Patient Blood Management in Elective Total Hip- and Knee-replacement Surgery (Part 2)

A Randomized Controlled Trial on Blood Salvage as Transfusion Alternative Using a Restrictive Transfusion Policy in Patients with a Preoperative Hemoglobin above 13 g/dl

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ABSTRACT

Background: Patient blood management is introduced as a new concept that involves the combined use of transfusion alternatives. In elective adult total hip- or knee-replacement surgery patients, the authors conducted a large randomized study on the integrated use of erythropoietin, cell saver, and/or postoperative drain reinfusion devices (DRAIN) to evaluate allogeneic erythrocyte use, while applying a restrictive transfusion threshold. Patients with a preoperative hemoglobin level greater than 13 g/dl were ineligible for erythropoietin and evaluated for the effect of autologous blood reinfusion.

Methods: Patients were randomized between autologous reinfusion by cell saver or DRAIN or no blood salvage device. Primary outcomes were mean intra- and postoperative erythrocyte use and proportion of transfused patients (transfusion rate). Secondary outcome was cost-effectiveness.

Results: In 1,759 evaluated total hip- and knee-replacement surgery patients, the mean erythrocyte use was 0.19 (SD, 0.9) erythrocyte units/patient in the autologous group (n = 1,061) and 0.22 (0.9) erythrocyte units/patient in the control group (n = 698) (P = 0.64). The transfusion rate was 7.7% in the autologous group compared with 8.3% in the control group (P = 0.19). No difference in erythrocyte use was found between cell saver and DRAIN groups. Costs were increased by €298 per patient (95% CI, 76 to 520).

Conclusion: In patients with preoperative hemoglobin levels greater than 13 g/dl, autologous intra- and postoperative blood salvage devices were not effective as transfusion alternatives: use of these devices did not reduce erythrocyte use and increased costs.
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PATIENT blood management involves the optimal and integrated use of transfusion alternatives as a multimodel strategy to reduce erythrocyte transfusions.[1] The effect on erythrocyte reduction 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.

Intraoperative use of a cell saver may recover up to 70% of the shed blood in orthopedic surgery,[10] 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.[2–5,11–15] The evidence for erythrocyte reduction by autologous salvaged blood reinfusion is generally based on small and/or underpowered studies

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 1,759 patients with a preoperative hemoglobin level greater than 13 g/dl (and therefore ineligible for erythropoietin) undergoing hip and/or knee arthroplasty, autologous intra- and postoperative blood salvage devices were not effective as transfusion alternatives.
- The use of these devices did not reduce erythrocyte use and increased costs.

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often not applying a restrictive transfusion threshold. We performed a multicenter study in patients undergoing elective total hip- or knee-replacement surgery. Here, we report the effect of autologous blood salvage on allogeneic erythrocyte use and cost-effectiveness of the use of these devices in patients with normal hemoglobin levels greater than 13 g/dl, while applying a restrictive transfusion policy to all patients. We hypothesized that a 30% reduction in both mean erythrocyte use and in proportion of transfused patients can be reached by use of autologous blood salvage devices.

Materials and Methods

The study design has been described elsewhere.[16] In summary, a randomized, multicenter, controlled study (ISRCTN 96327523) was performed in The Netherlands, and included adult patients (18 yr or older) scheduled for elective primary or revision total hip- or knee-replacement surgery. After providing written informed consent, 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. The study was approved by the University Hospital LUMC Committee of Medical Ethics and by the Medical Ethics Committees of the Albert Schweitzer Hospital, The Groene Hart Hospital, and the Slotervaart Hospital.

Patients were excluded if they had: Hb (hemoglobin) less than 13 g/dl, 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; 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.

