially. Patients were stratified according to the preoperative hemoglobin level with a hemoglobin cutoff level of 13 g/dl: patients in stratum I (low hemoglobin = hemoglobin level between 10 and 13 g/dl) were randomized for erythropoietin or no erythropoietin. Patients in stratum II (normal hemoglobin = hemoglobin level of 13 g/dl and higher) were not eligible for erythropoietin and effects of autologous blood use in this patient group are described elsewhere (part 2).[21] Because total knee–replacement procedures were performed using a pneumatic tourniquet, which was deflated after wound closure, intraoperative use of cell saver was not applicable in this group and consequently total knee–replacement surgery patients were excluded from randomization for cell saver. All patients were further randomized for two (total knee replacement) or three (total hip replacement) autologous modalities: (1) an intra- and postoperative autologous reinfusion device (cell saver) that washed, filtered, and reinfused the autologous shed blood (only in hip surgery), (2) a postoperative autologous reinfusion drainage system (DRAIN) that filtered and

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reinfused 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 was discarded. For practical purposes (after checking for homogeneity in the results obtained with the two devices), we present the modalities 1 and 2 as a combined autologous (AUTO) group. Within the AUTO group, both cell saver and DRAIN modalities were allocated randomly in a 1:1 ratio and randomization was completely balanced. The randomization resulted in the following four combinations: (1) erythropoietin+AUTO+; (2) erythropoietin+AUTO–; (3) erythropoietin–AUTO+; and (4) erythropoietin–AUTO– (*i.e.*, control group). A separate randomization list was created, using blocks of random length to avoid predictability of the random-treatment assignment toward the end of each block. All patients were transfused according to a restrictive transfusion policy as advised in the Dutch transfusion guidelines.* Preoperative anemia was defined according to the World Health Organization criteria[22] (for males: hemoglobin level <13 g/dl and for females: hemoglobin level <12 g/dl). Participating hospitals were free to choose the type of erythropoietin (*i.e.*, α-erythropoietin or β-erythropoietin) and the postoperative drainage system, but were obligated to use the same type throughout the study. The type of cell saver (OrthoPAT®; Haemonetics, Breda, The Netherlands) was uniform for all patients.

Transfusion Protocol and Procedures

The Dutch national transfusion protocol was applied for the use of allogeneic erythrocyte transfusions. This guideline considers age and comorbidity as triggers for transfusion. High risk included incapability to enlarge cardiac output to compensate for anemia, serious pulmonary disease, or symptomatic cerebrovascular disease. The following pretransfusion thresholds were used: hemoglobin level, 6.4 g/dl (4.0 mmol/l) for younger than 60 yr of age and normal risk; hemoglobin level, 8.1 g/dl (5.0 mmol/l) for age 60 yr or older and normal risk; hemoglobin level, 9.7 g/dl (6.0 mmol/l) in case of high risk irrespective of age. Hemoglobin values were derived from millimol per liter which is the standard unit to denote hemoglobin values in The Netherlands.

The protocol included a single-unit transfusion policy (erythrocyte units transfused one by one to reach a target hemoglobin level above the defined hemoglobin thresholds). Autologous blood was reinfused, independent of the hemoglobin value. A check for transfusion protocol adherence was included in the Case Report Form by verifying the pretransfusion hemoglobin, age, and cardiovascular history (for risk estimation) of the patient at every transfusion event. The erythrocyte units were prepared from whole blood donations. After centrifugation, followed by plasma and buffycoat removal, SAG-M (saline, adenine, glucose, mannitol) was added before prestorage leukocyte filtration, resulting in a final erythrocyte product with a hematocrit level between 0.50 and 0.65 l/l (40 to 54 g Hb), a total volume of 270 to 290 ml and less than 1 × 10E6 leukocytes per unit. All patients received 6 weeks of postoperative antithrombotic prophylaxis with subcutaneous low–molecular-weight heparin starting the day before surgery. Antiplatelet agents (nonsteroidal antiinflammatory drugs, 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 international normalized ratio values, which were required to be 1.8 or lower before surgery.

Treatment allocation was random using a uniform distribution and created a pregenerated list of sufficient length, based on the maximum expected sample size in each stratum. For each subject to be randomized, 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. Patients were recruited by the orthopedic surgeons and by the research nurses. 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 randomization list to check for selection bias. Total hip–replacement surgery patients who were randomized for cell saver were automatically assigned to postoperative autologous blood reinfusion, as the cell saver collected blood intra- *and* postoperatively.

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

Outcome Measures

The primary outcome measures were intra- and postoperative mean erythrocyte use and the proportion of transfused patients, up to 3 months after surgery. By comparing the mean erythrocyte use we quantified the "blood-sparing" effect, and by comparing the proportion of transfused patients, we quantified the "transfusion-avoiding" effect. Cost and cost-effectiveness were reported as secondary outcomes. All primary and secondary endpoints were scored until 3 months after surgery. Serious adverse events (SAEs) were reported up to 3 months as well and were defined as death, life-threatening events, (prolongation

* Available at: http://www.sanquin.nl/repository/documenten/en/prod-en-dienst/287294/blood-transfusion-guideline.pdf (p.169). Accessed October 3, 2011.

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of) hospitalization, and/or events resulting in persistent disability, and categorized into prosthesis related (dislocation, wound infection or deep prosthetic infection, fractures, or limitation in movement), thromboembolic (deep venous thrombosis diagnosed by ultrasound and not based on active surveillance, pulmonary emboli, stroke or transient ischemic attack, myocardial infarction), other cardiovascular events, allergy, infection/sepsis (not prosthesis related), malignancy, and other events.

