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Original research

Primary lower limb joint replacement and tranexamic acid: an observational cohort study

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ABSTRACT

Background: This work aimed to evaluate the efficacy and safety of routine tranexamic acid (TXA) use in elective orthopaedic lower limb joint replacement surgery.
Methods: This retrospective cohort study included all primary hip or knee replacement procedures by a single surgeon over a 6-year period. TXA was introduced during the study period as part of an enhanced recovery after surgery strategy.
Results: Of the 673 procedures, 446 cases (66.3%) received TXA. The median length of stay was 5 days (2-69) and 6 days (3-28) for the TXA and control groups, respectively ($P < .001$). Blood transfusion was required for 28 (6.3%) of the TXA cases versus 40 (17.6%) controls ($P < .001$). Complication rates were similar irrespective of TXA status. At multivariate analysis, TXA was significantly and independently associated with fewer blood transfusions (hazard ratio 0.309, 95% confidence interval: 0.168-0.568, $P < .001$), with a number needed to treat of 9 cases. TXA use was estimated to save between £67.89 and £155.90 per case.
Conclusions: Routine prophylactic TXA administration for elective primary hip and knee replacement reduces the likelihood of postoperative transfusion with a number needed to treat of 9. Cost savings may be as high as £155.90 per case, and no safety concerns were noted.

Introduction

Tranexamic acid (TXA) use for hemorrhage control was first described in the late 1950s [1] in patients with known clotting disorders. Tavenner [2] described improved hemorrhage control after dental extraction for patients with hemophilia or Christmas diseases after therapeutic TXA administration. TXA administration has become increasingly popular during resuscitation of major trauma patients and is associated with reduced mortality [3]. It is now recommended as an early hospital treatment for major trauma patients with a bleed [4] and as a therapeutic option after postpartum hemorrhage [5]. Furthermore, evidence is emerging for TXA use to treat other life-threatening hemorrhages, such as gastrointestinal bleeding [6].

More recently, TXA has been advocated for routine prophylactic use during gynecologic surgery [7,8], orthopaedic lower limb joint replacement surgery [9,10], and emergency orthopaedic hip surgery [11].

The primary aims of this work were to identify if routine TXA use in elective orthopaedic lower limb joint replacement surgery was associated with lower blood loss, reduced transfusion requirement and a shorter postoperative length of hospital stay. The secondary aim was to report a coupled economic analysis.

Material and methods

A retrospective cohort study was conducted including all patients who underwent primary hip or knee replacement by a single orthopaedic consultant operating at 2 district general hospitals. The cohort included males and females operated between February 2010 and April 2016, irrespective of age. TXA was

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introduced during the study period as part of an enhanced recovery after surgery (ERAS) program. Introduction was gradually dependant on adoption by individual anesthetists.

Authorization to conduct this work was granted by the research and development department of the University Health Board. All individual records were anonymized before analysis. Given the routine nature of the data collection to support service evaluation, formal ethical approval was not required.

Data collection

Patient data and relevant surgical information were abstracted from the digital theater management system. Further operative and outcome information was obtained from a prospectively updated arthroplasty database. Patient information was cross-referenced with the computerized hematology service system to provide preoperative and postoperative hemoglobin levels and details of blood transfusions. The case notes and anesthetic charts were reviewed to determine TXA dose and to validate that the requested blood for transfusion was administered.

Inclusions and exclusions

For the purpose of this work, the unit of analysis was "operation" rather than "patient" because some patients had undergone more than one joint replacement at different times (83, 2, and 1 patients had undergone 2, 3, and 4 joint replacements, respectively). Cases included all primary hip and knee joint replacements within the cohort when prophylactic TXA was administered (irrespective of dose). The remaining procedures that did not involve prophylactic TXA were recruited as the control group.

Emergency procedures, such as those following fractured neck of femur and revision procedures were excluded. Cemented hip replacement procedures were also excluded because these were only used for exceptional circumstances such as the management of metastatic disease or after radiotherapy. Complex primary procedures were included (such as hip dysplasia and removal of metalwork), provided that standard primary implants were used.

Outcome measures

The outcome measures for blood loss were a drop in hemoglobin from before to after surgery (measured in grams per liter, g/L) and blood transfusion requirement after surgery (during the postoperative inpatient stay). Length of stay (LOS) was measured in days from the date of surgery to discharge from hospital.

Complications

All complications within 90 days of surgery were included. For the purpose of this work, "total complications" included deaths and any complication within 90 days of surgery, irrespective of severity and type (both medical and surgical).

