Eur J Orthop Surg Traumatol (2014) 24:379–384
DOI 10.1007/s00590-013-1206-1

ORIGINAL ARTICLE

Can local administration of tranexamic acid during total knee arthroplasty reduce blood loss and transfusion requirements in the absence of surgical drains?

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Received: 6 December 2012 / Accepted: 1 March 2013 / Published online: 14 March 2013

Abstract Blood transfusions are frequently required following total knee arthroplasty. Tranexamic acid (TXA) inhibits fibrinolysis and has been shown to reduce blood loss and transfusion requirements when delivered intravenously. Topical and intra-articular applications directly target bleeding sites whilst limiting systemic uptake and theoretically reduce the risk of thromboembolic complications. However, in the absence of surgical drains, which increase post-operative blood loss, the efficacy of these techniques for reducing transfusion requirements is unclear. Our aim was to determine if locally administered tranexamic acid during total knee arthroplasty could reduce both blood loss and transfusion requirements in the absence of surgical drains. A retrospective review of 248 patients treated with primary unilateral cemented total knee arthroplasty was performed. Patients treated after January 2011 received topical and intra-articular tranexamic acid at the end of the procedure ($n = 136$). A second group of consecutive patients treated before this period acted as historical controls ($n = 112$). Patient groups were equivalent in terms of age, gender and ASA grade. There was a significant reduction in mean blood loss of 246 ml between the groups ($p < 0.01$). In addition, the requirement for post-operative allogenic blood transfusion was significantly reduced from 15.5 to 5.4 % after introduction of the tranexamic acid regimen ($p = 0.02$). This is the largest patient cohort reviewed to measure the efficacy of locally administered tranexamic acid during total knee arthroplasty and demonstrates that this is an effective technique for reducing both blood loss and transfusion requirements in the absence of surgical drains.

Keywords Arthroplasty · Knee · Tranexamic acid · Transfusion

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Introduction

Reports of mean post-operative blood losses following total knee arthroplasty range between 700 and 1,500 ml [1, 2]. Hyperfibrinolysis and post-operative bleeding are exacerbated by the use of a tourniquet, which causes release of tissue plasminogen activator from the vascular endothelium. [3, 4]. Blood transfusions are frequently required with the risks of incompatibility reactions, immunosuppression and disease transmission [5]. Techniques such as autologous blood donation, autologous drain transfusion and acute normovolaemic haemodilution have been utilised to reduce allogenic blood transfusion rates. However, their application is limited by their clinical and financial efficacy [5, 6].

Tranexamic acid (TXA) is a synthetic derivative of lysine that competitively blocks lysine binding sites on plasminogen, preventing the degradation of fibrin. Several meta-analyses have found that the intravenous use of this agent peri-operatively results in a reduction in both blood loss and the requirement for blood transfusion following total knee arthroplasty [7–9]. However, systemic administration has raised concerns regarding the theoretical increased risks of thromboembolic complications thereby limiting its appeal. In addition, most studies evaluating the benefit of TXA following total knee arthroplasty have involved the use of intra-articular drains [10–17], which

have been shown to increase post-operative blood transfusion requirements [18, 19]. Topical administration has the advantage of directly targeting surgically activated fibrinolysis [3, 4, 17], whilst limiting systemic absorption and avoiding intravenous dosing calculations and infusion regimes [1].

In 2010, Wong et al. [1] published the only study to have evaluated the benefit of topical TXA administration without concomitant use of a surgical drain. In this study, a wound irrigation technique was utilised and was shown to reduce blood loss but not transfusion requirements. Intra-articular administration has also been utilised as a method for local tranexamic acid delivery. Ishida et al. [16] demonstrated a reduction in blood loss following total knee arthroplasty using this technique. However, this study failed to demonstrate a significant reduction in transfusion requirements.

We performed a retrospective analysis of patients undergoing primary unilateral knee arthroplasty to determine if locally administered tranexamic acid can reduce both blood loss and transfusion requirements in the absence of surgical drains.