Interventions

A fixed weekly dose of 40,000 U was given to patients randomized for erythropoietin with simultaneous prescription of ferrofumarate 200 mg three times per day (195 mg Fe^{2+} a day) for 3 weeks before surgery. A total of four erythropoietin doses were administered by subcutaneous injection on days—21, 14, 7, and on the day of surgery (day 0), respectively. If the hemoglobin level, determined before the fourth dose, exceeded the value of 15 g/dl, the final erythropoietin dose was withheld. The erythropoietin preparations were Neorecormon® (erythropoietin-β; Roche Nederland BV, Woerden, The Netherlands) (three hospitals) or Eprex® (erythropoietin-α; Janssen-Cilag BV, Tilburg, The Netherlands) (one hospital). A protocol violation was scored if a patient, assigned to erythropoietin, did not receive erythropoietin. If at least one erythropoietin dose was given this was not regarded as violation.

The OrthoPAT® cell saver was used for both intra- and postoperative collection and reinfusion of autologous blood, collected up to 6 h after surgery, in total-hip–replacement surgery patients. The collected shed blood was washed, centrifuged, and concentrated to a hematocrit level of 60 to 80% before being returned to the patient. A protocol violation was scored if the cell saver was assigned but not used.

Two different DRAIN devices were used for reinfusion of collected autologous blood up to 6 h after surgery: 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 mmHg and just before reinfusion a double-shielded 40-μm filter (Pall Lipiguard® SB filter; Pall Medical USA, Ann Arbor, MI) entrapping lipids larger than 10 μm and 2 log of leukocytes. The Bellovac-ABT® system uses intermittent suction pressure by a manually expandable bag at a maximum pressure of 90 mmHg and three filters: a 200-μm filter, a secondary 80-μm filter, and before reinfusion a third 40-μm filter. In a feasibility and efficacy study, we found both systems to be comparable.[23] A protocol violation was scored if the device was assigned but not used.

† Available at: http://www.medicijnkosten.nl. Accessed October 7, 2011.

‡ Available at: http://www.cvz.nl/binaries/content/documents/zinl-www/documenten/publicaties/overige-publicaties/1007-handleiding-voor-kostenonderzoek/Handleiding+voor+kostenonderzoek.pdf. Accessed October 7, 2011.

Sample Size

On the basis of the assumption that 1 of 3 of the patients were erythropoietin eligible (hemoglobin levels, <13 g/dl), 2,250 participants were required for the total study (stratum I and stratum II), to detect a difference of 75% in mean erythrocyte use by erythropoietin (hypothesis 1) and a difference of 30% in mean erythrocyte use by autologous blood reinfusion by either cell saver or DRAIN (hypothesis 2), with statistical power of 90% at a 5% significance level. Mean transfusion rate was assumed to be 1.0 erythrocyte unit, with SD = 1.4 in control patients.[24] To demonstrate a reduction of 75% in the mean erythrocyte use (from 1.0 to 0.25 U erythrocyte), twice the number of 125 erythropoietin-eligible patients (250 patients) were required. For the comparison of autologous reinfusion *versus* no reinfusion, a total of 1,000 patients were needed (stratum I and stratum II together).

The study design allowed us to investigate the erythropoietin *versus* no-erythropoietin effect (comparison 1), the combined autologous *versus* no-autologous effect (comparison 2), and the cell saver *versus* DRAIN effect (comparison 3). The large calculated sample size allowed analysis of the separate strata (low hemoglobin stratum I and normal hemoglobin stratum II) in case of severe interactions between randomization and stratification factors. We increased the total sample size to 2,500 to account for a study dropout rate of 10%. An interim analysis was carried out by an independent Data Safety Monitoring Committee (LUMC, Leiden, The Netherlands) at the halfway mark (958 inclusions), using an α of 2.5% (instead of 5%). As predefined stopping criteria were not reached, neither for futility nor for efficacy, the Data Safety Monitoring Committee advised to continue the study until its prespecified number of patients was obtained.

Economic Evaluation

Costs were estimated from a hospital perspective, with a 3-month time horizon. Health care was valued at the 2011 price level, using market prices for erythropoietin, cell saver, and DRAIN (€1,293 for four doses,† €160, and €61, respectively) and using standard prices for allogeneic erythrocyte products, intensive care unit stay, and non*intensive care unit* stay (€207 per unit, €2,249 and €471 per day, respectively).‡ The total costs per unit of erythrocyte transfused was estimated at four times the product price (*i.e.*, €829 per unit) including costs of compatibility tests and handling, according to the article by Shander *et al.*[25]

Average costs were compared according to intention to treat (ITT), using nonparametric bootstrapping (programmed in Stata/IC 11.0 for Windows; StataCorp LP, College Station, TX). Both primary and revision surgery groups were included. 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 with the difference in costs. CIs for the cost-effectiveness ratio were calculated using net-benefit analysis.[26]

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Statistical Analysis

Statistical analyses were performed both according to ITT and as-treated. For erythropoietin, as-treated is defined as the actual administration of at least one dose of erythropoietin; for autologous reinfusion it is defined as the actual use of the device whether or not autologous blood had been reinfused to the patient.

Variables were described by frequencies, by mean and SD, and by median and interquartile range in case of a nonnormal distribution. Although erythrocyte use is nonnormally distributed, we also report means (and SD), because the power and sample size calculation was based on assumptions of these means. Ratios (dividing the mean erythrocyte units of two randomized groups to be compared) and 95% CIs were reported to calculate the proportional reduction of erythrocyte units between the groups. CIs for these highly nonnormally distributed ratios were obtained *via* bootstrapping methods. For additional nonparametric testing we used the Mann–Whitney test. When comparing the proportion of patients receiving erythrocyte transfusions, a Mantel–Haenszel procedure was applied, correcting for the stratification factors hip/knee and primary/revision surgery. This led to an overall, adjusted common odds ratio (OR) as a comparison of the probability of "receiving at least one erythrocyte unit" between the randomization arms. A linear mixed model was used for the primary outcome (erythrocyte use) as a function of the interventions, the stratification factors (hip *vs.* knee and primary *vs.* revision surgery) and their interactions with the intervention. In case of significant interaction, the calculations were based on the predefined subpopulations (stratified by the interacting term), for example, primary or revision surgery patients. In case of nonsignificant interactions, the stratification factor was retained in the model as a main term for adjustment. The stratification factor "center" was included as a random effect.