Patients were randomized for autologous blood reinfusion by cell saver or postoperative drain reinfusion device (DRAIN) (fig. 1). The cell saver and DRAIN groups are presented in this article as a combined autologous (AUTO) group. To have a balanced randomization, assignment was stratified for hospital and type of surgery (primary/revision as well as hip/knee). Knee-replacement procedures were excluded from use of cell saver, because this was not applicable due to negligible intraoperative blood loss resulting from the use of a tourniquet during surgery. All control patients received a low vacuum wound drain, of which the collected blood was discarded. Within the AUTO group, both cell saver and DRAIN modalities were allocated randomly in a 1:1 ratio and randomization was balanced for the study variables. Participating hospitals were free to choose the type of postoperative drainage system, but were obligated to use the same type throughout the study. 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 OrthoPAT® cell saver (Haemonetics, Breda, The Netherlands) was used in all four hospitals for both intra- and postoperative collection and reinfusion of autologous blood, collected up to 6 h after surgery, in hip surgery patients. The collected shed blood was washed, centrifuged, and concentrated to a hematocrit of 60 to 80% before being returned to the patient. The randomization resulted in the following two possibilities: AUTO+ or AUTO– (=control group). A protocol violation was scored if the cell saver or DRAIN device was assigned but not used.

Transfusion Protocol and Procedures

All patients were transfused according to a national protocol using a restrictive transfusion policy as advised by the Dutch transfusion guidelines. 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: Hb = 6.4 g/dl (=4.0 mmol/l) for age less than 60 yr and normal risk; Hb = 8.1 g/dl (=5.0 mmol/l) for age 60 yr older and normal risk; Hb = 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

