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ORIGINAL ARTICLE

Effectiveness of Primary Total Hip Arthroplasty Combined with Intra-articular and Intravenous Tranexamic Acid: A Retrospective Analysis of Number of Doses and Dose Strength

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Abstract

Introduction Total hip arthroplasty is a very effective reconstructive surgery but is often associated with massive perioperative bleeding, which leads to anemia. Tranexamic acid (TXA) minimizes bleeding and the need for blood transfusion. However, no universal standard TXA dosing regimen has been established. The objectives of this study were (1) whether there was a difference in the amount of decrease in perioperative mean hemoglobin (Hb) level between a single topical administration of TXA and intravenous and topical combination administration, and we also investigated whether there was a difference in the amount of decrease in the perioperative mean Hb level due to the difference in the local dose of TXA.

Methods We retrospectively reviewed 292 hips between June 2013 and October 2020. The decrease in Hb level (difference between the preoperative value and the 7-day postoperative value) was used to estimate total perioperative blood loss. The mean perioperative reduction in Hb was compared between hips that received intravenous TXA preoperatively and intra-articular TXA at wound closure (combination administration group) and those that received only intra-articular TXA (single dose group). It was also compared by different local doses of tranexamic acid.

Results The mean reduction in Hb was significantly smaller in the combination administration group than in the single dose group. However, no significant difference was observed due to the difference in the local dose of TXA administered at the time of wound closure.

Conclusion Reducing perioperative bleeding decreases the invasiveness of surgery, which is important from the perspective of medical safety.

Keywords Total hip arthroplasty · Perioperative bleeding · Tranexamic acid · Intra-articular administration · Intravenous administration · Medical safety

Introduction

Total hip arthroplasty (THA) is an effective surgical treatment for several hip disorders and has a high patient satisfaction rate. For example, THA can relieve pain and restore the function of the hip with damage due to arthritis or other conditions [1]. However, THA is often associated with massive perioperative bleeding, especially during surgery and in the first postoperative week, which leads to anemia [2] and may require blood transfusion. Patients who receive allogeneic blood transfusions are at risk of adverse reactions and infection [3].

Tranexamic acid (TXA) minimizes bleeding and the need for blood transfusion. It has been shown to be effective without increasing the risk of deep vein thrombosis or pulmonary

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embolism [4–11]. Synthesized in 1962 by Okamoto and Okamoto in Japan [12], TXA is now included on the World Health Organization Model List of Essential Medicines.

At our institution, up until June 2013, TXA was usually administered as a single intravenous (IV) dose immediately before THA and an intra-articular (IA) drain was inserted at the time of wound closure. After June 2013, IA drainage was discontinued and, in addition to preoperative IV administration of TXA, topical TXA was often administered when closing the wound. For patients at high risk of thromboembolic events, TXA was not administered IV preoperatively but was applied as a single topical dose when closing the wound.

There was been considerable research on the use of TXA in THA to define the optimal dosing regimen including the timing and frequency of dosing. However, the recommendations have been inconsistent and no uniform criteria have been established.

The aims of this retrospective study were to determine whether there was a difference in the amount of perioperative bleeding between a single dose and combination administration doses of TXA in patients undergoing primary THA, and also were to determine whether there was a difference in the amount of blood loss according to the topical dose administered at wound closure.

Materials and Methods

Primary THA was performed for 319 hips (269 female, 50 male) in 263 patients (222 female, 41 male) between June 2013 and October 2020. Nine of the 319 hips (2.8%) required allogeneic blood transfusion. Twenty seven of the 319 hips were excluded to make the patients as similar as possible. The reasons for these exclusions were as follows: surgery performed using a method other than the posterolateral approach ($n=11$); allogeneic blood transfusion performed perioperatively for preoperative anemia or another reason ($n=9$); topical TXA was not administered at the time of wound closure ($n=7$). The remaining 292 hips (247 female, 45 male) were included in the study (Fig. 1).