After data checking the database was frozen. SPSS (version 17.0 for Windows; SPSS Inc., Chicago, IL) was used for all analyses. For the final analysis of the primary endpoint, we used a correction according to Haybittle–Peto[27]: by specifying $\alpha = 0.025$ in the interim analysis at the halfway mark, the final analysis should declare a *P* value to be significant when it is less than or equal to 0.034. Together with a Bonferroni correction for multiple outcome measures for the primary endpoint (both mean erythrocyte use and proportion of transfused patients), a *P* value of less than 0.017 (0.034/2) was thus considered statistically significant. For the other endpoints, a *P* value of less than 0.05 was considered statistically significant.

Results

From May 2004 to October 2008, 3,165 patients were screened for eligibility to participate in the total study (stratum I and stratum II); of these, 586 patients were not enrolled (fig. 1). After completion of the study in October 2009, 2,579 patients had been randomized, of whom 2,442 (95%) were evaluated. Seven hundred thirty patients with a hemoglobin level lower than 13 g/dl (stratum I) had been randomized, of whom 683 (94%) were evaluated. Of the 47 not-evaluated patients, for the majority (83%) surgery had been cancelled or performed elsewhere, six of these patients had received at least one erythropoietin dose. Baseline characteristics of the 683 evaluated erythropoietin-eligible patients are shown in table 1. Sixty-two percent were hip procedures and 38% were knee procedures, 87% of the patients were female. Revision surgery took place in 10% patients (n = 70), equally divided among the randomization groups. Mean preoperative hemoglobin level at first outpatient visit was 12.6 g/dl (SD, 0.75) and mean hematocrit level 0.39 l/l (SD, 0.04). Table 2 shows the perioperative characteristics. The median volumes of reinfused blood were 100 ml for cell saver (interquartile range, 50 to 200 ml) with mean hematocrit level: 0.71 (SD, 0.12) and 320 ml for DRAIN (interquartile range, 200 to 500 ml) with mean hematocrit level:0.33 (SD, 0.15). Postoperative hemoglobin values on day+1 were comparable between the groups with (AUTO groups) or without autologous blood reinfusion (control groups). Revision surgery patients differed significantly from primary surgery patients for intraoperative blood loss ($P < 0.001$) and mean duration of surgery ($P < 0.001$), but not for the median reinfused volumes ($P = 0.42$) (table 2)

Primary Endpoint

Among the 683 evaluated patients, mean erythrocyte use was 0.61 units (U)/patient (SD 1.8) and median use was 0 U/patient (range, 0 to 27). Twenty-one percent (n = 144) of patients received in total 416 erythrocyte transfusions (median, 2.0 U [interquartile range, 2.0 to 2.0]). The majority of patients (n = 124; 86%) were postoperatively transfused between 1 and 14 days after surgery. The median erythrocyte units used and proportion of transfused patients are outlined in tables 2 and 3. No heterogeneity was found among the four participating hospitals with respect to the effect size in any comparison of the primary endpoint. Total-hip–replacement surgery patients were significantly more often transfused than total-knee–replacement surgery patients (26 *vs.* 14%) ($P < 0.001$).

Erythropoietin Treatment Effect

To investigate the overall erythropoietin effect, regardless of the use of autologous blood, pooled estimates were calculated comparing the erythropoietin+ and erythropoietin– groups (a test for heterogeneity was not significant) (table 3). ITT analysis showed that erythropoietin resulted in a statistically nonsignificant 29% reduction of mean erythrocyte use/patient (ratio, 0.71; 95% CI, 0.42 to 1.13; $P = 0.15$) and a statistically significant 50% relative reduction in transfused patients (OR, 0.5; 95% CI, 0.35 to 0.75; $P < 0.001$). Because of significant interaction between primary or revision surgery and the allocated treatments (erythropoietin and autologous reinfusion; $P < 0.001$), we analyzed these patient groups separately (613 primary and 70 revision surgery patients). Because the revision surgery group was too small and too

