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Tranexamic Acid and Bleeding Parameters Among High Tibial Osteotomy Patients: A Systematic Review and Meta-analysis

Yüksek Tibial Osteotomi Hastalarında Traneksamik Asit ve Kanama Parametreleri: Gözden Geçirme ve Meta-analiz

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ABSTRACT Objective: To clarify and elucidate the real correlation between tranexamic acid administration and post-operative bleeding parameters in high tibial osteotomy (HTO) patients. **Material and Methods:** Articles published in PubMed, Embase, and Cochrane Library were searched and included in our analysis under the eligibility criteria. Information related to bleeding parameters among HTO patients treated with tranexamic acid and placebo was collected and analyzed using random or fixed-effect models. **Results:** A total of five papers were included in our study. Our pooled calculations found that tranexamic acid was associated with reduced bleeding parameters in HTO patients including drainage volume on the first day (mean diff=1.47 [95% CI=0.33-2.65], p=0.0120), hemoglobin decline on the second day (mean diff=0.79 [95% CI=0.59-1.00], p=0.0000), and total blood loss (mean diff=2.25 [95% CI=0.59-3.91], p=0.0080) compared to control group. However, we failed to elucidate the correlation between tranexamic acid administration and hemoglobin decline on the first day among patients with HTO. **Conclusion:** Tranexamic acid is associated with reduced drainage volume on the first day, hemoglobin decline on the second day, and total blood loss among HTO patients.

Keywords: High tibial osteotomy; tranexamic acid; bleeding

ÖZET Amaç: Yüksek tibial osteotomi (YTO) hastalarında traneksamik asit uygulaması ile ameliyat sonrası kanama parametreleri arasındaki gerçek korelasyonu netleştirmek ve aydınlatmak. **Gereç ve Yöntemler:** PubMed, Embase ve Cochrane Kütüphanesinde yayınlanan makaleler taranmış ve uygunluk kriterleri kapsamında araştırmamıza dahil edilmiştir. Traneksamik asit ve plasebo ile tedavi edilen YTO hastalarında kanama parametreleriyle ilgili bilgiler toplanmış ve rastgele veya sabit etkili modeller kullanılarak analiz edilmiştir. **Bulgular:** Çalışmamıza toplam beş makale dahil edilmiştir. Havuzlanmış hesaplamalarımıza göre traneksamik asidin kontrol grubuna göre YTO hastalarında kanama parametrelerinde azalma ile ilişkili olduğu bulunmuştur; ilk gündeki drenaj hacmi (ortalama fark = 1.47 [% 95 CI = 0.33-2.65], p = 0.0120), ikinci gün hemoglobin düşüşü (ortalama fark = 0.79 [% 95 CI = 0.59-1.00], p = 0.0000) ve toplam kan kaybı (ortalama fark = 2.25 [95% CI = 0.59-3.91], p = 0.0080). Bununla birlikte, YTO'lu hastalarda traneksamik asit uygulaması ile hemoglobinde ilk günkü düşüş arasındaki ilişkiyi aydınlatamadık. **Sonuç:** Traneksamik asit YTO hastalarında ilk gün azalmış drenaj hacmi, ikinci gün hemoglobin azalması ve toplam kan kaybı ile ilişkilidir.

Anahtar Kelimeler: Yüksek tibial osteotomi; traneksamik asit; kanama

High tibial osteotomy (HTO) is considerably used to correct knee deformities such as gonarthrosis, osteonecrosis, posterolateral instability, osteochondritis dissecans, and chondral resurfacing. The primary goals of HTO are to unload diseased articular surfaces and to correct angular deformity at tibiofemoral articulation. Furthermore, HTO may be performed by either an opening wedge or a closing wedge technique.[1] Like other surgeries, HTO may have bleeding side effects. One of the most often side effects of HTO is a hematoma (4.7%).[2] Furthermore, HTO may lead to some vascular injury because the surgery site is near the popliteal artery.[3] The total blood loss volume of HTO has been estimated at

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383.3±181.3 mL.[4] The higher volume of perioperative bleeding may attribute to a higher cost.

