Acta Orthop. Belg., 2014, **80**, 228-233

ORIGINAL STUDY

Comparison of Intra-operative Regimes of Tranexamic Acid Administration in Primary Total Hip Replacement

John T. Machin, Vineet Batta, Juan A. Soler, Kannan Sivagaganam, Yegappan Kalairajah

From Luton & Dunstable University Hospital, Luton, United Kingdom

The administration of tranexamic acid to decrease blood loss in primary total hip replacement is established. In this observational study three different regimes of tranexamic acid were used to investigate the effects of combined intravenous and topical administration of tranexamic acid to a single intravenous bolus given at induction or closure. Group 1 (n = 50) received 1 g tranexamic acid intravenously at induction and 500 mg tranexamic acid topically during closure. Group 2 (n = 50) received 1 g tranexamic acid intravenously at induction. Group 3 (n = 50) received 1 g tranexamic acid at closure.

The mean haemoglobin loss was 2.83 g/dL (95% Confidence interval [CI] 2.51 to 3.15 g/dL) in Group 1, 2.92 g/dL (95% CI 2.65 to 3.19 g/dL) in Group 2 and 3.36 g/dL (95% CI 2.94 to 3.77 g/dL) in Group 3. No significant difference in mean haemoglobin loss was found (p = 0.123).

In this observational, non-randomised study we found no additional advantage to giving topical tranexamic acid at closure in addition to intravenous tranexamic acid given at induction.

Keywords : total hip replacement ; tranexamic acid ; blood loss ; transfusion.

INTRODUCTION

Primary total hip replacement (THR) is an established procedure, which has been proven to significantly improve a patient's quality of life (*8,17*). One of the common risks (2-5%) of THR is bleeding (*22*). Blood loss can vary depending on technique, surgeon and patient factors. Traditionally allogeneic blood transfusion has been the salvage treatment for patients with significant blood loss. This exposes the patient to risks including immunological reactions, renal failure, coagulopathy and can result in death (*5,15,16*).

Many different methods from regional anaesthesia to intra-operative blood salvage and anti-fibrinolytic agents have been used to reduce blood loss and decrease the not insignificant risks associated with allogeneic blood transfusion (*3*). Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine and competitively inhibits the activation of plasminogen to plasmin. Intra-operative administration of TXA has been shown by systematic review and meta-analysis of randomised control trials to significantly decrease intra-operative blood loss in primary THR and reduce transfusion rates (*23*). Currently there is no evidence that the use

■ John T. Machin MRCS.
■ Vineet Batta MRCS.
■ Juan A. Soler MRCS.
■ Kannan Sivagaganam FRCA.
■ Yegappan Kalairajah FRCS (Orth).

Department of Trauma & Orthopaedics, Luton & Dunstable University Hospital, Luton, United Kingdom.

Correspondence : Mr John T. Machin, Department of Trauma & Orthopaedics, Luton & Dunstable University Hospital, Lewsey Road, Luton, Bedfordshire LU4 0DZ, United Kingdom.

Email : johnmachin@doctors.org.uk

© 2014, Acta Orthopædica Belgica.

No benefits or funds were received in support of this study.

of TXA intra-operatively has significantly increased rates of venous thromboembolic events or any other complications at the recommended dose (under 30 mg/kg) in arthroplasty (*14,23*).

After excluding the additional nursing and other staff expenses a unit of packed red blood cells costs the NHS £125 while a 1g dose IV TXA (Cyklokapron) costs £3.10 (*4,20*). Studies have shown that the use of TXA would be cost effective, with savings of over £100,000 for some centres as a result of reduced transfusion costs even when taking into account the modest price of this agent (*6,11,13,21*).

In previous studies a number of regimes have been used when administering intravenous TXA including prolonged infusion, repeated boluses and boluses at induction or closure. There has also been a range of doses including 10-30 mg/kg or 1-2 g. However total blood loss and transfusion rate have not been shown to reduce with higher doses of TXA (*23*). Randomised control trials by Benoni *et al* suggested that the timing of the administration of intravenous TXA is important. In the first trial Benoni *et al* gave TXA at end of the operation and then three hours later and found this regime did not reduce total blood loss compared to a saline placebo (*2*). In contrast, in the second trial a bolus of TXA or placebo was given before the operation resulting in both a significant lower total blood loss and transfusion rate for those receiving TXA (*1*). Following this and other trials there has been a consensus that the administration of intravenous TXA before the surgical incision is more beneficial than at closure. TXA has a half life of 80 minutes in plasma and this combined with the CRASH 2 study of bleeding trauma patients has demonstrated that the use of TXA is time critical (*7,22*).