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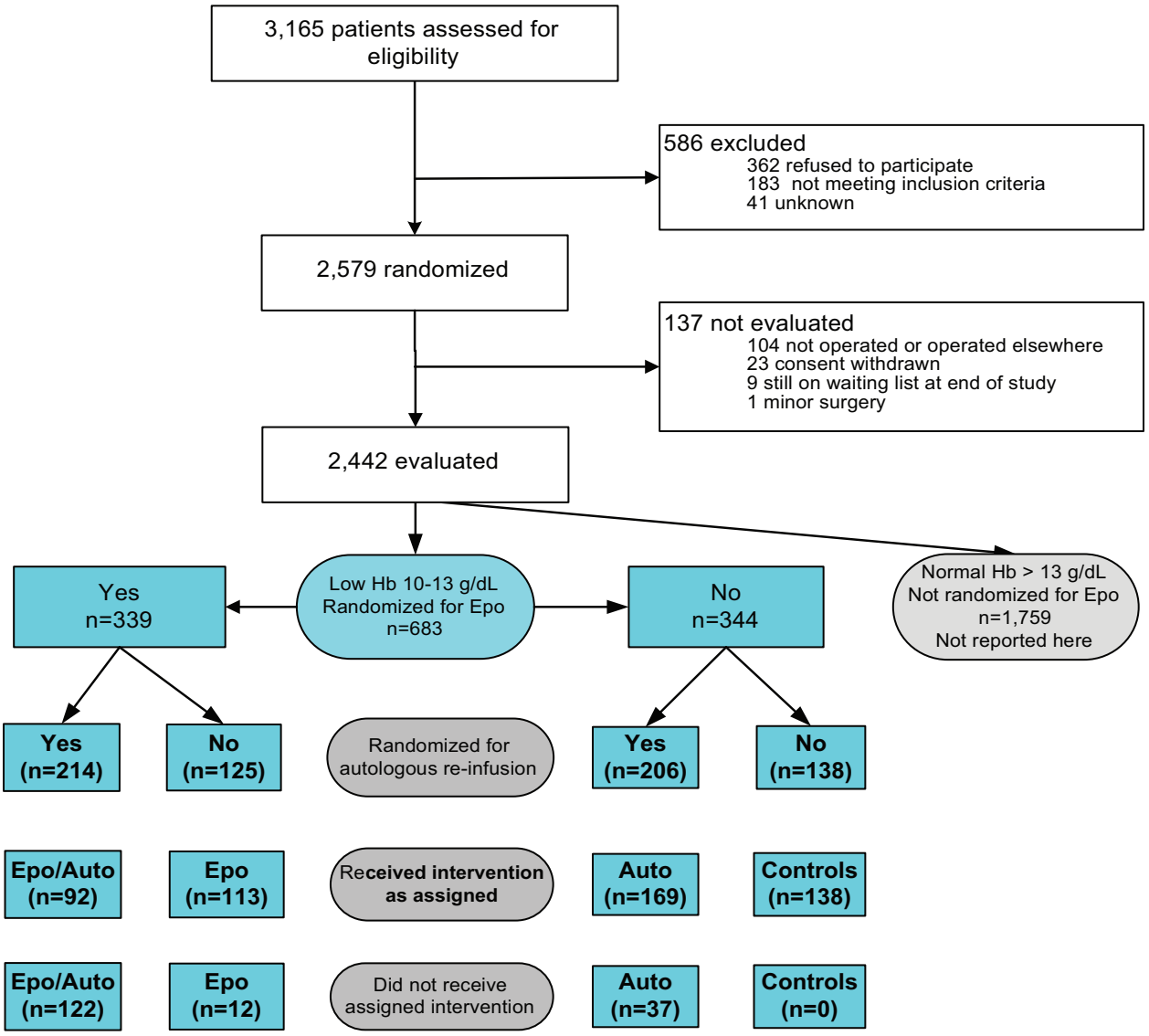

Fig. 1. Patient flow diagram. Auto = autologous reinfusion by cell saver or DRAIN; DRAIN = postoperative drainage and reinfusion device; Epo = erythropoietin; Hb = hemoglobin.

heterogeneous to draw valid conclusions, we separately present the results of the primary surgery group (n = 613) in table 4. This table shows, that erythropoietin significantly reduced mean erythrocyte use by 55% (ratio, 0.45; 95% CI, 0.28 to 0.69; $P < 0.01$) and significantly avoided transfusions in 55% of the patients (adjusted OR, 0.45; 95% CI, 0.29 to 0.72; $P < 0.001$). Fourteen percent of patients randomized for erythropoietin were transfused compared with 26% of patients not randomized for erythropoietin (absolute difference of 12%). In the as-treated analysis, where the actual use of erythropoietin and the actual use of the autologous blood reinfusion devices were analyzed, the erythropoietin effect was larger: a 62% reduction in mean erythrocyte use (ratio, 0.38, 95% CI, 0.19 to 0.66; $P = 0.01$) and a 70% reduction in proportion of transfused patients (adjusted OR, 0.30; 95% CI, 0.18 to 0.51; $P < 0.001$).

Autologous Blood Reinfusion Treatment Effect

The cell saver and DRAIN groups are reported as a combined autologous (AUTO) group. Autologous blood reinfusion neither resulted in a decrease of mean erythrocyte use nor in a decrease in proportion of transfused patients (tables 3 and 4). The separate cell saver and DRAIN effects were comparable (*not shown*). The combined use of erythropoietin and autologous blood reinfusion resulted in a erythrocyte reduction, which was mainly due to the erythropoietin effect. Analysis of the actual use of the autologous blood reinfusion devices (as-treated analysis) gave the same results as the ITT analysis.

Economic Evaluation

When surgery was unexpectedly rescheduled to a date within 3 weeks after randomization, no (further) erythropoietin was administered. As a result, only 66% of the patients randomized to receive erythropoietin actually received erythropoietin,

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Table 1. Baseline Characteristics of 683 Erythropoietin-eligible Patients by Treatment Group

N = 683		Low Hb (10< Hb<13 g/dl) Erythropoietin-eligible Group				
Patient Variables		1. Erythropoietin/AUTO	2. Erythropoietin	3. AUTO	4. Controls	*P* Value
Evaluated	683	214	125	206	138	
Total hip replacement	426 (62)	150 (70)	64 (51)	136 (66)	77 (56)	0.78*
Total knee replacement	257 (38)†	64 (30)	61 (49)	70 (34)	61 (44)	
Among primary hip	371 (61)	129 (68)	56 (50)	120 (65)	67 (53)	0.82*
Among primary knee	242 (39)	61 (32)	56 (50)	64 (35)	60 (47)	
Females	595 (87)	184 (86)	113 (90)	177 (86)	121(88)	0.67
Age (yr), mean (SD)	71 (12)	70 (13)	71 (12)	71 (12)	70 (11)	0.84
Preop Hb (g/dl), mean (SD)	12.6 (0.8)	12.5 (1.2)	12.5 (1.2)	12.3 (0.9)	12.6 (0.8)	0.10
Preoperative anemia	195 (29)	69 (32)	36 (29)	64 (31)	26 (19)	0.19
High risk‡	29 (4)	12 (6)	4 (3)	8 (4)	5 (4)	0.57
Cardiovascular history	329 (48)	96 (45)	54 (43)	111 (54)	68 (49)	0.04
COPD	63 (9)	23 (11)	10 (8)	14 (7)	16 (12)	0.64
Rheumatoid arthritis	142 (21)	45 (21)	25 (20)	47 (23)	26 (19)	0.76
Diabetes	104 (15)	33 (15)	20 (16)	26 (12)	25 (18)	0.74

