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RESEARCH

Dose optimisation of intravenous tranexamic acid for elective hip and knee arthroplasty

THE EFFECTIVENESS OF A SINGLE PRE-OPERATIVE DOSE

R. J. M. Morrison,
B. Tsang,
W. Fishley,
I. Harper,
J. C. Joseph,
M. R. Reed

Northumbria Healthcare NHS Foundation Trust, Northumberland, United Kingdom

Objectives

We have increased the dose of tranexamic acid (TXA) in our enhanced total joint recovery protocol at our institution from 15 mg/kg to 30 mg/kg (maximum 2.5 g) as a single, intravenous (IV) dose. We report the clinical effect of this dosage change.

Methods

We retrospectively compared two cohorts of consecutive patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA) surgery in our unit between 2008 and 2013. One group received IV TXA 15 mg/kg, maximum 1.2 g, and the other 30 mg/kg, maximum 2.5 g as a single pre-operative dose. The primary outcome for this study was the requirement for blood transfusion within 30 days of surgery. Secondary measures included length of hospital stay, critical care requirements, re-admission rate, medical complications and mortality rates.

Results

A total of 1914 THA and 2537 TKA procedures were evaluated. In THA, the higher dose of TXA was associated with a significant reduction in transfusion ($p = 0.02$, risk ratio (RR) 0.74, 95% confidence interval (CI) 0.58 to 0.96) and rate of re-admission ($p < 0.001$, RR 0.50, 95% CI 0.35 to 0.71). There were reductions in the requirement for critical care ($p = 0.06$, RR 0.55, 95% CI 0.31 to 1.00), and in the length of stay from 4.7 to 4.3 days ($p = 0.02$). In TKA, transfusion requirements ($p = 0.049$, RR 0.64, 95% CI 0.41 to 0.99), re-admission rate ($p = 0.001$, RR 0.56, 95% CI 0.39 to 0.80) and critical care requirements ($p < 0.003$, RR 0.34, 95% CI 0.16 to 0.72) were reduced with the higher dose. Mean length of stay reduced from 4.6 days to 3.6 days ($p < 0.01$). There was no difference in the incidence of deep vein thrombosis, pulmonary embolism, gastrointestinal bleed, myocardial infarction, stroke or death in THA and TKA between cohorts.

Conclusion

We suggest that a single pre-operative dose of TXA, 30 mg/kg, maximum 2.5g, results in a lower transfusion requirement compared with a lower dose in patients undergoing elective primary hip and knee arthroplasty. However, these findings should be interpreted in the context of the retrospective non-randomised study design.

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Article focus

- Intravenous (IV) tranexamic acid is routinely used in hip and knee arthroplasty.
- The optimum dose and route of administration is still debated.
- We have increased the dose used in our enhanced recovery (ER) protocol from 15 mg/kg to 30 mg/kg (maximum 2.5 g) as a single, IV dose. We report the clinical effect of this dosage change.

Key messages

- The higher dose of 30 mg/kg (maximum 2.5 g) as a single IV dose reduced transfusion requirements. It may also be associated with a reduction in length of stay, re-admission rate and requirement for critical care compared with a dose of 15 mg/kg (maximum 1.2 g).
- We did not see an increase in medical complications within 30 days of surgery,

R. J. M. Morrison, MBChB (Hons), BMSc (Hons), MRCS Ed, Specialist Registrar, Trauma & Orthopaedics Department,
B. Tsang, MBBS, MRCSEd Core Surgical Trainee,
W. Fishley, MBBS, MRCSEd Core Surgical Trainee,
I. Harper, MB, ChB, FRCA, Consultant Anaesthetist,
J. C. Joseph, FRCS (Tr&Orth), Consultant Orthopaedic Surgeon,
M. R. Reed, FRCS (Tr&Orth), Consultant Orthopaedic Surgeon,
Northumbria Healthcare NHS Foundation Trust, Woodhorn Lane, Ashington, Northumberland NE63 9JJ, UK.

Correspondence should be sent to R. J. M. Morrison; email: rorymorrison@nhs.net

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thromboembolic events within 60 days of surgery, or mortality within 90 days of surgery when using the higher dose.

