

Research Paper

Intraoperative Transfusion of Red Blood Cell Units Stored >14 Days is Associated with an Increased Risk of Prosthetic Joint Infection

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Abstract

Background: The aim of the present study was to evaluate the association between prosthetic joint infection (PJI) after joint arthroplasty and the length of red blood cell (RBC) storage, timing of RBC transfusion, and the number of RBC units transfused.

Study design and Methods: All patients who underwent a primary or revision joint arthroplasty between January 2000 and December 2012 were retrospectively reviewed. For this study, only patients who received RBC transfusions during the day of the surgery (early transfusion group) or within the first 4 days after surgery (late transfusion group) were included.

Results: A total of 9906 patients were reviewed. In the early transfusion group (n=1153, 11.6%), patients receiving 1 or 2 RBC units (3.5% vs 6.3%, P=0.041), 3 or 4 RBC (1.3% vs 13.3%, P=0.004) or ≥5 RBC units (5.0% vs 37.5%, P=0.026) had a higher PJI rate only when >50% of RBC units transfused had been stored >14 days. In the late transfusion group (n=920, 9.3%) these differences were not significant. Early transfusion of RBCs stored >14 days was an independent variable associated with an increased risk of PJI (OR:2.50, 95%CI:1.44-4.33)

Conclusion: Transfusion of RBC within the first 6h after joint arthroplasty was an independent variable associated with PJI risk when RBC units are stored >14 days. The rate of PJI increased with the number of old RBC units transfused within this critical period.

Key words: red blood cell storage, transfusion, prosthetic joint infection

Introduction

Prosthetic joint infection (PJI) is a devastating complication that occurs in 1-3% of arthroplasties. According to a recent retrospective study conducted in the United States, the frequency of PJI infection significantly increased from 2001 to 2009 ¹. This finding could be a consequence of the increasing number of revision ² procedures, aging population and a higher frequency of co-morbidities in patients undergoing arthroplasties in recent years ³. Identifying modifiable risk factors may guide

interventions aimed at reducing the risk of PJI after joint arthroplasty.

Blood transfusion has been associated with an increased risk of surgical-site infection after cardiac ⁴ and orthopedic surgery ^{5,6}. The mechanism for this deleterious effect remains unclear. Stored red blood cells (RBC) undergo a variety of biochemical and morphologic changes that impair their post-transfusion viability and biologic functions; however, the detrimental effect of such storage lesion at the

clinical level is still a matter of debate⁷. We previously reported⁸ an association between transfusion of old packed RBC and prosthetic joint infection in primary knee arthroplasties. Recent clinical trials in ill patients^{9,10}, undergoing cardiac surgery¹¹ or in hospitalized patients¹² did not identify any advantage of transfusing fresh versus older RBC units on survival or a composite score of morbidity and mortality. Of note, none of these trials dealt with the incidence of postoperative infection, a complication that has frequently been ascribed to RBC transfusion⁵.

The aim of the present study was to evaluate the association between PJI after joint arthroplasty and the duration of RBC storage, timing transfusion (during or after surgery) and the number of units transfused.

Materials and Methods

We retrospectively reviewed 9906 patients who underwent a primary or revision joint arthroplasty between January 2000 and December 2012. For this study, patients who received RBC transfusion(s) during the day of the surgery or within the first 4 days after surgery were included. Revision arthroplasties due to infection were excluded.

Relevant information about demographics (age and sex), site (hip, knee, shoulder, wrist or ankle), type (primary or revision) of arthroplasty, indication and duration of surgery were collected by standardized clinical data review. The number of RBC units transfused, date of transfusion and length of storage of each unit of RBC transfused were obtained from the database of our blood bank. Surgeries were performed in a non-laminar airflow operating room and all patients received prophylactic antibiotic according to a standardized protocol at our institution. Throughout the study period there were no variations in the operating theatres. After being discharged, patients were followed up according to a predetermined protocol at our hospital (one month, 3 months, 6 months and then yearly). Transfused blood consisted of pre-storage leuco-reduced RBC units stored in SAG Manitol for a maximum of 42 days. The concentration of hemoglobin that trigger RBC transfusion was 8 g/dL, although it could be higher in patients with risk factors (e.g. coronary heart disease) or poor tolerance to anemia.

Primary end-point was PJI within the first year after surgery defined according to the Musculoskeletal Infection Society criteria¹⁵. Time from index surgery to diagnosis of PJI was calculated and information about the microbiology was collected. The Ethical Committee of our institution approved the study.

