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Original article

Perioperative intravenous tranexamic acid reduces blood transfusion in primary cementless total hip arthroplasty

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Summary. *Background and aim of the work:* Blood loss and transfusion requirements are common in total hip arthroplasty. Tranexamic acid is one of the most interesting options to reduce the need for blood transfusions in a variety of surgical settings. The aim of this study was to assess the efficacy of perioperative intravenous traxexamic acid regarding blood transfusion rate and volume of transfused blood without increasing adverse events after primary elective cementless total hip arthroplasty. *Methods:* A comparative retrospective study was conducted in 86 healthy patients who had undergone primary cementless total hip artrhoplasty for severe joint diseases at a single institution. All surgical procedures were performed through an anterolateral Watson-Jones approach with the patient in supine position. Forty patients (TXA group) received tranexamic acid 1g as an intravenous bolus 10 minutes before skin incision and a further 1 g, diluted in 250 mL of saline solution, in continuous perfusion at 30 mL/h, following commencement of the surgery. Forty-six patients (control group) did not receive TXA. Outcome measures included BT rate, volume of transfused blood, deep vein thrombosis and occurrence of pulmonary embolism. *Results:* BT rate was significantly less for the TXA group (37.5%) compared with the control group (65%; p=0.011). The mean blood volume transfused was also significantly less for the TXA group (240 mL) compared with the control group (450mL; p=0.009). No adverse events occurred in any group. *Conclusions:* Perioperative intravenous tranexamic acid is effective in reducing blood transfusion rate and volume of transfused blood, without increasing the risk of thromboembolic events in patients undergoing primary cementless total hip arthroplasty. (www.actabiomedica.it)

Key words: tranexamic acid, intravenous, total hip arthroplasty, blood transfusion, blood loss

Introduction

Total hip arthroplasty (THA) is a widely used surgical procedure to treat painful and disabling hip diseases (1). THA can result in substantial amounts of intra and postoperative blood loss, which often entails a need for blood transfusion (BT) (2,3). BTs are associated with several possible complications and constitute a remarkable economic burden on healthcare systems(4,5).

The "patient blood management" advocates a conservative and limited use of blood products, aimed at preventing the need for BTs and improving patient outcome (5). A variety of perioperative blood conservation strategies have been developed to minimize blood loss and avoid postoperative allogeneic BTs, including autologous BT, patient positioning, controlled hypotensive anesthesia, intraoperative blood salvage and reinfusion drains (6,7). Furthermore, over the last few years, pharmacologic tools such as fibrin, erythropoietin, iron supplementation and tranexamic acid (TXA) have become popular (8).

Surgical trauma leads to activation of plasminogen inducing a state of hyperfibrinolysis which increases surgical site bleeding (9). TXA, an artificial synthetic derivative of the amino acid lysine, competitively inhibits both plasminogen activation and plasmin activity thus decreasing fibrinolysis process and

clot break-down (10). Perioperative intravenous (IV) TXA administration has proved to be effective in reducing blood loss and BT requirements in a variety of settings, including THA (7,11-15).

The aim of this study was to evaluate the ability of perioperative IV TXA administration (1 g preoperative loading dose and an additional 1 g infusion over 8 hours) in reducing BT rate and volume of transfused blood without increasing adverse events when used in primary elective cementless THA.

Materials and methods

We conducted a retrospective comparative study on patients undergoing primary cementless THA for severe joint diseases between December 2012 and December 2015 using our institutional blood conservation database, to evaluate the effect of perioperative IV TXA administration. All surgical procedures were performed at a single institution by two senior surgeons (DR, AS). This database included patients prior to and after the addition of TXA to our hospital. TXA dosing regimen was based on our TXA hospital's protocol used safely in bleeding trauma patients (16).

All patients undergoing primary elective cementless THA who were identified in our blood conservation database during the study period were considered for inclusion in the study. Exclusion criteria consisted of patients having history of cardiovascular disease, previous cerebral accident, coagulopathy, kidney and/or liver disease, thromboembolism, known drug reaction to TXA and patients receiving anticoagulant therapy. A total of 25 patients were excluded basing on these criteria.

