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Transfusion rates with intravenous tranexamic acid in total hip arthroplasty performed using the direct anterior approach

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**ABSTRACT**

**Introduction** Tranexamic acid (TXA) has been shown to reduce blood loss and transfusion requirements in patients undergoing total hip arthroplasty (THA). Most studies have focused on TXA in THA performed using a posterior approach (PA) or lateral approach. The aim of this study was to analyse the efficacy of TXA in patients undergoing THA using the direct anterior approach (DAA).

**Patients and Methods** Using our institutional database, a retrospective analysis was conducted on consecutive primary THA performed for osteoarthritis to determine transfusion rates in patients undergoing THA with the DAA with and without TXA..

**Results** 146 consecutive THA were performed using DAA: 83 (56.8%) patients had TXA and 63 (43.2%) did not have TXA. Among patients who had TXA, 1 patient required a blood transfusion compared to 7 patients among those who did not have TXA (1.2% vs 11.12%, p = 0.02). The relative risk of 0.11 (95% CI 0.01, 0.86) indicates an 89% reduction in the risk of requiring blood transfusion with TXA administration compared to no TXA.

**Conclusion** TXA is effective in reducing blood transfusion requirements for patients undergoing DAA THA. This is the first study to demonstrate a significant reduction in blood transfusion requirements when directly analysing TXA use in DAA THA.

**KEYWORDS**

Total hip arthroplasty; Direct anterior approach; Tranexamic acid; Blood transfusion

**INTRODUCTION**

There is strong evidence to support the use of tranexamic acid (TXA) in total hip arthroplasty (THA) to reduce perioperative blood loss and blood transfusion rates.1–7 TXA is an anti-fibrinolytic agent that inhibits plasminogen activation to reduce blood clot degradation.8 It has not been associated with increased rates of deep vein thrombosis or venous thromboembolism and has few contraindications for use (1,9–11)

There have been several randomised controlled trials that have compared TXA to placebo in THA and found significant reductions in blood loss and postoperative

blood transfusion requirements (2–4,7,12). Sukeik et al.1 found the use of TXA in THA has resulted in a 20% reduction in the proportion of patients requiring blood transfusion.

Allogenic blood transfusion post THA is costly, both from an economic and resource perspective. In Australia, the cost of a single unit of packed red blood cells is $AU401.13 Blood transfusion is also known to be associated with numerous adverse events including acute transfusion reactions, immunological reactions, transmission of infections, and transfusion-induced coagulopathy (14–16).

There is also evidence to suggest that patients who require blood transfusion post THA have greater morbidity, including higher rates of wound problems, respiratory infections, and increased length of hospital stay (LOS) (5,17–19).

THA can be performed through a variety of surgical approaches and in recent years the anterior approach has gained popularity. The anterior approach utilises intermuscular and inter-nervous planes,20,21 thereby avoiding dissection of muscle beds and possibly reducing local soft tissue trauma.22 Recent studies on blood loss and transfusion rates with regards to surgical approach for THA have not demonstrated consistent results (23).

At present, the vast majority of studies analysing the efficacy of TXA in THA have not independently evaluated the influence surgical approach has on its efficacy. In particular, there is little research looking into the efficacy of TXA in the direct anterior approach (DAA) to THA. The aim of our study, therefore, was to investigate the proportion of patients who had TXA compared to those who did not have TXA who required transfusion after DAA THA.

We hypothesised that intravenous TXA reduced transfusion requirements in patients undergoing DAA THA. Other measured outcomes included length of hospital stay

and reoperation for wound complications.

**PATIENTS AND METHODS**

**Study Sample**

Following ethics approval (University of Tasmania, H0016663), we performed a review of all consecutive primary THA operations performed at our institution between January 2011 and April 2017. TXA was variably used during this period before it became standard practice for all THA at our institution in 2017.

Eligibility criteria for the study included patients undergoing primary unilateral THA for osteoarthritis. Revision THA, THA performed for indications other than osteoarthritis, and simultaneous bilateral THA were excluded. Cases performed via the posterior approach were excludedfrom the analysis.