Statistical analysis

The Statistical Package for the Social Sciences was used [12]. Distributing the data by age revealed a negative skew; therefore, continuous data were described as median (range), and nonparametric statistical tests were employed.

Continuous and categorical data were compared with the Mann–Whitney U test and chi-squared (χ^2) test, respectively. The Wilcoxon signed rank test was used to compare preoperative and postoperative hemoglobin levels because these were related samples. Spearman's rho was used to test correlation. Linear discriminant analysis was used to compare continuous explanatory variables in relation to a binary outcome variable. To explore the factors associated with each outcome, 3 multivariate analyses were modeled. Model 1 consisted a binary logistic regression with blood transfusion status as the outcome variable, and hospital site, age, complex procedure, anesthetic type, preoperative Hb, TXA, gender, and joint type were entered as explanatory variables. Model 2 was a multiple linear regression with drop in Hb as the outcome variable, and hospital site, age, complex procedure, anesthetic type, preoperative Hb, TXA, gender, and joint type were entered as explanatory variables. Model 3 was also a multiple linear regression with LOS as the outcome variable, and hospital site, age, complex procedure, anesthetic type, preoperative Hb, TXA, gender, and joint type were entered as explanatory variables. The significance level was set at $P < .05$ for all tests.

The absolute risk reduction (ARR), relative risk reduction (RRR) and number needed to treat (NNT) were calculated according to the following formulas:

ARR = control event rate−experimental event rate
RRR = ARR/control event rate
NNT = 1/ARR (given as a whole number of "patients" as per convention)

Economic analysis

A simple cost-benefit analysis was conducted by exploring the monetary values of inpatient days and units of blood compared with the cost of TXA. This was done at a cohort level with average cost per operation given as the final output. Given the variation in cost for a hospital overnight stay (see below), the minimum and maximum costs were used, providing a simple sensitivity analysis.

Each unit of transfused blood in Wales was estimated to cost £149.07. An overnight stay at a hospital was estimated by the National Health Service Wales (NHS) Wales Informatics Service to cost £125 as a direct cost (used to calculate budget savings) and £378.14 as fully absorbed rate (the fee that would be charged to outside organizations or private patients). The NHS purchasing contract precludes disclosure by the Health Board of the exact payment for TXA in Wales. However, the most recent British National Formulary [13] quote the price from Pfizer as £1.55 per 500 mg, which is identical to the Monthly Index of Medical Specialties price quoted in the National Institute for Health and Care Excellence [14] guidelines on TXA in trauma. It was, therefore, decided to use this cost.

Results

During the study period, 674 primary total hip (THRs) or total knee replacements (TKRs) were performed. TXA status was not recorded for 1 operation, leaving 673 for analysis. The median age of the cohort was 68 years (range 27-90), 294 procedures (43.7%)

Table 1
Cohort breakdown of procedures.

Procedure	Number (%)
Primary THR	375 (55.7)
Conversion to THR (following previous fixation, such as dynamic hip screw; cannulated screws).	7 (1.0)
Complex primary THR (such as for hip dysplasia; severe osteoarthritis with bone loss).	11 (1.6)
Birmingham resurfacing hip replacement	1 (0.1)
Primary TKR	273 (40.6)
Complex primary TKR (such as for severe deformity)	6 (0.9)

were for males and almost two-thirds (n = 413, 61.4%) were operated at site 1. With regard to laterality, 360 (53.5%) and 313 (46.5%) were right and left lower limb, respectively (χ^2: 2.587, df: 1, $P = .108$). The breakdown of procedures is given in Table 1.

Most procedures received a spinal anesthetic (516, 76.7%), general anesthetic (145, 21.5%), or a combination of both (10, 1.5%). One procedure involved a nerve block and 1 a combined spinal epidural. The overall 90-day complication rate for the cohort was 4.3% (n = 29, 17 THR and 12 TKR). The mortality rate was 0.45% (n = 3); however, no deaths were associated with hemorrhage. The breakdown of complications by joint type and TXA status is given in Table 2.

Descriptive statistics of the cohort

With regard to exposure, 446 patients (66.3%) of the cohort received TXA. TXA was more frequently prescribed as the study time progressed (χ^2: 331.573, df: 6, $P < .001$), see Figure 1. With regard to outcomes, the median LOS was 5 days (range 2-69). The median preoperative and postoperative hemoglobin values were 136 g/L (range 96-179) and 113 g/L (60-160), respectively (Wilcoxon $P < .001$). Postoperative blood transfusion was required following 68 procedures (10.1%), with a median of 2 units transfused (range 2-13).

