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TRAC-24

Single Centre Randomised Controlled Trial To Assess The Effect Of The Addition Of Twenty-four Hours Of Oral Tranexamic Acid Post-operatively To A Single Intraoperative Intravenous Dose Of Tranexamic Acid On Calculated Blood Loss Following Primary Hip And Knee Arthroplasty (TRAC-24)

SHORT REPORT

List of Authors

David Beverland, Janet Hill, Paul Magill, Leeann Bryce, Rosie Hogg, Al Dorman, Gary Benson and the N.I. Clinical Trials Unit

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CONTENTS

EVIDENCE BRIEF

Why did we start?

We know that tranexamic acid (TXA) decreases blood loss in total hip and knee arthroplasty. However, there are two major issues. Firstly there is no universally accepted 'best-practice' protocol for timing or route of administration and secondly there has been no previous RCT which has specifically included patients with a history of thromboembolic disease. Consequently following evidence that 86% of blood loss in total knee arthroplasty (TKA) under tourniquet occurs in the first 24 post-operative hours and 80% of blood loss in total hip arthroplasty (THA) occurs in the period between skin closure and the first 24 post-operative hours the TRAC-24 clinical trial was established to identify if an additional 24-hour post-operative oral regime of TXA would be superior to a once-only intravenous dose at surgery. Furthermore patients with a history of thromboembolic disease were included.

What did we do?

We started a prospective, phase IV, single centered, open label, parallel group, controlled trial on patients undergoing primary elective THA and TKA. As above a history of thromboembolic, cardiovascular or cerebrovascular disease was not an exclusion criterion. The primary outcome was indirect calculated blood loss at 48 hours (IBL). 534 TKA and 534 THA patients were randomised on a 2:2:1 ratio over three different groups. Group 1 received an intravenous dose of TXA at the time of surgery and an additional 24-hour post-operative oral regime, group 2 only received the intra-operative dose and group 3 did not receive TXA. All analyses were carried out on an intention-to-treat basis.

What answer did we get?

We confirmed as expected that TXA is an effective medication for limiting blood loss in TKA and THA patients. This effect is independent of age, gender, BMI and surgeon. In TKA it is most effective when administered for 24 hours post-operatively and said regime can achieve approximately 40% reduction in blood loss over control while in THA there is no difference between single use and extended use over 24 hours of TXA, but patient weight may be a factor, further research is needed to determine this. Also and very significantly there were no safety signals with either active treatment regime in patients with a history of thromboembolic disease.

What should be done now?

From this study the following recommendations have been made:

1. The use of TXA should be considered in all patients undergoing primary THA and TKA.
2. Critically, that a history of thromboembolic disease should not be a contraindication to giving TXA.
3. That if a patient is receiving TXA, then all should receive one gram, intravenously prior to commencement of surgery.
4. Patients undergoing primary TKA should receive an additional one gram of TXA orally at 2hrs, 10hrs, 18hrs and 26hrs post knife to skin.

Although the additional oral doses made no difference in THA there was a trend for a positive effect in patients weighing >100Kg. We plan to look at this in more detail.

Background

Tranexamic acid (TXA) is a synthetic analogue of the amino acid lysine. It was first manufactured in 1964[1] to treat post-partum bleeding and it was very successful at doing so. Following the CRASH-2 trial publication in 2010[2] there was an exponential rise in TXA research by many subspecialties of medicine and surgery.

The supporting evidence for TXA at limiting medical and surgical blood loss is now irrefutable; it appears to be efficacious via intravenous, oral and topical routes[3] and it appears to be safe.[4] Its' success, however has led to the publication of multiple administration protocols with none having clear superiority.[5] Questions remain regarding the optimal protocol, in terms of route, dose, timing and duration. Questions also remain regarding its suitability in patients with a history of thromboembolic, cardiovascular and cerebrovascular disease because prospective data in this potentially high risk group is lacking. TRAC-24[6] was established to investigate an alternative protocol for patients undergoing elective primary total hip arthroplasty (THA) and total knee arthroplasty (TKA).