Strengths and limitations

- This study evaluates 1914 elective total hip arthroplasty procedures and 2537 total knee artrhroplasty procedures between May 2008 and January 2013.
- Our ER protocol is standardised across hospital sites and followed by all operating surgeons, thereby reducing variability in practice.
- This study is limited by the fact that it is a retrospective review of two different cohorts over two separate time periods.

Introduction

Accelerated rehabilitation using multimodal strategies can be employed in elective arthroplasty surgery to reduce morbidity, with a consequential reduction in length of hospital stay and improved patient satisfaction.[1] We have previously published our results following the introduction of an enhanced recovery (ER) programme within our unit for all patients undergoing elective total hip (THA) and knee (TKA) arthroplasty compared with our previous 'traditional' practice, demonstrating a reduction in length of stay and complications including mortality.[2] One element of this programme is the pre-operative use of intravenous (IV) tranexamic acid (TXA).

TXA is a synthetic form of lysine and prevents fibrinolysis by blocking the receptor site on plasminogen thus preventing binding to fibrin and subsequent clot degradation. Peak plasma concentrations are achieved fairly rapidly following IV administration. Half-life is approximately three hours, and $>$ 90% is excreted unchanged in urine. Reported effective plasma concentrations are between 5 µg/mL and 16 µg/mL, and an initial dose of 30 mg/kg followed by infusion in cardiac surgery has been shown to provide an effect for up to six hours post-operatively.[3,4]

The use of TXA throughout surgery in general,[5] and in elective arthroplasty surgery, is reported widely, most commonly in its IV form,[6-10] but also orally[11,12] and topically.[13,14] TXA has been shown to significantly reduce post-operative bleeding and thus the requirement for blood transfusion. Concerns remain regarding the safety of IV TXA, particularly regarding thromboembolic complications.[15]

We have amended our departmental protocol by increasing the dose of TXA used during surgery from 15 mg/kg to 30 mg/kg. Published work has shown the use of TXA 30 mg/kg to be effective in cardiac surgery patients with a high risk of bleeding.[16]

This present study aimed to evaluate the impact of a higher dose of TXA compared with the previously used lower dose. The primary outcome for this study is the requirement for blood transfusion within 30 days of surgery. Secondary outcomes to evaluate the impact of this change in terms of efficacy include medical complications, length of hospital stay, critical care requirements and re-admission rates.

Patients and Methods

Institutional Caldicott approval was granted for the review of our ER programme. For this before-and-after study, two series of primary hip arthroplasties over two different time periods were compared on an intention-to-treat basis. The control cohort between May 2008 and July 2011 received IV TXA at a dose of 15 mg/kg, maximum 1.2 g. We then changed the dose to 30 mg/kg, maximum 2.5 g, in August 2011 and allowed a six-month gap to ensure the change in practice had been adopted. Therefore, the intervention group, between February 2012 and January 2013, received the higher dose. An identical review was performed for primary knee arthroplasty.

Surgery was carried out at one of three hospitals. Surgeons, nurses and anaesthetic staff work between all three sites, and our ER protocol is standardised across each hospital. Each patient undertook our previously published ER programme,[2] which was the same for both cohorts. Briefly, this encompassed pre-operative patient education, a light general anaesthetic or low-dose spinal anaesthesia with sedation, and IV TXA (Cyclokapron injection; Pfizer, New York, New York) at the induction of anaesthesia. Contraindications to TXA are if the patient had a cardiac event, cerebrovascular accident, pulmonary embolism (PE) or deep vein thrombosis (DVT) within the last six months, a known history of thrombotic disorder, coronary stents, an allergy to TXA, disseminated intravascular coagulation, active cancer or overt haematuria. We used prophylactic IV antibiotics, 0.125% levobupivacaine local anaesthetic infiltration to the surgical site, regular oral analgesia and early mobilisation. Patients received prophylaxis against venous thromboembolism with both thromboembolic deterrent stockings and chemical prophylaxis. Tinzaparin (4500 units subcutaneously once daily) (Innohep; LEO Pharma A/S, Ballerup, Denmark) was used until 31 July 2009; this was then changed to rivaroxaban (10 mg orally once daily) (Xarelto; Bayer Schering Pharma AG, Wuppertal, Germany), before reverting to tinzaparin on 01 February 2010 to follow evolving National Institute for Care and Excellence (NICE) guidelines.[17] Patients were discharged once they were independently mobile with the help of appropriate walking aids and standard hospital discharge criteria had been met.