Group comparisons

The baseline characteristics of the groups (TXA received versus controls) are given in Table 3. The only significant difference at baseline was an association between surgery at site 1 and lower likelihood of receiving TXA.

Univariate analyses

The univariate analyses of outcomes are given in Table 4. TXA use was significantly associated with fewer transfusions, shorter LOS, higher postoperative hemoglobin levels, and lower drop in hemoglobin from before to after surgery. For procedures requiring transfusion, the requirement in terms of number of units was similar, irrespective of TXA status.

Advanced analysis

The factors associated with the 3 outcomes: receiving blood transfusion; Hb drop; LOS are given respectively in Table 5.

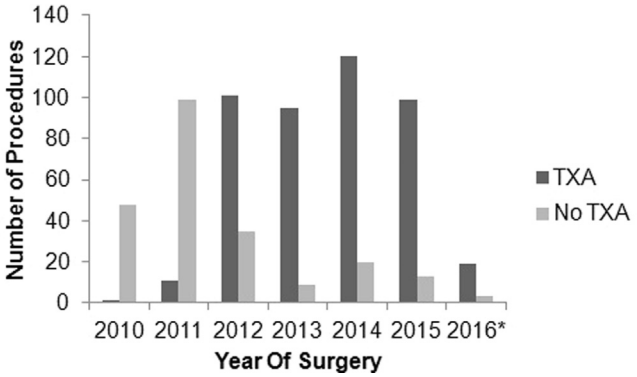

Figure 1. Numbers receiving TXA by year of surgery. *There are fewer cases in 2016 as incomplete year of data collection.

Receiving TXA was significantly and independently associated with not receiving a blood transfusion (model 1) and a lower drop in Hb (model 2), but not LOS (model 3).

Economic analyses

With regard to requiring a blood transfusion, the ARR, RRR, and NNT were 11.4%, 63%, and 9 patients, respectively. The breakdown of the cost-benefit analysis is given in Table 6. The minimum and maximum estimated savings per operation are £67.89 and £155.90, respectively, depending upon the cost used for bed stays (direct cost versus fully absorbed rate).

Discussion

The key findings were that routine prophylactic administration of TXA to patients undergoing elective hip or knee joint replacement was significantly and independently associated with fewer blood transfusions and a lower drop from preoperative to postoperative hemoglobin.

These findings are in keeping with other reports. Evangelista et al [15] compared total joint replacement patients in a cohort study and reported a reduction in blood transfusion from 22.7% to 11.9% and from 19.4% to 7.0% following hip and knee joint replacements, respectively. Similar findings have also been reported after prophylactic administration of TXA for other orthopaedic procedures. Shi et al [16] conducted a randomized trial of 100

Table 2
Recorded perioperative and early complications within 3 months of surgery.

	No TXA		TXA received	
	n	Complications	n	Complications
TKR	6	1 Death within 90 days. 1 PE. 1 COPD exacerbation. 1 Dislocation. 1 Pseudoaneurysm (stented) 1 Periprosthetic tibia fracture (Still's disease, conservative treatment).	6	1 Postoperative death (necrotic bowel). 2 Stitch abscesses (1 return to theater). 1 Readmission with cellulitis. 1 PE. 1 Late wound ooze (conservative management).
THR	5	1 Death (exacerbation COPD). 1 Dislocation. 1 Hematoma (conservative). 1 VF arrest, MI, and dislocation. 1 LRTI.	12	1 MI. 1 MI and dislocation. 2 DAIR procedures. 1 Massive transfusion (heparin for heart valve). 1 Traumatic periprosthetic femur fracture. 2 Dislocations. 2 LRTIs. 2 Readmissions (pain and minor wound issue).

PE, pulmonary embolus; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; VF, ventricular fibrillation; DAIR, debridement, antibiotics, and implant retention; LRTI, lower respiratory tract infection.

Table 3
Baseline group comparisons.