Statistics

Categorical variables were described by absolute frequencies and percentages and were compared using the Chi-square or the Fischer's exact test when necessary. All continuous variables were expressed as median and interquartile range (IQR) and were compared by the Mann-Whitney U test. Furthermore, continuous variables were categorized according to the median value as follows: age ≤ 75 or > 75 , duration of surgery ≤ 120 min or > 120 min and length of storage of RBC units ≤ 14 or > 14 days. Two groups of patients were identified: (i) those who were transfused during or within the first 6 hours after surgery (early transfusion group) and (ii) those that were transfused after the 6-hour period and during the first 4 postoperative days (late transfusion group). Both groups were categorized according to the number of RBC units received (1-2, 3-4 or ≥ 5 units) and according to the mean time of storage of packed red blood cell transfused (≤ 14 days vs > 14 days). A forward stepwise logistic regression model was performed to identify independent variables associated with PJI. Goodness of fit was explored based on the Hosmer-Lemeshow test. Statistical significance was defined as a two-tailed $P < 0.05$. The analysis was performed using SPSS, version 20.0 (SPSS, Inc., Chicago, IL, USA).

Results

A total of 2277 patients undergoing primary or revision joint arthroplasty and transfused with RBC units within the first four postoperative days were initially included in this study. In 1279 (56.2%) cases, patients were transfused during or within the first 6h after surgery (early transfusion group) and in 998 (43.8%) cases, patients were not transfused during this early period, but received at least one RBC unit within the first 4 days after surgery (late transfusion group). After exclusion of 194 patients (126 and 78 in the early and late transfusion groups, respectively) in whom the intervention was a revision surgery because of previous PJI, a total of 2073 patients were finally included in the study (figure 1). The median age was 74.9 years and 1546 (74.6%) were female. There were 914 (44.1%) hip and 1117 (53.9%) knee arthroplasties and 428 (20.6%) were revision surgeries. The median duration of surgery was 105 minutes. A total of 100 (4.8%) patients developed a PJI. Differences in baseline characteristics of patients between early and late transfusion group are displayed in table 1.

Early transfusion group

A total of 1153 patients received at least one RBC unit during or within the first 6h after surgery. The main patient and surgical characteristics of this group

are displayed in table 1. The median number of RBCs transfused in this early period was 2 (IQR: 2 - 2) units. According to the number of transfused RBC, 259 (22.4%) patients received 1 unit, 712 (61.8%) received 2 units, 154 (13.4%) received 3 or 4 units, and 28 (2.4%) received 5 or more units. The median length of storage of the RBC units transfused in this group was 14 (IQR: 7.25 - 21) days.

A total of 62 (5.4%) patients developed PJI within the first 365 days after surgery with a median of 23 (IQR: 14.8-37) days between surgery and PJI diagnosis. The infection was polymicrobial in 20 (32.3%) cases and the most frequently isolated micro-organisms were coagulase-negative staphylococci (24 cases, 38.7%), *Staphylococcus aureus* (20 cases, 32.3%), *Escherichia coli* (12 cases, 19.4%), *Pseudomonas* spp (11 cases, 17.7%) and *Enterococcus* spp (7 cases, 11.3%).

Table 2 shows the baseline characteristics and the rate of PJI a by the number of transfused units (1-2 vs 3-4 vs ≥ 5 RBC units) according to the mean time of storage of packed red blood cell transfused (≤ 14 days vs >14 days). Figure 2A clearly shows a progressive increase in the rate of PJI by increasing with the number of old RBC transfused units. Patients receiving 1 or 2 RBC units had a significantly higher PJI rate only when both units were stored for >14 days (3.5% vs 6.3%, $P=0.041$). This difference was also present in patients that have received 3 or 4 units of RBCs (1.3% vs 13.3%, $P=0.004$) or ≥ 5 RBCs units (5.0% vs 37.5%, $P=0.026$). Due to the long study period (13 years), the role of year of surgery was also assessed: Figure 3 shows the percentage of PJI according to the

year of surgery and mean storage time of packed red blood cell transfused during first 6 hours after surgery.