A cohort of 86 patients were included and reviewed (Table 1). Forty patients (TXA group) received IV TXA (Ugurol®, Rottapharm SpA, Milan, Italy). Forty-six patients (control group) did not receive TXA. All surgical procedures were performed through an anterolateral Watson-Jones approach with the patient in supine position under lumbar or general anesthesia (Table 2). Cementless stems and cups with ceramic-on-ceramic bearing (MicroPort Orthopedics Inc, Arlington, TN, USA) were used for all arthroplasties.

Patients in the TXA group received an intravenous bolus of 1 g of TXA 10 minutes before skin incision. A further 1 g, diluted in 250 mL of saline solution, was given in continuous perfusion at 30 mL/h, following commencement of the surgical procedure. All patients received preoperative antibiotic prophylaxis consisting of IV administration of 2 g dose of cefazolin (Cefamezin®, Pfizer srl, Latina, Italy; 1000mg/10ml) 30 minutes prior to the start of operation, followed by 1 g every 6 hours for 24 hours postoperatively. Deep vein thrombosis (DVT) prophylaxis was provided with subcutaneous enoxaparin sodium 4000 IU (Clexane®, Sanofi SpA, Milan, Italy) once daily for a minimum of 30 days, beginning on preoperative day. Active physiotherapy was instructed postoperatively in all cases.

Patients were classified by age, gender and surgical duration. The operative risk was assessed according to the American Society of Anesthesiologists (ASA) classification. Haemoglobin (Hb) levels were assessed preoperatively, at 6 hours, 24 hours, 48 hours, and 5 days postoperatively. Number of patients requiring BT, drop of Hb, volume of transfused blood and adverse effects were also recorded and compared. Patients with Hb levels <8 g/dL were considered for BT.

Outcome measures included BT rate, volume of transfused blood, deep vein thrombosis (DVT) and occurrence of pulmonary embolism (PE). DVT were screened for clinically with no investigations being performed unless there was clinical suspicion. After discharge, patients were checked up at 3 and 6 months postoperatively according to our routine follow-up.

Stata software (StataCorp LP, USA) was used for statistical analysis. Statistical differences between the TXA group and the control group were compared using χ^2 or Fisher exact test for categorical variables and Mann-Whitney U test for continuous variables, specifically. Results were expressed as the mean ± standard deviation. A value of $p<0.05$ was considered to be statistically significant.

Results

All the 86 patients were successfully reviewed (Tables 1, 2). No statistically significant differences were found between the two groups with regard to

Table 1. Patients' demographics and baseline characteristics

		TXA group	Control group	*p* value
N. of patients		40	46	NA
Gender	female/male	18/22	24/22	0.525
Age	years	65.2 ± 16.1	71.4 ± 9.1	0.215
ASA status	I/II/III/IV	4/36/0/0	3/43/0/0	0.749
Diagnosis	POA	26	30	0.983
	DDH	3	2	
	RA	3	2	
	FHN	7	12	
	AS	1	0	
Side	right/left	19/21	27/19	0.387
Operation time	minutes	115.25 ± 22.8	96.05 ± 5.9	0.000*

Legend POA: primary osteoarthritis; DDH: developmental dysplasia of the hip; RA: rheumatoid arthritis; FHN: femoral head necrosis; AS: ankylosing spondylitis; NA: not applicable; *statistically significant

Table 2. Patients' perioperative data

		TXA group	Control group	*p* value
N. of patients		40	46	NA
Type of anaesthesia	G	21	29	0.423
	L	14	12	
	G+L	5	5	
Preoperative Hb [g/dL]		13.7 ± 1.3	13.9 ± 1.3	0.332
Postoperative Hb [g/dL]				
immediate postoperative		10.6 ± 1.6	10.7 ± 1.4	0.762
48 hours		9.8 ± 1.1	9.6 ± 1	0.434
5^{th} day		9.9 ± 0.9	9.9 ± 1	0.978
Hb difference [g/dL]				
preoperative - immediate postoperative		3 ± 1.5	3.2 ± 1.3	0.548
preoperative - 48 hour postoperative		3.8 ± 1.3	4.3 ± 1.3	0.111
preoperative - 5^{th} day postoperative		3.7 ± 1.4	4 ± 1.5	0.374
N. of patients transfused		15	30	
BT rate (%)		37.5	65	0.011*
Volume of transfused blood [mL]		240 (0-1200)	450 (0-1500)	0.009*

Legend G: general; L: lumbar; NA: not applicable**;** *statistically significant

preoperative parameters (age, gender, side, ASA status, diagnosis, Hb level).

