

Retrospective Cohort Study

Cost benefit analysis of the use of tranexamic acid in primary lower limb arthroplasty: A retrospective cohort study

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Abstract

AIM: To examine the cost benefit conferred by the perioperative administration of intravenous tranexamic acid (TXA) in lower limb arthroplasty.

METHODS: This study evaluates the use of TXA in 200 consecutive lower limb arthroplasties performed in a single surgeon series. The initial 100 patients (control group) underwent surgery without perioperative administration of TXA while the subsequent 100 patients (TXA group) all received 1 g TXA at the time of induction of anaesthesia. Pre- and post-operative haemoglobin, platelet count, haematocrit, the use of blood product post-operatively, length of stay were examined. A financial analysis of both groups was then undertaken.

RESULTS: The mean age of patients in both groups was 63 ± 13 years. There were no significant differences between groups in terms of gender ($P = 0.47$), proportion of total hip replacement to total knee replacement ($P = 0.25$) or pre-operative haemoglobin ($P = 0.43$). In the control group, the transfusion rate was 22%. In the TXA group, the transfusion rate dropped to 2% ($P < 0.001$). The mean post-operative haemoglobin was 10.82 ± 1.55

g/dL in the control group vs 11.33 ± 1.27 g/dL in the TXA group ($P = 0.01$). The total cost of transfused blood products was €11055 and €603 respectively. The mean length of stay in the control group was 6.53 ± 5.93 d vs 5.47 ± 4.26 d in the TXA group ($P = 0.15$) leading to an estimated financial saving of €114586. There was one pulmonary embolus in the control group and one deep venous thrombosis in the TXA group.

CONCLUSION: Intravenous TXA reduces blood loss in lower limb arthroplasty. This leads to lower transfusion rates, shorter length of stay in hospital and significant financial savings.

Key words: Arthroplasty; Hip; Knee; Tranexamic acid; Cost-benefit analysis

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Core tip: Worldwide the demand for lower limb arthroplasty procedures is increasing in the context of a diminishing economic climate. Total hip replacement and total knee replacement have traditionally been associated with large volume blood loss and the need for transfusion. Use of perioperative intravenous tranexamic acid (TXA) has been shown to be a cost effective measure, which reduces the need for transfusion. In this study, TXA was found to significantly reduce the number of patients requiring blood transfusion post-operatively, which has both clinical and economic significance.

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INTRODUCTION

An aging population globally, coupled with an expansion of the indications for total hip replacement (THR) and total knee replacement (TKR) has meant that the demand for lower limb arthroplasty is expected to increase in the future^[1]. Against this, the economic climate worldwide has resulted in reduced healthcare funding whilst expecting increased productivity from the orthopaedic surgeon.

Surgical procedures such as THR and TKR may require allogeneic blood transfusion post-operatively^[2,3]. Perioperative transfusion of blood products not only adds expense to the procedure, but also places the patient at increased risk of wound infection, immune suppression and allergy, transfusion-related lung injury and transmission of viral pathogens^[4-6]. Efforts have therefore focused on maintaining post-operative haemoglobin levels and minimizing the need for blood transfusions.

Such measures may reduce overall surgical morbidity and length of in-hospital admission, while minimizing the burden of additional blood tests.

Perioperative tranexamic acid (TXA) has emerged as a useful adjunctive agent in reducing blood loss and the need for blood transfusion in lower limb arthroplasty. TXA is a synthetic derivative of the amino acid lysine, and exerts antifibrinolytic activity by competitively binding the lysine sites on plasminogen. It is thought that this makes blood clots more resistant to degradation, thereby preventing further blood loss.

Several recent studies have reported favourable outcomes for intravenous administration of TXA in both THR and TKR^[7,8]. Studies examining oral and topical administration of TXA have also demonstrated promising results^[9,10].

The primary aim of this study was to evaluate whether the use of intravenous TXA in elective primary THR and TKR in a single surgeon series resulted in reduced transfusion rate of packed red blood cells. Secondary aims included examining the effect of TXA on post-operative haemoglobin, haematocrit and platelet count, length of stay in hospital, rate of deep venous thrombosis (DVT) and pulmonary embolism and to assess whether its use is cost effective.