Baseline demographic data were recorded in a database for each patient including gender and age, and the following data were collected by professional medical coders: medical diagnosis, comorbidities, surgical procedure codes (OPCS) and complication codes (ICD-10). Recorded complications included mortality, stroke, myocardial

Table I. Baseline demographic and comorbidity characteristics between the two cohorts: 15 mg/kg and 30 mg/kg tranexamic acid

Characteristic	15 mg/kg (n = 2637)	30 mg/kg (n = 1814)	p-value
Mean age (yrs), n (range)	68.2 (19 to 93)	68.4 (22 to 98)	0.51*
Female, n (%)	1407 (*53.4*)	1030 (*56.8*)	**0.03**†
Total hip arthroplasty, n (%)	1106 (*41.9*)	808 (*44.5*)	0.09†
Mean pre-operative haemoglobin (g/dL), n (range)	13.7 (7.9 to 18.0)	13.7 (8.6 to 17.1)	1.00*
Hypertension, n (%)	1236 (*46.9*)	951 (*52.4*)	< **0.001**†
Atrial fibrillation, n (%)	146 (*5.5*)	105 (*5.8*)	0.67†
Ischaemic heart disease, n (%)	218 (*8.3*)	137 (*7.6*)	0.40†
Insulin-dependent diabetes, n (%)	30 (*1.1*)	10 (*0.6*)	0.08†
Non-insulin-dependent diabetes, n (%)	265 (*10.0*)	195 (*10.7*)	0.45†
Chronic obstructive pulmonary disease, n (%)	119 (*4.5*)	80 (*4.4*)	0.87†

Bold values are statistically significant
*Unpaired *t*-test
†chi-squared

infarction, and gastrointestinal bleeding. The incidence of those diagnosed with DVT or PE within 60 days was also recorded. Hospital Episode Statistics were used to record length of stay, as well as return to theatre or re-admission with an overnight stay within 30 days of surgery.

Pre-operative and day 1 post-operative haemoglobin (Hb) levels were accessed from the trust's pathology results system (Integrated Clinical Environment; Sunquest Information Systems Europe Ltd., Norwich, United Kingdom) for the purposes of this study by three authors (RJMM, BT, WF). Data for blood transfusion requirements of individual patients were also obtained from the trust's blood transfusion service database.

Drains are not used in our practice and so blood loss post-operatively could not be directly calculated. Therefore, to determine clinically relevant blood loss, we chose the requirement for allogeneic blood transfusion within 30 days of surgery as the primary outcome for this study.

Patients were transfused according to the trust's protocol. This protocol has remained the same since 2007, where either of the following leads to consideration of transfusion: patient has a Hb level of 8.0 g/dL or less; or patient has a Hb level between 8 g/dL and 10 g/dL and has a documented history of ischaemic heart disease or was deemed to be symptomatic from their anaemia.

Secondary outcomes included length of hospital stay, admission to critical care, and rate of re-admission (with overnight stay). Hip and knee arthroplasties were analysed together for the following secondary outcomes to increase power and the ability to detect a safety signal from the higher tranexamic dose: the incidence of myocardial infarction, stroke or gastrointestinal bleed occurring within 30 days of surgery; the incidence of DVT or PE within 60 days; and 90-day mortality rates.

Statistical analysis. This was carried out with significance taken as $p < 0.05$ with 95% confidence intervals (CI). Categorical data were analysed with chi-squared and Fisher's exact tests as dictated by sample size. Continuous data were analysed using Student's *t*-test or the Mann-Whitney U test according to normality.

Post hoc analysis was also performed to compare anaemic and non-anaemic patients, with anaemia defined as per the World Health Organisation (WHO) definition (Hb < 13 g/dL in male patients and < 12 g/dL in female patients).[18]

Results

This study evaluates 4451 elective THA and TKA procedures, between May 2008 and January 2013. The control groups who received 15 mg/kg of IV TXA, maximum 1.2 g, comprised 1106 THA procedures and 1531 TKA procedures. The intervention group, following the introduction of 30 mg/kg IV TXA, maximum 2.5 g, included 808 THA and 1006 TKA procedures.