For continuous variables mean (SD) is shown, for categorical variables numbers (percentages) are shown. Percentages are calculated within randomized group (columns). Preoperative anemia includes an Hb value <12 g/dl for women and an Hb value of <13 g/dl for men (World Health Organization standards).

* Within hip and within knee strata. † Six bilateral knee replacement. ‡ High risk denotes incapability to enlarge cardiac output to compensate for anemia, serious pulmonary disease, or symptomatic cerebrovascular disease.

AUTO = autologous blood reinfusion by cell saver or DRAIN; COPD = chronic obstructive pulmonary disease; DRAIN = postoperative drainage and reinfusion device; Hb = hemoglobin.

bringing the average erythropoietin costs to €851 per patient (table 5; 95% CI, 785 to 917). By using erythropoietin, the savings in costs for erythrocyte use and hospital stay were statistically nonsignificant and relatively small compared with the costs for the use of erythropoietin itself. The average total cost increase for the erythropoietin strategy was estimated at €785 per patient (95% CI, 262 to 1,309). With a decrease in the proportion of transfused patients by 10.8% (from 26.4 to 15.6%), erythropoietin avoided one transfusion in every nine patients, translating the cost estimate to €7,300 per avoided transfusion (95% CI, 1,900 to 24,000).

Autologous blood reinfusion was associated not only with a statistically significant decrease in erythropoietin use, but also with an increased length of the non*intensive care unit*

Table 2. Perioperative Patient Characteristics and Erythrocyte Transfusions by Randomized Group and by Surgery Type (Primary/Revision)

Intention-to-treat Analysis (n = 683)	Erythropoietin-eligible Group (10< Hb <13 g/dl)				
	1. Erythropoietin/AUTO N = 214	2. Erythropoietin N = 125	3. AUTO N = 206	4. Control N = 138	*P* Value
Duration of surgery (min), mean (SD)	101 (49)	98 (44)	102 (61)	102 (40)	0.71
% Cemented prosthesis	42	47	45	47	0.28
Blood loss *during surgery* (ml), median (IQR)	250 (0–500)	200 (0–500)	250 (0–500)	200 (0–500)	0.31
Total blood loss (ml), median (IQR)	650 (350–1,000)	650 (400–1,000)	650 (350–1,000)	650 (400–950)	0.75
Reinfused volume (ml), median (IQR)	225 (100–450)	NA	250 (100–450)	NA	0.83
Hb day+1 (g/dl), mean (SD)	10.4 (1.6)	10.8 (1.5)	9.6 (1.1)	9.5 (1.3)	0.05

	Primary Surgery	Revision Surgery	*P* Value
Duration of surgery (min), mean (SD)	97 (47)	131 (76)	<0.001
Blood loss *during surgery* (ml), median (IQR)	200 (0–450)	475 (175–700)	<0.001
Total blood loss (ml), median (IQR)	650 (350–975)	720 (400–1,100)	0.10
Reinfused volume (ml), median (IQR)	250 (100–450)	200 (50–350)	0.42

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

AUTO = autologous blood reinfusion by cell saver or DRAIN; DRAIN = postoperative drainage and reinfusion device; Hb = hemoglobin; IQR = interquartile range; NA = not applicable.

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Table 3. Intention-to-treat Analysis: Erythropoietin and AUTO Effect on Erythrocyte Use in Primary and Revision Surgery Together

Primary and Revision Surgery Patients					
N = 683	Mean Erythrocyte Use (U)	Mean Adjusted Difference* (95% CI)	Ratio† (95% CI)	Proportion Transfused (%)	Adjusted Odds Ratio‡ (95% CI)
No erythropoietin (n = 344)					
AUTO (n = 206)	0.76 (1.6)	0.10 (–0.25 to 0.45)	1.2 (0.7–2.0) *P* = 0.50	29	1.3 (0.8–2.2) *P* = 0.26
No AUTO (n = 138)	**0.64 (1.6)**			**23**	
With erythropoietin (n = 339)					
AUTO (n = 214)	0.65 (2.5)	0.34 (–0.10 to 0.78)	2.6 (1.2–6.5) *P* = 0.02	19	2.2 (1.1–4.4) *P* = 0.02
No AUTO (n = 125)§	0.25 (0.9)			10	
Pooled erythropoietin effects					
With erythropoietin (n = 339)	0.50 (2.1)	–0.22 (–0.50 to 0.05)	0.71 (0.42–1.13) *P* = 0.15	16	0.50 (0.35–0.75) *P* < 0.001
No erythropoietin (n = 344)	0.71 (1.6)			26	

Control group is outlined in bold.

* Adjusted for primary/revision surgery, hospital, and knee/hip surgery; CIs for reference purposes only (assuming normality). † Ratio was defined as the quotient of mean erythrocyte units of two groups being compared; all estimates and robust standard errors were obtained *via* bootstrapping in R (http://www.r-project.org/). Accessed August 14, 2013. ‡ All estimates and standard errors were obtained using the Mantel–Haenszel procedure, stratifying by the prespecified stratification factors primary/revision and knee/hip surgery. § Denotes erythropoietin-alone group.

