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Magill, P., Cunningham, E. L., Hill, J. C., & Beverland, D. E. (2018). Identifying the period of greatest blood loss after lower limb arthroplasty. *Arthroplasty Today*, *4*(4), 499-504. https://doi.org/10.1016/j.artd.2018.09.002

Published in:
Arthroplasty Today

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Arthroplasty Today 4 (2018) 499–504

Contents lists available at ScienceDirect

Arthroplasty Today

journal homepage: http://www.arthroplastytoday.org/

Original research

Identifying the period of greatest blood loss after lower limb arthroplasty

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ARTICLE INFO

Article history:
Received 5 August 2018
Received in revised form
30 August 2018
Accepted 3 September 2018
Available online 16 October 2018

Keywords:
Arthroplasty
Hip
Knee
Blood loss
Tranexamic acid

ABSTRACT

Background: The use of tranexamic acid (TXA) in total hip replacement (THR) typically reduces blood loss by approximately 400 mL, and typical total blood loss is still approximately 1 L. A barrier to harnessing the full potential of TXA is disagreement on the optimum timing of administration. To address this, we aimed to identify the period of greatest blood loss.

Methods: We analyzed the perioperative data of 870 patients who had undergone THR, total knee replacement, or unicompartmental knee replacement just before the introduction of TXA to our unit. Total blood loss was calculated on postoperative day (POD) 1 and POD2 using an equation based on change in hematocrit.

Results: Average total blood loss at POD2 was 1505, 1322, and 611 mL for THR, total knee replacement, and unicompartmental knee replacement, respectively. Between 86% and 96% of this blood loss occurred in the period between skin closure and POD1. Intraoperative loss did not correlate with total loss at POD2. Blood transfusion was more likely if the patient was female (odds ratio [OR], 6.8) or if they had preoperative anemia (OR, 8.3) than if there was a high-volume blood loss (OR, 1.6).

Conclusions: Approximately 90% of blood loss occurs between skin closure and the first postoperative 24 hours. "Intraoperative blood loss" and "transfusion rate" are not reliable markers of total blood loss. The full potential of TXA could be harnessed by using it during the period of greatest blood loss, that is, during the first postoperative 24 hours.

Introduction

Total hip replacement (THR) and total knee replacement (TKR) are associated with mean total blood losses of approximately of 1.0 to 1.5 L [1-4]. Postoperative anemia is directly related to increased morbidity and mortality [5]. Although blood transfusion is an effective treatment, it carries an immunological risk [6], increases the risk of periprosthetic infection [7], and is an expensive, limited resource.

Tranexamic acid (TXA) effectively decreases perioperative blood loss via intravenous [8], oral [9], and topical [10] routes and appears to be safe [11,12]. One of the earliest randomized studies demonstrating the efficacy of TXA in reducing blood loss after total joint arthroplasty was published in 1997 [13], and it has since been adopted in many medical and surgical specialties [14]. However, it has much greater potential than we are currently harnessing [15]. For example, after THR, the reduction in blood loss we are currently achieving with TXA use is a modest 250 to 400 mL [4,10,16]. There is a remarkable lack of consensus on the optimal protocol of administration [17,18]. In the last 12 months alone, several randomized controlled trials have investigated the efficacy of TXA in reducing blood loss during orthopedic surgery comparing various multiple-dose intravenous administration [4], various multiple-dose oral administration [19], multiple oral doses (preoperative and postoperative) versus intraarticular administration [20], oral dose versus intravenous dose [21], and preoperative oral dose versus preoperative intravenous dose versus topical administration [22]. The American Academy of Orthopedic Surgeons guidelines on the surgical management of osteoarthritis of the knee stated that

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.artd.2018.09.002

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https://doi.org/10.1016/j.artd.2018.09.002

Table 1
Data extracted.