Baseline demographic data comparing cohorts were recorded (Table I). The higher-dose group comprised a larger percentage of female patients overall compared with the control group (56.8% *versus* 53.4%, p = 0.03, chi-squared). Except for a significantly higher incidence of hypertension (52.4% *versus* 46.9%, p < 0.001, chi-squared) in the intervention cohort, all other variables were matched. In those patients who used anticoagulants such as warfarin pre-operatively, it is our unit's practice that these are discontinued in the pre-operative period, with surgery only commencing if a coagulation blood test on the day of surgery has normalised.

Post-operative outcomes were recorded for THA patients (Table II). Transfusion requirements were significantly less in the higher-dose group (p = 0.02). The mean post-operative Hb in the intervention group was 11.24 g/dL *versus* 10.89 g/dL in the control group (p < 0.001). There was a significant reduction in 30-day re-admission rate (p < 0.001), overall length of stay (p = 0.02), and a non-significant trend towards reduction in the requirement for critical care admission with the higher dose (p = 0.06). There was no difference in other outcomes.

The use of higher-dose TXA in TKA surgery is also of benefit (Table III). In the higher-dose group, there was a significant reduction in transfusion rate (2.7% *versus* 4.2%, p = 0.049). The mean post-operative Hb in the intervention group was 12.01 g/dL *versus* 11.69 g/dL in

Table II. Outcomes for each cohort following total hip arthroplasty

Outcome	15 mg/kg (n = 1106)	30 mg/kg (n = 808)	RR (95% CI)	p-value
Transfusion, n (%)	149 (*13.5*)	81 (*10.0*)	0.74 (0.58 to 0.96)	**0.023***
Post-operative Hb (g/dL), mean (range)	10.89 (5.4 to 15.3)	11.24 (6.6 to 15.1)	Difference 0.36 (0.22 to 0.49)	**< 0.001†**
LOS (mean days), n (range)	4.7 (0 to 61)	4.3 (1 to 93)	-	**0.020‡**
Re-admission 30 days, n (%)	112 (*10.1*)	41 (*5.1*)	0.50 (0.35 to 0.71)	**< 0.001***
RTT 30 days, n (%)	22 (*2.0*)	13 (*1.6*)	0.81 (0.41 to 1.60)	0.607*
Aspiration	1 (*4.5*)	0 (*0.0*)	-	-
Dislocation	4 (*18.2*)	2 (*15.4*)	-	-
Wound debridement	17 (*77.3*)	10 (*76.9*)	-	-
Sciatic nerve exploration	0 (*0.0*)	1 (*7.7*)	-	-
Critical care admission, n (%)	37 (*3.3*)	15 (*1.9*)	0.55 (0.31 to 1.00)	0.063*

*chi-squared
†Unpaired *t*-test
‡Mann-Whitney U test
Bold values are statistically significant
Hb, haemoglobin; RR, risk ratio; CI, confidence interval; LOS, length of stay; RTT, return to theatre

Table III. Outcomes for each cohort following total knee arthroplasty (TKA)

Outcome	15 mg/kg (n = 1531)	30 mg/kg (n = 1006)	RR (95% CI)	p-value
Transfusion, n (%)	64 (*4.2*)	27 (*2.7*)	0.64 (0.41 to 0.99)	**0.049***
Post-operative Hb (g/dL), mean (range)	11.69 (7.1 to 16.1)	12.01 (7.8 to 16.2)	Difference 0.32 (0.20 to 0.42)	**< 0.001†**
LOS (mean days), n (range)	4.6 (0 to 81)	3.6 (0 to 61)	-	**< 0.001‡**
Re-admission 30 days, n (%)	109 (*7.1*)	40 (*4.0*)	0.56 (0.39 to 0.80)	**0.001***
RTT 30 days, n (%)	13 (*0.8*)	5 (*0.5*)	0.59 (0.21 to 1.64)	0.344*
Aspiration	2 (*15.4*)	0 (*0.0*)	-	-
Wound debridement	11 (*84.6*)	5 (*100*)	-	-
Critical care admission, n (%)	36 (*2.4*)	8 (*0.8*)	0.34 (0.16 to 0.72)	**0.003***

*chi-squared
†Unpaired *t*-test
‡Mann-Whitney U test
Bold values are statistically significant
Hb, haemoglobin; RR, risk ratio; CI, confidence interval; LOS, length of stay; RTT, return to theatre

the control group ($p < 0.001$). There were significant reductions in re-admission rate (4% *versus* 7%, $p < 0.001$) and requirement for critical care (0.8% *versus* 2.4%, $p = 0.003$) when compared with 15 mg/kg.