Tranexamic acid (TXA), an amino acid lysine synthetic, has an antifibrinolytic effect by blocking the lysine binding sites on plasminogen molecules.[5] The application of TXA in orthopedic surgery is to reduce blood loss and blood transfusion requirements. TXA may be administered intravenously, orally, or topically. TXA has been widely studied in orthopedic surgery, including total hip arthroplasty, total knee arthroplasty, hip fracture surgery, shoulder arthroplasty, and fracture related to trauma. The evidence revealed that TXA provided efficacy to reduce blood loss and the risk of blood transfusion requirements.[6,7] However, studies assessing the correlation between TXA and post-operative bleeding parameters in HTO patients are rarely reported. The previous meta-analysis also found that TXA could reduce blood loss and hemoglobin decline. However, inconsistency and the potential of bias were found across the studies.[8]

Our present study aimed to assess the correlation between TXA administration and post-operative bleeding parameters in HTO patients using a meta-analysis approach. Our present study was intended to elucidate the real correlation between TXA administration and post-operative bleeding parameters in HTO patients.

MATERIAL AND METHODS

STUDY DESIGN

We conducted a meta-analysis study from September to November 2020 to assess the correlation between TXA administration and post-operative bleeding parameters among HTO patients. Articles published in PubMed, Embase, and Cochrane Library were collected for determining the correlation and the calculation of pooled mean difference and 95% confidence interval (95% CI). Our current study protocols were performed based on the checklist from Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA).[9] Our present study was conducted following the principles of Helsinki Declaration, and approved by local ethics committee (No: 048/Liv/K.3/308/2020).

SEARCH STRATEGY

Papers concerning the association between TXA administration and post-operative bleeding parameters among HTO patients were searched on the primary scientific website (PubMed, Embase, and Cochrane Library) up to November 10th, 2020. Language restriction was not applied. If articles neither in English nor Indonesia were found, a consultation to the Language Centre in our University was performed. A comprehensive search of the papers was performed using the keywords conformed to medical subject heading [“HTO”] and [“TXA”] and [“bleeding”]. If papers with the same study data were found, we included an article with the largest sample size. Moreover, we also performed a manual search for the reference list of related articles.

ELIGIBILITY CRITERIA

The inclusion criteria for this study were: (1) patients who underwent the HTO procedure (2) comparing the bleeding parameters between with and without administration of TXA, (3) available full text, and (4) having required data for the calculation of correlation and effect estimates. On the other hand, the exclusion criteria for this study were: (1) unrelated titles and abstracts, (2) involving patients with coagulopathy, (3) incomplete data, and (4) low-quality papers. Moreover, we also excluded case reports, editorials, reviews, letters to the editor, and animal studies.

QUALITY ASSESSMENT

The quality of papers was appraised using the Newcastle Ottawa Scale (NOS) in cohort studies, conducted by FR (Ferdian Rizaliansyah), FF (Farahdina Farahdina), and JUA (Justika Usmadhani Aulya) independently.[10] The NOS assessment had three main factors: sample recruitment (4 points), comparison (2 points), and exposure (3 points). The interpretation of the NOS assessment was high quality (score ≥7), moderate quality (score 5-6), or low quality (score ≤4). If we found a discrepancy, we established a consensus and consultation with a senior researcher [JKF (Jonny Karunia Fajar)].

DATA EXTRACTION

The data on study characteristics (first authors, year of publication, randomization methods, sample size,

age, ethnicity, and tranexamic dose) were extracted. Three independent investigators (FR, FF, JUA) conducted data collection to avoid human errors. If a discrepancy was found, we established a consensus and consultation with a senior researcher (JKF).

OUTCOME MEASURE

The predictor variable in our present study was TXA administration. While, the outcome measures were bleeding parameters, including drainage volume on the first day, hemoglobin decline on the first day, hemoglobin decline on the second day, and total blood loss among HTO patients. All covariates in our current study were determined by initial searching. Covariates having required criteria for the calculation of correlation and effect estimates were included for our meta-analysis.

STATISTICAL ANALYSIS

The pooled mean difference calculation was used to assess the correlation between TXA administration and post-operative bleeding parameters among HTO patients**.** The heterogeneity was assessed using a Q test to determine the effect model (fixed or random effect model). The p value of less than 0.10 indicated that the heterogeneity among studies existed, and a random effect model should be used to determine the correlation. Conversely, if we found no heterogeneity among studies (p heterogeneity >0.10), the correlation was assessed using a fixed-effect model. Furthermore, we employed an Egger's test to assess the publication bias among studies. The p value of less than 0.05 indicated that publication bias among studies was found. All analyses were confirmed by two softwares: Comprehensive Meta-Analysis [CMA, New Jersey, USA] version 3.3 and Review Manager [Revman Cochrane, London, UK] version 5.4.