AUTO = autologous blood reinfusion by cell saver or DRAIN; DRAIN = postoperative drainage and reinfusion device; U = units.

hospital stay by 0.82 days (95% CI, 0.09 to 1.55; *P* = 0.03; table 6). The total cost increase for the autologous blood reinfusion strategy was estimated at €537 per patient (95% CI, 45 to 1,030; *P* = 0.03), without a reduction in erythrocyte use.

Study Protocol Adherence

Intervention Adherence. A total of 171 patients did not receive the intended intervention. Of the 339 patients assigned to erythropoietin, 114 did not receive erythropoietin (34%), 225 patients assigned to erythropoietin received at least one dose and of these 97% received at least three erythropoietin doses. Twenty-two of 136 (16%) assigned patients did not receive cell saver (with or without erythropoietin) and 37 of 184 (20%) assigned patients did not receive DRAIN (with or without erythropoietin). Most common reasons for not receiving the intended intervention were earlier rescheduling of surgery in case of erythropoietin, technical problems with the cell saver device (broken or incomplete device) for cell saver, and not using the proper drain device or not placing a drain at all.

Transfusion Protocol Adherence. In more than 95% of the patients, the transfusion protocol was correctly used according to hemoglobin-level, age, and risk-group assessment of the patient before transfusion. Transfusion protocol

Table 4. Intention-to-treat Analysis: Erythropoietin and AUTO Effect on Erythrocyte Use in Primary Surgery

Primary Surgery Patients					
N = 613	Mean Erythrocyte Use (U) (SD)	Mean Adjusted Difference* (95% CI)	Ratio† (95% CI)	Proportion Transfused (%)	Adjusted Odds Ratio‡ (95% CI)
No erythropoietin (n = 311)					
AUTO (n = 184)	0.78 (1.7)	0.15 (–0.22 to 0.52)	1.3 (0.8–2.3) *P* = 0.70	29	1.4 (0.7–2.1) *P* = 0.41
No AUTO (n = 127)	**0.61 (1.6)**			23	
With erythropoietin (n = 302)					
AUTO (n = 190)	0.36 (1.1)	0.09 (–0.15 to 0.32)	1.5 (0.7–4.0) *P* = 0.35	17	1.9 (0.9–4.0) *P* = 0.10
No AUTO (n = 112)§	0.24 (0.9)			9	
Pooled erythropoietin effects					
With erythropoietin (n = 302)	0.32 (1.0)	–0.39 (–0.61 to –0.18)	0.45 (0.28–0.69) *P* < 0.01	14	0.43 (0.29–0.66) *P* < 0.001
No erythropoietin (n = 311)	0.71 (1.6)			26‖	

Control group is outlined in bold.

* Adjusted for hospital and for knee/hip surgery; CIs for reference purposes only (assuming normality). † Ratio was defined as the quotient of mean erythrocyte units of two groups being compared; all estimates and robust standard errors were obtained *via* bootstrapping in R (http://www.r-project.org/). Accessed August 14, 2013. ‡ All estimates and standard errors were obtained using the Mantel–Haenszel procedure, stratifying by the prespecified stratification factors knee/hip surgery. § Denotes erythropoietin-alone group. ‖ 12% absolute difference in transfusion avoidance.

AUTO = autologous blood reinfusion by cell saver or DRAIN; DRAIN = postoperative drainage and reinfusion device; U = units.

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Table 5. Estimated Costs per Patient for the Strategies with and without Erythropoietin

N = 683	Volumes of Health Care*		Costs (in €)			
	With Erythropoietin (n = 339)	No Erythropoietin (n = 344)	With Erythropoietin (n = 339)	No Erythropoietin (n = 344)	Difference (95% CI)	*P* Value
Erythropoietin	66%	0.6%†	858	8	851 (784–917)	<0.001
AUTO	63%	60%	56	52	4 (–4 to 13)	0.30
Erythrocyte use (%/mean units)	15.6%/0.50	26.5%/0.71	418	591	–172 (–401 to 57)	0.14
ICU stay (%/mean days)	3.2%/0.04	2.3%/0.04	100	98	1 (–99 to 102)	0.98
Non-ICU stay (%/mean days)	100%/8.87	100%/8.66	4,182	4,081	101 (–256 to 459)	0.57
Total costs			5,615	4,829	785 (262–1,309)	0.003

* Volume = percentage of patients/mean erythrocyte usage or hospital days per patient. † Two patients received erythropoietin while not randomized for erythropoietin.

AUTO = autologous blood reinfusion by cell saver or DRAIN; DRAIN = postoperative drainage and reinfusion device; ICU = intensive care unit.

violations were equally distributed among all randomization groups.

Serious Adverse Events

A total of 33 SAEs were reported in 30 patients (three patients suffered two SAEs) (table 7). One patient did not undergo surgery because of a stroke after one erythropoietin dose (hemoglobin value of 12.2 g/dl) and one patient was not further evaluated due to assignment of a wrong randomization number. These two patients are included in table 6. A total of eight thromboembolic events occurred, all within 1 month after surgery. Five thromboembolic events (three myocardial infarctions and two strokes) occurred in the erythropoietin group (1.5%), all in patients with hemoglobin levels of 12.2.g/dl or less, two of these events occurred after only one erythropoietin dose. The proportion of thromboembolic events (1.5%) in the erythropoietin group was not significantly different from that in the nonerythropoietin group (0.9%) (OR, 1.7, 95% CI, 0.40 to 7.2; $P = 0.50$). Nonthromboembolic-related SAEs were mostly prosthesis related: hip dislocation, prosthesis infections, or wound infections, limited knee flexion needing manipulation, or fractures. Other events included cardiovascular events (arrhythmia, blood pressure instability), allergic events, nonprosthesis-related infections or sepsis, bleeding, or malignancy. Autologous blood reinfusion–related complications were not related to sepsis or infection. In the as-treated analysis, SAE differences between groups remained nonsignificant.