There were no differences in medical complications, venous thromboembolic events or death between the two groups for either THA or TKA surgery. Due to the small numbers of complications, these have been collated for each cohort (Table IV).

The higher dose of TXA led to a reduction in the primary outcome measure of transfusion, but in THA patients the rate was still 10%. Those patients in the intervention cohort requiring blood transfusion had a significantly lower pre-operative Hb than those who did not require transfusion ($p < 0.001$, unpaired *t*-test). Therefore, the outcome of those patients classified as anaemic on their pre-operative screening bloods compared with those with normal Hb levels undergoing THA is shown in Table V.

From this *post hoc* unadjusted analysis in the higher-dose group, anaemic patients were significantly older and more likely to require blood transfusion. They had an increased length of stay and higher rate of admission to critical care following surgery than non-anaemic patients (all $p < 0.001$).

Table VI demonstrates the results showing that the use of the higher dose of IV TXA in non-anaemic patients still led to significant reductions in transfusion requirement, length of stay, 30-day re-admission and requirement for critical care (all $p < 0.01$), when compared with the lower dose.

Discussion

In this study comprising more than 4400 patients, we have demonstrated that in both THA and TKA, those patients who received a single pre-operative dose of TXA of 30 mg/kg had significant reductions in transfusion requirements following surgery compared with the group who received the lower dose of 15 mg/kg. We recognise that in TKA the requirement for transfusion is not as great compared with THA. This may be due to associated factors such as the use of a tourniquet during surgery, which was not investigated as part of this study. However, the higher dose of TXA in TKA patients still led to a significant reduction in transfusion requirement by one-third.

In both THA and TKA, we did not demonstrate a difference in thromboembolic events up to 60 days, or mortality up to 90 days, following surgery between the two cohorts; however, this was not the primary aim and thus no power calculation was made in this regard. These

Table IV. Complications for each cohort following surgery (combined total hip and knee arthroplasty)

Outcome	15 mg/kg (n = 2637)	30 mg/kg (n = 1814)	RR (95%CI)	p-value
MI 30 days, n (%)	12 (*0.5*)	3 (*0.2*)	0.36 (0.10 to 1.29)	0.117*
Stroke 30 days, n (%)	6 (*0.2*)	3 (*0.2*)	0.73 (0.18 to 2.90)	0.652*
GIB 30 days, n (%)	8 (*0.3*)	3 (*0.2*)	0.55 (0.14 to 2.05)	0.542*
DVT 60 days, n (%)	11 (*0.4*)	7 (*0.4*)	0.93 (0.36 to 2.38)	0.872†
PE 60 days, n (%)	29 (*1.1*)	13 (*0.7*)	0.65 (0.34 to 1.25)	0.194†
Death at 90 days, n (%)	10 (*0.4*)	1 (*0.1*)	0.15 (0.02 to 1.13)	0.066*

*Fisher's exact test
†chi-squared
RR, risk ratio; CI, confidence interval; MI, myocardial infarction; GIB, gastrointestinal bleed; DVT, deep vein thrombosis; PE, pulmonary embolism

Table V. Comparison of anaemic and non-anaemic patients in the intervention (30 mg/kg) total hip arthroplasty group

