Intravenous versus Intra-Articular Tranexamic Acid in Primary Total Hip Arthroplasty: A Prospective Randomised Double Blinded Non-Inferiority Trial

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Abstract

Background: Tranexamic acid (TXA) has been shown to be effective in reducing post-operative blood loss after hip replacement surgery. Clinicians can be reluctant to administer intravenous (IV) TXA to high risk patients and intra-articular (IA) administration has been proposed as an alternative mode of delivery. This study was conducted to compare the efficacy of IV versus IA administration of TXA.

Methods: This prospective, double blinded, randomised non-inferiority trial, compared 69 patients undergoing primary total hip arthroplasty (THA) who received either 3 doses of 15mg/kg of IV TXA or 3 g of IA TXA after capsular closure. The primary outcomes were change in Hb and the rate of blood transfusion. The secondary outcome was the rate of VTE.

Results: The mean haemoglobin level change from pre-operative to day 1 post-operative for the IV group was 26.7g/L and for IA group was 27.3g/L. No statistically significant difference was detected between the two groups ($p=0.82$). No patients required a transfusion or developed a VTE.

Conclusions: IA administration of TXA can be equally effective as IV in the reduction of blood loss and the prevention of post-operative anaemia in primary THA.

Background

Tranexamic acid (TXA), an antifibrinolytic agent that has been in clinical use since the 1960s, has become commonly used in orthopaedic surgery over the last decade, often as a component of a multimodal blood loss management strategy. Post operative anaemia is common following hip arthroplasty surgery with some studies reporting transfusion rates of 24.4% prior to the introduction of TXA [1]. Allogeneic transfusions are associated with complications including immunosuppression, perioperative infections and transfusion-related reactions [2,3]. Among patients with acute coronary syndromes, there is an increased risk of myocardial infarction and death [4,5]. Furthermore, anaemia may slow a patient's postoperative rehabilitation and prolong the length of hospital stay with additional costs [6].

Intravenous (IV) administration of TXA during arthroplasty surgery has been shown to decrease peri-operative blood loss, thereby reducing transfusion rates [7-10]. The decreased transfusion requirements and length of stay is cost effective and the routine use of TXA is recommended [11,12].

Keywords: Tranexamic Acid, Hip Arthroplasty, Intravenous, Intra-Articular, Topical, Blood Loss
Level of Evidence: II

The proposed advantages of a single dose IA (intra-articular) TXA administration include targeted therapeutic delivery with lower plasma concentration of TXA [13] potentially mitigating the risk of systemic adverse events and eliminating the requirement for repeated post-operative IV administration. Common medical conditions such as previous venous thromboembolism, renal impairment, cerebrovascular and myocardial disease preclude universal administration of IV TXA despite no evidence of risk to these patients [14]. This population with medical co-morbidities would benefit from the prevention of post-operative anaemia.

IA administration of TXA has been compared to IV use in total hip arthroplasty with variable results [12,15,16]. North et al and Xie et al observed that IA was not as effective as IV administration at reducing post-operative haemoglobin drop [12,16]. However, all 3 studies observed equal transfusion rates amongst the IV and IA cohorts [15]. All three studies used only a single dose of IV TXA. It is standard at our institution to give 3 doses at 8 hourly intervals, a multi-dosing approach which has been associated with improved effectiveness [7]. Given the uncertainty in the literature, this study aims to confirm if IA can be an effective and equal substitute for IV multi-dose administration.

The purpose of this prospective, randomised non-inferiority trial was to compare the efficacy of intravenous (IV) versus intra-articular (IA) administration of TXA in patients undergoing primary total hip arthroplasty by comparing the post-operative haemoglobin (Hb) change and transfusion requirement.

Materials & Methods

Patients

The study design was a prospective double blinded, randomised non-inferiority trial. Between June 2016 and October 2017, patients were recruited from Wakefield Orthopaedic Clinic, a metropolitan private hospital. All patients undergoing primary total hip arthroplasty for osteoarthritis were included. Independent Ethics Board approval was granted from the Calvary Health Care Adelaide Human Research Ethics Committee (Ref no. 16-CHREC-F001) and the trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12616000907448).

Exclusion criteria included those with acquired defective colour vision, previous subarachnoid haemorrhage, active intravascular clotting, or hypersensitivity to TXA (which are the product specified contra-indications), as well as those with a hypercoagulable tendency (history of

arterial or venous thromboembolic disease such as CVA, DVT or PE, or fibrinolytic disorder requiring anti-fibrinolytic treatment), coagulopathy (PLT <150, INR >1.4) or cognitive impairment. Patients on continued anticoagulation agents were excluded to eliminate this confounding factor. Patients with renal impairment (creatinine >120mmol/L) were also excluded to keep the administered dose the same for all patients. The exclusion criteria was based on previous similar studies investigating the effectiveness of TXA in order to produce a comparable cohort.