Factor	TXA received	No TXA (controls)	*P* value
Number	446	227	-
Gender, n (%):			.140
Male	204 (69.4)	90 (30.6)	
Female	242 (63.9)	137 (36.1)	
Age in years, median (range)	67.3 (27-90)	68.7 (42-88)	.164
Hospital site, n (%):			<.001
Site 1	251 (60.8)	162 (39.2)	
Site 2	195 (75.0)	65 (25.0)	
Laterality, n (%):			.141
Right	248 (68.9)	112 (31.1)	
Left	198 (63.3)	115 (36.7)	
Joint, n (%):			.102
Hip	276 (70.1)	118 (29.9)	
Knee	170 (60.9)	109 (39.1)	
Complex procedure, n (%)	11 (64.7)	6 (35.3)	1.00
Anesthetic n (%):			.381
Spinal	350 (67.8)	166 (32.2)	
GA	87 (60.0)	58 (40.0)	
Other	9 (75.0)	3 (25.0)	
Hemoglobin preoperative (range)	136 (100-179)	136 (96-171)	.236
Total complications, n (%)	18 (4.5)	11 (4.0)	.930
Hemorrhage-related complication, n (%)	2 (0.45)	1 (0.44)	.988
90-day mortality, n (%)	1 (0.22)	2 (0.88)	.227

patients undergoing posterior lumbar surgery and identified a significantly reduced perioperative blood loss in the intervention arm. They did not notice a significant variation in transfusion requirement; however, their caseload may have been too low to detect such a difference. Yu et al [17] also reported significantly lower postoperative blood loss after TXA administration in a retrospective cohort study of cervical laminectomy patients. The similar quantity of units of blood given to those requiring transfusion irrespective of TXA status in our study may be influenced by the hospital policy requiring transfusions to consist of at least 2 units of blood.

TXA administration in our study was associated with a shorter LOS at univariate analysis, although this association was lost after adjustment. Readmission was not specifically considered in our study; however, reduced readmission rate after hip replacement has been associated with TXA administration [9].

The NNT with TXA to avoid 1 transfused case was 9. From an economic perspective, it was estimated that receiving TXA could save between £67.89 and £155.90 per operation. With 187,879 primary hip and knee replacements performed in England and Wales in 2015 [18], a saving of £12.7-£29.3 million per annum may be possible across the NHS with routine TXA administration. Hospital bed costs in England were estimated at £400 per night following a freedom of information request. Therefore, TXA may result in greater financial savings in England. However, each unit of transfused blood in Wales was estimated to cost £149.07 compared with £120 (but will increase to £124.46 in April 2017 according to the NHS Blood and Transplant service) in England. Therefore, estimated savings with regard to blood transfusion costs may be lower in England. Estimated savings of $3,083 (approximately £2,386) and $2,582 (approximately £1,998) per case have been reported for THR and TKR, respectively, with TXA use in the US [15].

Table 4
Univariate analyses of outcomes in relation to TXA.

Factor	TXA received	No TXA (controls)	*P* value
Transfusion, n (%)	28 (6.3)	40 (17.6)	<.001
Median LOS, days (range)	5 (2-69)	6 (3-28)	<.001
Median Hb postoperative, g/L (range)	115 (70-160)	110 (60-149)	<.001
Median Hb drop, g/L (range)	21 (−7 to 57)	26 (−5 to 62)	<.001
Median transfusion, units (range)	2 (2-13)	2 (2-5)	.973

Table 5
Multivariate analyses final models of factors associated with receiving blood transfusion, Hb drop, and LOS.

Factor	Hazard ratio	*P*-value
Model 1: receiving blood transfusion		
Hospital site	0.376 (95% CI: 0.187-0.757)	.006
Age	1.056 (95% CI: 1.020-1.094)	.002
Preoperative hemoglobin	0.913 (95% CI: 0.890-0.938)	<.001
TXA	0.309 (95% CI: 0.168-0.568)	<.001
Joint type (knee versus hip)	0.403 (95% CI: 0.207-0.784)	.007
Model 2: hemoglobin drop		
Hospital site	−1.952 (SE: 0.766)	.011
Preoperative hemoglobin	0.275 (SE: 0.029)	<.001
TXA	−6.627 (SE: 0.792)	<.001
Gender	2.642 (SE: 0.822)	.001
Joint type (knee versus hip)	−8.078 (SE: 0.753)	<.001
Model 3: length of stay		
Hospital site	−1.503 (SE: 0.379)	<.001
Age	0.105 (SE: 0.018)	<.001
Preoperative hemoglobin	−0.032 (SE: 0.013)	.016

CI, confidence interval; SE, standard error

No TXA-related side effects or safety issues were identified in our study. Duncan et al [19] retrospectively studied more than 13,000 elective THR and TKR patients in the US and identified no increased risk of venous thromboembolism or 30-day mortality after TXA administration. However, adverse events, such as an aortoiliac thrombosis after the use of TXA with internal iliac balloon occlusion to control postpartum hemorrhage [20] have been reported. Other authors have highlighted that the safety profile of TXA should be further investigated [21].