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

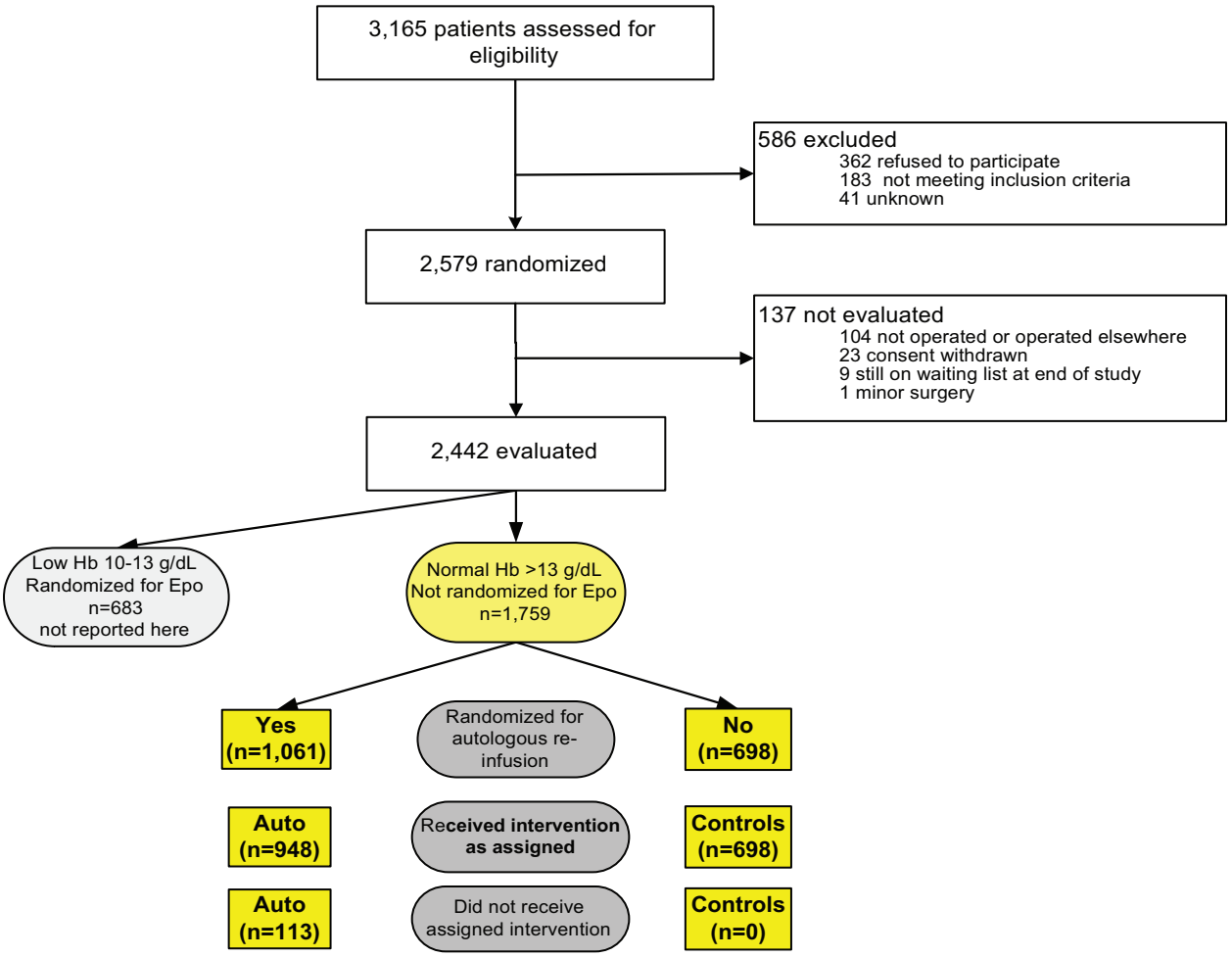

Fig. 1. Patient flow diagram. Auto = autologous reinfusion by cell saver or DRAIN; DRAIN = postoperative drainage and reinfusion device; Epo = erythropoietin; Hb = hemoglobin.

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. Intraoperative transfusions were prescribed by the anesthesiologist and postoperative transfusions by the orthopedic surgeon. A check for transfusion protocol adherence was included in the case report form by verifying the pretransfusion hemoglobin level, age, and cardiovascular history (for risk estimation) of the patient at every transfusion event. The erythrocyte products contained 40 to 54 g Hb in SAG-M (Saline, Adenine, Glucose-Mannitol) and less than $1 \times 10E6$ leukocytes per unit by prestorage leukocyte filtration as previously described. 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. Patients were recruited by orthopedic surgeons and by research nurses.

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 outcome measures. All endpoints were scored until 3 months after surgery. Serious adverse events were reported up to 3 months as well and were defined as death, life-threatening events, (prolongation 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.

Sample Size

For this part of the study, 1,000 participants were required to detect a difference of 30% in mean erythrocyte use by autologous blood reinfusion by either cell saver or DRAIN, with statistical power of 90% at a 5% significance level.

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 cell saver and DRAINS (€160 and €61, respectively) and using standard prices for allogeneic erythrocyte products, intensive care unit stay, and nonintensive care unit stay (€207 per unit, €2249, 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 study by Shander *et al.*[17] Average costs were compared according to intention to treat, using nonparametric bootstrapping (programmed in Stata/IC 11.0 for Windows; StataCorp LP, College Station, TX). Both primary and revision surgery patients 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 to the difference in costs. CIs for the cost-effectiveness ratio were calculated using net benefit analysis.[18]

Statistical Analysis

Statistical analyses were performed in SPSS (version 17.0 for Windows; SPSS Inc., Chicago, IL) according to intention-to-treat and as-treated analysis. As-treated 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. 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. 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 as a comparison of the probability of "receiving at least one erythrocyte unit" between the randomization arms. For the final analysis of the primary endpoint, we used a correction according to Haybittle–Peto[19]: 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.

† 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.

Results

Of the total group of patients (n = 2,442), 1,759 had a preoperative hemoglobin level greater than 13 g/dl. Baseline characteristics are shown in table 1. The cell saver and DRAIN groups are reported as a combined autologous (AUTO) group. Fifty-nine percent of the procedures were hip replacement and 41% were knee replacement, 63% of the patients were female. Revision surgery took place in 6.5% patients (n = 114), equally distributed among the groups. Mean preoperative hemoglobin level at first outpatient visit was 14.4 g/dl (SD, 0.92) and mean hematocrit: 0.43 l/l (SD 0.03). 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: 0.70 (SD, 0.09) and 350 ml for DRAIN (interquartile range, 150 to 500 ml) with mean hematocrit: 0.31 (SD, 0.13). Postoperative hemoglobin values on day+1 were comparable between the groups with (AUTO groups) or without autologous blood reinfusion (control groups) in the two strata. Revision surgery patients differed significantly from primary surgery patients with respect to intraoperative blood loss (*P* = 0.001) and mean duration of surgery (*P* < 0.001), but not for the median reinfused volumes of blood (*P* = 0.93; table 2).

