Chapter 2

A randomized comparison of transfusion triggers in elective orthopaedic surgery using leucocyte-depleted red blood cells

CynthiaSo-Osman, Rob Nelissen, Ron Te Slaa[†], L. Coene, R. Brand and Anneke Brand

The Department of Research and Development, Sanquin Blood Bank South West Region, Leiden, the Netherlands
The Department of Orthopaedic Surgery, Leiden University Medical Centre (LUMC), Leiden, the Netherlands
The Department of Orthopaedic Surgery, Reinier de Graaf Groep, Delft ([†]passed away), the Netherlands
The Department of Orthopaedic Surgery HAGA Hospital, Leyenburg location, Den Haag, the Netherlands
The Department of Medical Statistics and BioInformatics, Leiden University Medical Centre (LUMC), Leiden, the Netherlands.

Vox Sang 2010; 98: 56-64

ABSTRACT

Objective: In elective orthopaedic hip- and knee replacement surgery patients, we studied the effect of implementation of a uniform transfusion policy on RBC usage.

Study design and methods: A randomized, controlled study. A new uniform, restrictive transfusion policy was compared with standard care, which varied among the three participating hospitals. Only prestorage leukocyte-depleted RBC(s) were used. Primary end-point was RBC usage, related to length of hospital stay. Secondary end-points were Hb levels, mobilisation delay and postoperative complications.

Results: 603 patients were evaluated. Adherence to the protocol was over 95%. Overall mean RBC usage was 0.78 U/patient in the new policy group and 0.86 U/patients in the standard care policy group (mean difference 0.08; 95% CI [-0.3; 0.2]; p=0.53). In two hospitals the new transfusion policy resulted in a RBC reduction of 30% (0.58U RBC/patient) (p=0.17) and 41% (0.29 U RBC/patient) (p=0.05), respectively. In the third hospital, however, RBC usage increased by 39% (0.31 U RBC/ patient) (p=0.02) with the new policy, due to a more restrictive standard care policy in that hospital. Length of hospital stay was not influenced by either policy.

Conclusions: Implementation of a uniform transfusion protocol for elective lower joint arthroplasty patients is feasible, but does not always lead to a RBC reduction. Length of hospital stay was not affected.

INTRODUCTION

Concerns about transfusion-associated complications have stimulated the use of drugs and devices to reduce peri-operative blood transfusions [1-3]. To value such interventions they must be compared with an appropriate and uniform use of allogeneic RBC transfusions. In itself, one of the tools to accomplish a reduction in allogeneic RBC transfusions is a standardized protocol for the use of a restrictive transfusion trigger. Studies on the use of such a protocol in (orthopaedic hip fracture) surgery report an allogeneic RBC reduction between 40 and 80%, depending on the type of restriction used [4-6]. In elective orthopaedic surgery, a randomized study in which different transfusion trigger protocols are compared has never been performed. Additionally, except for studies in paediatric and neonatal patients, all previous studies that compared different transfusion triggers used non leukocyte-depleted RBC units [4,5,7]. We only used pre-storage leukocyte-depleted (LD) RBC(s) and conducted a randomized controlled trial among elective orthopaedic surgery patients in three Dutch hospitals to investigate the effect of a new, restrictive transfusion protocol compared with the standard care on the magnitude of reduction in RBC transfusions and its effects on length of hospital stay (LOHS), postoperative complications and rehabilitation.

PATIENTS AND METHODS

Outcome measures

Primary objective was to investigate whether or not a reduction of RBC usage was associated with a prolonged hospital stay.

Primary outcome was RBC usage. With the new transfusion policy we aimed at a reduction of 40% in RBC use without increasing hospital stay. Secondary end-points were: postoperative Hb values (g/dL) at day +1, day +4 and day +14, mobilization delay (days) and postoperative complication rate.

Inclusion criteria:

All patients of 18 years and older scheduled for a primary or revision total hip replacement (THR)- or total knee replacement (TKR) surgery of three Dutch participating hospitals were eligible for inclusion.

Exclusion criteria:

Refusal of allogeneic transfusions (e.g. Jehovah's witnesses).

Study design

A randomized open study stratified by hospital, type of surgery and risk group. Eligible patients were informed during the preoperative intake at the orthopaedic outpatient clinic and after obtaining informed consent were randomly assigned to a new transfusion policy (protocol A) or standard care (protocol B). The new policy, which was risk level based and uniform among the three participating hospitals, is described in Table 1, and was meant to include the more restrictive transfusion policy. In this policy, age and co-morbidity were determinants for the used risk levels for transfusion. Three clinical risk groups (low, intermediate and high) were defined: age groups less than 50 years, 50 to 70 years, and older than 70 years or presence of significant co-morbidity (i.e. cardiovascular and pulmonary disease, and/or insulin dependent diabetes). The standard care policies, which varied among hospitals, are described in Table 2, and were supposed to include the more liberal transfusion policies. Randomization took place as follows: all patients were stratified by hospital, type of surgery (primary/revision THR/TKR) and risk group. For each stratum a separate randomization list was created, using blocks of variable length to avoid predictability of the random treatment assignment towards the end of each block. Treatment allocation was random using a uniform distribution for 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. 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.