Since several patient- and surgical-related risk factors for PJI were significantly different among the groups represented in table 2, we performed a multivariable binary logistic regression model including potential confounders in order to assess the independent effect of RBC units storage duration on the incidence of PJI. Covariates analyzed in the logistic regression model included the patients' sex, age, anatomical site of the arthroplasty, duration of surgery, primary vs. revision procedure, and mean time of storage and number of packed red blood cell transfused. As outlined in table 3, transfusion of packed RBC stored > 14 days was associated with an increased rate of PJI (OR: 2.069; 95%CI: 1.08– 3.98; $p=0.0029$). The other factor that was associated with an increased rate of PJI was revision surgery.

Late transfusion group

A total of 920 patients did not received a blood transfusion during surgery or within the first 6 hours, but received at least one RBC unit within the first 4 days after surgery. The main patient and surgical characteristics of these patients are summarized in table 1. Thirty-eight (4.1%) patients were diagnosed with PJI within the first postoperative year. As shown in figure 2B, in this group of patients the rate of PJI did not change with the total number of transfused RBC nor with the proportion of units stored for more than 14 days, despite the overall median age of transfused RBCs was older as compared to the early transfusion group (table 1).

Discussion

To our knowledge, this is the largest study evaluating the influence of the storage time of transfused RBC on infection rate after joint arthroplasty and the first one evaluating also the timing of the transfusion. We have analyzed a large cohort of patients who underwent a joint arthroplasty and were transfused with RBC within the first four post-operative days according to whether the transfusion was performed during surgery or the first 6 hours after surgery (early transfusion group; $n=1153$) or later than 6 hours (late transfusion group; $n=920$). A recent, randomized trial in cardiac surgery did not find any detrimental

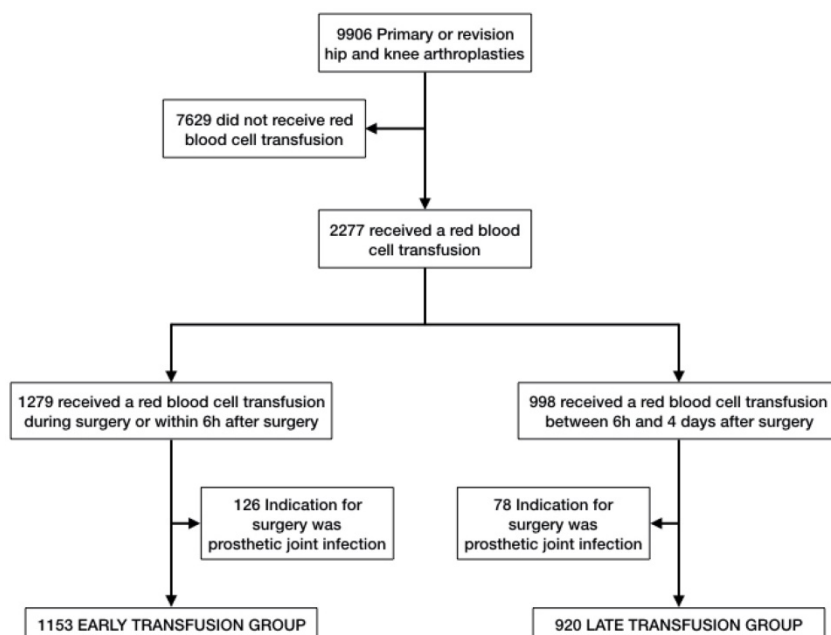


Figure 1. Flowchart of selected patients

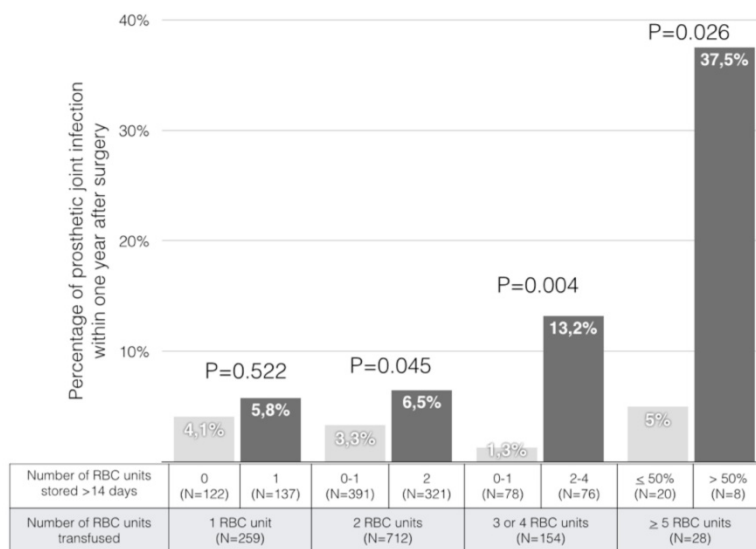
effect of transfusing old RBC. However, the study did not evaluate the impact on surgical site infection and did not take into account the timing of transfusion in relation to surgery ¹¹. In contrast, a clinical trial excluding cardiac surgery (abdominal, orthopedic, vascular and urological surgeries) that randomized 199 patients to receive fresh (≤ 14 storage days) or old (>14 days) RBC demonstrated that wound infections were significantly less frequent among patients receiving fresh RBC (RR, 3.09; CI, 1.17-8.18) ¹⁶,