Data	Source	Definition
ASA grade	Anesthetists' operative report	As decided by anesthetist at the time of surgery
Weight (kg)	Anesthetists' operative report	Measured day of surgery
Height (m)	Anesthetists' operative report	Measured day of surgery
Preoperative Hb (g/L)	Computerized laboratory results	77% within 24 hours before surgery; 100% within 3 mo before surgery
Preoperative Hct	Computerized laboratory results	77% within 24 hours before surgery; 100% within 3 mo before surgery
Intraoperative blood loss (mL)	Anesthetists' operative report	Total from suction and weighing swabs. Measured only for THR because TKR and UKR performed with tourniquet inflated
POD1 Hb (g/L)	Computerized laboratory results	Collected between 7 AM and 9 AM on the day after surgery
POD1 Hct	Computerized laboratory results	Collected between 7 AM and 9 AM on the day after surgery
POD2 Hb (g/L)	Computerized laboratory results	Collected between 7 AM and 9 AM on day 2 after surgery
POD2 Hct	Computerized laboratory results	Collected between 7 AM and 9 AM on day 2 after surgery
Volume and timing of postoperative transfusions	Medical and nursing notes	Any blood transfusion administered during hospital admission
Chemical thromboprophylaxis	Postoperative medical Kardex	Decided by surgeon according to risk stratification protocol (see text in Materials and methods)

Hct, hematocrit.

although there is strong evidence to support treatment with TXA to decrease postoperative blood loss and to reduce the need for transfusion, there is considerable variability in dosing, route, and timing of administration. Therefore, there is a clear lack of consensus regarding the administration of TXA.

The vast majority of TXA studies to date have focused on the intraoperative period [23,24]. We hypothesize that the postoperative phase is the period of greatest blood loss and that, therefore, this is the optimal time for the administration of TXA. To test this theory, we sought to identify the period of greatest blood loss during hip and knee arthroplasty in a large patient cohort that did not receive TXA.

Material and methods

Before June 2013, TXA was used rarely in our unit and only in cases where there was specific clinical concern. Therefore, we elected to study data from the 1000 consecutive patients who had undergone THR, TKR, or unicompartmental knee replacement (UKR) just before this time point. In this group, TXA had been administered to 98 patients, so these were excluded from the analysis. Of the remaining 902 patients, a complete data set was available on 870 patients (393 THR, 403 TKR, and 74 UKR).

Data were extracted from electronic hospital information systems and patient notes (Table 1). Blood loss was calculated indirectly using a modification of previously documented methods of Nadler, Gross, and Mercuriali [25-28]. This method is based on the change in hematocrit levels between 3 different time points. The first time point was before the procedure, the second time point was postoperative day 1 (POD1) and the last time point was postoperative day 2 (POD2). The postoperative phlebotomy service runs daily between 7 AM and 9 AM, so the time range for POD1 was 15 to 24 hours postoperatively, and for POD2, it was 39 to 48 hours.

Calculation used for total blood volume loss [25-28]

Step 1: Calculate patient blood volume (PBV)

$$PBV = \left(k_1 \times h^3\right) + (k_2 \times w) + k_3,$$

where PBV = patient blood volume (L), h = height (m), w = weight (kg), $k_1 = 0.3669$ for men and 0.3561 for women, $k_2 = 0.03219$ for men and 0.03308 for women, $k_3 = 0.6041$ for men and 0.1833 for women.

PBV is then converted to milliliters before the next step.

Step 2: Calculate volume of red blood cell volume loss (RBC)

$$RBC = PBV \times \left(Hct_{pre-op} - Hct_{post-op}\right),$$

where RBC = red blood cell volume loss (mL), $Hct_{pre\text{-}op}$ = preoperative hematocrit, $Hct_{post\text{-}op}$ = postoperative hematocrit, either day 1 or day 2 time point.