Table 1. Baseline Characteristics of Patients with Preoperative Hb >13 g/dl by Treatment Group

N = 1,759 Patient Variables	Preoperative Hb >13 g/dl		
	AUTO	Controls	*P* Value
Evaluated (n = 1,759)	1,061	698	
Total hip replacement*	695 (66)	342 (49)	<0.001‡
Total knee replacement†	366 (34)	356 (51)	
Among primary hip	643 (65)	319 (48)	<0.001‡
Among primary knee	344 (35)	339 (52)	
Females	694 (65)	410 (59)	0.005
Age (yr), mean (SD)	69 (10)	68 (10)	0.04
Preoperative Hb (g/dl), mean (SD)	14.3 (0.9)	14.5 (1.0)	<0.001
High risk§	40 (4)	23 (3)	0.60
Cardiovascular history	538 (51)	358 (51)	0.81
COPD	81 (8)	53 (8)	0.98
Rheumatoid arthritis	85 (8)	60 (9)	0.66
Diabetes	116 (11)	66 (10)	0.32

For continuous variables mean (SD) is shown, for categorical variables numbers (percentages) are shown. Percentages are calculated within randomized group (columns).

* One bilateral hip surgery. † Eight bilateral knee surgeries. ‡ Within hip and within knee strata. § 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.

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

	Preoperative Hb >13 g/dl		
Intention-to-treat Analysis (n = 1,759)	AUTO (n = 1,061)	Control (n = 698)	*P* Value
Duration of surgery (min), mean (SD)	98 (42)	97 (40)	0.63
% Cemented prosthesis	37	43	0.05
Blood loss *during surgery* (ml), median (IQR)	200 (0–400)	250 (0–450)	0.001
Total blood loss (ml), median (IQR)	650 (400–950)	700 (400–1,000)	0.12
Reinfused volume (ml), median (IQR)	250 (100–450)	NA	NA
Hb day+1 (g/dl), mean (SD)	11.0 (1.3)	11.0 (1.3)	0.30
	Primary Surgery	Revision Surgery	*P* Value
Duration of surgery (min), mean (SD)	96 (40)	124 (56)	<0.001
Blood loss *during surgery* (ml), median (IQR)	200 (0–450)	300 (50–600)	0.001
Total blood loss (ml), median (IQR)	650 (380–970)	700 (450–1,100)	0.08
Reinfused volume (ml), median (IQR)	250 (100–450)	250 (100–450)	0.93

For continuous variables mean (SD) is shown, and median (IQR) 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.

Table 3. Intention-to-treat Analysis: Autologous Blood Reinfusion Effect on Erythrocyte Use

		Primary and Revision Surgery Patients			
N = 1,759	Mean erythrocyte use (U)	Mean adjusted difference* (95% CI)	Ratio† (95% CI)	Proportion transfused (%)	Adjusted odds ratio‡ (95% CI)
AUTO (n = 1,061)	0.19 (0.9)	−0.06 (−0.15 to 0.02)	0.9 (0.6–1.3) *P* = 0.64	7.7	0.79 (0.55–1.1) *P* = 0.19
No AUTO (n = 698)	**0.22 (0.9)**			8.3	
		Primary Surgery Patients			
N = 1,645	Mean erythrocyte use (U) (SD)	Mean adjusted difference* (95% CI)	Ratio† (95% CI)	Proportion transfused (%)	Adjusted odds ratio‡ (95% CI)
AUTO (n = 987)	0.16 (0.7)	−0.08 (−0.16 to −0.01)	0.73 (0.48–1.1) *P* = 0.13	7.1	0.74 (0.5–1.1) *P* = 0.11
No AUTO (n = 658)	**0.22 (0.9)**			8.2	

Control groups are outlined in bold.