Discussion

In elective total hip– and knee–replacement surgery patients with preoperative hemoglobin levels between 10 and 13 g/dl, three widely used erythrocyte transfusion alternatives were compared using a baseline restrictive transfusion threshold. Erythropoietin contributed significantly in avoiding erythrocyte transfusions, but not in mean erythrocyte reduction. Autologous reinfusion by two different devices did not result in a clinically relevant decrease in erythrocyte use. On the basis of the results of the ITT analysis, both alternative hypotheses 1 and 2 (a 75% reduction in mean erythrocyte use and proportion of transfused patients by erythropoietin and a 30% reduction in mean erythrocyte use and proportion of transfused patients by autologous reinfusion, respectively), were rejected.

Because the revision surgery group was too small and effects were too heterogeneous, valid conclusions on erythrocyte use could only be drawn for the large primary surgery group (90% of the total cohort). Because we stratified by primary *versus* revision surgery, no major imbalance in covariates

Table 6. Estimated Costs per Patient for the Strategies with and without Autologous Blood Reinfusion

N = 683	Volumes of Health Care*		Costs (in €)			
	AUTO n = 420	No AUTO n = 263	AUTO n = 420	No AUTO n = 263	Difference (95% CI)	*P* Value
Erythropoietin	27%	43%	351	556	–205 (–300 to –109)	<0.001
AUTO	100%	0.4%	88	1	87 (83 to 92)	<0.001
Erythrocyte use (%/mean units)	23.8%/0.70	16.7%/0.46	584	378	206 (–5 to 417)	0.06
ICU stay (%/mean days)	3.3%/0.05	1.9%/0.03	123	60	63 (–29 to 155)	0.18
Non-ICU stay (%/mean days)	100%/9.08	100%/8.26	4,280	3,894	386 (41–731)	0.03
Total costs			5,426	4,888	537 (45–1,030)	0.03

* Volume = percentage of patients/mean erythrocyte usage or hospital days per patient.

AUTO = autologous blood reinfusion by cell saver or DRAIN; DRAIN = postoperative drainage and reinfusion device; ICU = intensive care unit.

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Table 7. Reported Serious Adverse Events: TE Complications,* Non-TE Complications,† and Total Numbers

Intention-to-treat (Numbers)	TE Events (%)	Myocardial Infarction	Stroke/TIA	DVT	Pulmonary Emboli	Other	Non-TE Events (%)	Total Numbers SAEs (%)
Erythropoietin/AUTO (214)	1 (0.5)	1	0	0	0	0	11 (5.1)	12 (5.2)
Erythropoietin (125)	4 (3.2)	2	2	0	0	0	1 (0.8)	5 (4.0)
Total, erythropoietin groups (339)	*5 (1.5)*						*12 (3.5)*	*17 (5.0)*
AUTO only (206)	2 (1.0)	1	0	0	1	0	9 (4.3)	11 (5.3)
Control group (138)	1 (0.7)	1	0	0	0	0	4 (2.9)	5 (3.6)
Total, nonerythropoietin groups (344)	3 (0.9)						*13 (3.8)*	*16 (4.7)*
Grand total (683)	8 (1.2)	5	2	0	1	0	25 (3.7)	33 (4.8)

Percentages are calculated within randomized groups (rows). Six SAE patients did not actually receive the intervention.

* TE complications were categorized in: myocardial infarction, stroke/TIA, DVT, pulmonary emboli, or other. † 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, *etc*.

AUTO = autologous reinfusion by cell saver or DRAIN; DRAIN = postoperative drainage and reinfusion device; DVT = deep venous thrombosis; SAE = serious adverse event; TE = thromboembolic; TIA = transient ischemic attack.

will occur for this primary surgery group. Use of erythropoietin in primary surgery patients resulted in a significant 12% absolute and a 55% relative reduction in transfused patients irrespective of the use of autologous reinfusion. The as-treated analysis, based on the patients who did receive erythropoietin, confirmed the results of the ITT analysis. These results confirm earlier reports that erythropoietin has a significant benefit as a transfusion-avoiding strategy (avoidance of exposure to allogeneic erythrocyte transfusions) as well as a significant blood-sparing effect (mean units of erythrocyte reduction; not statistically significant in our study). A recent meta-analysis of erythropoietin in 26 hip- and knee-surgery trials (n = 3,560) showed an overall reduction in erythrocyte transfusion rate of 52% (relative risk, 0.48; 95% CI, 0.38 to 0.60; $P < 0.00001$), which was in line with our results.[28] Our finding of a low and nonsignificant mean erythrocyte reduction is probably related to our restrictive transfusion protocol, which uses a one-unit transfusion policy. The combined use of erythropoietin and autologous blood reinfusion resulted in an erythrocyte reduction, which was mainly due to the erythropoietin effect.

Our finding that neither cell saver nor DRAIN resulted in a clinically relevant erythrocyte reduction may be explained by relatively low (visible) blood loss and a low volume of recovered shed blood in combination with the applied restrictive transfusion threshold. The total blood loss is still considerable, because the amount of nonvisible blood loss can reach the same amount as the visible blood loss.[29,30] Slight adaptations of surgical techniques (*i.e.*, less extensive incisions) to minimize blood loss and increased awareness among orthopedic surgeons may also have contributed to a low autologous blood collection volume. This finding is consistent with a recent survey on the effect of blood salvage programs among 20 hospitals in the United States, which observed that the volume of returned blood in total joint surgery was small.[31]

Neither erythropoietin nor blood salvage were cost-effective. From a hospital perspective, the additional costs for the erythropoietin strategy in patients with low hemoglobin levels were estimated at €785 per patient, mainly the additional erythropoietin costs. Erythropoietin avoided one transfusion in about every nine patients, translating the cost estimate to €7,300 per avoided transfusion.