The mean operation time was 115.25±22.8 minutes for the TXA group and 96.05±5.9 minutes for the control group (p=0.000). The mean preoperative Hb level was 13.7±1.3 g/dL in the TXA group and 13.9±1.3 g/dL in the control group (p=0.332). The mean immediate postoperative Hb level was similar in both TXA and control groups, 10.6±1.6 g/dL vs 10.7±1.4 g/dL, respectively (p=0.762). The mean 48-hour postoperative Hb level was higher in the TXA group, 9.8±1.1 g/dL vs 9.6±1 g/dL (p=0.434). Mean 5th-day postoperative Hb reached similar values: 9.9±0.9 g/dL in TXA group vs 9.9±1 g/dL in the control group (p=0.978). The highest difference between mean pre- and postoperative variation of Hb was measured 48 hours after surgery, 3.8±1.3 g/dL in the TXA group and 4.3±1.3 g/dL in the control group, although it was not statistically significant (p=0.111). Compared with control group, patients who received TXA had a significant reduction in BT rates (65% vs 37.5%, p=0.011) and lower mean blood volume transfused (450 mL vs 240 mL, p=0.009). No TXA allergy and thromboembolic complications occurred in any group.

Discussion

THA is associated with major blood loss and frequently requires BTs for postoperative anemia, and BT rates varies between 21% and 80% (2,3,17). In OSTEO study, Rosencher et al. (17) investigated a total of 2640 hip arthroplasty patients quantifying perioperative blood loss at mean 1934 mL total blood. Allogeneic BTs have several risks like transfusion-related reactions, infections, and immunomodulatory effects (18). Additional health cost is also a rising concern (5).

Several blood conservation techniques have been employed to reduce blood loss and the exposure to BTs (6,7). A possible pharmacological option to prevent surgical bleeding in hip replacement surgery is the use of TXA (13,15). TXA, originally discovered in 1962 by Utako Okamoto (19), exerts its antifibrinolytic effect by a reversible interaction with plasminogen and the active protease, plasmin, inhibiting the activation of the plasminogen and retarding the fibrinolysis cascade process (10).

IV delivery is the most common route for TXA administration in published studies regarding total joint arthroplasties (20). Andersson et al. (21) showed that in healthy patients receiving a single bolus of TXA (10 mg/kg dose) the highest plasma concentration was measured within 1 hour, with 30% excreted in the urine after 1 hour, 55% at 3 hours, and 90% after 24 hours. The half-life of IV TXA is 2 hours (22). Furthermore, TXA diffuses rapidly in the joint fluid and synovial membrane, reaching the same concentration in the synovial fluid as in the serum 15 minutes after IV administration (23).

We found that BT rates and mean volume of transfused blood were less in the TXA group compared to the control group: 37.5% vs 65% (p=0.011) and 240 mL vs 450 mL (p=0.009), respectively, although the median surgical time was statistically significantly longer for the TXA group. These results were consistent with previous studies (13,20). In a systematic review and meta-analysis, Sukeik et al. (13) investigated the efficacy of IV TXA vs placebo in reducing blood loss and BT in THA, and showed that preoperative IV TXA reduced intraoperative blood loss by a mean of 104 mL, postoperative blood loss by a mean of 172 mL, and total blood loss by a mean of 289 mL, leading to a 20% reduction in the proportion of patients who required BTs. Moskal et al. (20) focused on IV TXA administration vs placebo in primary THA, analyzing only data of randomized controlled studies. IV TXA was more beneficial than placebo for blood loss intraoperatively, blood loss through drains, and total blood loss during hospitalization, in addition to reducing allogeneic BT rates (8.20% vs 19.52%).