TXA has been applied topically to the operative field during closure. Wong *et al* randomised 124 patients receiving Total Knee Replacements (TKR) to topical application of TXA or placebo directly into the surgical wound. Topical TXA was found to significantly reduce postoperative blood loss (*27*). Gilbody *et al* found topical TXA reduced length of stay, blood loss and transfusion rate in both primary THR and TKR (*9*).

However there is no study in the literature comparing the combined intra-operative administration of both intravenous and topical TXA administration in THR. Our observational study is based on the change of administration of TXA in the practice of one surgeon in the context of an evolving evidence base. The aim of this study was to compare the effects of combined intravenous and topical administration of TXA to single intravenous bolus given at induction or closure.

MATERIALS & METHODS

Selection criteria

This study retrospectively reviewed 153 primary THRs performed by the same surgeon at one centre from August 2008 until June 2012. Patients were excluded who had a clotting disorder, a previous thromboembolic event, bleeding diathesis, allergy to TXA, were taking warfarin or had renal failure (CrCl < 30 ml/min). The above criteria resulted in 3 patients being excluded. Patients receiving any form of revision or trauma surgery were not considered.

Patients received either a fully uncemented hip replacement (Trident acetabular PSL cup and Accolade stem) or a hybrid hip replacement (Trident acetabular PSL cup and Exeter stem – Stryker Orthopaedics, Mahwah, New Jersey, U.S.A.) based on the judgement of the senior author.

The procedures were performed through a modified Hardinge approach. A combination of 0.25% buvipicaine and 1:200,000 adrenaline was injected into the joint and soft tissues. Standard transosseos closure was carried out. No drains were used. Anaesthetic techniques used included spinal anaesthesia, general anaesthesia and regional blocks. These techniques were used individually or in combination depending on the anaesthetic assessment.

For venous thromboembolic event prophylaxis all patients received dabigatran unless contraindicated or declined by the patient. In place of dabigatran this small minority of patients received 40 mg enoxaparin subcutaneously once daily. Dabigatran was given as a half dose 3-4 hours post surgery and a full dose of 220 mg once daily from the first day post-operation onwards. Patients over 75 years old, using amiodarone or verapamil received a lower dose of 150 mg as recommended by the manufacturer (Boehringer Ingelheim Limited, Berkshire, United Kingdom.)

Three different regimes of TXA administration were used. The first fifty cases with each of the three regimes

were included in the study after exclusions. Group 3 contained our first 50 patients who received 1 g TXA at closure, which had previously been our standard protocol. Group 2 contained 50 patients who received 1 g TXA intravenously at induction. This was an interim group of patients who were treated chronologically after Group 3 but before group 1. Group 1 contained 50 patients who received 1 g TXA intravenously at induction and 500 mg TXA topically during closure, which is our current practice.

Outcome

Patients with haemoglobin (Hb) less than 8 g/dl or those who were symptomatic with anaemia, had history of ischeamic heart disease and Hb less than 10 g/dl were transfused. Hb loss was calculated using a method developed at the Mayo Clinic (Rochester, Minnesota, USA). This formula gives an indirect measure of blood loss using pre-operative and first day post-operative blood samples together with the units of Red Blood Cells transfused between blood samples (*18*).

Hb loss = Pre-op Hb – Post-op Hb + Units of Red Blood Cells Transfused

This formula assumes Pre-op Hb = preoperative Hb (g/dL), Post-op Hb = Hb the next day after the surgical procedure (g/dL). Units of Red blood Cells transfused assuming 1 unit = 1 g/dL Hb and Hb loss is secondary to the THR only.

The length of stay, transfusion rate and complications including thromboembolic events were also reviewed by interrogating our discharge letters and database of investigations from an electronic reporting system. Ultrasound Doppler examination of deep veins and CT pulmonary angiograms were not carried out routinely but only on clinical suspicion guided by the Wells' score (*26*).