**Data Collection**

Data was extracted from our institution’s electronic medical record by standard form. Patient characteristics including age, gender, BMI, comorbidities, smoking status, the use of anticoagulant or anti-platelet medications and pre-operative haemoglobin were collected. At the time of operation, ASA score, operative side, operative diagnosis, surgical approach, and data pertaining to the use of TXA were recorded. Post-operative data included TXA administration, day one haemoglobin level, transfusion requirement and length of hospital stay. Documentation of return to the operating theatre for any reason within four weeks of the index operation was also recorded.

**Administration of TXA**

As the use of TXA was not standard protocol during the study period, surgeons administered it at their discretion. When administered, 1g of TXA was given intravenously at the start of the operation. Post-operative TXA was prescribed based on surgeon preference, and if used it was given in two further doses of 1g intravenously at both eight hours and 16 hours post commencement of surgery.

**Transfusion Protocol**

A standard transfusion protocol was followed at our institution. This had the following indications for transfusion of packed red blood cells: haemoglobin less than 70g/dL; haemoglobin 70-100g/dL during surgery associated with major blood loss or symptoms of impaired oxygen transport.

**Outcomes**

The primary outcome was post-operative *blood transfusion rate*, determined as the percentage of patients within each analysis group who required one or more units of packed red blood cells (PRBC). The number of units of PRBC administered was also recorded. Other recorded outcomes included post-operative haemoglobin decrease compared to pre-operative values, length of hospital stay and reoperation for wound complications. *Haemoglobin decrease*was calculated by subtracting post-operative day 1 haemoglobin levels from pre-operative values, all of which were measured within three months pre-operatively. *Length of hospital stay* was measured as the number of days spent in hospital from operation (day 0) until discharge, with each night in hospital after the day of operation being recorded as one day. *Reoperation* was defined as return to the operating theatre within four weeks post-operatively for wound-related complications. Within each of the study groups, outcomes were analysed in cases performed without the use of TXA and compared to those performed with TXA.

**Statistical Analysis**

Stata 15.1 was used for data analysis (24). Means were investigated in the DAA without TXA compared to the DAA with TXA group using independent *t*-tests). Crosstabs were used to investigate proportions for categorical variables and chi-square tests were produced to test for significant differences across the two groups (or Fisher’s exact tests where appropriate). Post-operative outcomes were investigated among the TXA vs. no TXA groups. Tests were considered significant at p< 0.05 level. Relative risks with 95% confidence intervals were calculated for outcomes that were significantly different in those who had TXA compared to the without TXA group.

**RESULTS**

A total of 541 THA operations were performed within the study period. Following application of exclusion criteria, 205 posterior approach operations were excluded. The remaining 146 THA performed via the direct anterior approach were included in the analysis. These operations were performed by a total of five surgeons.

There were no significant differences in mean patient age, BMI, comorbidities or use of anticoagulants/anti-platelet agents between the with TXA and without TXA groups (Table 1). There were also no significant differences in mean pre-op haemoglobin between the groups.

TXA was first used at our institution in August 2015. With no administration protocol, there was variability between surgeons first adopting TXA such that the use between this time and the end of the study period was intermittent. In operations where TXA was given, 56.8% also received post-operative TXA.

In the group without TXA, 7 of 63 patients (11.1%) required post-operative blood transfusion, compared to one of 83 (1.2%) when TXA was used (*p*= 0.02) (Table 2). The relative risk of requiring blood transfusion in those who had TXA was 0.11 (95% CI 0.01, 0.86).

There was a significantly greater reduction in mean haemoglobin level (pre-operative to one day post-operative) in those patients who did not have TXA (mean 37.9, SD 11.8) compared to those who did have TXA (mean 32.6, SD 11.4) (*t*(144)=2.74, *p*=0.007).There was no significant difference in hospital LOS when TXA was used compared to not used (3.9 vs 4.2 days, *t*(144)=1.03, *p*=0.31).

Investigation of differences in the mean number of packed red blood cell (PRBC) units and mean day 1 haemoglobin within each group was not possible as only one patient in the TXA group required a transfusion.