The median LOS for the cohort (5 days) was long compared with contemporary rates for many other arthroplasty units. This may be explained by the retrospective inclusion of patients who received surgery before the introduction of ERAS protocols, the age of the patients, and the deprivation levels of the communities served by both centers. Both hospitals serve parts of the South Wales valleys that have some of the highest deprivation levels in the country. These communities expanded rapidly with the growth of the coal and steel industry during the industrial revolution. However, most heavy industries ceased in the 1980s, leading to mass unemployment. Many patients will have medical comorbidities and social circumstances that may have dictated their hospital LOS.

The main strength of this work was the inclusive pragmatic nature of the study to reflect a consultants' workload. Furthermore, as the data reflected the workload of a single consultant surgeon, operative practice was unlikely to differ except for the exposure of interest.

Despite the strengths, several limitations must be noted. First, this was an observational study, and without randomization confounding

Table 6
Cost-benefit analysis breakdown by component costs.

Costs	Without TXA (n = 227)	With TXA (n = 446)
Bed stays		
Minimum	1616 × £125 = £202,000	3020 × £125 = £377500
Maximum	1616 × £378.14 = £611074.24	3020 × £378.14 = £1141982.80
Blood	87 × £149.07 = £12969.09	87 × £149.07 = £12969.09
TXA	-	519.94 × £3.10 = £1611.814
Total cohort costs		
Minimum	£214,969.09	£392,080.90
Maximum	£624,043.33	£1156563.70
Cost per case		
Minimum	£947.00	£879.11
Maximum	£2,749.09	£2,593.19

cannot be excluded. This risk was minimized by adjusting for known and potential confounders (such as hospital site and age respectively) at analysis. However, residual confounding from unadjusted factors such as deprivation remains a possibility. Also, low body mass index has been associated with requiring a blood transfusion [22], and such data were not available to adjust in this study. Confounding by intention should also be considered because TXA may have been prescribed more frequently in complex cases in the earlier days of ERAS implementation. However, this would have diluted the findings toward the null, underestimating the benefits of TXA.

Second, potential bias must be highlighted. ERAS programs were introduced during the study period and included several components in addition to TXA that may have impacted upon the numbers of transfusions and LOS. A trend in reduction of postoperative blood transfusion rates from 2007 to 2015 after hip and knee arthroplasty has been reported in the US [23]. This trend was attributed to a combination of factors that also included changes to the transfusion trigger and hydration protocols [23]. Furthermore, bias may have occurred if social reasons that influence LOS or regular anticoagulation medication status varied systematically between the 2 groups.

Third, as all available cases were included, a power calculation was not used. Therefore, the study may have been underpowered to detect all investigated differences between the groups, such as LOS (type II statistical error). We performed multiple analyses without a statistical correction, increasing the likelihood of observing a significant result in the absence of a true difference. Although, such type I statistical errors are unlikely because obtained *P*-values were highly significant.

Fourth, we may have oversimplified the data by converting several variables to binary variables. For example, we did not consider the dose of TXA and therefore, could not explore the possibility of a dose-response relationship. Randomized control trial level evidence has reported that 2 g is an effective and safe dose for hip and knee arthroplasty [24]. Furthermore, we considered any postoperative blood transfusion. However, we did not consider the indication. Blood may have been transfused for an indication unrelated to the orthopaedic surgery. However, data for both cases and controls were gathered consistently, and arguably, the nature of the bleed is irrelevant if the TXA helps to prevent such bleeds.

Finally, the economic analysis was limited to the costs of TXA, LOS, and blood transfusion. The most up-to-date estimates were used, rather than retrospectively applying costs according to the date of surgery. Furthermore, LOS was retained in the analyses based on the median durations, although it was not independently associated with TXA at adjusted analysis. All our patients received TXA via the intravenous route; however, alternative routes have similar efficacy and side effect profiles [25], and oral administration is cheaper [26]. However, debate remains and the optimum administration route may vary, for example, reserving topical administration to patients at higher risk of thromboembolic events [27].

Conclusions

In conclusion, routine prophylactic administration of TXA for elective primary THR and TKR reduces the likelihood of postoperative transfusion with an NNT of 9. Cost savings may be as high as £155.90 per case. Although no issues have been identified within our study, some debate remains, and the safety profile of TXA for this indication should continue to be monitored.

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