RESULTS

ELIGIBLE STUDIES

Our final search identified five papers compatible with the calculation of our meta-analysis. They were retrieved from the searching in PubMed, Embase, and Cochrane Library after selected following our eligibility criteria. In the first searching, we collected 109 potentially relevant articles. Of those, 99 papers were excluded because of irrelevant titles or abstracts, one paper was excluded due to being a review, and one paper was excluded because of insufficient data. Figure 1 illustrated the selection flowchart of our meta-analysis. All articles included in our analysis had moderate-high quality. Baseline characteristics of papers included in our meta-analysis are outlined in Table 1.

DATA SYNTHESIS

Five papers recording 274 controls and 258 cases were enrolled for our analysis. All five papers included knee osteoarthritis patients with varus deformity and were treated with medial opening-wedge HTO.[11-15] Our findings revealed that TXA administration was correlated to lower drainage volume on the first day (mean diff=1.47 [95% CI=0.33-2.65], p=0.0120), lower hemoglobin decline on the second day (mean diff=0.79 [95% CI=0.59-1.00], p=0.0000), and lower total blood loss (mean diff=2.25 [95% CI=0.59-3.91], p=0.0080), compared to without TXA administration among HTO patients. While, for hemoglobin decline on the first day, we failed to show the correlation with the use of tranexamic acid among HTO patients (mean diff=1.01 [95% CI=0.7-1.25], p=0.0000). Our calculations in Review Manager [Revman Cochrane, London, UK] version 5.4 are presented in Figure 2 while the summary of the correlation between tranexamic acid and post-operative bleeding parameters in HTO patients are presented in Table 2. Moreover, we also found that

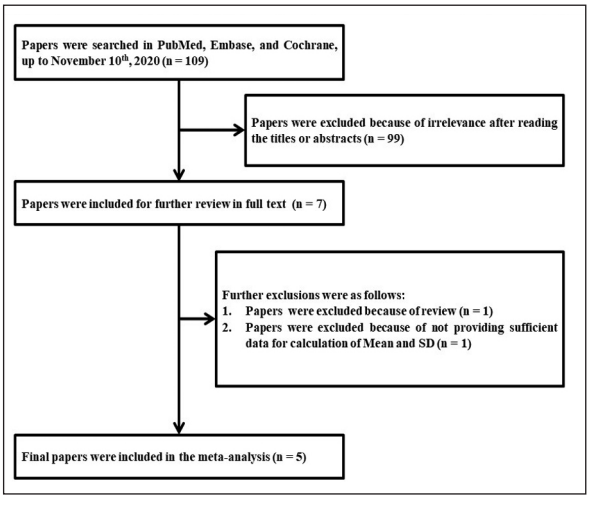

FIGURE 1: Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram.

TABLE 1: Baseline characteristics of the studies included in our study.

Author & year	Sample size Control	TXA	NOS	Age (mean±SD)	Anesthesia Route	TXA dose	Main findings
Chen et al. 2020	48	52	7	57.5±10.3	NR	1 g TXA was administered intravenously before tourniquet inflation and 1 g topically at the osteotomy site	Administration of TXA is beneficial to patients undergoing open-wedge HTO via decreasing length of stay, reducing blood loss, and maintaining higher post-operative Hb levels
Ni et al. 2020	50	50	9	52.7±3.0	Continuous epidural anesthesia	50 mg/kg intravenously, 10 min before the tourniquet deflated	Intravenous TXA can effectively and safely reduce blood loss and bleeding-related complications after HTO and was beneficial for the blood management of HTO
Palanisamy et al. 2018	86	66	7	57.5±5.5	Spinal anesthesia with the femoral nerve block	2 g were infused intravenously 10 min before tourniquet applicated and the same dose was repeated 3 hours after an initial dose	This study demonstrates that the systemic administration of TXA reduces postoperative blood loss in medial opening wedge HTO
Kim et al. 2018	75	75	9	55.4±6.2	NR	10 mg/kg was dissolved in 100 mL of normal saline for intravenous administration. The patient received three doses. First, before tourniquet deflated; second, 6 hours after surgery; and third, 24 hours after surgery	The intravenous administration of TXA reduced hemoglobin drop, postoperative drain amount, and total blood loss without thromboembolic complications in patients undergoing open-wedge HTO
Suh et al. 2018	15	15	6	58.0±5.7	Spinal anesthesia	2 g TXA in 20 mL saline was administrated at the osteotomy site through the applied Hemovac line.	Topical TXA was effective for reducing postoperative bleeding after medial open HTO.

TXA: Tranexamic acid; NOS: Newcastle-Ottawa Scale; SD: Standard deviation; HTO: High tibial osteotomy; NR: Not reported; Hb: Hemoglobin.