**DISCUSSION**

There is increasing evidence to suggest that TXA is effective in reducing blood transfusion rates in THA (1–7). Transfusion following THA is costly and may be a harbinger of increased morbidity and increased length of hospital stay (5,17–19).

The vast majority of studies analysing the efficacy of TXA in THA have involved operations performed by posterior or lateral surgical approaches. By contrast there is a paucity of evidence on the utility of TXA in the DAA. The aim of this study, therefore, was to investigate whether TXA reduced the rate of blood transfusion in patients undergoing DAA THA. Our study found that the use of TXA in DAA THA resulted in a significantly lower proportion of patients requiring transfusion. The relative risk of 0.11 indicates that patients who had TXA had an 89% reduced risk of

requiring blood transfusion compared to those who did not have TXA. In a randomised control trial, Fraval et al.(25) analysed 101 DAA THA in 50 patients that received TXA and 51 that did not. Although the authors demonstrated that blood transfusion rate was reduced in the TXA group, their finding was not statistically significant. Other studies have found the use of TXA in THA performed using other

approaches significantly reduces transfusion rates (2,4,5,26)

Our findings are in accordance with these studies. The transfusion rate of 1.2% when TXA was used is lower than that reported in other studies (2–4,27–29). Despite the small number of patients requiring a transfusion (7 in the without TXA group and 1 in the with TXA group), it is reassuring that there were no significant differences in the baseline characteristics of the with TXA versus without TXA groups. This provides reassurance that the main outcome (transfusion) was independently associated with TXA use. However, this requires further investigation

in a study with a large sample population in order to identify sufficient numbers of patients with the outcome of interest in each group, and to adjust for potential confounding variables.

A 2nd significant difference between the groups was in change in mean haemoglobin, with a reduction of 37.9 in the without TXA group compared to a reduction of 32.6 in the with TXA group. This reduction in haemoglobin in the

TXA group is higher than values reported in other studies (2,3,29,30).

Our study also found that there was no significant difference in mean LOS when TXA was used. Other studies have suggested that the use of TXA can reduce hospital LOS.31,32 The impact of TXA use on hospital LOS requires further exploration in a prospective randomised controlled trial. We found no significant differences in rates of patients returning to theatre for wound-related complications between groups, however these events occurred in low numbers making it difficult to draw valid

conclusions.

There are several limitations to our study. Its retrospective design makes it difficult to control for confounding factors and also makes it subject to selection bias. The DAA group that did not receive TXA, for example, had a significantly greater proportion of males and consequently higher mean preoperative haemoglobin levels, which may

have introduced bias when transfusion is considered postoperatively.

The timing of administration of TXA prior to skin incision was also not recorded which may have influenced results. It is also possible that hospital practices may have changed over time influencing the outcomes of more recent cases when TXA was commonly used. Finally, although larger than many other studies in this area, our

study sample size is relatively small and larger studies are equired to validate our findings.

**CONCLUSION**

We have provided evidence to support the use of TXA to reduce blood transfusion requirements in DAA THA. This s the 1st study to demonstrate a significant reduction in blood transfusion requirements when directly analysing intravenous TXA use in the anterior approach to THA. Further study with a prospective, randomised design that includes a large number of patients is required to validate this observation.

**REFERENCES**

1. Sukeik M, Alshruda S, Haddad F, et al. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. J Bone Joint Surg Br 2011; 93: 39–46.

2. Johansson T, Pettersson L and Lisander B. Tranexamic acid in total hip arthroplasty saves blood and money. Acta Orthopaedica 2005; 76: 314–319.

3. Rajesparan K, Biant L, Ahmad M, et al. The effect on an intravenous bolus of tranexamic acid on blood loss in total hip replacement. J Bone Joint Surg Br 2009; 91: 776–783.

4. Benoni G, Fredin H, Knebel R, et al. Blood conservation with tranexamic acid in total hip arthroplasty: a randomized, double-blind study in 40 primary operations. Acta Orthop Scand 2001; 72: 442–448.