Due to a universal leukocyte-depletion policy in the Netherlands, our data comprises only pre-storage LD- RBC(s). Intra-operative transfusions were guarded by the anaesthesiologist and post-operative transfusions by the orthopaedic surgeon. Both were informed about the treatment assignment in order to avoid protocol violations, but they were not involved in the coordination and evaluation of the study. The chart data were written on the Clinical Research Form and placed in the database by the research nurse, who had access to the medical records in which the study assignment was noted. The study investigators, however, were blinded for the randomization arm. Transfusion trigger deviations were regarded as protocol violations. The following postoperative complications were scored: infections, ICU stay, transfusion reactions (defined by the national hemovigilance association), neuro-psychiatric, cardiovascular, haemorrhagic and drug related complications, and death. Post-operative infections were defined according to the CDC criteria [8]. Wound infections were scored according to Gaine et al [9]. Mobilisation was defined according to the hospital protocols (hospital number 1: mobilisation from day +2 onwards, hospitals number 2 and 3: mobilisation from day +1 onwards) and was recorded by the orthopaedic surgeon on the ward. Postoperative discharge from the hospital was based on physical properties of the

patient: they had to be ambulated with a crutch and had to be able to walk a staircase with ease. Hospital number 2 used a short-stay protocol for the most healthy and mobile patients. Follow up ended at the outpatient clinic 14 days after surgery or (in case of a hospital stay of more than 14 days) at final discharge. All patients provided informed consent, and the trial was conducted according to good clinical practices and the Declaration of Helsinki. The study was approved by the Medical Ethical Committees of the three participating hospitals.

Table 1. Transfusion policies: new, uniform restrictive transfusion policy (Protocol A)

Low risk group (patients younger than 50 years of age)					
Within 4 hours of surgery			After 4 hours of surgery		
If Hb	≥6.4 g/dL:	0 RBC	If Hb	≥6.4 g/dL:	0 RBC
	4.8 - <6.4:	1 RBC		5.6 - <6.4:	1 RBC
	<4.8:	2 RBC(s)		<5.6:	2 RBC(s)
Intermediate risk group (patients from 50 to 70 years of age)					
Within 4 hours of surgery			After 4 hours of surgery		
If Hb	≥7.2 g/dL:	0 RBC	If Hb	If Hb ≥8.1g /dL:	0 RBC
	6.4 - <7.2:	1 RBC		7.2 - <8.1:	1 RBC
	<6.4:	2 RBC(s)		<7.2:	2 RBC(s)
High risk group[a] (see below)					
Within 4 hours of surgery			After 4 hours of surgery		
If Hb	≥8.9 g /dL:	0 RBC	If Hb	If Hb ≥9.7 g /dL:	0 RBC
	8.1 - <8.9	1 RBC		8.9 - <9.7:	1 RBC
	7.2 - <8.1:	2 RBC(s)		8.1 - <8.9:	2 RBC(s)
	<7.2:	3 RBC(s)		<8.1:	3 RBC(s)

Hb values were originally in mmol/L (e.g. 4.0 / 5.0 / 6.0 mmol/L) which is common use in the Netherlands
[a]High risk includes one or more of the following:
(i) any heart rhythm different than sinus rhythm.
(ii) unstable cardiac ischemia (by history or ECG)
(iii) myocardial infarction < 6 months
(iv) heart failure
(v) heart valve disease
(vi) age (from 70 years onwards)
(vii) serious peripheral arterial disease, including large vessel surgery (aortic aneurysm, peripheral vessels).
(viii) cerebral arterial disease (CVA or TIA in history)
(ix) hypertension with left ventricular hypertrophy (LVH) (shown on ECG/ echocardiogram)
(x) serious pulmonary disease, expressed in polyglobulism (emphysema / pulmonary fibrosis)
(xi) insulin dependent diabetes mellitus

Table 2. Transfusion policies: standard care transfusion policies (Protocol B)

Hospital number 1 (University Medical Center):

Peri-operative transfusion policy (day 0):
if Hb between 8.1 and 9.7 g /dL and dependent on blood loss: 1-2 RBC(s).

Post operative transfusion policy (from day 1):
if Hb <9.7 g /dL : 2 RBC(s), independent of age, risk status

Hospital number 2 (general hospital):

Peri-operative transfusion policy (day 0):

I keep Hb >6.4 g/dL in case of age < 60 years and ASA[a] class 1

II keep Hb >8.1 g.dL in case of age ≥ 60 years and ASA[a] class 1, 2, 3

III keep Hb >9.7 g/dL in case of ASA[a] class 4 or serious cardiopulmonary disease

[a]American Society of Anesthesiologists

Post operative transfusion policy (from day 1):

I keep Hb > 9.7 g/dL in case of co-morbidity as: IC / CCU admission, uremia, serious heart-, lung- or vessel disease:

II If no co-morbidity exists, the transfusion trigger is age-dependent:

Age (years)	**Hb (g/dL)**
>70	10.5
50-70	9.7
25-50	8.9
<25	8.1

Hospital number 3 (general hospital):

Peri-operative transfusion policy (day 0):
if Hb <9.7 g/dL and dependent on (expected) blood loss: 2 RBC(s)

Post operative transfusion policy (from day 1):

I Patients with cardiac history:

if Hb <9.7 g/dL: 2 RBC(s)

II Patients without cardiac history if symptomatic (nausea, dizziness, tachycardia, general malaise, paleness):

if Hb 7.2 g/dL – 8.1 g/dL: 2 RBC(s)

III If Hb ≤7.2 g/dL: 2 RBC(s)

Sample size calculation

The initial sample size calculation (power 0.90; alpha 0.05) was based on pilot data of hospital number 1, from which a 40% RBC reduction (in terms of RBC units divided by the total patients in each randomization group) was expected by introducing the new transfusion policy. Since the main statistical analysis is a comparison of group means, the reduction for which the study was powered, was transformed to an absolute reduction from an estimated mean RBC use of 2.6 units (SD 2.4) in one group to a mean RBC use of 1.6 units (SD 2.4) in the

other group. A t-test with adjustment for possibly non-normally distributed data needed 2 groups of 125 patients to achieve 90% power for a treatment effect of 1 RBC unit at a pooled SD of 2.4, while at the same time powering with 90% for equivalence in length of stay with a delta of at most four days between the groups. At the time the study protocol was designed a mean hospital stay of 10 to 12 days was usual, therefore a prolongation of hospital stay of more than four days was not acceptable from a clinical point of view. To adjust for non-evaluable patients, each of 3 hospitals had at least to randomize 100 patients. An interim analysis was performed after the first 125 patients became evaluable. A formal stopping rule was pre-specified to enable the trial to stop for futility as well as efficacy, using a simple Bonferroni correction for multiple testing (alpha=0.025). This pre-specified rule also included the condition of a maximal prolongation of hospital stay of four days in the new policy group, which was expected to include the most restrictive transfusion policy: so if RBC use was significantly lower in the new policy group, but hospital stay increased by more than four days, the new transfusion policy was considered not to be clinically nor economically beneficial. A much lower percentage of patients who were actually transfused (33% in stead of the expected 75%, which was calculated from the pilot study), irrespective of hospital and trial arm, resulted in an adjustment of the group sizes, leading to two groups of 300 evaluable patients.

Statistical analysis

Analysis was performed on an intention-to-treat basis and for the parametric analyses stratified by all stratification factors in the design. Frequencies were described as mean and SD, and in addition median and interquartile range in case of a non-normal distribution. Analysis of laboratory parameters between patients and other numerical end-points was performed with the ANOVA-test for between-group comparisons and by a paired t-test (or a mixed model) for within-patients effects. Differences between the groups in the number of RBC transfusions and the total number of units RBC transfusions given were analysed with the non-parametric Mann-Whitney test. Categorical end-points were tested using the Chi-square test or Fisher's Exact test. LOHS and age were analysed as a continuous variable. In case of heterogeneity between the three hospitals concerning the primary and secondary end-points, subgroup analyses by hospital will be performed.

Regarding the primary end-point, a P-value of less than 0.05 was considered statistically significant. For the analysis of the secondary end-points we used a Bonferroni correction to adjust for multiple testing (significant P-value of less than 0.01). Data were analysed using the SPSS statistical program (version 11.0) for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Patient enrolment and baseline characteristics

From 2001 to 2003, 713 patients were assessed for eligibility of which 619 consecutive patients were included. Sixteen patients were not analysed because of the following reasons: cancellation of surgery in seven, death before surgery in one, consent withdrawn before surgery in six and charts missing in two cases (Figure 1: Flow chart).

Baseline characteristics of the excluded group were comparable with the analysed group (data not shown). The included patients were equally assigned to the randomization groups within each hospital.

Baseline characteristics between the two randomization groups (protocol A and protocol B) were comparable, except for female patients, who were represented more in the new policy group (P=0.01) and for patients with rheumatoid arthritis, who were represented more in the standard care group (P=0.02) (Table 3).

The baseline characteristics between hospitals were comparable, except for hospital number 1, the university medical centre, who included a significantly higher proportion of Rheumatoid Arthritis (RA) patients (31.7% versus 9.2% and 3.3% in the other hospitals, respectively; P<0.001). Also, hospital number 1 included patients with a lower mean age (SD) than the other hospitals (67.1 (11.7) versus 71.1 (9.8) and 70.5 (9.9); p<0.001). This age difference can be explained by the larger RA patient population, who are generally younger when indicated for joint replacement surgery. Co-morbidities such as hypertension, myocardial infarction, heart failure, diabetes, stroke, peripheral arterial disease and arrhythmia were all comparable among hospitals, as well as use of medication (steroids, non-steroidal anti-inflammatory drugs (NSAID's), anticoagulants etc). Autologous re-infusion by cell saver was used in two hospitals in a total of 9 cases (2% of total; twice in hospital number 2 and seven times in hospital number 3).