For TKA, the use of TXA has been reported to reduce blood loss by up to 60% beyond a control group[7] but total losses are still high at 600 to 900ml.[8-10] Previous THA studies reported that TXA could save approximately 30% blood loss but losses were still high at almost 1 litre.[11] TRAC-24 aimed to improve upon this by addressing a number of deficiencies in the TXA evidence base. Firstly, the majority of studies try to limit blood loss during the intra-operative period,[9, 10, 12,13] but since we know that only 13% of blood loss with THA occurs intra-operatively[14] and if using a tourniquet for TKA intra-operative blood loss is minimal, we hypothesised that extending TXA use to the 24 hour post-operative period would result in less blood loss. We chose the oral route as it is the cheapest, easiest to administer and appears to be equally as efficacious as the intravenous route.[15] Secondly, many studies choose incidence of blood transfusion as their primary outcome measure. Blood transfusion is a poor outcome measure because it is now universally uncommon in modern arthroplasty care and the decision to administer is often subjective. Consequently, our primary outcome measure was indirect calculated blood loss at 48 hours post-operatively.

With regards to safety, orthopaedic studies have, to date, excluded patients with a history of thromboembolic, cardiovascular and cerebrovascular disease as they are considered too high risk. We argue that not only is there no convincing evidence to support this but there is good level 1 data supporting its safe use in coronary artery surgery,[16] patients who, by definition would be excluded from orthopaedic studies. Potentially these patients have the most to gain from reduced blood loss so in designing TRAC-24 we consulted with national and international colleagues to decide the exclusion criteria. Consequently patients with a history of thromboembolic, cardiovascular and cerebrovascular disease were included if otherwise fit for surgery.

Aims and Objectives

The overall aim of this study was to reduce blood loss in THA and TKA patients using TXA. While TXA has been shown to reduce blood loss in THA/TKA patients, the optimum method of delivery, optimum number of doses and optimum period of use is not clear. A previous audit of patients under the care of the chief investigator demonstrated that five sixths of the blood loss occurs post wound closure. Therefore, hypothetically if TXA was given to a patient for over 24 hours following surgery it should further reduce blood loss as compared to TXA dosing in the immediate peri-operative period.

The primary objective was to determine if the use of oral TXA post-operatively for up to 24h hours would confer a reduction in calculated blood loss at 48 hours beyond an intra-operative intravenous bolus alone for patients undergoing unilateral primary total hip or knee replacement.

The secondary objective was to determine if the addition of oral TXA post-operatively to an intra-operative intravenous bolus of TXA produced any change in other measurable parameters as compared to those observed either with an intra-operative intravenous bolus alone or no TXA for patients undergoing unilateral primary THA/TKA.

Methods

Study design and participants

The trial was registered on ClinicalTrials.gov (NCT03690037) and ISRCTN (ISRCTN58790500) and the protocol was published prior to trial completion.[6] This was a phase IV, single centered, open label, parallel group, randomised controlled trial on patients undergoing primary elective TKA or THA. An independent clinical trials unit (CTU) monitored the trial from design to closure. Four surgeons from Musgrave Park Hospital consented to recruitment of their patients and any patient attending for THA and TKA under their care was invited to join the trial.

The full list of exclusion criteria are listed in the study protocol.[6] Patients with a history of thromboembolism, cardiac disease or cerebrovascular disease, other than that which precluded fitness for surgery, were not excluded.

Randomisation and masking

Stratification was performed prior to randomization. TXA undergoes renal clearance so in order to prevent overdosing, participants were stratified to a lower dose if their creatinine was elevated, according to set criteria.[6] Participants were also stratified according to their surgeon. Once the participant was appropriately stratified they were then randomised on a 2:2:1 ratio to one of three groups. This was performed by picking, in sequence, a sealed envelope with a tamper-proof label. The trial statistician generated the randomisation sequence.