5. Husted H, Holm G and Jacobsen S. Predictors of length of stay and patient satisfaction after hip and knee replacement surgery: fast-track experience in 712 patients. Acta Orthop 2008; 79: 168–173.

6. Ido K, Neo M, Asada Y, et al. Reduction of blood loss using tranexamic acid in total knee and hip arthroplasties. Arch Orthop Trauma Surg 2000; 120: 518–520.

7. Lemay E, Guay J, Côté C, et al. Tranexamic acid reduces the need for allogenic red blood cell transfusions in patients undergoing total hip replacement. Can J Anaesth 2004; 51: 31–37.

8. Henry D, Carless P, Moxey A, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2011; 16: CD001886.

9. Ho K and Ismail H. Use of intravenous tranexamic acid to reduce allogeneic blood transfusion in total hip and knee arthroplasty: a meta-analysis. Anaesth Intensive Care 2003; 31: 529–537.

10. Zhou X, Tao L, Li J, et al. Do we really need tranexamic acid in total hip arthroplasty? A meta-analysis of nineteen randomized controlled trials. Arch Orthop Trauma Surg 2013; 133: 1017–1027.

11. Gandhi R, Evans H, Mahomed S, et al. Tranexamic acid and the reduction of blood loss in total knee and hip arthroplasty: a meta-analysis. BMC Res Notes 2013; 6: 184.

12. Ekback G, Axelsson K, Ryttberg L, et al. Tranexamic acid reduces blood loss in total hip replacement surgery. Anesth Analg 2000; 91: 1124–1130.

13. Australian Red Cross Blood Service. 2016/17 blood bag cost indicators, <https://transfusion.com.au/bsib_july2016_3> (2017, accessed 03 July 2018).

14. Lemaire R. Strategies for blood management in orthopaedic and trauma surgery. J Bone Joint Surg Br 2008; 90: 1128–1136.

15. Cardone D and Klein AA. Perioperative blood conservation. Eur J Anaesthesiol 2009; 26: 722–729.

16. Fernandez MC, Gottlieb M and Menitove JE. Blood transfusion and postoperative infection in orthopedic patients. Transfusion 1992; 32: 318–322.

17. Weber EW, Slappendel R, Prins MH, et al. Perioperative blood transfusions and delayed wound healing after hip replacement surgery: effects on duration of hospitalization. Anesth Analg 2005; 100: 1416–1421.

18. Bierbaum B, Callaghan J, Galante J, et al. An analysis of blood management in patients having a total hip or knee arthroplasty. J Bone Joint Surg Am 1999; 81: 2–10.

19. Pedersen A, Mehnert F, Overgaard S, et al. Allogenic blood transfusion and prognosis following total hip replacement: a population-based follow up study. BMC Musculoskelet Disord 2009; 10: 167.

20. Kennon RE, Keggi JM, Wetmore RS, et al. Total hip arthroplasty through a minimally invasive anterior surgical approach. J Bone Joint Surg Am 2003; 85: 39–48.

21. Matta JM, Shahrdar C and Ferguson T. Single-incision anterior approach for total hip arthroplasty on an orthopaedic table. Clin Orthop Relat Res 2005; 441: 115–124.

22. Bremer AK, Kalberer F, Pfirrmann CW, et al. Soft-tissue changes in hip abductor muscles and tendons after total hip replacement: comparison between the direct anterior and the transgluteal approaches. J Bone Joint Surg Br 2011; 93: 886–889.

23. Meermans G, Konan S, Das R, et al. The direct anterior approach in total hip arthroplasty: a systematic review of the literature. Bone Joint J 2017; 99: 732–740.

24. StataCorp. Stata 15.1 Statistics/Data Analysis. College Station, TX: StataCorp LLC, 2017.

25. Fraval A, Effeney P, Fiddelaers L, et al. OBTAIN A: outcome benefits of tranexamic acid in hip arthroplasty. A randomized double-blinded controlled trial. J Arthroplasty 2017; 32: 1516–119.