MATERIALS AND METHODS

This study was a retrospective review of a cohort of 200 consecutive primary total knee and hip replacements performed by a single orthopaedic surgeon at a single institution between September 2013 and March 2015. The initial 100 joints were all performed without perioperative administration of TXA (control group). The subsequent 100 joints were all performed with additional perioperative TXA (TXA group). Revision joints, arthroplasties performed for fracture, and simultaneous bilateral procedures were excluded from the analysis.

Preoperative antibiotic prophylaxis followed local institutional protocol and consisted of intravenous cefuroxime, or alternatively teicoplanin if there was a history of cephalosporin or penicillin allergy. Vancomycin was utilised in select cases where there was a history of Methicillin Resistant *Staphylococcus Aureus* (MRSA) present. Preoperative antibiotics were administered at induction of anaesthesia, within one hour of skin incision.

All THRs were performed following a uniform technique using anterolateral approach to the joint. Both uncemented and cemented techniques were utilised as determined by the operating surgeon. All TKRs were performed through a medial parapatellar approach to the knee. One gram of TXA was administered parentally at the time of preoperative antibiotic administration in the TXA group. Intraoperative surgical drains were placed routinely in all joints, and removed on the first post-operative day. DVT prophylaxis consisted of thrombo-embolic deterrent stockings worn for 6 wk post-operatively and chemical prophylaxis consisting of

Table 1 Patient demographics

	Control group (n = 100)	TXA group (n = 100)	P value
Male/female	49/51	44/56	0.47
Age in years	62.57 ± 12.14	62.9 ± 12.6	0.86
THR/TKR	60/40	52/48	0.25
Pre-operative Hgb	13.61 ± 1.42	13.77 ± 1.41	0.43
Pre-operative Hct	0.41 ± 0.04	0.41 ± 0.04	0.32
Pre-operative platelets	253.01 ± 55.87	256.85 ± 69.75	0.67

THR: Total hip replacement; TKR: Total knee replacement; Hgb: Haemoglobin; Hct: Haematocrit; TXA: Tranexamic acid.

subcutaneous low molecular weight heparin for three days while an in-patient on the ward. Oral rivaroxaban was then commenced on the fourth post-operative day and continued until the end of the second week post-operatively for TKR, and the end of the fifth week post-operatively for THR, as per National Institute for Health and Care Excellence guidelines. On the second post-operative day, a full blood count was performed. The hospital transfusion protocol was initiated where a patient's haemoglobin was less than 8 g/dL or the patient was symptomatic with anaemia.

The following variables were ascertained following retrospective review of data: Age, gender, pre-operative and post-operative haemoglobin, pre-operative and post-operative haematocrit, pre-operative and post-operative platelet counts, transfusions of blood product, length of stay in days and thrombotic complications including DVT or pulmonary embolus.

In consultation with our hospital blood bank and purchasing department, the cost of a vial of 1 g of TXA was determined at €0.75 at our institution. One unit of packed red blood cells cost €201, and a single "bed-day used" (BDU) at our institution was valued at €1081. "Bed-days used" is a measure of hospital activity. A single BDU may be defined as a patient occupying an in-patient bed for all or part of one 24-h period. All figures were correct in respect of 2015.

Descriptive statistics were used to represent the data including proportions, means and standard deviations. Independent sample *t*-tests were used to assess continuous outputs, and two sample tests of proportion were used for binary outcomes. Statistical analysis was performed using Stata statistical software package, version 13 (StataCorp, Texas, United States). A value of $P < 0.05$ was considered to be statistically significant.