* Adjusted for revision/nonrevision 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 November 8, 2013). ‡ All estimates and standard errors were obtained using the Mantel–Haenszel procedure, stratifying by the prespecified stratification factors knee/hip surgery (and primary/revision for the upper part of the table).

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

Primary Endpoint

Mean erythrocyte use of the total group was 0.20 U/patient (SD, 0.88) and 8% of patients (n = 140) were transfused. Among the autologous group, mean erythrocyte use was 0.19 U/patient (SD, 0.86) and 7.7% were transfused (table 3). Among the control group, mean erythrocyte use was 0.22 U/patient (SD, 0.9) and 8.3% were transfused. Because of significant interaction between primary or revision surgery and the allocated treatments (autologous reinfusion; $P < 0.001$), we analyzed these patient groups separately (1,645 primary and 114 revision surgery patients). Because the revision surgery group was too small and too heterogeneous to draw valid conclusions, we separately present the results of the primary surgery group (n = 1,645) in table 3. Among the primary surgery group, mean erythrocyte use in the autologous group was 0.16 U/patient (SD, 0.7) and 7.1% were transfused. Among the control group that underwent primary surgery, mean erythrocyte use was 0.22 U/patient (SD, 0.9) and 8.2% were transfused. The majority was transfused (n = 122, 87%) in the postsurgery period between 1 and 14 days. Hip surgery patients were significantly more often transfused (11%) than knee surgery patients (4.1%) ($P < 0.001$). In primary surgery patients, autologous blood reinfusion resulted neither in a meaningful erythrocyte sparing (0.08 units mean erythrocyte decrease) nor in transfusion avoidance (1.1% absolute decrease). The separate cell saver and DRAIN effects showed no difference in primary outcome (table 4). In the as-treated analysis, a statistically nonsignificant reduction in transfused patients of 31% (adjusted odds ratio, 0.69; 95% CI, 0.47 to 1.0; $P = 0.05$) from 8.8 to 6.2% (2.6% absolute difference) was observed.

Economic Evaluation

Autologous blood reinfusion resulted in an statistically significant increased length of the nonintensive care unit hospital stay by 0.45 days (95% CI, 0.08 to 0.82; $P = 0.02$; table 5). The total cost increase for the autologous blood reinfusion

Table 4. ITT Analysis of Separate Cell Saver and DRAIN Effect in Primary Hip Surgery Patients

	Primary Hip Surgery Patients				
AUTO N = 642	Mean Erythrocyte Use (U) (SD)	Mean Adjusted Difference* (95% CI)	Ratio† (95% CI)	Proportion Transfused (%)	Adjusted Odds Ratio‡ Cell Saver *vs.* DRAIN (95% CI)
Cell saver (n = 321)	0.25 (0.5)	−0.12 (−0.23 to −0.01)	0.73 (0.48–1.1)	7.2	0.67 (0.4–1.2)
DRAIN (n = 321)	0.13 (0.7)		*P* = 0.12	10.3	*P* = 0.16

* Adjusted for hospital; CIs for reference purposes only (assuming normality). † Ratio was defined as the quotient of mean erythrocyte values of two groups being compared; all estimates and robust standard errors were obtained *via* bootstrapping in R (http://www.r-project.org/. Accessed November 8, 2013). ‡ All estimates and standard errors were obtained using the Mantel–Haenszel procedure, stratifying by the prespecified stratification factor hospital. Because knee surgery was excluded from cell saver use, for better comparison to exclude bias, only hip surgery patients were analyzed.

AUTO = autologous blood reinfusion by cell saver or DRAIN; DRAIN = postoperative drainage and reinfusion device; ITT = intention-to-treat; U = units.