Step 3: Convert red cell volume into total blood volume loss

To convert red blood cell volume loss into total blood volume loss, the RBC must be divided by the average hematocrit. In addition, volume of transfused blood must be taken into account. An average unit of blood contains 280 mL with an Hct of 0.6, which is the red cell equivalent of 168 mL with an Hct of 1.0. As this is diluted by patient blood volume, the value must again be divided by average hematocrit.

$$\text{Total blood volume loss} = \frac{RBC}{Hct_{avg}} + \frac{\text{Number of units of blood transfused}}{Hct_{avg}},$$

where $Hct_{avg} = (Hct_{pre\text{-}op} + Hct_{post\text{-}op\ day\ 2})/2$.

All surgeries were performed under the care of the senior author (D.E.B.). A cementless CORAIL stem and a cementless Pinnacle cup (DePuy Synthes, Warsaw, IN) were used in all THRs, which were performed via the posterior approach using a 12- to 14-cm incision [29]. Cementless LCS implants (DePuy Synthes, Warsaw, IN) were used for all TKRs via a medial Insall approach under tourniquet, released at capsule closure [30,31]. Cementless Oxford Microplasty medial unicompartmental implants (Biomet Ltd., Bridgend, UK) were used for all UKRs via a distal medial parapatellar approach under tourniquet, released at capsule closure [32]. No drains were used in any case. All TKRs and UKRs were placed in a knee flexion device for a period of 6 hours postoperatively to limit blood loss [33].

Mechanical thromboprophylaxis consisted of pneumatic calf compression devices and full weight–bearing mobilization as soon as possible after surgery. Chemical thromboprophylaxis commenced at 10 PM on the day of surgery based on a risk stratification with high-risk patients (personal history of thromboembolic disease or on treatment for active cancer) receiving enoxaparin, and all others receiving aspirin [34]. If a low-risk patient had an allergy or was intolerant to aspirin, then no chemical agent was given.

Table 2
Patient demographics.

Variable	THR (n = 393)	TKR (n = 403)	UKR (n = 74)
Gender			
Female, n (%)	230 (58.5)	251 (62.3)	35 (47.3)
Male, n (%)	163 (41.5)	152 (37.7)	39 (52.7)
Age, mean (SD)	68.5 (10.4)	69.5 (9.7)	68.1 (9.5)
ASA grade			
1	25	13	3
2	310	337	61
3	58	53	10
BMI, kg/m^2, mean (SD)	29.0 (5.5)	31.8 (5.4)	31.6 (4.2)
Chemical thromboprophylaxis			
Aspirin	349	358	74
Enoxaparin	37	40	0
Nil	7	5	0

No patients received an intraoperative transfusion. The decision to administer a blood transfusion postoperatively was subjective. Although each patient was preoperatively assigned a "transfusion trigger" hemoglobin (Hb) level, this was not considered absolute, and the final decision also took into account symptoms of anemia and the cardiac risk profile of the patient.

Data analysis was conducted using SPSS (IBM SPSS Statistics for Windows, version 22.0; IBM Corp., Armonk, USA), and all relevant data were assessed for normality. Normally distributed data are presented as mean with standard deviation (SD), whereas nonparametric data are presented as median with interquartile range. Continuous data were analyzed using two-tailed Students' t-test, and the nonparametric alternative (Mann-Whitney U tests) was used where data were not normally distributed. Blood transfusion data were examined with a binary outcome (transfused yes/no) multiple stepwise regression model with the variables gender, preoperative Hb, age, body mass index (BMI), blood loss at POD1 and POD2 (in deciliters), and American Society of Anesthesiologists (ASA) grade. Significance level was set at $P < .05$.

This project was registered with the Belfast HSC Trust's Standards, Quality and Audit Department (Audit Reference number 4232).