Statistical Analysis

Data analysis was carried out using SPSS version 7 (*24*). Normality of blood loss and hospital stay was tested using Shapiro-Wilks test. Blood loss satisfies the normality, while hospital stay rejects the normality assumption. Welch test was applied to compare the mean across the three groups for blood loss because variances were not homogeneous across the three groups (tested by Levene's test, P = 0.018). Kruskal Wallis test was used for hospital stay. Multiple comparisons for blood loss were done using Dunnett's T3 and Mann-Whitney U test with Bonferroni correction for hospital stay. In subgroup analysis, blood loss was homogeneous across the three groups ; one-way analysis of variance followed by Tukey's test was applied to compare the mean across the three groups. Fisher's exact test was applied to compare the proportion of low transfusion rate and thromboembolic events among groups. P-value less than 0.05 were considered as significant.

Sample Size Calculation

The sample-size calculation was based on the differences in the primary outcome (i.e. the post-operative decrease in haemoglobin) among the three study groups. Using the study done by Wong *et al* (*20*), total blood loss of 1610 ± 325 ml and a reduction of 250 ml in total loss were considered as clinical important, and therefore, sample size of 22 was required in each group. The sample size was calculated using PASS software and for fixed effect, one-way ANOVA variance design was used. It was assumed that standard effect size d = 0.39, the level of alpha (two-tailed) = 0.05, and power = 80%. In addition the standard deviation within each arm was taken as 300. It was calculated that a minimum of 23 patients was required in each arm. Therefore with 50 patients in each group we are satisfied that our study has sufficient power.

RESULTS

Table I summarises the distribution of 150 patients between groups. Dabigatran was given to 141 patients (94%) with the remaining 9 patients (6%) receiving enoxaparin. Spinal anaesthetic was given to 83 patients (55%), general anaesthetic was given to 31 patients (20%) and the remainder had a combination of blocks, general anaesthetic, epidural, and spinal anaesthetic1.

The mean Hb loss was 2.83g/dL (Standard deviation (SD) 1.12 g/dL) in Group 1, 2.92 g/dL (SD 0.95 g/dL) in Group 2 and 3.36 g/dL (SD 1.47 g/dL) in Group 3 (Fig. 1). The Welch test showed no significant difference in mean Hb loss across the groups, P = 0.123. Subgroup analysis by procedure revealed that there was no significant difference in Hb loss when considering patients receiving hybrid THRs when comparing Groups 1-3. However analysis of the uncemented subgroup using the post hoc Tukey's test showed there is significant difference in mean blood loss between the group 1 and group 3 (p = 0.037). There was no significant

Table I. — Patient Distribution

	Group 1 (n = 50)	Group 2 (n = 50)	Group 3 (n = 50)
Tranexamic acid Regime	**1 g IV at induction + 500 mg Topical**	**1 g IV at induction**	**1 g IV at closure**
Male	18	17	19
Female	32	33	31
Mean Age (years)	61	66	69
Number of patients receiving Hybrid THR	20	32	15
Number of patients receiving Uncemented THR	30	18	35
Anaesthetic – Spinal	33	29	21
– GA	7	7	17
– GA + Spinal	3	9	4
– GA + Regional Block	4	3	4
– Spinal + epidural	3	2	3
– Unknown	0	0	1

difference in mean blood loss between group 1 and group 2 ($p = 0.968$) or group 2 and group 3 ($p = 0.1441$).

Groups 1 and 2 who both received IV TXA at induction had lower transfusion rates of 6% (n = 3) compared to 10% (n = 5) of group 3 that received IV at closure but this was not statistically significant ($p = 0.71$). This was consistent with Groups 1 and 2 having a lower Hb loss.

The mean length of stay was 4.3 days (range 2-13 days) for Group 1, 5.0 days (range 1-26 days) for Group 2 and 5.8 days (range 2-26 days) for Group 3. Overall there was no significant difference in length of stay between the three groups ($p = 0.214$). There were a number of outliers who had length of stays much greater than expected due to a number of medical complications including urinary tract infections, lower respiratory tract infection and renal failure, extending their recovery period.

There was no significant difference ($p = 1.00$) in thromboembolic events between groups with no patients being diagnosed with venous thromboembolic events in groups 1 and 2. In group 3 only 1 patient was diagnosed with a deep vein thrombosis and there was no diagnosis of pulmonary embolism. In addition, we did not find an increased incidence of any other complications including previously reported neurological sequelae in higher doses of TXA (*19*).