Mean age at surgery was 69.7 (range 49–90) years, and mean body mass index (BMI) was 25.1 (16.8–35.6) kg/m^2. One hundred and seventy hips (58.2%) were on the right and 122 (41.8%) were on the left. The most common indications for THA were osteoarthritis ($n=270$, 92.5%), rheumatoid

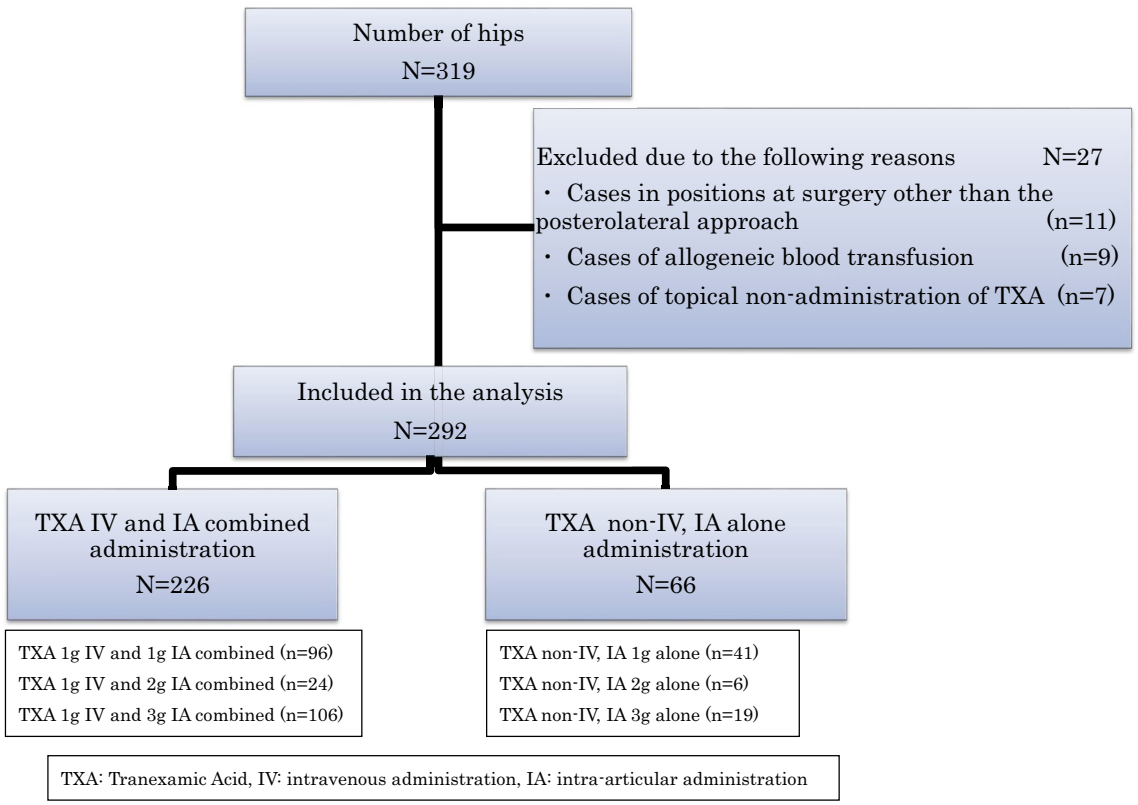

Fig. 1 Flowchart showing differences in the TXA dose and administration method in patients undergoing primary total hip arthroplasty. *TXA* tranexamic acid, *IV* intravenous administration, *IA* intra-articular administration

arthritis ($n=6$, 2.1%), necrosis of the femoral head ($n=15$, 5.1%), and unilateral ankylosis (Table 1).

Immediately before surgery, 1 g of TXA was administered IV for 226 hips (77.4%). Sixty-six patients (22.6%) at high risk for thromboembolic events did not receive IV TXA preoperatively. TXA was administered IA at the time of wound closure in all cases; the dose was 1 g for 96 hips, 2 g for 24 hips, and 3 g for 106 hips.

Patients were categorized into a group that received preoperative IV TXA and IA TXA at wound closure (combination administration group) and a group that received only IA TXA at wound closure (single dose group). Intraoperative bleeding was compared between the two groups. Mean perioperative reduction in hemoglobin (Hb) was also compared. The mean perioperative reduction in Hb was also compared according to whether the IA TXA dose was 1 g, 2 g, or 3 g. Perioperative blood loss was estimated from the decrease in Hb, which was calculated as the difference between the preoperative Hb level and the Hb level on postoperative day 7. All patients were investigated for pulmonary thromboembolism as a postoperative complication.

We investigated the occurrence of pulmonary thromboembolism, myocardial infarction, and cerebral infarction as perioperative complications during and immediately after surgery. In addition, on postoperative day 7, lower extremity venous ultrasound was performed to investigate the presence or absence of deep vein thrombosis.

This research was approved by the IRB of the authors' affiliated institution. All participants provided written informed consent.