however, they did not consider the timing of transfusion. Our study shows that transfusion of RBC units stored >14 days during surgery or early afterwards is an independent predictor of PJI (OR:2.50, 95%CI: 1.44-4.33). The rate of PJI progressively increased with the number of old RBC units transfused during this critical period. In contrast, no differences were found among patients who received young RBC units (Figure 2A) or in those receiving older units when transfused after the 6th

postoperative hour (Figure 2B). Considering these findings together, they suggest that transfusion of old RBC units during surgery or within the first 6h after surgery is harmful by itself. Storage time progressively impairs the physiological properties of red cells ¹⁷ becoming depleted of 2,3-diphosphoglycerol and nitric oxide, and evolving into rigid spherocytocytes⁸. Once transfused to the patient, these red cells may cause slugging and occlusion of the microcirculation ⁷, thereby precluding a good oxygenation of the surgical wound as well as the arrival of bactericidal leukocytes and prophylactic antibiotics and increasing the deposition of free iron; factors involved in the progression from wound contamination to wound infection ^{17,18}. Indeed, the first few hours after tissue contamination by bacteria are critical for wound infection to be established ¹⁹. In agreement with our finding, events associated with damaging the phagocytic capacity of leucocytes during surgery or early postoperative period like high glucose level ²⁰, low body temperature ²¹ or low oxygen tissue concentration ²² have been associated with a higher infection risk. These findings show that there is a "critical period" where any adverse event impacting on immune cells favors the invasion by contaminating bacteria. It is, therefore, biologically plausible that transfusion of old RBC units in this early and critical period results in more wound infections.

According to previous studies ^{5,23-25}, male sex, surgical duration and revision surgery were risk factors associated with PJI. The influence of blood transfusion on the infection rate is always difficult to evaluate since transfusion is frequently associated with some of these risk factors (longer surgical time or revision surgery) and may act as a confounder variable. Table 2 shows that there were no

A. Early transfusion group



B. Late transfusion group

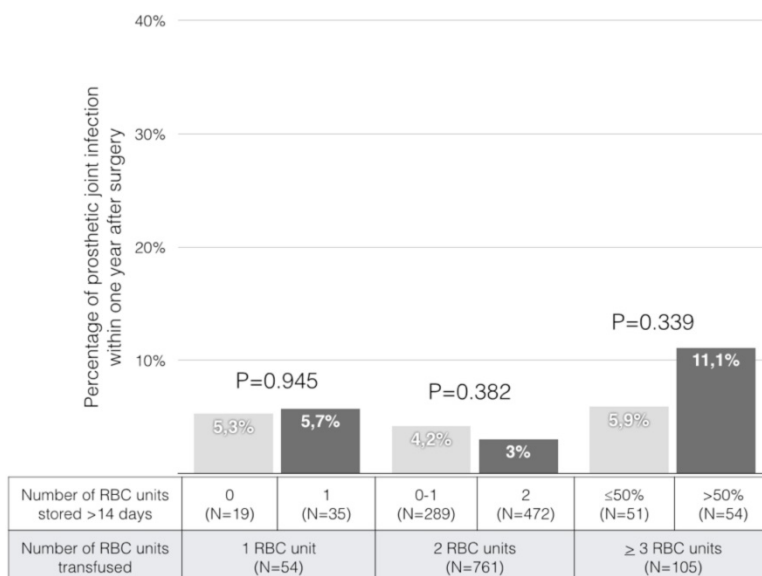


Figure 2. Rate of prosthetic joint infection within the first 365 days after joint arthroplasty according to the number of red blood cell (RBC) units transfused and the proportion of such units stored >14 days. (A) Patients transfused during surgery or within the first 6 hours after surgery; (B) patients transfused only later than 6 hours after surgery and up to the 4th postoperative day.

differences between patients who received $\leq 50\%$ or $>50\%$ of RBC units stored >14 days regarding sex, duration of surgery and type of surgery despite a significantly higher PJI rate in patients receiving $>50\%$ of old RBC units (7.7% vs 3.3%, $P=0.001$).