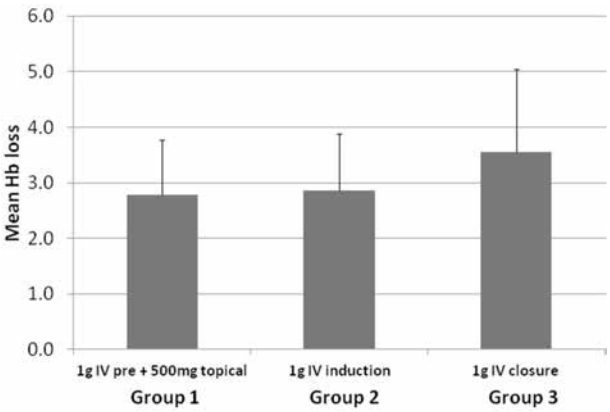

Fig 1. — Calculated Mean Hb loss of Groups1-3 with error bars indicating 1 standard deviation.

DISCUSSION

This observational study compares the use of topical and intravenous regimes of TXA. Although the mean Hb loss was lowest in group 1 and highest in group 3, a significant reduction in blood loss, as indicated by change in Hb, was only seen in the subgroup analysis of uncemented THRs when comparing groups 1 and 3. Previous randomised controlled trials have found a significant reduction in total blood loss when intravenous TXA is given at induction rather than closure when using cemented THR (*1,2*).

The uncemented group had a higher percentage of males with 52% (n = 43) compared to 16% (n = 11) in the hybrid population. There is evidence men accumulate more blood loss in THR and therefore if this is the case may benefit from an additional topical dose of TXA more than women (*10*). This higher percentage of males could be a contributing factor to the significant reduction of Hb loss found when topical TXA was given in addition to intravenous TXA in the uncemented subgroup. Another explanation could be the difference in anaesthetic technique as Group 3 patients had a high proportion of general anaesthetics compared to group 1 (34% compared to 14% respectively). Due to the lack of randomisation it is possible that this study was unable to find a significant difference across other groups due to other confounders.

The variation of uncemented and hybrid implants could be a possible confounder as traditional teaching has been that cemented or hybrid THRs have a lesser total blood loss than uncemented THRs. However this is not universally accepted. Interestingly a retrospective study of THRs found that when comparing hybrid, cemented and uncemented THRs there was no evidence of differing blood requirements between cemented and uncemented (*25*).

A trend of increasing length of stay from Groups 1 to 3 could be expected due to the lower transfusion rates in Groups 1 and 2. However there was no significant difference between groups. This could be due to a minority of outliers including 2 patients who unfortunately stayed 26 days as a result of lower respiratory tract infections leading to multi-organ failure and ITU admission.

In our study the addition of topical TXA for Group 1 did not increase the frequency of thromboembolic events compared to intravenous TXA given alone. It should be noted though that our study was not of sufficient power to definitively detect differences in complication rates.

In summary this study found no increased benefit of giving a topical dose at closure in addition to an intravenous dose at induction. The body of evidence suggests that TXA given intravenously at induction or topically can reduce blood loss without increasing thromboembolic events. This study offers a preliminary review of regimes for the use of TXA in THR. However further work comparing intravenous, topical as well as oral regimes in a randomised controlled trial would be welcomed by the authors. Determining the most efficacious regime will enable the already proven benefits of decreased blood loss and financial savings to be maximised.