Table 1 Patient characteristics

Patient demographics	Baseline data ($N=292$)
Gender (hips)	
Female	247 (84.6%)
Male	45 (15.4%)
Mean age at operation (years) (range)	69.7 ± 8.6 (49–90)
Mean body mass index (kg/m^2) (range)	25.1 ± 3.8 (16.8–35.6)
Laterality (hips)	
Right	170 (58.2%)
Left	122 (41.8%)
Primary disease (hips)	
Osteoarthritis	270 (92.5%)
Rheumatoid arthritis	6 (2.1%)
Osteonecrosis	15 (5.1%)
Ankylosis	1 (0.34%)

Surgical Technique

In all patients, surgery was performed using the same technique via a posterolateral approach in the lateral decubitus position. Cementless fixation was used for all implants. No drainage tube was inserted in the joint when the wound was closed to prevent the TXA solution inside the joint from draining to the outside.

Statistical Analysis

Continuous variables were compared using Student's *t* test, and categorical variables were compared using the chi-square test. We performed statistical correction using Bonferroni correction to avoid bias in the subgroup analysis between the three groups using *t* test. All statistical analyses were performed using Microsoft Excel 365 (Microsoft, Redmond, WA, USA). A P value of less than 0.05 was considered statistically significant.

Results

The mean intraoperative blood loss was significantly less in the combination administration group than in the single dose group (308.7 ± 121.1 mL vs 363.5 ± 137.2 mL; $P<0.001$). The mean perioperative decrease in Hb also was significantly less in the combination administration group than in the single dose group (2.25 ± 1.02 g/dL vs 2.49 ± 0.96 g/dL; $P=0.0468$; Table 2).

With or without preoperative TXA administration, there was no significant difference due to the difference in the intra-articular dose of TXA administered at the time of wound closure (Table 3). TXA 2 g IA alone group

Table 2 Comparison between the two groups regards to intraoperative bleeding volume, and amount of decrease in hemoglobin level during the perioperative period

$N=292$	TXA IV and IA combined groups ($N=226$)	TXA IA alone groups (single dose groups) ($N=66$)	P value (*$P<0.05$, **$P<0.01$)
Intraoperative bleeding volume (ml) (mean ± SD)	308.7 ± 121.1	363.5 ± 137.2	< 0.001**
Mean Hb levels decrease between pre-op and post-op day 7 (g/dL) (mean ± SD)	2.25 ± 1.02	2.49 ± 0.96	0.0468*

TXA tranexamic acid, *IV* intravenous administration, *IA* intra-articular administration

Table 3 Comparison between the two groups about the reduction in mean Hb levels during the perioperative period

N = 120	TXA 1 g IV, 1 g IA combined (*n* = 96)	TXA 1 g IV, 2 g IA combined (*n* = 24)	*P* value
Mean Hb levels decrease between pre-op and post-op day 7 (g/dL) (mean ± SD)	2.18 ± 1.12	2.12 ± 1.17	1.0000
N = 202	TXA 1 g IV, 1 g IA combined (*n* = 96)	TXA 1 g IV, 3 g IA combined (*n* = 106)	*P* value
Mean Hb levels decrease between pre-op and post-op day 7 (g/dL) (mean ± SD)	2.18 ± 1.12	2.34 ± 0.80	0.8459
N = 130	TXA 1 g IV, 2 g IA combined (*n* = 24)	TXA 1 g IV, 3 g IA combined (*n* = 106)	*P* value
Mean Hb levels decrease between pre-op and post-op day 7 (g/dL) (mean ± SD)	2.12 ± 1.17	2.34 ± 0.80	1.0000
N = 125	TXA 1 g IV, 3 g IA combined (*n* = 106)	TXA 3 g IA alone (*n* = 19)	*P* value
Mean Hb levels decrease between pre-op and post-op day 7 (g/dL) (mean ± SD)	2.34 ± 0.80	2.64 ± 0.67	0.0836
N = 137	TXA 1 g IV, 1 g IA combined (*n* = 96)	TXA 1 g IA alone (*n* = 41)	*P* value
Mean Hb levels decrease between pre-op and post-op day 7 (g/dL) (mean ± SD)	2.18 ± 1.12	2.35 ± 1.01	0.2014
N = 60	TXA 1 g IA alone (*n* = 41)	TXA 3 g IA alone (*n* = 19)	*P* value
Mean Hb levels decrease between pre-op and post-op day 7 (g/dL) (mean ± SD)	2.35 ± 1.01	2.64 ± 0.67	0.1371

TXA 2 g IA alone group (*n* = 6) was excluded from statistical processing due to the small number of cases

TXA: tranexamic acid, IV: intravenous administration, IA: intra-articular administration

(*n* = 6) was excluded from statistical processing due to the small number of cases.