The main limitation of our study is the retrospective nature of our work. This limitation is of particular importance since retrospective evaluation of RBC units transfused could be difficult using the medical records only. However, for the present study, the number of RBC units administered to the patients and data regarding the length of storage was obtained from the anesthesia report, medical history and matched with the database of our blood bank. Furthermore, despite the fact that patients were not randomized to receive old (>14 days) or young (≤ 14 days) RBC units, both groups were similar in gender, age, duration of surgery, site and type of prosthesis and this work was performed in a single institution in a uniform environment. The second limitation of our study is that the cut off used for the analysis of the storage time (≤ 14 days or >14 days) were based on statistical parameters (median value). However, other authors in previous literature have also used this cut off point^{8,26,27}. The third limitation is that other parameters associated with infections like body mass index or some comorbidities such as diabetes mellitus or parameters associated with the need for RBC transfusion, such as preoperative hemoglobin, were

not available.

In conclusion, transfusion of RBC units stored >14 days during surgery or within the first 6h after surgery was a variable independently associated to PJI after joint arthroplasty. Rate of PJI increased with the number of old RBC units transfused during this critical period. If confirmed in prospective clinical trials, these results can influence on the current transfusion practice in joint arthroplasty.

Table 1. Baseline characteristics of patients according to the group of patients transfused during surgery or within the first 6 hours after surgery (early transfusion group) and group of patients transfused between 6 and 96 hours after surgery (late transfusion group).

	Early transfusion group (N=1153)	Late transfusion group (N=920)	P-value
Median (IQR) age (years)	75.4 (68.9-80.2)	74.4 (67.8-79.7)	0.008
Female gender	873 (75.7)	673 (73.2)	0.183
Site			
Hip	547 (47.4)	367 (39.9)	<0.001
Knee	597 (51.8)	520 (56.5)	
Other	9 (0.8)	33 (3.6)	
Type of prosthesis			
Primary surgery	837 (72.6)	808 (87.8)	<0.001
Revision surgery	316 (27.4)	112 (12.2)	
Fracture	128 (10.8)	134 (14.6)	0.009
Median (IQR) duration of surgery (min)	120 (85-195)	95 (75-120)	<0.001
Median (IQR) time of storage (days)	14 (7.25-21)	17.5 (11.1-24.5)	<0.001
Prosthetic Joint Infection	62 (5.4)	38 (4.1)	0.188

Table 2. Baseline characteristics of patients receiving a blood transfusion during surgery or within the first 6 hours after surgery according to the number of red blood cells (RBC) units transfused and the number of RBC units stored more than 14 days.