REFERENCES

1. **Benoni G, Fredin H, Knebel R, Nilsson P.** Blood conservation with tranexamic acid in total hip arthroplasty : a randomized, double-blind study in 40 primary operations. 2001 ; 72 : 442-8.
2. **Benoni G, Lethagen S, Nilsson P, Fredin H.** Tranexamic acid, given at the end of the operation, does not reduce postoperative blood loss in hip arthroplasty. 2000 ; 71 : 250-4.
3. **Blood Conservation in Elective Orthopaedic Surgery.** *British Orthopaedic Association* 2005.
4. **British National Formulary.** Arrival at http://www.bnf.org
5. **Cardone D, Klein AA.** Perioperative blood conservation. 2009 ; 26 : 722-9.
6. **Chang RW, Pellisier JM, Hazen GB.** A cost-effectiveness analysis of total hip arthroplasty for osteoarthritis of the hip. *JAMA* 1996 ; 20 : 858-65.
7. **CRASH-2 trial collaborators** Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2) : a randomised, placebo-controlled trial. 2010 ; 376 : 23-32.
8. **Finalised Patient Reported Outcome Measures (PROMs) in England - April 2009 to March 2010.** Pre- and post-operative data : Experimental Statistics. Arrival at http://www.ic.nhs.uk/statistics-and-data-collections/hospital-care/patient-reported-outcome-measures-proms/finalised-patient-reported-outcome-measures-proms-in-england-april-2009-to-march-2010-pre-and-post-operative-data-experimental-statistics.
9. **Gilbody J, Dhotar HS, Perruccio AV, Davey JR.** Topical Tranexamic Acid Reduces Transfusion Rates in Total Hip and Knee Arthroplasty. *J Arthroplasty* 2013 ; S0883-5403 : 00649-9.
10. **Grosflam JM, Wright EA, Cleary PD, Katz JN.** Predictors of blood loss during total hip replacement surgery. *Arthritis Care Res* 1995 ; 8 : 167-173.
11. **Helm AT, Karski MT, Parsons SJ, Sampath JS, Bale RS.** A strategy for reducing blood-transfusion requirements in elective orthopaedic surgery. Audit of an algorithm for arthroplasty of the lower limb. 2003 ; 85 : 484-9.
12. **Hiippala S, Strid L, Wennerstrand M *et al.*** Tranexamic acid (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. 1995 ; 74 : 534-7.

13. **Irisson E, Hémon Y, Pauly V *et al.*** Tranexamic acid reduces blood loss and financial cost in primary total hip and knee replacement surgery. *Orthop Traumatol Surg Res* 2012 ; 98 : 477-83.
14. **Ker K, Edwards P, Perel P, Shakur H, Roberts I.** Effect of tranexamic acid on surgical bleeding : systematic review and cumulative meta-analysis. *BMJ* 2012 ; 17 ; 344 : e3054.
15. **Kumar A.** Perioperative management of anemia: limits of blood transfusion and alternatives to it. 2009 ; 76 Suppl 4 : S112-8.
16. **Lemaire R.** *J Bone Joint Surg Br* 2008 ; 90 : 1128-36.
17. **Malchau H, Garellick G, Eisler T, Karrholm J, Herberts P.** "Presidential guest address : the Swedish Hip Registry : increasing the sensitivity by patient outcome data." *Clin Orthop Relat Res* 2005 ; 441 : 19-29.
18. **Maniatis A, Hardy J, van der Linden P.** Alternatives to Blood Transfusion in Transfusion Medicine, 2nd Edition, Hoboken : Wiley-Blackwell, 2011 : 65.
19. **Murkin JM, Falter F, Granton J, *et al.*** High-dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients. *Anesth Analg* 2010 ; 110 : 350-353.
20. **NHS Blood and Transplant.** Arrival at http://www.nhsbt.nhs.uk/news/2011/newsrelease060911.html
21. **Niskanen RO, Korkala OL.** Tranexamic acid reduces blood loss in cemented hip arthroplasty : a randomized, double-blind study of 39 patients with osteoarthritis. 2005 ; 76 : 829-32.
22. **Orthoconsent.com**. Arrival at http://www.orthoconsent.com
23. **Sukeik M, Alshryda S, Haddad FS, Mason JM.** Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. 2011 ; 93 : 39-46.
24. **SPSS.** Arrival at http://www-01.ibm.com/software/analytics/spss/
25. **Trice ME, Walker RH, D'Lima DD, Morris BA, Colwell CW Jr.** Blood loss and transfusion rate in noncemented and cemented/hybrid total hip arthroplasty. Is there a difference ? A comparison of 25 matched pairs. 1999 ; 22 : s141-4.
26. **Venous thromboembolic diseases.** NICE Clinical Guideline CG144 (June 2012). Arrival at http://guidance.nice.org.uk/CG144
27. **Wong J, Abrishami A, El Beheiry H et al *et al.*** Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty : a randomized, controlled trial. 2010 ; 92 : 2503-13.