Clinical studies investigating the effect of intravenous TXA in THA are heterogeneous regarding dosage schedules and timing of administration. The contrasting results highlight the importance of the appropriate timing of administration. In a randomized double-blind trial, Benoni et al. (24) reported that IV use of TXA at the end of the operation and 3 hours later did not reduce postoperative blood loss, demonstrating inadequate timing of TXA administration. On the other hand, a similar placebo-controlled study conducted by Ekback et al. (25) demonstrated that IV TXA prior to

the start of the surgical procedure showed significant benefit for both intra- and postoperative blood loss in the TXA group. Yamasaky et al. (26) and Rayesparan et al. (27) reported that a 1 g IV TXA, given at the induction of anaesthesia, reduced postoperative blood loss but did not reduce intraoperative blood loss. Firstly, Imai et al. (7) evaluated the effects of TXA examining the timing of its administration during THA. One hundred seven patients were randomly divided into 5 groups: no TXA administration (control group), single administration (either preoperative or postoperative phase), and double administration (preoperative or postoperative and 6 hours after first administration). They found that the intraoperative blood loss in the preoperative TXA administration groups was significantly lower than both control and postoperative groups. They concluded that two administrations of TXA, 1 g given 10 minutes before surgery and 6 hours later, significantly reduced blood loss without increasing the risk of thromboembolic events. Similarly, in our study, patients received TXA as a loading intravenous bolus dose of 1 g over 10 minutes prior to skin incision, followed by an additional 1 g, diluted in 250 ml of saline solution, given in continuous perfusion at 30 mL/hour. The rationale for this protocol is that the preoperative TXA bolus should help the surgeons to take advantage of the 120 minutes of TXA plasmatic half-life. Moreover, the continuous 8-hour TXA supplementary infusion should be able to maintain the therapeutic plasma concentration of TXA and stabilize the postoperative hematoma, further preventing the postoperative blood loss.

In the present study, immediate postoperative Hb levels were similar in both groups, as previously reported by other authors (26,27). The highest variation of pre- and postoperative Hb difference between the TXA group and the control group, although not statistically significant, was observed at 48 hours after surgery (3,84 g/dL vs 4,29 g/dL, p= 0,111). The postoperative hematoma is likely to become unstable after 48 hours because of the cessation of the TXA effect. This could explain the frequent need of BTs on the second or third day following surgery. Hb level decrease did not significantly differ between the two groups 5 days postoperatively, as the beneficial effect of TXA in preventing blood loss could be counterbalanced by the larger amount of transfusions to the control group.

TXA is contraindicated in patients with history of hypersensitivity and allergy to TXA, previous venous or arterial thrombosis, risk for thrombosis or thromboembolism, heart disease, hepatic dysfunction, and acute renal failure(7,28). The major concern of using TXA is an increased risk of thromboembolic events. The current investigation and most previous studies have excluded patients with significant risk factors, such as a history of cardiovascular disease, thromboembolic events, and renal failure. According to our findings and literature data, IV TXA administration in healthy patients undergoing THA did not appear to increase the incidence of thomboembolic events compared with the placebo groups (13,20,29). However, studies of TXA in THA have failed to adequately evaluate its effects on the risk of DVT, because in most of them the patients had only a clinical evaluation, and this should to be the subject of future research.

The limitations of the current study include the retrospective review of the data and the small sample sizes. Moreover, the total intraoperative bleeding was not measured, and the diagnosis of DVT or PE was based only on clinical evaluation. However, the two groups of patients were well matched for age, sex, diagnosis, and comorbidities. Furthermore, all patients were operated on by the same surgeons using the same surgical approach and standard cementless THA, thus excluding possible surgical factors affecting blood loss.

Conclusions

BTs requirements in THA can be reduced with various blood conservation techniques. TXA is one of the most interesting options to decrease the need for BTs. The current study found that perioperative IV administration of TXA in patients undergoing primary elective cementless THA resulted in reduction of BT rate and volume of transfused blood, without increasing the risk of thromboembolic events. Prospective randomized trials with larger patient populations are required to confirm our preliminary findings, define the optimal drug regimen, and verify the safety and cost-effectiveness of TXA in THA.

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