Primary outcome

RBC usage

Overall RBC usage in the group with the new policy was 0.78 U/patient (SD 1.4) and 0.86 U /patient (SD 1.6) in the standard care group, with an overall mean difference of 0.08 (95% CI of mean difference [-0.3, 0.2]; P=0.53). LOHS was comparable between the groups (mean difference of - 0.6 days (95% CI of mean difference [-1.2, 0.5]; P=0.21)) (Table 4).

Secondary outcome

Results of all categorical, secondary end-points were not significantly different between the new policy and the standard care policy (P>0.05) (Table 4).

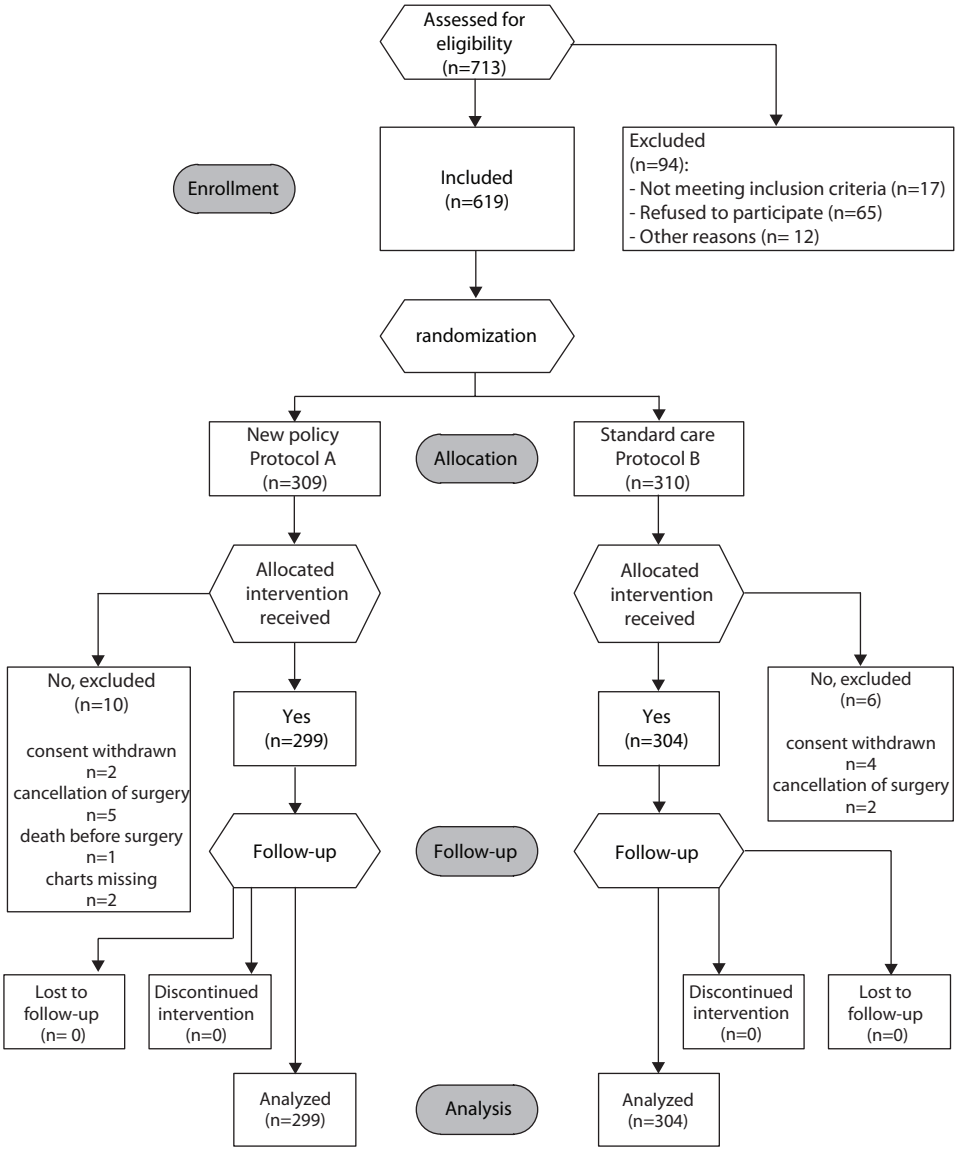

Figure 1. Flowchart

The flowchart shows the progress of all participants in the trial, from the time they are assessed for eligibility until the end of their involvement. In hospital #1 and hospital l#2, the new policy (protocol A) was the most restrictive policy, as expected. In hospital #3 the standard care policy (Protocol B) turned out to be the most restrictive policy.