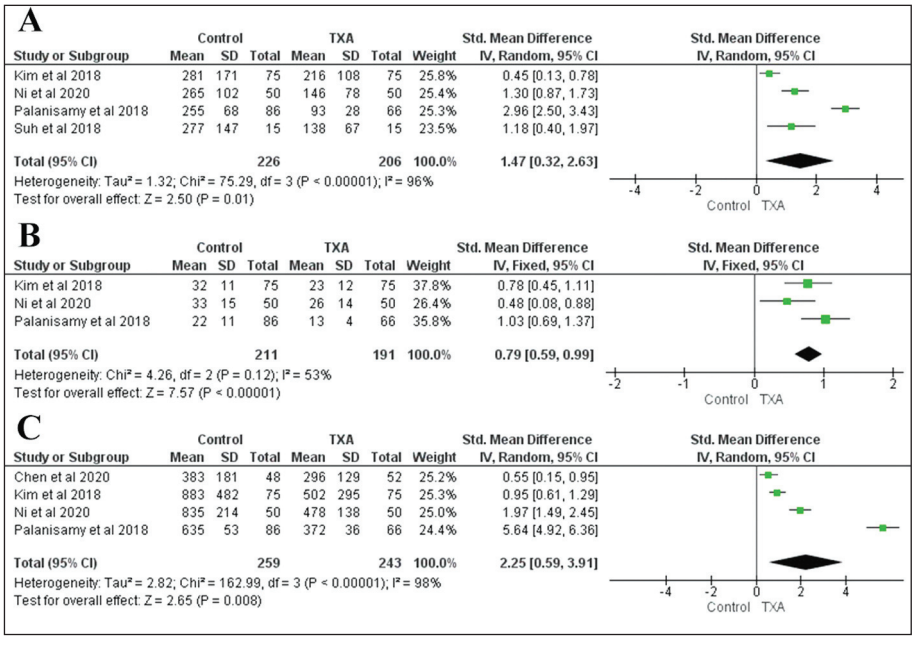

FIGURE 2: Forest plot of the associations between tranexamic acid and bleeding parameters. **A)** Drainage volume on 1st day. **B)** Hemoglobin decline on 2nd day. **C)** Total blood loss.

TABLE 2: Summary of the association between tranexamic acid and post-operative bleeding parameters among patients with high tibial osteotomy in our study.

			Outcome measure						
Bleeding parameters	**NS**	**Model**	**Control**	**TXA**	**Std diff in mean**	**95%CI**	**pE**	**pHet**	**p value**
Drainage volume on 1st day	4	Random	269.5±122.0	148.3±70.3	1.47	0.33-2.65	1.1530	0.0000	0.0120
Hemoglobin decline on 1st day	3	Fixed	2.3±0.9	1.3±1.0	1.01	0.76-1.25	0.0000	0.7970	0.0000
Hemoglobin decline on 2nd day	3	Fixed	2.9±1.2	2.1±1.0	0.79	0.59-1.00	0.1940	0.1170	0.0000
Total blood loss	4	Random	700.3±292.3	425.3±187.3	2.25	0.59-3.94	1.6930	0.0000	0.0080

Note, data were presented in mean±SD: Standart deviation; NS: Number of studies: TXA: Tranexamic acid: CI: Confidence interval; pE: p egger; pHet: p heterogeneity.

TABLE 3: Summary of other bleeding parameters or wound complications.

Author & year	**Control**	**TXA**
Chen et al. 2020	4 patients had thromboembolism	2 patients had thromboembolism
	5 patients had hematoma	2 patients had hematoma
	2 patients had infection	1 patient had superficial wound infection
	1 patient had infection	
Ni et al. 2020	1 patient had wound hematoma	
	1 patient received blood transfusion due to	
	hemoglobin levels below 7 g/dL	-
Palanisamy et al. 2018	1 patient had superficial wound infection	
	1 patient had tense wound hematoma	-
Kim et al. 2018	2 patients received a blood transfusion	-
Suh et al. 2018	1 patient had wound hematoma	-

TXA: Tranexamic acid.

complications were found less in the tranexamic acid group (Table 3).

SOURCE OF HETEROGENEITY

The random-effect model was applied to assess the correlation between TXA administration, post-operative drainage volume on the first day, and post-operative total blood loss among HTO patients due to the evidence of heterogeneity. On the other hand, due to no heterogeneity evidence, the correlation between TXA administration and hemoglobin decline both on the first and second days among HTO patients was assessed using the fixed-effect model. The evidence of heterogeneity in our present study is described in Table 2.