Results

Demographics and patient characteristics

There were more females than males for both THR and TKR, whereas just under half of UKR patients were female. The mean patient age for each surgery subgroup was in the late sixties, whereas the ages reached up to 94 years, 92 years, and 89 years for THR, TKR, and UKR, respectively. In each surgical subgroup, the majority of patients were classed as ASA grade 2. The mean BMI for all patients was 30.4 with 29, 31.8, and 31.6 for THR, TKR, and UKR, respectively. The mean preoperative Hb was normal in each subgroup; however, 16.0%, 16.1%, and 14.9% of patients had a Hb level in the anemia range (<130 g/L for males, <115 g/L for females) for THR, TKR, and UKR, respectively. Patient demographics are detailed in Table 2. Date of surgery ranged from February 2012 to June 2013.

Blood loss data

Patients undergoing THR had a significantly greater blood loss at POD2 than those undergoing TKR, whereas patients who had UKR had the least blood loss. For all groups, approximately 90% of blood loss had occurred by POD1. Blood loss data are detailed in Table 3. For those undergoing THR, intraoperative loss represented 13% of the total POD2 loss. There was no correlation between intraoperative loss for THR and POD2 loss (Spearman's rho = 0.07, $P = .11$, controlled for baseline Hb).

The choice of chemical thromboprophylaxis did not affect blood loss. Mean POD2 loss for patients on aspirin was 1373 mL (SD, 580 mL), and for those on enoxaparin, it was 1302 mL (SD, 601 mL), $P = .34$.

There was no significant difference in median blood loss between ASA grades for any group (Table 4). There was no relationship between BMI and blood loss for any group (Spearman's rho = 0.001, $P = .97$).

Blood transfusions

Of all, 12.5% of THR patients, 5.5% of TKR patients, and 0% of UKR patients received a blood transfusion. Of those transfused, none were transfused intraoperatively, 62% were transfused in the first postoperative 24 hours, and the rest were transfused between 24 hours and discharge. There was no relationship between intraoperative blood loss in THR and subsequent transfusion ($P = .95$); however, those who were transfused had a significantly lower preoperative Hb than those who were not transfused, and the majority of those who were transfused were female (Table 5).

Binary logistic regression analysis included only THR and TKR patients. The binary outcome was blood transfusion while in hospital (yes/no), and the variables included were gender, preoperative Hb, age, BMI, blood loss at POD1 and POD2 (in deciliters), and ASA

Table 3
Blood loss details for THR, TKR, and UKR.

Variable	THR (n = 393)		TKR (n = 403)		UKR (n = 74)	
Preoperative Hb, g/L (SD)	13.5 (1.4)		13.2 (1.4)		13.5 (1.6)	
Mean Hb at POD1, g/L (SD)	10.2 (1.5)		10.6 (1.4)		12.2 (1.5)	
Mean Hb at POD2, g/L (SD)	9.8 (1.4)		10.1 (1.3)		11.9 (1.5)	
Mean loss at POD2, mL (SD)						
Overall	1505 (560)		1322 (539)	$P < .001$[a]	611 (358)	$P < .001$[b]
Male	1661 (578)	$P = .01$	1501 (632)	$P < .001$	628 (385)	$P = .01$
Female	1483 (539)		1214 (440)		594 (313)	
Mean loss at POD2 as a percentage of patient blood volume (SD)						
Overall	34 (14)		28 (12)	$P < .001$[a]	13 (7)	$P < .001$[b]
Male	31 (11)	$P < .001$	27 (11)	$P = .2$	11 (7)	$P = .004$
Female	37 (14)		29 (11)		14 (8)	
Mean loss at POD1, mL (SD)	1381 (550)		1094 (450)	$P < .001$[a]	548 (340)	$P < .001$[b]
Mean loss at POD1 as a percentage of loss at POD2 (SD)	91 (27)		86 (35)		96 (55)	
Mean intraoperative loss, mL (SD)	179 (137)		NA		NA	
Mean intraoperative loss as a percentage of loss at POD2 (SD)	13 (11)		NA		NA	

NA, not applicable.
[a] Comparing THR and TKR.
[b] Comparing TKR and UKR.