26. Yamasaki S, Masuhara K and Fuji T. Tranexamic acid reduces postoperative blood loss in cementless total hip arthroplasty. J Bone Joint Surg Am 2005; 87: 766–770.

27. Wind TC, Barfield WR and Moskal JT. The effect of tranexamic acid on transfusion rate in primary total hip arthroplasty. J Arthroplasty 2014; 29: 387–389.

28. Wei W and Wei B. Comparison of topical and intravenous tranexamic acid on blood loss and transfusion rates in total hip arthroplasty. J Arthroplasty 2014; 29: 2113–2116.

29. North WT, Mehran N, Davis JJ, et al. Topical vs intravenous tranexamic acid in primary total hip arthroplasty: a double-blind, randomized controlled trial. J Arthroplasty 2016; 31: 1022–1026.

30. Cao G, Huang Q, Huang Z, et al. The efficacy and safety of multiple-dose oral tranexamic acid on blood loss following total hip arthroplasty: a randomized controlled trial. Int Orthop. Epub ahead of print 10 April 2018. DOI: 10.1007/s00264–018–3925–8.

31. Konig G, Hamlin BR and Waters JH. Topical tranexamic acid reduces blood loss and transfusion rates in total hip and total knee arthroplasty. J Arthroplasty 2013; 28: 1473–1476.

32. Ralley FE, Berta D, Binns V, et al. One intraoperative dose of tranexamic acid for patients having primary hip or knee arthroplasty. Clin Orthop Relat Res 2010; 468: 1905–1911.

**TABLES**

**Table 1:** Patient demographic characteristics and details

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **DAA without TXA (n=63)** | **DAA with TXA (n=83)** | **p-value** |
| **n (%) or mean (SD)** | **n (%) or mean (SD)** |  |
| Age (mean years) | 64.5 (12.4) | 68.0 (9.3) | 0.07 |
| Gender (%)MF | 37 (58.7)26 (41.3) | 39 (47.0)44 (53.0)  | 0.16 |
| BMI (mean) | 28.9 (5.2) | 30.7 (6.1) | 0.07 |
| Comorbidities (%)DiabetesIHDCOADMalignancy | 12 (19.0)7 (11.1)9 (14.3)4 (6.3) | 10 (12.0)13 (15.7)16 (19.3)12 (14.5) | 0.240.430.430.12 |
| Smokers (%) | 14 (22.2) | 24 (28.9) | 0.36 |
| ASA (%)1234 | 4 (6.3)32 (50.8)26 (41.3)1 (1.6) | 3 (3.6)45 (54.2)435 (42.2)0 (0) | 0.63 |
| Anticoagulants/antiplatelet (%)†NilAnti-plateletWarfarinNOAC | 47 (74.6)13 (20.6)4 (6.3)0 (0) | 64 (77.1)17 (20.5)1 (1.2)1 (1.2)  | 0.730.980.171.00 |
| Surgical side (%)RL | 34 (54.0)29 (46.0) | 46 (55.4)37 (44.6) | 0.26 |
| Pre-op Hb (mean) | 144.5 (14.5) | 140.8 (13.8) | 0.13 |
| Post-op TXA used (%) | - | 83 (56.8) | - |

† note: one patient was receiving treatment with more than one type of anticoagulant/antiplatelet

**Table 2:** Outcome measures

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **Anterior without TXA (n=63)** | **Anterior with TXA (n=83)** | **p-value** |
|  | **n (%) or mean (SD)** | **n (%) or mean (SD)** |  |
| Hb change (mean) | 37.9 (11.8) | 32.6 (11.4) | 0.007 |
| Return to theatre | 1 (1.6) | 1 (1.2) | 1.00 |
| LOS (mean days) | 4.2 (2.1) | 3.9 (1.9) | 0.31 |
| Transfusion | 7 (11.1) | 1 (1.2) | 0.02 |
| No. units PRBC (total) | 1.4 (0.5) | 1.0 (0.0) | \* |
| Day one Hb of those transfused (mean) | 86.4 (17.2) | 84.0 (0.0) | \* |

\*unable to calculate due to ≤2 patients in one sub-group