RESULTS

A total of 200 patients were included in this study. One hundred patients were included in the control group, who did not receive perioperative TXA. One hundred patients were included in the TXA group, who received TXA at the time of surgery. The average age of participants in both groups was 63 ± 13 years. Table 1 displays the baseline characteristics of patients. There were no statistically significant differences between the

Table 2 Differences between the groups following surgery

	Control group (n = 100)	TXA group (n = 100)	P value
Post-operative Hgb	10.82 ± 1.55	11.33 ± 1.27	0.01
Post-operative Hct	0.32 ± 0.05	0.34 ± 0.04	0.01
Post-operative platelets	204.32 ± 44.68	212.22 ± 52.49	0.25
Mean length of stay in hospital in days	6.53 ± 5.92	5.47 ± 4.26	0.15

Hgb: Haemoglobin; Hct: Haematocrit; TXA: Tranexamic acid.

groups across all variables at baseline. The control group ($n = 100$) comprised 40 TKR and 60 THR. The TXA group ($n = 100$) consisted of 48 TKR and 52 THR.

Primary outcome - proportion of patients requiring transfusion

There was a highly significant difference between the groups ($P < 0.001$) in the proportion of patients who required transfusion following surgery (22 patients in the control group vs 2 patients in the TXA group). However, the number of units of blood received by those individuals that required transfusion did not differ significantly between the groups ($P = 0.34$).

Secondary outcomes

Table 2 indicates that there were significant differences in haemoglobin and haematocrit levels between the groups following surgery ($P = 0.01$). Differences in post-operative platelet counts between the groups were not statistically different ($P = 0.25$). The mean length of stay in hospital, equivalent to BDUs, for the TXA group was 5.47 ± 4.26 d vs 6.53 ± 5.92 d for patients in the control group, although this difference was not statistically significant ($P = 0.15$).

In the control group, one patient developed multiple pulmonary emboli on the second post-operative day following TKR. In the TXA group, one patient developed a DVT in the peroneal vein one week post-operatively following TKR. Both patients recovered uneventfully.

Two patients in the TXA group required blood transfusion. One patient was a 72-year-old lady who underwent uneventful left TKR. Her pre-operative haemoglobin dropped from 10.4 g/dL to 7.4 g/dL. Although asymptomatic, she activated the transfusion protocol and was transfused two units of blood. The second patient transfused blood was a 78-year-old lady who underwent uneventful right THR. She had a background history of a myelodysplastic syndrome and B12 deficiency. She was transfused perioperatively on the advice of the haematology service.

Cost analysis

This study analyzed the financial benefit of TXA in terms of reduction in transfusion rate and reduction in length of stay in hospital. At a cost of €0.75 per 1 g of TXA, the total cost burden for use of TXA for 100 arthroplasties was calculated at €75. There was a 20% difference in

Table 3 Cost analysis

	Control group (<i>n</i> = 100)	TXA group (<i>n</i> = 100)	Difference
No. of patients transfused	22	2	20
No. of units transfused	55	3	52
Total cost of transfusion	€11055	€603	€10452
BDU	653	547	106
Total cost of BDU	€705893	€591307	€114586

BDU: Bed days used; TXA: Tranexamic acid.

transfusion rate between the control and TXA group, in favour of the latter. A total of 55 units of blood were transfused in the control group, in contrast to 3 units of blood in the TXA group. With a cost of €201 per unit of packed red cells, we therefore estimated the savings in terms of transfusion following TXA administration at €10452. When this figure was offset against the cost of TXA, we estimated overall savings of €10377, equivalent to €103.77 per patient.

On average, the control group remained in hospital for 6.53 d, equivalent to 653 BDUs in total for this cohort. The TXA group averaged 5.47 d, or 547 BDUs in total in hospital. It was therefore calculated that for 100 patients given TXA perioperatively, a total of 106 d were saved, at a cost of €1081 per BDU. On this basis, we estimated savings of €114586, or €1145.86 per patient. Table 3 summarizes our cost analysis.

DISCUSSION

Elective THR and TKR are among the most common surgical procedures that may lead to considerable blood loss requiring transfusion^[11,12]. Blood loss following lower limb arthroplasty remains a concern for orthopaedic surgeons, although the rates of significant blood loss have improved over the past quarter of a century^[13]. Despite this, blood losses of up to 1500 mL or higher following TKR have been reported^[14].