A consistent blood management protocol was used. The protocol included pre-operative Hb assessment and optimization if required. All patients were advised to cease anti-inflammatory medications and health supplements ten days prior to surgery. Spinal anaesthetic was used with normotensive or hypotensive control. Normothermia was maintained. TXA was administered to all patients at 15mg/kg approximated to 1g aliquots which translated to a total dose of 3g for all patients. Post operative Hb was measured on the morning the day after surgery. We adhered to an evidence-based transfusion protocol, whereby patients were transfused if they had a Hb <70g/L, or Hb <100 g/L with symptoms of cardiovascular or cerebrovascular ischemia [17,18].

All surgeries were performed by 2 experienced arthroplasty surgeons using their usual surgical technique and implant. Drains were not used. VTE prophylaxis included bilateral pneumatic calf compression devices and 100mg Aspirin commencing day 1 post-operative for a minimum of four weeks. Median length of stay was 4 days for both surgeons. Both surgeons had similar surgical techniques and post-operative protocols.

Randomisation and Administration

Allocation was determined using an electronic randomizer in blocks of 20 and envelopes were then numbered consecutively. Envelopes were opened by the anaesthetist in the operating theatre who prepared the treatment and placebo IV and IA solutions. Patients were assigned to one of two groups; the IV group received IV TXA 15mg/kg 8 hourly for three doses commencing at induction of anaesthesia plus a placebo of 40ml normal saline injected intra-articular in a single sterile syringe. The IA group received 3g of TXA mixed with 40ml normal saline in a single sterile syringe that was administered IA plus a placebo of similar volume IV normal saline. IA application was performed by injecting the 40mL solution intra-articular after capsular closure. The second and third doses of IV solution (TXA or saline) was prescribed by the anaesthetist and administered by the ward nurses. The surgeon and patient remained blinded throughout this process.

Outcomes

The primary outcome was the Hb change comparing preoperative Hb and day 1 post-operative Hb. Secondary outcomes were the rate of transfusion and the incidence of inpatient venous thromboembolism. A restrictive investigation protocol was routine practice and patients were investigated with limb venous ultrasonography if they demonstrated clinical symptoms and signs of VTE.

Statistical Analysis

Sample size was calculated using a two-sample means test, setting a non-inferiority margin for Hb change of 8g/L with a standard deviation of 12.6g/L. These parameters have been used by others [19,20]. In order to achieve 90% power at the 0.05 level of significance, 32 patients per study arm were required.

Unadjusted and adjusted linear regression models were performed to detect a statistically significantly different (P value <0.05) change in Hb. Fisher's Exact Test was used to find an association between TXA treatment group and transfusion requirement.

Results

Patient Cohort

Of the 86 patients deemed eligible, 13 patients were excluded and the remaining 73 patients were randomised to either IV or IA application (Figure 1). The final analysis consisted of 35 patients in the IV and 34 patients in the IA treatment arm.

The patient demographics and surgical parameters are listed in Table 1. The two cohorts were similar. The average age was 67.6 years. The majority of hip arthroplasties were uncemented, performed via a posterior approach.

Haemoglobin change

There was a mean Hb drop of 26.7g/L for the IV group and 27.3 g/L for the IA group (Table 2). An unadjusted linear regression of Hb change versus TXA treatment group, adjusting for Hb pre-surgery, did not show a statistically significant difference in Hb change between the 2 cohorts (P value=0.7665). An adjusted linear regression of Hb change versus TXA treatment group, adjusting for Hb pre-surgery, age, BMI, surgeon, approach, stem fixation and operation time was performed. Adjusting for these variables, there was no statistically significant difference

Figure 1. Participant flow

Table 1: Baseline Characteristics of Study Population

	IV (n= 35)	IA (n=34)	Total (n=69)
Patient Demographics			
Male	14	14	28 (41%)
Female	21	20	41 (59%)
Average age	70.0 ± 10.2	65.2 ± 10.5	67.6 ± 10.5
BMI	27.7 ±	29.1 ± 6.1	28.4 ± 5.5
ASA			
1	2	3	5 (7%)
2	20	16	36 (52%)
3	13	14	27 (41%)
4	0	1	1 (1%)
Surgical Parameters			
Surgeon 1	25	26	51 (74%)
Surgeon 2	10	8	18 (26%)
Posterior	33	30	63 (91%)
Anterior	2	4	6 (9%)
Uncemented	30	30	60 (87%)
Cemented	5	4	9 (13%)
Average op time			
(mins)	72.6 ± 18.4	74.5 ± 15.1	73.5 ± 16.8

Table 2: Outcomes of the Two Groups – Mean and Standard deviations

	IV (n=35)	IA (n=34)	P value
Pre-op Hb (g/L)	138.1 ± 10.5	137.6 ± 12.0	0.86
Post-op Hb (g/L)	111.5 ± 13.3	110.3 ± 14.7	0.73
Hb drop (g/L)	26.7 ± 12.2	27.3 ± 11.8	0.82
Transfused	0	0	0.00
DVT	0	0	0.00

in Hb change between the two treatment groups (P value=0.6298).

Transfusion and Venous thromboembolism rate

None of the patients in this study required a transfusion. Additionally, none of the patients developed an inpatient venous thromboembolism.