Materials and methods

All patients included underwent elective unilateral cemented total knee arthroplasty (P.F.C.® Sigma® Depuy Synthes) by or under the direct supervision of the senior author between February 2009 and May 2012. In view of the growing of evidence supporting the use of tranexamic acid in knee arthroplasty, and in particular the reported efficacy of topical regimens, the senior author adopted a technique of local TXA administration in November 2010. The patient cohort was therefore divided into two groups, those treated before November 2010 (Group 1) and those treated from January 2011 (Group 2) and the estimated blood loss and transfusion requirements compared.

Patient data were collected from the operative database system (Theatre Manager, Bluespeir International, UK) regarding age, gender, ASA grade, weight and height. All patients taking warfarin, acetylsalicylic acid and other anti-platelet agents had been advised to stop these drugs 5 days pre-operatively. Patients with evidence of abnormal clotting, thrombocytopenia or a history of venous thromboembolic disease were excluded from the analysis. The choice of either spinal or general anaesthesia was decided according to the preference of the anaesthetist. In all cases, limb exsanguination was performed and a pneumatic tourniquet inflated to 300 mm/hg. A medial para-patellar approach was utilised. All components were cemented, and the patellar articular surface replaced in every case. No surgical drains were used. The wound was infiltrated with 150 mls of 0.2 % ropivacaine and 0.1 % adrenaline solution prior to closure. Subcutaneous 3–0 monocryl was used for skin closure in all cases. The tourniquet was released after pressure dressings were applied. All patients received two post-operative intra-articular injections of 20 ml 0.75 % ropivacaine for analgesia, 8 and 16 h post-operatively via a wound catheter. Routine thromboprophylaxis was administered according to the local protocol with 5,000 units subcutaneous dalteparin once daily for 10 days with the first dose given 6 h after wound closure.

All patients in Group 2 received wound irrigation with approximately 80 mls of 10 mg/ml TXA-saline solution for a minimum of 5 min whilst the cement set as per the technique of Wong et al. [1]. The wound was subsequently washed with saline using pulsatile lavage, and once the capsule had been closed, a further 20 mls of 10 mg/ml TXA solution was injected into the joint cavity.

A maximum total dose of 1 g TXA was administered. Any thromboembolic complications (deep vein thrombosis, pulmonary embolus, cerebrovascular accident, myocardial infarction) were identified from follow-up questionnaires sent to all patients at 6 weeks post-operatively as per normal departmental practice.

Patient's Oxford knee scores were obtained independently of the surgical team by the research department at the Elective Orthopaedic Centre (Epsom, Surrey, UK) both pre-operatively and at a minimum follow-up of 1 year. Two custom pathology database search programmes were used to collect all patient's peri-operative haemoglobin results up to 1 month post-operatively, together with records of all allogenic blood transfusion events.

Outcome measures

The minimum haemoglobin level between post-operative days one to five (Hb_{min} g/L) was compared with pre-operative baseline levels ($Hb_{initial}$ g/L). Total haemoglobin loss in grams ($HbGms_{loss}$ g) was estimated using the formula for total blood volume (ml) given by Nadler et al. [20] and the method of Good et al. [11] correcting for units of blood transfused ($HbGms_{trans}$-approximating 54 g Hb per unit [21]).

$$\text{Blood vol.}\,(\text{ml}) = (\text{A} \times \text{H}^3) + (\text{B} \times \text{W}) + \text{C}$$

$$\text{H} = \text{height}\,(\text{m}),\ \text{W} = \text{weight}\,(\text{Kg})$$

$$\text{Males}: \ \text{A} = 0.3669,\ \text{B} = 0.03219,\ \text{C} = 0.6041$$

$$\text{Females}: \ \text{A} = 0.3561,\ \text{B} = 0.03308,\ \text{C} = 0.1833$$

$$\text{HbGms}_{\text{loss}} = \text{Blood vol.} \times (\text{Hb}_{\text{initial}} - \text{Hb}_{\text{min}}) \times 0.001 + \text{HbGms}_{\text{trans}}$$

$$\text{Blood loss}\,(\text{mL}) = 1,000 \times \text{HbGms}_{\text{loss}}/\text{Hb}_{\text{initial}}$$