Table 3. Patient characteristics (by type of policy and of total group)

Parameter Numbers (%) or mean (SD)	New policy (Protocol A)	Standard care (Protocol B)	All patients
Patients			619
Evaluated	299	304	603
Females (%)	215 (71.9)	186 (61.2)[d]	401 (66.5)
Mean age (years)	70.7 (10.2)	70.3 (9.7)	70.4 (9.9)
Mean weight (kg)	78.1 (13.4)	79.0 (13.2)	78.6 (13.2)
Smoking	43 (14.3)	47 (15.5)	90 (15.2)
THR	167 (55.9)	172 (56.6)	339 (56.2)
TKR	111 (37.1)	113 (37.2)	224 (37.1)
Revision THR	18 (6.0)	16 (5.2)	34 (5.6)
Revision TKR	3 (1.0)	3 (1.0)	6 (1.0)
Low risk[a]	14 (4.7)	12 (3.9)	26 (4.3)
Intermediate[b]	80 (26.8)	81 (26.6)	161 (26.7)
High risk[c]	205 (68.6)	211 (69.4)	416 (69.0)
Rheumatoid arthritis	24 (8.0)	43 (14.1)[e]	67 (11.1)
COPD	21 (7.0)	25 (8.3)	46 (7.6)
Mean pre-operative Hb (g/dL)	13.7 (1.4)	13.7 (1.4)	13.7 (1.3)
Mean pre-operative Hct (L/L)	0.41	0.41	0.41

Percentages are within policy group.
[a] low risk: patients younger than 50 years of age without risk factors indicated in Table 1
[b] intermediate risk: patients from 50 to 70 years of age without risk factors indicated in Table 1
[c] high risk: see definition in Table 1.
[d] P=0.01
[e] P=0.02

Subgroup-analysis at individual hospital

Due to heterogeneity of the effects on primary outcome across the three hospitals (P=0.008), we performed a subgroup-analysis by hospital.

Primary outcome

RBC use and the proportion of transfused patients were highest in hospital number 1 (Table 5). In two hospitals (number 1 and 2), the new policy (protocol A) was more restrictive than the standard care, but resulted in a non-significant RBC reduction of 30% in hospital number 1 (P=0.17) and a nearly significant reduction of 41% in hospital number 2 (P=0.05). In the third hospital, however, the standard care was more restrictive, which led to an increase of 39% in RBC usage (P=0.02) and to an increase in the proportion of transfused patients as well (P=0.001). The effect on RBC use differed significantly per hospital (test on interaction; P=0.008). An interaction of RBC use with risk group was found in hospital number 1:

compared to the high risk group, the effect size (this is the difference between the new policy and standard care) was larger in the lowest risk group, namely -4.9 RBC(s) (95% CI [-7.1, -2.7]; P<0.001) and -2.1 RBC(s) (95% CI [-3.2, -1.0]; P<0.001) in the intermediate risk group. In hospital number 2 and 3, no clinical significant interaction with a particular risk group was found. Within each hospital, mean duration of surgery and median blood loss were comparable between randomization groups. Total LOHS differed between hospitals due to the different hospital protocols. Hospital number 2 used a short-stay protocol, which resulted in the shortest LOHS. Due to a non-normal distribution of data, median values are shown, which were comparable within randomization groups. In all hospitals, LOHS was not affected by any transfusion protocol.

Table 4. Results of primary and secondary end-points by randomized group

Parameters	New policy (Protocol A) n=299	Standard care (protocol B) n=304
RBC (units) / patient	0.78 (1.4)	0.86 (1.6)[a]
LOHS (days)	9.6 (5.0)	10.2 (7.4)[b]
Hb day +1 (g/dL)	10.5 (1.6)	10.3 (1.4)
Hb day +4 (g/dL)	10.5 (1.1)	10.5 (1.1)
Hb at discharge (g/dL)	11.4 (1.1)	11.4 (1.3)
Infections	18 (6.0 %)	31 (10.1%)
Cardiovascular complications	34 (11.4%)	23 (7.6%)
Respiratory complications	6 (2.0%)	15 (4.9%)
Neuropsychiatric complications	11 (3.7%)	13 (4.2%)
Hemorrhage	10 (3.3%)	12 (3.9%)
Delayed mobilisation	22 (7.4%)	36 (11.8%)
Mortality	1 (0.3%)	2 (0.7%)
Composite complications	99 (33.1%)	104 (34.2%)

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

[a] mean difference 0.08 (95% CI of mean difference: -0.3 to 0.2; P=0.53)

[b] mean difference -0.6 (95% CI of mean difference: -1.2 to 0.5; P= 0.21)

For all categorical complications (infections etc) no difference between groups was found (P-values were all >0.05).

Secondary outcome

Mean post-operative Hb levels were comparable between hospitals and within each hospital between randomization groups. For hospital number 1 mean values were: 9.8 g/dL (SD 1.3) at day +1, 10.3 g/dL (SD 1.1) at day +4 and 10.9 g/dL (SD 1.1) at day +14. For hospital number 2 these values were: 10.8 g/dL (SD 1.6), 10.9 g/dL (SD 1.1) and 11.8 g/dL (SD 1.3),

respectively and for hospital number 3 these values were: 10.5 g/dL (SD 1.3), 10.3 g/dL (SD 1.1) and 11.3 g/dL (SD 1.1), respectively.