The patients' transfusion trigger, which is a haemoglobin (Hb) level below which one should consider blood transfusion, was decided prior to randomisation. This enabled us to count the number of patients who dropped below the transfusion trigger as a blinded secondary outcome. However, the decision to transfuse remained subjective and clinicians were not blinded. The only staff blinded to group allocation were the offsite laboratory staff processing the blood samples.

Procedures

Group 1 had IV TXA within 30 minutes before knife to skin (KTS) and an additional four post-operative oral doses. The first post-operative oral dose was two hours after skin closure then eight-hourly for the three further oral doses. Group 2 had IV TXA within 30 minutes before KTS and no post-operative doses. Group 3 had no TXA, which had been standard practice in the unit prior to trial commencement. Following an independent interim analysis, the data monitoring and ethics committee (DMEC) recommended cessation of group 3. Approval was granted to change the protocol and randomisation for the remainder of the trial was on a 1:1 ratio to groups 1 and 2 only.

Other than the trial drug, there were no other changes to surgical practice for TRAC-24 although individual surgeon practice varied in terms of implant choice. With regards to chemical thromboprophylaxis one surgeon used Aspirin 150mg daily for 6 weeks and the other three, 40mg of Enoxaparin (60mg if ≥100Kg) once daily for 28 days.

Outcomes

Indirect calculated blood loss 48 hours post-operatively (IBL) was the primary outcome measure. This was calculated based on a change in haematocrit (Hct)[17–19] and transfused blood was taken into account. The equation is published in the trial protocol.[6] Pre-operative Hct was performed on admission. Day of surgery (DOS) blood tests were taken at 8 hours +/- 30 minutes following KTS and Day 2 blood tests were taken at 48 hours +/- 2 hours following KTS. The timing of day 1 tests and day 3, 4 tests (if performed) were not defined a priori.

Incidence of post-operative Hb falling below the transfusion trigger (irrespective of transfusions), 90-day mortality rate and 1-year mortality rate were included as secondary outcome measures. Further outcome measures were termed exploratory and these included intra-operative blood loss, blood transfusion data, change in Hb, incidence of deep vein thrombosis (DVT), incidence of pulmonary embolism (PE), incidence of repeat admission to hospital (defined as any cause) and change in Oxford hip score and knee score. DVT and PE were screened for only if indicated by patient symptoms.

Statistical analysis

Based on a mean (standard deviation) of 1,225 (499) mls of blood loss[20] and a clinically significant difference of 150 ml (12%) between the 2 TXA groups, the trial required 233 patients per group at 90% power and 0.05 level of significance. Due to the proven greater blood loss in the 'no TXA' group the allocation ratio was 2:2:1, resulting in half the number of participants in this group (n=117). This resulted in a total of 1,166 patients (583 TKA, 583 THA).

Following the interim analysis and DMEC recommendation, randomisation of recruited patients to group 3 was stopped. The revised sample size was 1,066; 932 in groups 1 & 2 with 134 having been recruited to group 3. NQuery Version 3.0 was used for the sample size analysis.

Analyses were conducted on an intention-to-treat basis and at a significance level of 0.05.There was no adjustment for multiple testing. Baseline characteristics and outcome measures were summarised as mean & SD, median & inter-quartile range (IQR) or numbers & proportions (%) depending on the scale of measurement.

For the primary outcome, a t-test was used to investigate the difference between the intervention groups and also the difference between the intervention groups combined versus the control group. The primary outcome was also compared between the three groups using ANOVA (and post-hoc test if significant differences were identified). The differences between the combined intervention and control were also confirmed using ANOVA with contrasts. Analysis of covariance was used to adjust for age, weight, surgeon and recruitment period. The covariates were not specified in the statistical analysis plan (SAP).

Subgroup analyses were performed on the primary outcome measure for creatinine, age, gender, BMI and surgeon. A statistical interaction test was used to assess differences in treatment effects between the subgroups and were reported using 99% CI.

Continuous secondary and exploratory outcomes were compared between the three groups using ANOVA (and post-hoc tests if significant differences) or non-parametric equivalent if appropriate. If a significant difference was found between the three groups we investigated the difference between the intervention groups.