Patients receiving pre- and peri-operative blood transfusions due to pre-operative anaemia were included

in the analysis correcting the pre-operative haemoglobin levels accordingly. Rates of allogenic blood transfusions, the number of units transfused, thromboembolic events and changes in Oxford knee scores were compared between the groups. Indications for patient transfusion varied depending on the clinical picture but occurred in any patient with an absolute haemoglobin level of less than 8 mg/dL, or in patients with symptoms of anaemia or evidence of inadequate tissue oxygenation.

Statistical methods

Statistical analysis for continuous data was performed using either the students *t* test or Mann–Whitney U test depending on the normality of data distribution. Fisher's exact test was used to determine the significance of differences in anaesthetic technique and incidence of thromboembolic events. All other categorical data were analysed using Pearson's Chi-squared test. A p value of less than 0.05 was considered significant.

Results

A total of 248 patients underwent primary unilateral total knee arthroplasty during the study period. 112 patients were treated between February 2009 and October 2010 (Group 1), and 136 patients were treated between January 2011 and May 2012 (Group 2) receiving TXA at the end of the surgical procedure. No significant differences were identified between the groups regarding age ($p = 0.87$), gender ($p = 0.16$) or ASA grade ($p = 0.28$) (Table 1). Patients in Group 2 had a greater body mass index (BMI) (30.4) on average than those in Group 1 (28.9) ($p = 0.02$). There was no significant difference in the proportions of patients receiving spinal or general anaesthesia for Group 1 (96.4 % Spinal) compared with Group 2 (93.4 % Spinal) ($p = 0.39$).

Table 1 Baseline demographics and haemoglobin levels

	Group 1 ($n = 112$)	Group 2 ($n = 136$)
Age[a]	72.3 ± 9.5	72.1 ± 7.9
Gender (male/female)	51/61	50/86
ASA Grade 0-II/III-IV	101/11	118/18
Weight (Kg)[a]	79.6 ± 17.6	81.9 ± 15.0
Height (m)[a]	1.66 ± 0.11	1.64 ± 0.10
BMI[a]	28.9 ± 5.3	30.4 ± 4.7
Pre-op Hb (g/dL)[a]	13.4 ± 1.2	13.7 ± 1.2
Pre-op Oxford knee scores[a]	22.6 ± 8.8	22.2 ± 8.0

Baseline patient demographics and haemoglobin levels

[a] Means ± standard deviations

The mean blood loss for Group 1 was 1,251 ml compared with 1,004 ml for Group 2 ($p < 0.01$) (Table 2). 15.5 % of patients in Group 1 received one or more blood transfusions compared with only 5.4 % in Group 2 ($p = 0.02$). The mean pre-transfusion haemoglobin level was 8.5 mg/dL for both Group 1 and Group 2 ($p = 0.90$). The median number of units transfused per patient was 2 in both groups.

Data regarding Oxford knee scores at one-year follow-up were available for 95 patients in Group 1 and 38 patients in Group 2 with a mean change between pre- and post-operative scores of 14.6 and 18.4, respectively (Table 2). However, this difference did not reach statistical significance ($p = 0.08$). 94.4 % of all patients responded to a 6-week follow-up questionnaire regarding thromboembolic events. The VTE incidence between the two groups was not significantly different ($p = 0.46$).

Discussion

The beneficial effect of TXA for the reduction of blood loss and transfusion requirement following total knee arthroplasty was first demonstrated by Benoni et al. [22] in 1995. Several randomised controlled trials and meta-analyses have since confirmed this effect [7–9]. However, the routine use of TXA has not been widely adopted, in part due to concerns regarding the theoretical increase in risk of thromboembolic complications. No studies to date have demonstrated an increased thromboembolic risk, although caution has been recommended in patients with pre-existing risk factors [9]. Nonetheless, alternative methods of TXA administration to limit systemic uptake have been introduced, including both topical wound irrigation and intra-articular injection techniques.