Outcome	Not anaemic (n = 688)	Anaemic (n = 120)	RR (95% CI)	p-value
Mean age (yrs), n (range)	67.6 (22 to 98)	72.1 (38 to 92)	Difference 4.56 (2.49 to 6.63)	< **0.001***
Female, n (%)	405 (*58.9*)	81 (*67.5*)	1.45 (0.96 to 2.18)	0.075†
Pre-operative Hb (g/dL), mean (range)	13.9 (12 to 17.1)	11.6 (8.6 to 12.9)	8.8 (6.2 to 12.7)	< **0.001***
Transfusion, n (%)	36 (*5.2*)	45 (*37.5*)	10.9. (6.60 to 17.90)	< **0.001**†
LOS (mean days), n (range)	3.8 (1 to 45)	7.5 (1 to 93)	-	< **0.001**‡
Re-admission 30 days, n (%)	35 (*5.1*)	6 (*5.0*)	0.98 (0.42 to 2.29)	0.968†
RTT 30 days, n (%)	12 (*1.7*)	1 (*0.8*)	0.48 (0.06 to 3.64)	0.476§
Critical care admission, n (%)	4 (*0.6*)	11 (*9.2*)	17.26 (5.10 to 55.16)	< **0.001**§
MI 30 days, n (%)	2 (*0.3*)	0 (*0.0*)	1.14 (0.06 to 23.58)	0.933§
Stroke 30 days, n (%)	2 (*0.3*)	0 (*0.0*)	1.14 (0.06 to 23.58)	0.933§
GIB 30 days, n (%)	1 (*0.1*)	1 (*0.8*)	5.73 (0.36 to 91.05)	0.216§
DVT 60 days, n (%)	3 (*0.4*)	0 (*0.0*)	0.81 (0.04 to 15.65)	0.891§
PE 60 days, n (%)	5 (*0.7*)	1 (*0.8*)	1.15 (0.14 to 9.73)	0.905§
Death at 90 days, n (%)	1 (*0.1*)	0 (*0.0*)	1.90 (0.08 to 46.32)	0.729§

*Unpaired *t*-test
†chi-squared
‡Mann-Whitney U test
§Fisher's exact test
Bold values are statistically significant
Hb, haemoglobin; RR, risk ratio; CI, confidence interval; LOS, length of stay; RTT, return to theatre; MI, myocardial infarction; GIB, Gastrointestinal bleed; DVT, deep vein thrombosis; PE, pulmonary embolism

findings with regard to thromboembolic events are similar to those reported elsewhere.[19]

TXA can be administered intravenously, orally or topically. Published work has suggested benefits of oral TXA when compared with IV, including reduced cost and a greater reduction in transfusion requirements, while maintaining a similar safety profile. However, this was based on a small cohort due to the opportunistic nature of the study, undertaken when there was a lack of IV TXA. There is a paucity of similar studies investigating the oral form.[11]

Topical administration of TXA is safe and effective, and a systematic review has suggested that the topical form is better than IV, although the authors conclude this was an indirect comparison.[13] However, applying TXA topically after the procedure has no effect on intra-operative blood loss. Topical TXA also has the potential to adversely affect implants, although this does not appear to be the case when assessed in an *ex vivo* setting.[20] It may be that a combination of IV and topical TXA could be of potential benefit.[21]

We use a single dose of TXA at induction of anaesthesia and a single dose has been shown to have good effect in reducing transfusion requirements and post-operative complications.[22,23] To date, no clear consensus on the optimum method or the timing, frequency or dose of administration exists in the published literature.[14,24-26]

While we recognise that this is a retrospective study assessing two groups during two different time periods, we have included all unselected patients operated in the study timeframe, thus removing any selection bias and ensuring the results are representative. Except for the difference in TXA dose, practice remained unchanged. Consequently, we feel this strengthens our findings as it removes heterogeneity in our study methodology. We do acknowledge that, as the two consecutive cohorts were treated at different timepoints, with the passage of time other unknown factors may have influenced outcomes. In addition, we have not audited the compliance with the protocol in terms of drug timing and dosing, and the results are described on an intention-to-treat basis.

A number of methods are described in the literature to calculate post-operative blood loss, and most depend on an estimation of calculated blood volume such as the Nadler method.[27] We were unable to calculate blood loss directly as drains are not used post-operatively and we felt that the most clinically relevant way to assess blood loss was the requirement for blood transfusion, rather

Table VI. Comparison between cohorts of non-anaemic patients undergoing total hip arthroplasty