Categorical secondary and exploratory outcomes were compared between the three groups using chi-square (or fishers exact if appropriate) to test the difference in the proportions. If a significant difference was found between the three groups we investigated the difference between the intervention groups.

The number of adverse events (AEs), adverse reactions (ARs), serious AEs (SAEs), serious ARs (SARs), suspected unexpected SARs (SUSARs) and number (%) of patients experiencing the events were reported. Chi-square test (or Fisher's exact test if appropriate) and proportion test was used to check whether incidences of adverse events differ between the groups. Relative risk and 95% CI were reported. This was performed for intervention groups combined versus the control group and difference between intervention groups.

Personal and Public Involvement (PPI)

The Primary Joint Unit Patient Liaison Group (PLG) were involved in the design of TRAC-24 and reviewed all patient documentation. In addition, a member of the PLG sat on the Trial Steering Committee for TRAC-24. The PLG received regular updates about the study at their quarterly meetings. The PLG were also involved in how best to share the results of the study with the public. Information about the study has also been disseminated to patients and the public by the Belfast Arthroplasty Research Trust through social media, newsletters and their website.

Findings

Primary Outcome

Table 1 shows the results of the primary outcomes. TRAC-24 confirmed that TXA can safely deliver a 38% reduction in blood loss in TKA and THA. There was a statistically significant difference in indirect blood loss at 48 hours between intervention 1, intervention 2 and control for all patients ($p<0.001$), THA patients ($p<0.001$) and TKA patients ($p<0.001$). This effect was independent of age, gender, BMI and surgeon. The primary objective of TRAC-24 was to test if prolonging the post-operative administration of TXA for 24 hours would further reduce blood loss and we conclude that it did for TKA patients.

Thus for TKA patients the extension of TXA administration for 24 hours decreased the blood loss by a further mean volume of 126ml, an extra 11% beyond a standard pre-operative dose which itself gave a 28% reduction in blood loss as compared to no TXA. Again, this 11% additional benefit was independent of age, gender, BMI and surgeon. In contrast for THA however, there was no difference between single use and prolonged use of TXA irrespective of patient age, gender, creatinine level or surgeon. BMI and more specifically weight possibly has an influence as we observed a non-statistical but clinically significant benefit of extended TXA in patients weighing 100kg or more.

Table 1 Anova results for primary outcome

Primary outcome	Treatment Group			p-value	Post-hoc comparison of group 1 and group 2
	Intervention 1	Intervention 2	Control		
All patients; indirect blood loss at 48 hours	790.4(428.8) (n=456)	851.7(423.1) (n=454)	1282.4(592.0) (n=133)	*<0.001*	*0.030*
THA patients; indirect blood loss at 48 hours	848.4(463.8) (n=226)	843.7(478.7) (n=221)	1370.9(630.1) (n=66)	*<0.001*	*0.92*
TKA patients; indirect blood loss at 48 hours	733.5(384.0) (n=230)	859.2(363.6) (n=233)	1195.2(542.6) (n=67)	*<0.001*	*<0.001*

Secondary Outcomes

For TKA patients there was no significant difference between the groups in the incidence of reaching the transfusion trigger or 1-year mortality. There was one death within 90 days in group 3 due to a perforated bowel and no deaths in either intervention group within 90 days. For THA patients there was no significant difference between the groups regarding the incidence of reaching the transfusion trigger or in overall mortality. There was one death within 90 days in group 1 due to heart failure.

Exploratory Outcomes

For TKA patients the incidence of blood transfusion was significantly higher in group 3 patients when compared to intervention group 1 and intervention group 2, p=0.001, the post hoc comparison of group 1 and group 2 was not significant (p=0.09). Transfusion was not blinded so to evaluate for potential bias we looked at the number of patients in each group that fell below the transfusion trigger but who did not receive a transfusion and found that all groups were comparable.