Orthopaedic surgeons have generally tended to minimize the use of allogeneic blood transfusion in THR and TKR on the basis of concerns for potentially serious complications including sepsis^[15], increased length of stay in hospital^[16], and mortality^[17]. Efforts have therefore focused on the use of pharmacological agents and other methods to minimize blood loss. Autologous transfusion^[18], cryotherapy^[19], hypotensive anaesthesia^[20], fibrin tissue adhesive^[21] and erythropoietin alpha^[22] have been studied in this regard.

The first reported successful use of TXA in knee arthroplasty by Benoni *et al.*^[23] in 1995 has led to increased interest in the use of antifibrinolytics in lower limb arthroplasty. A number of studies including retrospective and systematic reviews have supported the use of TXA in arthroplasty^[8,9,24,25]. This study examined the affect of perioperative intravenous TXA on blood loss in lower limb arthroplasty. A statistically significant difference ($P < 0.001$) was identified in the number of

patients transfused in the control group ($n = 22$) vs the TXA group ($n = 2$). This has clinical significance for the patient. With a drop in the number of patients transfused from 22% to 2%, patients were at reduced risk of recognized transfusion related complications. These figures are similar to the findings of Tuttle *et al.*^[10] and Gillette *et al.*^[26] who have reported transfusion rates post TXA of 17.5% vs 5.5% and 21.6% vs 8.9%, respectively.

Statistically significant differences were also found between pre-operative and post-operative haemoglobin ($P = 0.01$) and haematocrit ($P = 0.01$). Higher post-operative haemoglobin may reduce the number of laboratory tests performed during admission, while also reducing patient fatigue, hypotensive episodes, and length of stay in hospital^[26]. This may result in improved savings in overall cost.

Financial savings may also be made in terms of the cost of blood products, the expense of additional blood tests and laboratory labour, and the overall length of stay in hospital. The use of TXA in this series resulted in estimated savings of the cost of blood products of €104.52 per patient. Although the difference in length of stay in hospital between the control and TXA groups only trended towards statistical significance ($P = 0.15$), in financial terms there was a significant difference. Patients in the TXA group left hospital on average one day earlier than those in the control, with estimated savings of €1145.86 per patient. Larger studies may demonstrate statistical difference in terms of length of stay. Nevertheless, these findings support the growing body of evidence supporting the cost effectiveness of both intravenous and topical formulations of TXA^[10,26]. Recent evidence further suggests TXA is also safe in high-risk arthroplasty patients^[27].

There are potential limitations to this study. The findings of this study are inherently limited by its retrospective nature. Moreover, patients were not randomized into either the control or TXA groups, and this potentially introduces a selection bias. However, the 200 patients included in this analysis were consecutive, and underwent arthroplasty following a standardized technique, and in a single surgeon series. Additionally, no statistically significant differences in baseline variables between the groups were found.

In conclusion, the addition of perioperative intravenous TXA has been shown to reduce the rate of blood transfusion post-operatively while also generating considerable cost savings.

COMMENTS

Background

Hip and knee arthroplasty can potentially result in large volume blood loss, with the consequent need for transfusion of blood products. This carries increased risk to the patient, while also is a costly intervention. Antifibrinolytic agents such as tranexamic acid (TXA) were originally described in the trauma setting to prevent blood loss.

Research frontiers

There has been increased interest among in the use of TXA as a means of reducing blood loss in lower limb arthroplasty. Concerns remain, however, regarding possible increased risk of thromboembolic disease.

Innovations and breakthroughs

In a large single surgeon series of 200 consecutive lower limb arthroplasties, the perioperative use of TXA resulted in significant financial savings. There was no increased rate of thromboembolic disease following the use of TXA.

Applications

In a time of increasing demand being placed on diminishing health resources, measures that result in cost savings should be encouraged. However, care must be taken to ensure that the use of newer agents is safe to patients. Perioperative TXA appears to provide a favourable cost-benefit profile, while also being safe in lower limb arthroplasty. Further study is required to evaluate the thromboembolic risk of TXA in lower limb arthroplasty.

Terminology

TXA is an abbreviation for tranexamic acid, an antifibrinolytic agent. It stabilizes clot by competitively binding to plasminogen.

Peer-review

This is a good article.

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