Table 5. Subgroup analysis of primary outcome measurements at individual hospital

Primary end-point	New policy (Protocol A)	Standard care (Protocol B)
Median RBC use[a] (25-75% range):		
Hospital #1	0.5 (0.0-2.0)	2.0 (0.0-2.3)
Hospital #2	0.0 (0.0-0.0)	0.0 (0.0-2.0)
Hospital #3	0.0 (0.0-2.0)	0.0 (0.0-0.0)
Proportion transfused patients in %:		
Hospital #1 (n=123)	50.8 (n=61)	54.8 (n=62)
Hospital #2 (n= 206)	20.8 (n=101)	30.8 (n=105)
Hospital #3 (n=274)	38.7 (n=137)	19.7 (n=137)[c]
Median LOHS[b] (25-75% range):		
Hospital #1	10.0 (9.0-13.0)	11.0 (10.0-13.3)
Hospital #2	6.0 (6.0-8.0)	6.0 (6.0-8.0)
Hospital #3	9.0 (8.0-10.0)	9.0 (8.0-10.0)

In hospital#1 and hospital#2, the new policy was the most restrictive policy, as expected. In hospital #3 the standard care policy turned out to be the most restrictive policy.

[a] Mean RBC use (U/patients) (SD): in hospital #1 was 1.34 (2.2) with the new policy and 1.92 (2.4) with standard care. In hospital #2 mean RBC use was 0.42 (1.0) and 0.72 (1.2), respectively and in hospital #3 mean RBC use was 0.80 (1.2), and 0.49 (1.1) (P=0.02), respectively

[b] LOHS must not be prolonged for more than four days in the most restrictive policy group.

[c] P=0.001

In 203 patients (33.7%) a postoperative complication was observed, which was highest in hospital number 1 (83/123=67%). Between transfusion policies, differences were found in composite complications in hospital number 2, which were slightly more represented in the standard care group that had the most liberal policy (n=35 versus n=21 in the new policy group; P=0.04) (Table 6). In hospital number 1, respiratory complications were more observed in the standard care group, that had the most liberal transfusion policy (n=13 versus n=3 in the new policy group; P=0.008). Furthermore, delayed mobilization (i.e. different from the standard ambulation protocol) was reported more frequent in the standard care group of hospital number 3 (n=18 versus n=8 in the new policy group; P=0.04), which contained the most restrictive transfusion policy. Infections occurred in 47 (7.8%) of all patients, which were mostly urinary tract infections (24 cases); 16 patients had wound infections, of which 5 were deep prosthetic infections. The remaining wound infections consisted of mostly superficial wound infections, which resolved uneventful: mild, grade 2 infections (haematoma with or without evident inflammation, but no bacterial growth) and in two cases more severe infections: one grade 3 (bacterial growth with a haematoma, but

Table 6. Subgroup analysis of secondary outcome measurements at individual hospital

Secondary end-points	New policy (Protocol A) n=299	Standard care (Protocol B) n=304
Composite complications[a]		
Hospital #1 (n=123)	43	40
Hospital #2 (n=206)	21	35[b]
Hospital #3 (n=274)	35	29
Infections		
Hospital #1	8	16
Hospital #2	4	9
Hospital #3	6	4
Cardiovascular complications		
Hospital #1	18	10
Hospital #2	8	9
Hospital #3	8	4
Respiratory complications		
Hospital #1	3	13[c]
Hospital #2	1	1
Hospital #3	2	1
Delayed mobilisation		
Hospital #1	12	14
Hospital #2	2	4
Hospital #3	8	18[d]

Stated values are numbers of patients
[a] patients could experience more than one complication
[b] P=0.04
[c] P=0.008 (significant P-value of less than 0.01 (Bonferroni correction for multiple comparisons)).
[d] P=0.04

no evident inflammation) and one grade 4 infection (evident inflammation and bacterial growth). Furthermore, one patient suffered from a pneumonia and in six patients a systemic bacterial infection (n=3) or a localized infection (n=3) was found. One patient had two infections. Respiratory complications were pulmonary embolism in one, pneumonia in one, five cases of transfusion associated cardiac overload (TACO), three cases of respiratory insufficiency due to opiates for pain reduction, bronchospasm in COPD in two and shortness of breath without evident clinical substrate in nine cases. Of all complications, ICU stay of more than 1 day (n=3) and transfusion reactions (n=3) were negligible (<1%). Mortality was found in three cases, one in each hospital, which all occurred in the groups who were transfused with the most liberal policies. The proportion of patients who had a delay in mobilisation differed per hospital, but within hospitals, delay was comparable between randomization groups in hospitals number 1 and 2. In hospital number 3, however, more patients (n=18) were delayed in the group with the most restrictive transfusion policy compared to the patients in the group transfused with the most liberal policy (OR 2.4 (95%

CI [1.0, 5.8]); P=0.008). Nevertheless, total hospital stay in hospital 3 was comparable in both groups. This delay in mobilisation could not be explained by a difference in post-operative Hb level of these patients: mean Hb level at day +1 was 10.2 g/dL with delay and 10.5 g/dL without delay (NS). Other complications as neuropsychiatric and haemorrhage were not different between randomization groups within each hospital.