To justify such costs from a health economic perspective, transfusion would have to be associated with a considerable health risk. Accepting a threshold of €40,000 per quality-adjusted life year, 1 in every 100 transfused patients would have to incur an average life expectancy loss of approximately 20 yr (100 × 7,300/40,000). According to hemovigilance registries, allogeneic blood transfusions currently seem considerably safer.[32]

In our trial, autologous blood reinfusion did not reduce allogeneic erythrocyte transfusions as a single intervention, and from a health economic perspective the associated cost increase is not justified. The use of autologous blood reinfusion was associated with significantly increased length of the hospital stay by 0.82 days. Short-term fever associated with autologous reinfusion may play a role in this increased hospital stay.

Strengths and Limitations of the Study

Strengths of our study were the randomization, inclusion, and evaluation of sufficient numbers of patients, the balancing of study variables across the randomization groups, and the study power of 90%. The complex design of the study was optimally consistent with current clinical practice, allowing the evaluation of the combined and separate effect of three widely used transfusion alternatives, which fits in the multimodel approach of current patient blood management strategies. Adherence to the restrictive transfusion protocol was more than 95%, in contrast to the 34% (n = 114) nonadherence to the erythropoietin randomization. This is a major weakness, which was mainly due to the surgery date being brought forward when surgery time became suddenly available, resulting in lack of time to prescribe 3 weeks of erythropoietin therapy. This situation may be typical for The Netherlands: during this study the waiting list for elective orthopedic surgery was short (<2 months).

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Because the results are based on ITT analyses, this nonadherence to erythropoietin may provide an underestimation of its effect. As a consequence of major protocol deviations, the ITT analysis differed from the as-treated analysis, analyzed in addition as complementary analysis.

Nonadherence to cell saver and DRAIN occurred in 16% (n = 22) and 20% (n = 37) of patients, respectively. Of the patients who did receive the device, some did not receive any autologous blood due to insufficient collection of shed blood. A further limitation is that the study population was scheduled for elective total joint surgery, excluding hip-fracture surgery patients, and results can therefore not be extrapolated to the latter group. Another limitation is the combined primary endpoint: mean erythrocyte use was taken as primary endpoint to calculate sample sizes. However, from a clinical point of view the proportion of transfused patients is as or even more important. We used both as primary endpoints for erythrocyte use and corrected for multiple testing.

Another limitation may be that only study investigators were blinded and not the clinical team, which was informed of the assigned randomization. It is unlikely that nonblinding of erythropoietin administration has influenced the decision to transfuse, because clinicians adhered to the transfusion protocol and violations were equal in all randomization groups. Because the study was not powered for safety evaluation, we are unable to draw valid conclusions on the incidence of adverse complications. All patients in our study received thrombosis-prophylaxis, which may have influenced the proportion of thromboembolic complications in the erythropoietin group. This finding is in contrast to a safety study in orthopedic spine surgery patients not receiving anticoagulant prophylaxis, which reported a higher incidence of postoperative thrombotic events (deep vein thrombosis in particular) in patients after erythropoietin treatment compared with a control group.[33] Also, most transfusion trials are complicated by the fact that randomization occurs before surgery, while the majority of included patients do not reach the trigger level for transfusion. Consequently, a large number of the randomized patients may not be transfused at all (in this study 71 to 90% of patients). This disadvantage, however, does not invalidate in any respect the ITT approach.[34]

The generalizability of economic evaluations to other settings may be limited. For example, we estimated relatively low hospital costs. Nevertheless, we consider our results robust as the cost-effectiveness of erythropoietin is primarily determined by the price of the erythropoietin itself and that price would need to decrease drastically to make a strategy with erythropoietin cost-effective. Autologous blood salvage devices did not reduce erythrocyte use and increased the duration of the hospital stay, so results remain unfavorable for blood salvage regardless of healthcare prices.

Implications for Clinicians and Other Researchers

This study may serve as a valid estimate for the elective total hip– and knee–replacement surgery population in The Netherlands (16.6 million inhabitants), where approximately 50,000 total hip and knee replacements are performed annually, expected to rise to more than 100,000 in 2030.[35]

Our results confirm that patients with preoperative hemoglobin levels between 10 and 13 g/dl are more likely to receive a erythrocyte transfusion (23% of 138 control group patients compared with 8.3% of control patients with hemoglobin levels above 13 g/dl)[21] and up to 32.4% of patients with overt preoperative anemia required an erythrocyte transfusion.[29,36–39] For these truly anemic patients, erythropoietin is recommended in recently published guidelines, after excluding treatable causes of anemia.[37] We did not investigate the cost-effectiveness of erythropoietin in our true anemic subpopulation (195 patients), nor did we evaluate correction of anemia in those patients. Therefore, we propose to await additional data to decide on the use of erythropoietin in this subpopulation. Furthermore, research should focus on clinical outcomes as well, such as postoperative complications rather than on product outcome like erythrocyte use.

Conclusions

In elective total hip– and knee–replacement surgery patients with preoperative hemoglobin levels between 10 and 13 g/dl, even with a restrictive transfusion policy, erythropoietin significantly contributed as a transfusion alternative, but at unacceptably high costs. No clinically relevant decrease in erythrocyte use was found by using autologous blood salvage by cell saver or DRAIN, which consequently only increased costs.

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Competing Interests

The authors declare no competing interests.

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