Outcome	15 mg/kg (n = 942)	30 mg/kg (n = 688)	RR (95% CI)	p-value
Transfusion, n (%)	84 (*8.9*)	36 (*5.2*)	0.59 (0.40 to 0.86)	**0.005***
LOS (mean days), n (range)	4.4 (0 to 61)	3.8 (1 to 45)	-	**0.005†**
Re-admission 30 days, n (%)	96 (*10.2*)	35 (*5.1*)	0.50 (0.34 to 0.73)	< **0.001***
RTT 30 days, n (%)	21 (*2.2*)	12 (*1.7*)	0.78 (0.39 to 1.58)	0.594*
Critical care admission, n (%)	31 (*3.3*)	4 (*0.6*)	0.18 (0.06 to 0.50)	< **0.001‡**
MI 30 days, n (%)	4 (*0.4*)	2 (*0.3*)	0.68 (0.13 to 3.73)	0.661‡
Stroke 30 days, n (%)	3 (*0.3*)	2 (*0.3*)	0.91 (0.15 to 5.45)	0.920‡
GIB 30 days, n (%)	3 (*0.3*)	1 (*0.2*)	0.46 (0.05 to 4.38)	0.643‡
DVT 60 days, n (%)	5 (*0.5*)	3 (*0.4*)	0.82 (0.20 to 3.43)	0.787‡
PE 60 days, n (%)	4 (*0.4*)	5 (*0.7*)	1.71 (0.46 to 6.35)	0.506‡
Death at 90 days, n (%)	4 (*0.4*)	1 (*0.1*)	0.34 (0.04 to 3.06)	0.404‡

*chi-squared
†Mann-Whitney U test
‡Fisher's exact test
Bold values are statistically significant
Hb, haemoglobin; RR, risk ratio; CI, confidence interval; LOS, length of stay; RTT, return to theatre; MI, myocardial infarction; GIB, Gastrointestinal bleed; DVT, deep vein thrombosis; PE, pulmonary embolism

than to calculate an estimation. We accept that there may have been variability in transfusion depending on the treating clinician's view of what is 'symptomatic anaemia' when a patient's post-operative Hb is between 8 g/dL and 10 g/dL. The transfusion protocol was well established when the study began and so we feel that this approach pragmatically represents current clinical practice, thus making the results more clinically relevant.

As well as a decline in transfusion rates, the 30 mg/kg cohort had an overall reduction in mean length of stay of 0.4 days for THA and one day for TKA, as well as significant reductions in admission to critical care and 30-day hospital re-admission. In addition to being of clear benefit to patients, these reductions will also be associated with significant financial savings for trusts. However, we concede that the reduction in length of stay and re-admissions may not be fully attributable to the increase in TXA dose. As our unit's experience of an ER protocol has grown since its introduction in 2008, length of stay has reduced over that time. Also, a specific programme to reduce re-admissions in the trust was implemented in March 2012, and so these reasons may also account for the improvements seen in length of stay and re-admission.

Despite a significant reduction with 30 mg/kg TXA, 10% of THA patients still required blood transfusion. There was a significant requirement for transfusion in anaemic patients compared with non-anaemic patients (38% *versus* 5%), and so correcting this pre-operatively will likely be an important factor in further reducing the transfusion rate. However, TXA should still be used in addition to correcting pre-operative anaemia, as we have shown the higher dose of IV TXA still had a significant effect on reducing transfusion requirements in non-anaemic patients.

In conclusion, TXA is now widely accepted for use in arthroplasty surgery, and a single dose of IV TXA at 30 mg/kg, maximum 2.5 g, is associated with a significant reduction in transfusion requirements for both THA and TKA surgery. Its use may also be associated with reductions in length of stay, 30-day re-admission rate and requirement for critical care admission. In this study, we did not demonstrate an increase in thromboembolic events up to 60 days following surgery, or mortality at 90 days. Pre-operative anaemia also has a significant effect on outcome and its impact should be considered. These findings, although robust, should be considered in the context of the retrospective non-randomised nature of the current study.

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Author Contributions

- R. J. M. Morrison: Data collection, Analysis, Writing and editing of manuscript.
- B. Tsang: Data collection, Analysis, Review of manuscript.
- W. Fishley: Data collection, Analysis, Review of manuscript.
- I. Harper: Introduction of dose change, Analysis, Editing of manuscript.
- J. C. Joseph: Introduction of dose change, Analysis, Editing of manuscript.
- M. R. Reed: Introduction of dose change, Analysis, Writing and editing of manuscript.

Conflicts of Interest Statement

- None declared