DISCUSSION

Implementation of a new restrictive transfusion protocol in three different hospitals compared with the standard care did not result in an overall significant reduction of RBC transfusions, however, this study shows that a uniform transfusion policy can be implemented with great reliability, as deviations from the trigger protocol were only 4.5%. By implementing a new presumably restrictive transfusion trigger, we aimed at a reduction in RBC use, but one of the hospitals (number 3) showed an increase instead. This can not be explained by a population difference or a staff compliance difference to the protocol, because patients characteristics (age, gender) were not different from hospital number 2 which was the other general hospital. Hospital 1 and 2 had a liberal standard care transfusion policy. However, hospital 3 turned out to have a different more restrictive standard care policy. Furthermore that policy did not consider age as a risk factor. Thus, their current standard policy resulted in a lower RBC use. As a result, the overall difference in RBC use between the original randomization groups was negligible. Due to heterogeneity between hospitals in primary outcome we performed a subgroup analysis by hospital. Hospital number 1 had a modest RBC reduction, but showed a significant interaction of RBC use with risk group. This is explained by the difference in Hb trigger of age-matched patients between randomization groups in this hospital: the difference was largest in the low risk group (age<50 years): transfusion trigger of 6.4 g/dL with the new protocol and 9.7 g/dL with standard care. In the intermediate group (age 50-70 years) these were 8.1 g/dL and 9.7 g/dL, respectively and 9.7 g/dL in both arms for the high risk group (>70 years). The standard care policy advocated to give two RBC(s) per transfusion against one RBC in the new protocol. In hospital number 2, a high mean age of the patient population (71.1 years) resulted in a large population of high risk patients who were transfused with a trigger of 9.7 g / dL according to the new, restrictive policy (protocol A) compared a trigger of 10.5 g/dL according to standard care (protocol B). Despite this small difference, still an overall reduction of transfused RBC units was found, but not a reduction of the percentage of transfused patients. In none of the three hospitals, the Hb level of the transfusion triggers was identical between randomization arms for age-matched patients, except for high risk patients (age from 70 years onwards). Hospital number 1 had a trigger of 9.7 g/dL in either arm, but differed in number of units transfused (one versus two). The largest difference in

transfusion protocol effect was seen in hospital number 3, due to the exclusion of age in the standard care protocol (protocol B), which resulted in a more restrictive RBC use compared to the new, age-dependent protocol (protocol A).

A reduction of RBC use would not be acceptable at the cost of an increased hospital stay (due to increased morbidity from anaemia). However, the most restrictive transfusion policies were safe and LOHS was not affected by either of the two transfusion policies, although ambulation in hospital number 3 was slightly slowed down in the standard care group that used the most restrictive transfusion policy.

The impact of different transfusion triggers on postoperative complications (e.g. infection rate) in elective orthopaedic surgery patients has not been previously reported. Allogeneic RBC transfusions were found to be associated with a higher post-operative infection rate compared to non- transfused patients [10-15], but these studies were observational and/or retrospective and performed with non leukocyte-reduced RBC(s). Subgroup-analysis by hospital showed that in hospital number 1, respiratory complications were significantly higher in the group with the most liberal transfusion policy. This association should be further studied in future trials.

Of the total of respiratory complications, in 14 of 21 cases the respiratory complications might be explained by the RBC transfusion itself: 5 cases were classified as transfusion related (TACO), whereas in the 9 cases of unclassified hypoxemia, a subclinical TACO or a transfusion related acute lung injury (TRALI) might have been present [16]. The occurrence of post-operative infections was not significantly different between randomization groups. Age appeared no risk factor for post-operative complications, as shown by data of hospital number 3, who had a standard care policy that was more restricted and not age-dependent, but was not associated with an increase in post-operative complications, although mobilisation was significantly delayed in this group. Other factors, such as pre-existent cardiovascular disease may play a role, however the current study was not powered to identify such an effect. In the FOCUS trial [17], an ongoing randomized, multi-centre study on elderly hip fracture patients (from 50 years of age onwards), patients with cardiovascular disease or cardiovascular risk factors are studied to investigate the impact of a restrictive transfusion trigger in this specific patient population with functional outcome as the primary end-point.

This study has some limitations. First, our data can not be extrapolated to other hospitals in general, as the hospital's standard care transfusion policy turned out to be very different between hospitals and therefore, it is unlikely that these three hospitals do represent the overall transfusion policy in the Netherlands. Second, our study was not powered to evaluate mortality or cardiovascular outcomes. Third, it is possible that our assessment of secondary end-points was biased since the trial and classification of outcomes was not blinded. However, the secondary end-points were scored by use of pre-defined objective criteria by the orthopaedic residents not performing the surgery. Fourth, to take RBC usage

as a primary end-point can be seen as a limitation, because transfusion less blood is the intended intervention of a restrictive policy. However, to use another well-accepted primary outcome such as mortality or post-operative complications is difficult, because of the low prevalence of such end-points in this study population. Although it seemed logically that a new, restrictive policy would always result in a RBC reduction, this was not the case in one hospital.