Our results demonstrate that a combined approach of topical and intra-articular TXA administration following capsular closure in patients undergoing total knee arthroplasty reduces hidden blood loss on average by 246 ml. Good et al. [11] have previously reported that TXA reduces only drain output but not hidden blood loss when given intravenously during total knee arthroplasty. However, the results of our study indicate to the contrary and are supported by other authors investigating this effect [1, 10, 16, 17].

Studies by both Ishida et al. [16] and Roy et al. [15] administered intra-articular TXA through the surgical drain at end of the procedure demonstrating a reduction in drain output and transfusion requirements. However, like many studies investigating the effect of TXA in total knee arthroplasty, their results may have been influenced by the

Table 2 Mean post-operative blood loss, transfusion and outcome measures

	Group 1 ($n = 112$)	Group 2 ($n = 136$)	p value
Minimum post-op Hb (g/dL)[a]	9.8 (9.6–10.0)	10.7 (10.5–10.9)	<0.01
Total blood loss (ml)[a]	1,250 (1,175–1,326)	1,004 (943–1,066)	<0.01
Pre-transfusion Hb (g/dL)[b]	8.5 ± 1.4	8.5 ± 1.0	0.90
Rate of blood transfusions	15 (15.5 %)	7 (5.4 %)	0.02
Increase in Oxford knee scores	14.9 (12.6–17.1)[c]	18.4 (15.7–21.1)[d]	0.08
DVT/PE	1/1 ($n = 107$)	2/3 ($n = 127$)	0.46

Mean post-operative blood loss, transfusion requirements, changes in Oxford knee scores and thromboembolic complications

[a] Mean ± 95 % CI

[b] Mean ± standard deviations

[c] Mean value and 95 % CI based on 95 patients

[d] Mean value and 95 % CI based on 38 patients

use of surgical drains, known to increase post-operative blood transfusion requirements [18, 19]. The use of drains may therefore has the potential to inflate the apparent efficacy of anti-fibrinolytic agents in total knee arthroplasty, and the results of such studies may not be applicable to the patient cohort in which surgical drains are not used.

To our knowledge, only two studies have previously evaluated the benefit of TXA following total knee arthroplasty without the use of surgical drains [1, 23]. Sasanuma et al. [23] demonstrated a reduction in transfusion requirement comparing intravenous TXA with placebo controls. However, the authors report that this benefit was not significantly different to patients in whom a surgical drain was used. Wong et al. [1] also demonstrated the benefit of TXA for reducing post-operative blood loss without concomitant use of a surgical drain. Their technique of topical application immediately prior to wound closure also reduced systemic serum TXA concentrations by approximately 70 % when compared with the intravenous route. This method may therefore enable direct targeting of bleeding sites whilst also reducing potential systemic thromboembolic risks.

The only other study to investigate topical TXA administration compared this technique with different intravenous regimens [17]. Maniar et al. [17] demonstrated a significant reduction in post-operative blood loss. However, in this study, patients were treated with surgical drains, and no significant differences in post-operative transfusion rates were observed.

In contrast to Wong et al., our results demonstrated a significant reduction in post-operative transfusion requirement with only 5.4 % of patients receiving TXA (Group 2) requiring a blood transfusion, compared with 15.5 % for patients not receiving TXA (Group 1). There was no significant difference in pre-transfusion haemoglobin levels between the groups indicating that the decision thresholds for post-operative transfusion had not changed during the period analysed. It is important to recognise that although Wong et al. [1] and Maniar et al. [17] were unable to demonstrate any benefit of topical TXA in reducing allogenic blood transfusions, a trend towards a reduction in transfusion requirement was observed. Therefore, failure to identify any benefit in this regard may be a reflection of small sample group sizes and limited study power rather than a genuine lack of effect.