Table 5. Estimated Costs per Patient for the Strategies with and without Autologous Blood Reinfusion, among Patients with Hemoglobin Levels >13 g/dl

	Volumes of Health Care*		Costs (in €)			
N = 1,759	AUTO n = 1,061	No AUTO n = 698	AUTO n = 1,061	No AUTO n = 698	Difference (95% CI)	*P* Value
AUTO	100%	0.3%	90	0	89 (86–92)	<0.001
Erythrocyte use (%/mean units)	7.7%/0.19	8.3%/0.22	159	185	−27 (−96 to 42)	0.46
ICU stay (%/mean days)	1.5%/0.02	0.7%/0.01	53	29	24 (−26 to 74)	0.36
Non-ICU stay (%/mean days)	100%/7.83	100%/7.38	3,690	3,479	212 (38–385)	0.02
Total costs			3,992	3,694	298 (76–520)	0.008

* 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.

strategy was estimated at €298 per patient (95% CI, 76 to 520). With the nonsignificant decrease in the proportion of transfused patients by 0.6% (from 8.3 to 7.7%; *P* = 0.19), the cost difference translates to €51.000 per avoided transfusion (95% CI, 3,000 to infinity).

Study Protocol Adherence

A total of 113 patients did not receive the intended intervention. Forty of 348 (11%) assigned patients did not receive cell saver and 73 of 713 (10%) assigned patients did not receive DRAIN. Most common reasons for not receiving the intended intervention were 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. In more than 95% of the patients, the transfusion protocol was correctly followed according to hemoglobin level, age, and risk group assessment of the patient before transfusion. Transfusion protocol violations were equally distributed among the randomization groups.

Serious Adverse Events

A total of 77 serious adverse events were reported in 72 patients (five patients suffered two serious adverse events; table 6). Autologous blood reinfusion–related complications were not sepsis or infection related. The proportion of thromboembolic events in the AUTO group (1.4%) was not significantly different from that in the control group (1.1%) (odds ratio, 1.2; 95% CI, 0.52 to 2.9; *P* = 0.63). Four cases of myocardial infarction (1 in control group and 3 in autologous group) were reported.

One serious anaphylactic reaction occurred in the DRAIN group after postoperative refusion of 50 ml, which was treated with adrenalin and fluid resuscitation, and resolved uneventfully. In the as-treated analysis, serious adverse event differences between groups remained nonsignificant.

Discussion

In elective total hip- and knee-replacement surgery patients with a preoperative hemoglobin level greater than 13 g/dl, the use of autologous reinfusion by cell saver or DRAIN device did not result in a statistically and clinically significant erythrocyte reduction. On the basis of the results of the intention-to-treat analysis, the alternative hypothesis of a 30% reduction in mean erythrocyte use or in proportion of transfused patients by autologous reinfusion was rejected.

Possible explanations of our finding that neither cell saver nor DRAIN resulted in a clinically relevant erythrocyte reduction may be: (1) the relatively low (visible) blood loss and a low volume of recovered shed blood, although total blood loss is still considerable, because the amount of nonvisible blood loss can reach the same amount as the visible blood loss[20,21]; (2) the applied restrictive transfusion threshold; (3) increased awareness of the orthopedic surgeons regarding blood management and intraoperative

Table 6. Reported Serious Adverse Events: TE Complications*, Non-TE Complications†, and Total Numbers (%)

Intention-to-treat (Numbers) n = 1,759	TE Events (%) n = 23	Myocardial Infarction n = 4	Stroke/TIA n = 10	DVT n = 4	Pulmonary Emboli n = 4	Other n = 1	Non-TE Events (%) n = 54	Total SAEs (%) n = 77
AUTO (1,061)	15 (1.4)	3	7	1	3	1‡	32 (3.0)	47 (4.4)
Control group (698)	8 (1.1)	1	3	3	1	0	22 (3.2)	30 (4.2)

Percentages are calculated within randomized groups (rows).

* 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*. ‡ Denotes an arterial occlusion.