Discussion

We found that IA TXA was equally effective as IV administration in total hip arthroplasty in restricting post-operative blood loss as measured by drop in Hb. In this study a single 3g dose of IA TXA administered during surgery was not inferior to the three separate 15mg/kg doses of IV TXA. There was no clinically significant difference in the post-operative haemoglobin decrease, post-operative haemoglobin value or transfusion requirements.

Strategies to limit blood loss associated with arthroplasty surgery are increasingly used by arthroplasty surgeons and TXA is commonly used for coagulation cascade manipulation [1]. Multiple studies have been published with universal demonstration of its clinical efficacy, however the ideal route and timing of administration are less clear. IA administration is a potential option to mitigate systemic TXA effects. Wong et al found the plasma concentration of TXA after topical application was 70% less than the same dose of TXA administered by IV injection [13]. While there is good evidence to support the use of TXA in all patients, with no evidence of adverse effects, there is some reluctance for routine use of IV TXA amongst clinicians less familiar with the data due to theoretical concerns of a prothrombotic effect.

No clinical studies, meta-analyses or registry studies have demonstrated an association with an increased risk of VTE or arterial thrombosis [21] but many clinical trials have excluded patients considered to be of increased risk. Whilst there is no data to suggest an increased risk with universal TXA use [14], the converse is less clear: i.e. whether there is an increased risk of medical complications by withholding TXA in the 'high risk' patient group. Two recent clinical studies addressing the use of TXA in the 'high risk' group have not demonstrated an increased complication rate [22,23]. IV TXA was not associated with an increased risk of VTE in patients with a history of VTE [22]. Further, a Danish registry study has demonstrated not only a reduced risk of arterial thrombosis (myocardial infarction and ischaemic stroke), but reduced rate of all-cause mortality, if TXA is still administered in these patients [24].

Despite the paucity of evidence of harm, Patel et al [25] observed that TXA was considered a contraindication in over 25% of patients. Further, Ho et al [26] observed 6% of patients had a failure of a universal administration protocol citing concern from clinical staff (such as anaesthesia) and were denied TXA treatment.

There are limited prospective studies assessing the efficacy of intra-articular TXA in hip arthroplasty patients and comparison of these is difficult due to the variety of doses and dosing regimens used. König et al and Wei and Wei used three separate 1g injections instilled after acetabular preparation, after femoral broaching and before/after fascial closure [15,27]. Wei and Wei reported 3g IA was equally effective as the same dose IV at reducing total blood loss (958 ml [IV] vs 963ml [IA]) and the transfusion rate (5.94% [IV], 5.88% [IA]), but did not report on the effect on Hb change [15]. North et al used a lower dose of 2g TXA, and bathed the wound with TXA after component placement and observed an inferior blood sparing effect when compared to the IV group (Hb drop 3.1g/dL [IV] vs 3.5g/dL [IA], transfusion rate 11% [IV] vs 18% [IA] [12]. Xie et al observed a significantly smaller Hb change in a 1.5g IV dose group compared to 3g IA group (2.98g/dL [IV] vs 3.36g/dL [IA]) [16]. They also showed a combination of 1g IV and 2g IA administration was more effective than either IA or IV in isolation (Hb drop 3.89g/dL [IV and IA]) [16]. Similarly, Yi et al found that a combination of IV and IA administration was more effective than IV delivery alone at reducing postoperative bleeding and the transfusion rate (16% [IV] vs 2% [IV and IA] [28].

This study found an overall smaller Hb change and transfusion rate across both treatment groups compared to previous studies which may be the result of the effectiveness of our strict blood management protocol. Unlike North et al and Xie et al, we found IA application was not inferior to IV in preventing post-operative anaemia.

This study design differs from others being a non-inferiority trial comparing a single 3g TXA IA injection following capsule closure (a contemporary dosage regime) to three 15mg/kg IV doses (the manufacturer recommended regime). This is also consistent with the method used in a study of knee arthroplasty patients (3g TXA IA compared to three divided IV doses) which also demonstrated no difference in blood loss [29,30].

We acknowledge the limitations of this study. This study was powered to detect a primary outcome of the day 1 postoperative fall of Hb level setting a non-inferiority margin of 8g/L that was validated with a post hoc analysis. The requirement for blood transfusion could not be studied due to the low frequency of this event (as anticipated with the inclusion of TXA and a contemporary blood manage-

ment protocol) [17]. Similarly we did not design the study to detect medical or surgical complications and we did not compare clinical outcomes. Our results on VTE rate are consistent with previously published data; it is a relatively uncommon event and difficult to demonstrate a statistically significant association with any route of TXA administration.

Conclusion

This study shows IA administration is an effective alternative to IV administration for TXA. IA administration may have a particular place for patients where there are concerns about possible systemic side-effects from IV use.

Acknowledgements

We thank Christine Schultz for assisting with data collection and logistics and Suzanne Edwards, Data Management and Analysis Centre at the University of Adelaide, for her help with the statistical analysis of the collected data.

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SUBMISSION HISTORY

Submitted: July 22, 2020
 Reviewed: August 8, 2020
 Revised November 10, 2020
 Accepted: December 4, 2020
 Published: January 30, 2021

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AUTHOR DISCLOSURES

- The authors certify that no benefits or funds were received in direct or indirect support of this article.

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