N° packed RBC transfused	1-2		3-4		>4		all cases					
Categorization	Median ≤ 14 days (n=498)	Median >14 days (n=473)	p-value	Median ≤ 14 days (n=80)	Median >14 days (n=74)	p-value	Median ≤ 14 days (n=18)	Median >14 days (n=10)	p-value	Median ≤ 14 days (n=596)	Median >14 days (n=557)	p-value
Median (IQR) age (years)	74 (68-80)	77 (71-81)	0.853	74 (68-78)	73 (66-77)	0.842	78 (74-81)	75 (63-78)	0.974	74 (68-80)	76 (70-81)	0.798
Age > 75 years	237 (47.6)	274 (57.9)	0.001	35 (43.8)	30 (40.5)	0.745	14 (77.8)	5 (50.0)	0.210	286 (48.0)	309 (55.5)	0.011
Sex												
Male	115 (23.1)	101 (21.4)	0.515	24 (30.0)	32 (43.2)	0.088	7 (38.9)	1 (10.0)	0.194	146 (24.5)	134 (24.1)	0.862
Female	383 (76.9)	372 (78.6)		56 (70.0)	42 (56.8)		11 (61.1)	9 (90.0)		450 (75.5)	423 (75.9)	
Site												
Hip	214 (43.0)	237 (50.1)	0.021	45 (56.2)	34 (45.9)	0.180	11 (61.1)	6 (60.0)	1.000	270 (45.3)	277 (49.7)	0.238
Knee	278 (55.8)	235 (49.7)		35 (43.8)	38 (51.4)		7 (38.9)	4 (40.0)		320 (53.7)	277 (49.7)	
Other	6 (1.2)	1 (0.2)		0 (0)	2 (2.7)		-	-		6 (1.0)	3 (0.5)	
Type of prosthesis												
Primary surgery	391 (78.5)	347 (73.4)	0.060	46 (57.5)	44 (59.5)	0.805	6 (33.3)	3 (30.0)	1.000	433 (74.3)	394 (70.7)	0.172
Revision surgery	107 (21.5)	126 (26.6)		34 (42.5)	30 (40.5)		12 (66.7)	7 (70.0)		153 (25.7)	163 (29.3)	
Prosthesis indicated due to fracture	56 (11.2)	56 (11.8)	0.772	7 (8.8)	2 (2.7)	0.170	1 (5.6)	2 (20.0)	0.284	64 (10.7)	60 (10.8)	0.985
Median (IQR) duration of surgery (min)	105 (80-150)	120 (85-198)	0.895	135 (110-180)	137 (115-198)	0.913	250 (145-262)	198 (160-232)	0.620	115 (85-170)	125 (90-198)	0.683
Duration of surgery >120 min	127 (37.5)	175 (47.8)	0.006	40 (61.5)	35 (62.5)	0.913	13 (86.7)	35 (62.5)	1.000	180 (43.0)	218 (50.6)	0.026
Outcome												
Prosthetic Joint Infection	18 (1.9)	29 (3.0)	0.068	2 (1.3)	9 (5.8)	0.020	0 (0)	4 (40.0)	0.010	20 (1.7)	42 (3.6)	0.002

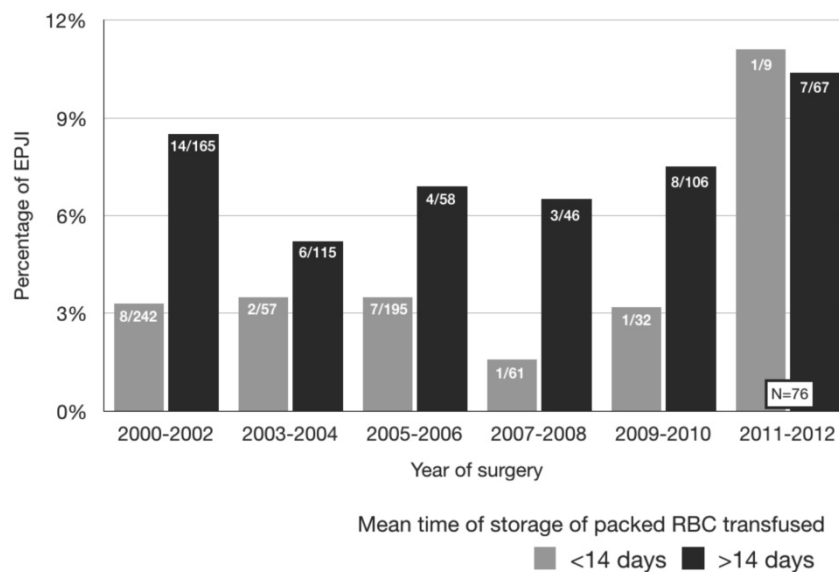


Figure 3. Percentage of early prosthetic joint infection (EPJI) within the first 365 days after joint arthroplasty according to year of surgery and mean time of storage (≤ 14 days or >14 days) of packed red blood cell transfused during surgery or within the first 6 hours after surgery.

Table 3. Step-wise forward logistic regression model results of each subgroups of patients transfused during surgery or within the first 6 hours after surgery.

Multivariable analysis	p-value	OR	CI 95%
Age > 75 years	-	-	-
Male gender	-	-	-
Site (Knee/other vs Hip)	-	-	-
Revision surgery	0.001	2.854	1.54-5.29
Fracture	-	-	-
Duration of surgery	-	-	-
Mean time packed RBC storage >14 days	0.029	2.069	1.08-3.98
Numer of packed RBC storage transfused	-	-	-

RBC, Red blood cells; OR, Odds Ratio; CI95%, Confidence Interval 95%.

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Competing Interests

The authors have declared that no competing interest exists.

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