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

blood loss: blood management in orthopedic surgery was declared as one of the key indicators for quality assessment in hip and knee arthroplasty surgery by the healthcare authority‡; and (4) slight adaptations of surgical techniques (*i.e.*, less extensive incisions), which might also minimize blood loss. Our findings are 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 orthopedic total joint surgery was small.[21]

We did not find any interaction between the AUTO *versus* control groups, primary *versus* revision groups and hemoglobin groups with either a low hemoglobin level (<13 g/dl) or normal hemoglobin level (hemoglobin level 13 g/dl and higher) on the transfusion rate. Although the group of primary surgery patients consists of a subgroup of the patient population, the analysis of these patients cannot be regarded as a typical subgroup analysis as such, because the distinction between primary and revision groups is a defined stratification factor in the study protocol, and separate reporting of the primary group is an effect of the result that the AUTO treatment effects differed significantly between primary and revision surgery patients (significant interaction). We further observed that the use of autologous blood reinfusion was associated with a small, but significantly longer hospital stay of 0.45 days. Such a small increase in hospital stay was also found in the erythropoietin-eligible patient group with a low level of preoperative hemoglobin.[16] We could not identify a particular cause. Because adverse reactions (mostly mild fever) have been reported in up to 30% of patients, and severe reactions may occur (one patient in the study), returning autologous blood may not be harmless.[22]

Although a restrictive transfusion policy was used, four cases were reported with a postoperative myocardial infarction (0.2%).

Strengths and Limitations of the Study

Our study has several strengths and limitations. Strengths were that the study was randomized, sufficient numbers of patients were included and evaluated, the patients were balanced considering the study variables across the randomization groups, and that the power of the study was 90%. Adherence to the restrictive transfusion protocol was more than 95%. A limitation of the study was the approximately 10% nonadherence to the randomization arms, which occurred equally in all participating centers for both autologous reinfusion devices. Of the patients who did receive the device, a number of patients did not receive any autologous blood due to insufficient drainage and/or collection of shed blood. Another limitation may be that the study was unblinded. It is unlikely that this affected transfusion policy, because there was good adherence to the transfusion protocol and violations were equal in the randomization groups. Furthermore, because the study was not powered for safety evaluation, we are unable to draw valid conclusions on the incidence of complications regarding safety. No difference in this complication rate that could explain the slightly longer hospital stay in receivers of autologous salvaged blood was found. All patients in our study received thrombosis-prophylaxis, which may have had an effect on the low proportion of thromboembolic complications. A further limitation is that the study population was scheduled for elective hip- and knee-replacement surgery, excluding the hip fracture surgery patients, and results cannot be therefore extrapolated to this latter group.

Many transfusion trials are complicated by to the fact that randomization occurs before surgery. In this group of patients with a preoperative hemoglobin levels greater than 13 g/dl undergoing elective surgery, the transfusion rate is below 10%. To demonstrate further reduction of transfusions by interventions needs very large studies. This, however, does not invalidate in any respect the intention-to-treat approach.[23] The generalizability of economic evaluations to others settings may sometimes be limited. For example, we expect our hospital costs to be relatively low compared with those of many other countries. Nevertheless, we expect our results to be very robust. Autologous blood salvage devices did not significantly reduce erythrocyte use and increased the duration of the hospital stay, so results will be unfavorable for blood salvage regardless of the healthcare prices.

‡ Available at: www.zichtbarezorg.nl. Accessed March 18, 2012.

This study may serve as a valid estimate for the elective 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 more than 100,000 in 2030.[24] Considering the fact that autologous blood reinfusion devices are used in up to 80% of Dutch hospitals (year 2007),[25] and that we found no blood-sparing benefit, omission of these devices from blood management protocols may result in a considerable decrease in healthcare costs.

Conclusions

Autologous blood reinfusion in elective total hip- and knee-replacement surgery patients with preoperative hemoglobin levels greater than 13 g/dl did not result in a clinically meaningful reduction in allogeneic erythrocyte use, was not cost-effective, and therefore should be reconsidered for these patients. Using a restrictive transfusion protocol, it was observed that the proportion of transfused patients is below 10%.

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Competing Interests

The authors declare no competing interests.

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