Table 4
Median POD2 blood loss in milliliters (IQR) per ASA group.

Operation group	ASA1	ASA2	ASA3	*P* value[a]
THR	1497 (1156-1781)	1423 (1069-1781)	1672 (1144-1993)	.09
TKR	1250 (1041-1434)	1264 (951-1565)	1433 (1088-1895)	.06
UKR	565 (NA)[b]	648 (463-831)	667 (543-751)	.95

IQR, interquartile range; NA, not applicable.
[a] *P* value comparing median blood loss across the 3 ASA groups, calculated with independent samples Kruskal-Wallis test.
[b] Only 3 UKR patients graded ASA1.

grade. Being female, having a low preoperative Hb, higher age, low BMI, and higher POD2 blood loss volume were identified as independent risk factors for receiving a blood transfusion. ASA grade was not predictive of receiving a blood transfusion (Table 6).

Discussion

This study calculated perioperative blood loss in a large database of THR, TKR, and UKR patients who did not receive TXA, identifying the first postoperative 24 hours as the period during which approximately 90% of blood loss occurs for all 3 surgery groups. Based on these data, administration of TXA for 24 hours could have the greatest impact on reducing perioperative blood loss.

In 1996, the requirement for blood transfusion to treat postoperative blood loss was reportedly as high as 37% for THR and 25% for TKA [35]. The results of the present study show that in a modern arthroplasty service without TXA, a much lower rate of 12.5% for THR and 5.5% for TKR is expected. Some studies now suggest that with the addition of TXA, the rate can be brought closer to zero [36].

This implies that TXA use, regardless of the administration protocol used, has fully addressed the problem, but this is not correct. The use of "rate of blood transfusion" as a surrogate for "volume of blood loss" is unreliable. Blood transfusion rates are determined by subjective decision-making and are too infrequent to accurately interpret. We, like other studies [7,37,38], have shown that the strongest predictor of a transfusion is not blood loss but a low preoperative Hb and being female of low BMI. So, although TXA has undoubtedly contributed to a reduction in transfusion rates, it should not be interpreted that TXA has reduced blood loss to an insignificant level. Future studies should focus on a more objective measure, such as whether postoperative Hb drops below a predetermined "transfusion trigger".

Blood loss is still a clinically significant issue in patients who receive TXA. Yue et al. [10] found a mean total blood loss of 945.5 ± 331.7 mL in THR patients receiving 3 g of topical TXA. Lee et al. [9] found a mean total blood loss of 847 ± 413 mL in THR patients receiving 3 g of oral TXA. Wei and Wei [16] found a mean total blood loss of 958.5 ± 422 mL in THR patients receiving 3 g of intravenous TXA. We, like others, believe that these figures can be improved further [15].

The limitations to this study include that this was a retrospective review of a prospectively maintained data, which renders our data potentially underpowered for any given variable. However, the numbers involved were large enough to provide meaningful preliminary investigation of multiple variables as presented, and the retrospective nature reduces potential measurement biases. A major strength of this study is the absence of TXA. The existence of our comprehensive historic database allows investigation of non-TXA patients, which, due to the now near-universal use of TXA, may not be easily replicated in future studies.

Blood loss during the postoperative period, often referred to as "hidden loss" because it is not visualized [1], is likely to be a combination of on-going bleeding and hyperfibrinolysis [39]. The latter is triggered by surgically induced vascular hypoxia, hypotension, and cytokine release. After THR or TKR, it is thought to peak at 6 hours postoperatively and persist until 18 hours [39]. Our findings compliment this work, providing a blood volume measurement for this fibrinolytic process.

Because TXA inhibits plasminogen and therefore acts as an antifibrinolytic agent, it is practical to use TXA during the period of greatest fibrinolysis.