POTENTIAL PUBLICATION BIAS

The analysis of publication bias among the included studies was assessed using Egger's test. We found that publication bias was observed in hemoglobin decline on the first day. For other covariates, including total blood loss, hemoglobin decline on the second day, and drainage volume; we found no evidence of potential publication bias. The summary of publication bias analysis among the studies is presented in Table 2.

DISCUSSION

We identified five compatible papers regarding the association between TXA and post-operative bleeding parameters in HTO patients. Three bleeding parameters (drainage volume on the first day, hemoglobin decline on the second day, and total blood loss) were observed higher in patients without TXA administration compared to patients receiving TXA. Our current findings were consistent with Yao et al.[8] They found that TXA could reduce total blood loss, and they found that thromboembolic events were not found, suggesting that TXA administration provided efficacy and safety for patients with HTO. Theoretically, the antifibrinolytic effect of TXA may

occur by interrupting plasminogen molecules by blocking the lysine binding site. Thereafter, it may inhibit the interaction between plasminogen and the heavy chain of plasmin with lysine residues on fibrin's surface. While plasmin may still be established under these circumstances, it cannot bind and degrade fibrin.[5] This mechanism may bridge our findings, showing that TXA was associated with reduced bleeding parameters among HTO patients.

Some meta-analyses revealed that the use of TXA in orthopedic surgeries provided the efficacy to reduce blood loss and the risk of transfusion requirements.[6,7] However, the incidence of venous thromboembolism was considered the most common condition why TXA was not routinely applied in orthopedic surgery. In our present meta-analysis, we also provided evidence that fewer patients receiving TXA had venous thromboembolism compared to those without TXA administration among HTO patients. Meanwhile, previous studies in this context had quite different results. They found that the incidence of venous thromboembolism was similar between patients receiving TXA and without TXA among patients who underwent orthopedic surgery.[6,7,16] Therefore, in our current study, TXA administration was proven to provide the safety and efficacy to reduce drainage volume on the first day, hemoglobin decline on the second day, and total blood loss compared to patients without TXA administration among HTO patients.

Our current study emphasized that TXA administration provided potential effects to reduce bleeding in patients undergoing the HTO procedure. The previous meta-analysis in this context had been performed.[8] However, several crucial issues were observed. First, their study had a smaller sample size. Second, we found an non-proportional data presentation. Our current study had a larger sample size, and our data were proportional, conformed with the primary source. Therefore, our current study might provide a better correlation. However, until now, the only FDA (U.S. Food and Drug Administration)-approved indication for tranexamic acid is for heavy menstrual bleeding and short-term bleeding prevention in patients with hemophilia.[17] Moreover, there is no guideline for orthopedic surgeons to administer TXA before the HTO procedure. Shortly soon, we expected that our current findings might be considered the initial clue to investigate the potency of TXA further to prevent blood loss in HTO patients.

There were several limitations to our meta-analysis. First, the dosage of TXA varied among studies. We found five different doses in our study. Therefore, the combination of our data should be carefully interpreted. Second, our sample size was relatively small, and therefore, the risk of bias might occur. Third, the surgery operator factor that might also have a crucial role governing bleeding parameters was not included and controlled for in our analysis. Because of the limitations, up-coming studies by eliminating the limitation factors might be needed to clarify the better association.

CONCLUSION

Our study reveals that TXA is associated with reduced bleeding parameters, including drainage volume on the first day, hemoglobin decline on the second day, and total blood loss among high tibial osteotomy patients. Our results may clarify a better correlation related to TXA benefit in HTO patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ferdian Rizaliansyah;* ***Design:*** *Ferdian Rizaliansyah;* ***Control/Supervision:*** *Ferdian Rizaliansyah, Justika Usmadhani Aulya;* ***Data Collection and/or Processing:*** *Ferdian Rizaliansyah, Farahdina Farahdina, Justika Usmadhani Aulya, Jonny Karunia Fajar;* ***Analysis and/or Interpretation:*** *Ferdian*

Rizaliansyah, Farahdina Farahdina, Justika Usmadhani Aulya, Jonny Karunia Fajar; ***Literature Review:*** *Ferdian Rizaliansyah, Farahdina Farahdina, Jonny Karunia Fajar;* ***Writing the Article:*** *Ferdian Rizaliansyah, Farahdina Farahdina, Justika Usmadhani Aulya, Jonny Karunia Fajar;* ***Critical Review:*** *Ferdian Rizaliansyah, Jonny Karunia Fajar;* ***References and Fundings:*** *Farahdina Farahdina, Justika Usmadhani Aulya;* ***Materials:*** *Farahdina Farahdina, Justika Usmadhani Aulya.*

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