Regardless of the dose or frequency of TXA, no serious perioperative complications such as pulmonary thromboembolism, myocardial infarction, or cerebral infarction related to TXA administration were observed in either group during the perioperative period up to postoperative day 7. In addition, there was no significant difference between the groups in the presence of deep vein thrombosis on postoperative day 7 (*P* = 0.2087; Table 4).

Discussion

In this study, we found that a combination of preoperative IV TXA and IA TXA at wound closure was more effective than IA TXA alone at wound closure for controlling perioperative bleeding. Furthermore, with or without preoperative TXA administration, there was no significant difference due to the difference in the intra-articular dose of TXA administered at the time of wound closure regarding to the mean perioperative decrease in Hb levels.

TXA is used to treat or prevent excessive blood loss as a result of major trauma, postpartum hemorrhage, surgery, tooth extraction, epistaxis, and heavy menstruation [13]. TXA is

Table 4 Thromboembolic complications during the perioperative period

Complications, *N* = 292	TXA 1 g IV and TXA 1 g IA combined (combination administration group) *n* = 96	TXA 1 g IV and TXA 2 g IA combined (combination administration group) *n* = 24	TXA 1 g IV and TXA 3 g IA combined (combination administration group) *n* = 106	TXA non-IV, IA only (single dose group) *n* = 66	*P* value
Pulmonary thromboembolism	0	0	0	0	
Myocardial infarction	0	0	0	0	
Cerebral infarction	0	0	0	0	
Deep vein thrombosis	16/96 (16.7%)	3/24 (12.5%)	9/106 (8.5%)	5/66 (7.6%)	0.2087

TXA tranexamic acid, *IV* intravenous administration, *IA* intra-articular administration

now routinely used to prevent bleeding in patients undergoing primary THA. However, there is currently no uniform dosing regimen. There have been other reports suggesting the effectiveness of combined IV and IA administration of TXA [14–20]. The IV route is the most widely used during surgery. The advantages of topically administered TXA are that it can be targeted directly to a bleeding site, accumulate in the surgical area, and inhibit local fibrinolytic activity, which helps to stabilize the fibrin clot and reduce blood loss [21]. Zhang et al. reported that IV administration of TXA may be particularly effective but also suggested that topical TXA may be preferable in patients who are at high risk of a thromboembolic event [6].

No serious perioperative complications occurred in this study, suggesting that the use of TXA does not have high risk for elderly patients. When administering TXA, however, caution should be exercised in administering the drug to elderly patients with impaired renal function because the half-life of TXA (1.9 h) is prolonged in the presence of renal dysfunction. In addition, TXA also has the effect of suppressing fibrinolysis (i.e., enzymatic breakdown of blood clots) in vivo [21]. Therefore, careful administration is required for patients with a history of cerebral thrombosis, myocardial infarction, thrombophlebitis, or other thromboembolic events. The current protocol for the use of TXA at our hospital is a combination of 1 g of IV TXA administered preoperatively and 3 g of TXA administered topically at the time of wound closure. In patients at high risk of thromboembolic events, preoperative IV administration is not performed and only a single dose of 3 g of TXA is administered topically at the time of wound closure.

This study has several limitations. First, the topical doses of TXA were not randomly selected. The reason is as follows. Prior to this study, a single dose of TXA intravenously was given immediately before surgery. From the beginning of the study period in June 2013, we started the combination therapy with additional topical administration of TXA at the time of wound closure. We initially used a dose of 1 g of TXA. Thereafter, the topical dose of TXA was increased to 2 g from June 2016 and then to 3 g from June 2017 after confirming that there were no serious vascular complications. Thus, to seek the most effective dose, the local dosage was gradually increased over time while checking for safety. The second limitation is as follows. Autologous blood was stored for some of the patients in the study and varied in amount from case to case. Preoperative Hb levels were measured before doing autologous blood storage to minimize the effects of blood storage.

Conclusion

In this study, patients undergoing THA who received both IV TXA preoperatively and IA TXA at the time of wound closure showed a smaller perioperative decrease in Hb than those who only received IA TXA at wound closure. This finding suggests that preoperative administration of IV TXA and an additional topical dose when closing the wound is more effective for controlling blood loss in these patients. Furthermore, with or without preoperative TXA administration, there was no significant difference due to the difference in the intra-articular dose of TXA administered at the time of wound closure regarding to the mean perioperative decrease in Hb levels. Further studies are needed to determine the optimal TXA dosing regimen. Reducing perioperative bleeding decreases the invasiveness of THA, which is important in terms of medical safety.

Declarations

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

Ethical standard statement This article does not contain any studies with human or animal subjects performed by the any of the authors.

Informed consent For this type of study informed consent is not required.

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