Several studies have attempted to compare different regimes of TXA administration in terms of route, timing and duration of treatment. However, despite significant differences in blood loss and transfusion requirements compared with placebo controls, the evidence supporting one TXA regimen over another has been less clear. Maniar et al. did not demonstrate any significant differences between a topical TXA regimen and various intravenous TXA regimens [17]. Similarly, Zohar et al. [14], comparing oral and intravenous TXA regimens, was unable to identify any significant differences. It is possible that again owing to small sample group sizes in these studies, true differences in regimen benefits may have been missed. Regardless, it is clear that locally administered TXA is an effective method for reducing both post-operative blood loss and transfusion requirement.

There were no significant differences in patient outcomes in terms of Oxford knee scores or incidence of thromboembolic complications between the two groups analysed. Indeed, although there are concerns regarding an association between TXA administration and thromboembolic risk, currently there is no evidence to support this. Alshryda et al. [8] have estimated that in order to identify a 1 % increase in thromboembolic risk, a study enrolling more than 5,000 patients would be required. Nonetheless, local administration has been shown to reduce systemic TXA uptake [1],

Table 3 Comparison of costs with and without TXA administration

	Transfusion cost per patient without TXA	Transfusion cost per patient with TXA	Estimated saving per patient
Good et al. [11]	£67.08	£11.93	£55.15
Ralley et al. [24][a]	£59.31	£22.93	£36.38
Lozano et al. [25][b]	£109.43	£24.89	£84.54
Craik et al.	£49.08	£16.25	£32.84

Published data and study results comparing the cost of blood transfusions per patient with and without a tranexamic acid administration regimen

[a] 2009 Exchange rate £1 per $1.787 (Canadian Dollars)

[b] 2008 Exchange rate £1 per €1.361

and therefore, this technique may allay the concerns of some surgeons regarding potential thromboembolic risks.

Several studies have evaluated the cost efficacy of TXA. Correcting for exchange rates at the time of publication, and excluding the costs of adverse effects to allogenic transfusion, estimates of savings range between £36 and £84 per patient [11, 24, 25]. The cost for one unit of allogenic blood is £125 at our hospital, compared with £3.71 for 1 g of TXA. On average, 1,240 primary knee arthoplasties are performed per year at our institution, and adopting this technique could save in excess of £40,000 (saving approximately £32.84 per patient) and protect 125 patients from the risks associated with allogenic blood transfusion per annum (Table 3). These figures exclude associated transfusion administration and complication costs, and therefore, the true values are likely to be much greater.

This audit has several limitations. Firstly, although the two groups are equivalent in terms of age, gender and ASA grade, we cannot guarantee the absence of other unidentified confounding factors. In addition, the retrospective audit design and lack of patient randomisation or blinding of the operating surgeon to tranexamic acid administration at the time of treatment could be potential sources of bias. Blood loss has also been estimated using the patients weight, height and changes in haemoglobin level, and therefore, the volumes calculated may be affected by perioperative intra-venous fluid administration. Nonetheless, this is the largest patient cohort reviewed to measure the efficacy of tranexamic acid in total knee arthroplasty, and therefore, the impact of variations in post-operative fluid management may be limited. In addition, our results relate to a single surgeon's practice, and therefore, one would expect that with a consistent surgical technique, the potential for subsequent blood loss would be comparable between the groups.

Conclusion

A combination of both topical and intra-articular administration of 1 g tranexamic acid is effective in reducing post-operative blood loss and transfusion requirements following total knee arthroplasty. This technique is also safe and highly cost-effective.

Acknowledgments Lydia Jones—Consultant Haematologist, Epsom General Hospital; Joan Desborough—Consultant Anaesthetist, Epsom General Hospital; Paul Bassett—Medial Statistician, Statsconsultancy Ltd; Zoe Beer—Elective Orthopaedic Centre Research Department; Gaye Hadfield—Elective Orthopaedic Centre Research Department; Katherine Scouler—Epsom General Hospital Blood Transfusion Department; Simon Easton—Pathology IT Manager, Epsom General Hospital.

Conflict of interest The authors declare that they have no conflict of interest.

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