And finally, there is a limitation concerning the un-transfused patients, which is a general problem concerning all transfusion medicine trials: due to the early time of randomization, prior to surgery, the majority of patients included in the study did not meet any of the criteria for transfusion. In our study, this concerns a large part (45 to 80%) of the randomized patients. Ideally a patient should only be randomized when a transfusion is inevitable, but in practice this is very difficult to perform. However, by comparing the randomized patients according to the intention-to-treat principle, both groups remain balanced in terms of the levels of all known confounding factors [18].

In conclusion, implementation of a new, intentionally restrictive transfusion protocol in elective hip and knee replacement surgery is feasible and safe without lengthening the hospital stay. Whether a more restrictive transfusion policy is associated with less post-operative complications should be investigated in further studies which are powered to find this effect.

Acknowledgements

The authors thank Tineke van der Heide for data collection and the Orthopaedic staff of the Leiden University Medical Center, The HAGA Hospital Leyenburg and the Reinier de Graaf Gasthuis for participating in this study.

The authors state that none of them had any conflict of interest or financial involvement with this manuscript.

REFERENCES

1. Keating EM. Current options and approaches for blood management in orthopaedic surgery. Instr Course Lect 1999; 48:655-65.
2. Goodnough LT, Shander A, Spence R. Bloodless medicine: clinical care without allogeneic blood transfusion. Transfusion 2003; 43:668-676.
3. Shander A and Goodnough LT. Objectives and limitations of bloodless medical care. Curr Opin Hematol 2006; 13 (6):462-470.
4. Carson JL, Hill S, Carless P, Hebert P, Henry D. Transfusion triggers: a systematic review of the literature. Transf Med Rev 2002; 16(3):187-199.
5. Hill SR, Carless PA, Henry DA, Carson JL, Hebert PC, McClelland DB, Henderson KM. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 2002; (2):CD002042.
6. Eindhoven GB, Diercks RL, Richardson FJ, van Raaij JJAM, Hagenaars JAM, van Horn JR, de Wolf JThM. Adjusted transfusion triggers improve transfusion practice in orthopaedic surgery. Transfus Med 2005; 15:13-18.
7. Lacroix J, Hébert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, Gauvin F, Collet JP, Toledano BJ, Robillard P, Joffe A, Biarent D, Meert K and Peters MJ, for the TRIPICU Investigators, the Canadian Critical Care Trials Group, and the Pediatric Acute Lung Injury and Sepsis Investigators Network. Transfusion Strategies for Patients in Pediatric Intensive Care Units. New Engl J Med 2007; 356:1609-19.
8. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol 1992; 13 (10):606-608.
9. Gaine WJ, Ramamohan NA, Hussein NA, Hullin MG, McCreath SW. Wound infection in hip and knee arthroplasty. J Bone Joint Surg Br 2000; 82(4):561-565.
10. Murphy P, Heal JM, Blumberg N. Infection or suspected infection after hip replacement surgery with autologous or homologous blood transfusions. Transfusion 1991; 31(3); 212-217.
11. Fernandez MC, Gottlieb M, Menitove JE. Blood transfusion and postoperative infection in orthopedic patients. Transfusion 1992; 32;318-322.
12. Vignali A, Braga M, Gianotti L, Radaelli G, Gentilini O, Russo A, Di Carlo V. A single unit of transfused allogeneic blood increases postoperative infections. Vox Sang 1996; 71(3);170-175.
13. Duffy G and Neal KR. Differences in post-operative infection rates between patients receiving autologous and allogeneic blood transfusion: a meta-analysis of published randomized and nonrandomized studies. Transfus Med 1996; 6 (4);325-328.
14. Triulzi DJ, Vanek K, Ryan DH, Blumberg N. A clinical and immunologic study of blood transfusion and postoperative bacterial infection in spinal surgery. Transfusion 1992; 32 (6);p.517-524.
15. Innerhofer P, Klinger A, Klimmer C, Fries D, Nussbaumer W. Risk for postoperative infection after transfusion of white blood cell-filtered allogeneic or autologous blood components in orthopedic patients undergoing primary arthroplasty. Transfusion 2005; 45;103-110.
16. Kopko PM, Marshall CS, MacKenzie MR, Holland PV, Popovsky MA. Transfusion-related acute lung injury. Report of a clinical look-back investigation. JAMA 2002; 287(15):1968-1971.
17. Carson JL, Terrin ML, Magaziner J, Chaitman BR, Apple FS, Heck DA, Sanders D; FOCUS Investigators. Transfusion trigger trial for functional outcomes in cardiovascular patients undergoing surgical hip fracture repair (FOCUS). Transfusion 2006; 46(12):2192-206.
18. Vamvakas EC. Rationale for randomized controlled trials and for intention-to-treat analysis in transfusion medicine: are they one and the same? Vox Sang 2008; 95:165-73.