For TKA patients the incidence of PE was highest in control group compared to the intervention groups. The number of PEs recorded for the control group was beyond the expected rate for a sample size of only 68 patients. There was also a higher incidence of repeat hospitalisation or unplanned admission to critical care in group 3 compared to intervention group 1 and intervention group 2.

It is also notable from TRAC-24 data that the rate of hospital readmission or unplanned admission to critical care was higher for TKA patients in the control group than in the intervention groups combined, p<0.001. The admission diagnosis of these patients was varied and we have no evidence to link them to the lack of TXA or increased blood loss but there is a clinical rationale for a further RCT on high-risk patients.

For THA patients, intra-operative blood loss and incidence of blood transfusion was higher in group 3 however, there was an equitable rate of with-holding transfusion when the patient was below the transfusion trigger. There was a single diagnosis of DVT within 90 days of surgery (group 2) and a single diagnosis of PE within 90 days of surgery (group 3), but there were more hospital readmissions in the intervention groups.

Safety

Overall there were no events to cause an immediate safety concern with TXA. In addition the safety profile of TXA was comparable in all groups. For TKA patients there were 269, 331 and 98 AEs in Group 1, 2 and 3 respectively, of which over 66% were nausea and vomiting or dizziness on mobilising. There were 22 SAEs in both Group 1 and Group 2 and 13 in group 3. There were 2, 3 and 0 SARs in group 1, 2 and 3 respectively. There were no SUSARs in any group. For THA patients there were 242, 256 and 65 AEs in Group 1, 2 and 3 respectively, of which 61 % were gastro-intestinal (nausea and vomiting) or neurological (dizziness on mobilising) symptoms. There were 21 and 34 SAEs in Group 1 and Group 2 and 7 in group 3. There were 1, 3 and 0 SARs in group 1, 2 and 3 respectively. There were no SUSARs in any group. Of note though there was a statistically significant difference in the number of AEs reported for Blood and Lymphatic System Disorders between intervention combined and control for THA patients.

Conclusion

TXA is an effective medication for limiting blood loss in TKA and THA patients. This effect is independent of age, gender, BMI and surgeon. In TKA it is most effective when administered for 24 hours post-operatively and said regime can achieve approximately 40% reduction in blood loss over control while in THA there is no difference between single use and extended use over 24 hours of TXA, but patient weight may be a factor, further research is needed to determine this.

We found no safety concerns and a history of thromboembolic disease should not be a contraindication to the use of TXA with either dosage regime.

Practice and Policy Implications/Recommendations

As of December 2019, following the analysis of the results of TRAC-24 the following local policy was agreed for all patients undergoing elective primary hip or knee replacement in Musgrave Park Hospital:

1. The use of TXA should be considered in all patients undergoing primary THA and TKA.
2. Critically, that a history of thromboembolic disease should not be a contraindication to giving TXA.
3. That if a patient is receiving TXA, then all should receive one gram, intravenously prior to commencement of surgery and prior to tourniquet inflation if being used.
4. Patients undergoing primary TKA should receive an additional one gram of TXA orally at 2hrs, 10hrs, 18hrs and 26hrs post knife to skin.

Pathway to Impact

Initial results were presented internationally at the Association of Bone and Joint Surgeons annual meeting in Rhode Island, USA, July 2019. This is a high impact orthopaedic meeting in the calendar year which was a good opportunity to present the TRAC-24 findings and discuss them amongst international peers. Locally the results of this research have been disseminated to all orthopaedic surgeons and anaesthetists in the Belfast Trust via email and presented at an Audit meeting in November 2019. The work has also been presented nationally at the British Hip Society in Cardiff in March 2020 and won the McKee prize for best podium presentation. The British Hip society annual meeting is well attended by UK orthopaedic surgeons and an

ideal opportunity to present the results of the hip replacement arm of the trial and discuss the use of tranexamic acid in UK arthroplasty practice.

Two publications are now in preparation for the hip and knee arms of the trial and will be submitted to the Lancet by June 2020.

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Acknowledgements/Relevant Logos

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