Hyperfibrinolysis after THR has been documented since 1991 [40], but the clinical relevance of this has perhaps been underappreciated, especially with regard to TXA administration. A group from China has recently published the results of using postoperative TXA in 150 THR [3] and 159 TKR procedures [41], and in both trials, it was concluded that the greatest reduction in blood loss was when TXA administration was extended by up to 12 hours postoperatively. Based on the results of the present study, we have started a randomized controlled trial (ISRCTN58790500) to study

Table 5
Blood transfusion data.

Variable	THR (n = 393)		TKR (n = 403)		UKR (n = 74)
Patients who received a blood transfusion					
Number of patients	49		22		0
% of total patients	12.5		5.5		0
% female	91.8		68.2		NA
Mean preoperative Hb, g/dL (SD)					
Female	12.9 (1.2)	*P* < .001	12.8 (1.3)	*P* < .001	12.7 (1.6)
Male	14.4 (1.1)		14.1 (1.1)		14.4 (1.5)
Transfused	11.9 (1.4)	*P* < .001	11.9 (1.3)	*P* < .001	NA
Not transfused	13.8 (1.2)		13.3 (1.2)		13.6 (1.6)
Mean blood loss at POD2, mL (SD)					
Transfused	2023 (667)	*P* < .001	2180 (756)	*P* < .001	NA
Not transfused	1491 (489)		1273 (465)		611 (351)
Mean blood loss at POD1, mL (SD)					
Transfused	1978 (764)	*P* < .001	1789 (559)	*P* < .001	NA
Not transfused	1292 (445)		1047 (404)		538 (340)
Mean intraoperative blood loss, mL (SD)					
Transfused	172 (230)	*P* = .95	NA		NA
Not transfused	180 (118)		NA		NA
Mean intraoperative blood loss as % patient blood volume (SD)					
Transfused	5.3 (6.3)	*P* = .15	NA		NA
Not transfused	3.9 (2.5)		NA		NA

NA, not applicable.

Table 6
Results of binary regression analysis with transfusion while in hospital, (yes/no) as the binary outcome.

Variable	*P* value	OR	95% CI	Interpretation
Female gender	.002	6.8	2.1-22.3	Females are 6.8 times more likely than males to receive a transfusion
Preoperative Hb	<.001	0.12	0.07-0.21	With an increase in Hb of 1 g/dL, a patient is 8.3 times less likely to receive a transfusion (ie, 1/0.12)
Age	.002	1.09	1.03-1.15	With an increase in age of 1 y, a patient is 1.09 times more likely to receive a transfusion
BMI	<.001	0.86	0.80-0.93	With an increase in BMI of 1 kg/m^2, a patient is 1.16 times less likely to be transfused (ie, 1/0.86)
Blood loss at POD1 in deciliters	.001	1.19	1.08-1.31	With an increase in POD1 loss of 100 mL, a patient is 1.2 times more likely to receive a transfusion
Blood loss at POD2 in deciliters	<.001	1.56	1.36-1.78	With an increase in POD2 loss of 100 mL, a patient is 1.6 times more likely to receive a transfusion
ASA grade	.2	0.52	0.18-1.45	No influence on odds of transfusion

CI, confidence interval.

the effect of 24 hours of postoperative TXA on total calculated blood loss. We powered our study to detect a difference of 500 mL between 2 treatment groups and will report on the results of 1066 patients. Recruitment has just finished.

Conclusions

We have shown that in lower limb arthroplasty, approximately 90% of blood loss occurs between skin closure and the first postoperative 24 hours. We have also shown that "intraoperative blood loss" and "transfusion rate" are unreliable surrogates for total blood loss, so they should not be used to gauge the success of blood conservation methods. The implications of these findings have relevance to TXA. Although there is evidence that TXA is effective, it is only by a modest amount, and we should not be misguided by reduced transfusion rates. We believe that the efficacy of TXA use can be optimized by using it during the period of greatest blood loss, that is, during the first postoperative 24 hours.

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