Is tranexamic acid safe and reliable during tibial intramedullary nailing?

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ABSTRACT

BACKGROUND: The aim of this study was to determine if the use of tranexamic acid (TXA) during intramedullary reaming treatment for tibial diaphyseal fractures was safe, reduced blood loss, or affected cost effectiveness.

METHODS: A total of 70 patients with a tibia diaphysis fracture were randomized into 2 groups and prospectively followed for data on blood loss, thrombosis, and fracture healing. Preoperative TXA was administered intravenously to Group A, and Group B served as the control group.

RESULTS: While there was no significant difference between the preoperative and postoperative 1-hour hemoglobin (Hb) and hematocrit (Hct) levels of the patients, there was a statistically significant difference in the comparison of the postoperative 24-hour and 48-hour Hb and Hct levels. There was no need for an allogenic blood transfusion to any patient in Group A; however, 2 patients in Group B each received 1 unit of erythrocyte suspension because their Hct values dropped below 27%. There was no deep vein thrombosis or embolism observed in any of the patients.

CONCLUSION: The application of intravenous TXA during the preoperative period in the treatment of tibial fractures with intramedullary nailing reduced the bleeding seen in the postoperative period. It did not lead to intravascular thrombosis in the postoperative period, and had no adverse effect on bone healing.

Keywords: Intramedullar nailing; tibia diaphyseal fracture; tranexamic acid.

INTRODUCTION

Tranexamic acid (TXA) is a popular antifibrinolytic agent used by orthopedic surgeons.[1] Greater efficacy in arthroplasty procedures and reduced need for blood replacement in trauma patients are common surgical goals.[2] However, many questions about the use of TXA remain, including the effective dose, the dose interval, whether intravenous (IV) or intra-articular application is optimal, and whether the drug should be delivered in a bolus or perioperative infusion. Few relevant studies have been published in the literature.

Tibial diaphysis fractures are commonly seen in emergency departments. The treatments include plate fixation, the use of screws, intramedullary nailing (IMN), and the use of external fixators and plaster (conservative treatments). Currently, the most commonly used treatment options are fixation with IMN and plate fixation. Nails are superior to plates in terms of early loading.[3]

Tibial fractures are often associated with hemorrhage, hematoma, and superficial/deep infections.[4] The objective of this study was to examine whether TXA could be used safely to treat patients with tibial diaphyseal fractures treated via...
IMN, and if it reduced blood loss and increased cost-effectiveness.

**MATERIALS AND METHODS**

All of the study procedures met the ethical standards of the institutional and national research committees and all of the tenets of the 1964 Helsinki declaration and later amendments thereto, and/or comparable ethical standards. Written informed consent was obtained from all of the participants. We did not use any animals in the present research. The study was approved by the ethics committee of Beykoz State Hospital (number: 177/C).

A total of 80 patients were enrolled. All were admitted to the emergency department with leg pain and were thought to have a tibial fracture based on a physical examination, had a tibial diaphysis fracture confirmed on X-ray, and agreed to participate in the study. Closed fractures were categorized using the AO/OTA Classification of Fractures and Dislocations system[5] and open fractures were classified using the Gustilo/Anderson system.[6] The inclusion criteria were: an isolated diaphyseal fracture displacing both the tibia and the fibula, fixation using the IMN system, use of a trans-tendinous approach, and an international normalized ratio of 0.8–1.2. The exclusion criteria were: polytrauma, a need for open reduction, a need for additional orthopedic surgical intervention, a Gustilo/Anderson type 2 or 3 fracture, any contraindication for the use of TXA (chronic renal or liver failure), an American Society of Anesthesiologists score ≥4, and/or any cerebrovascular event. An American Society of Anesthesiologists score ≥4, and/or any cerebrovascular event. The 80 patients were randomly divided into 2 groups and followed up prospectively. Nine patients (3 with multi-trauma, 3 with Gustilo/Anderson type 3b–c open fractures, 1 on acetylsalicylate medication, 1 with a pathological fracture, 1 with sickle-cell anemia, and 1 with incomplete follow-up) were excluded. One patient was also lost to follow-up. In all, 70 patients were included in the study. Randomization to TXA treatment was performed with a sealed envelope, which was opened in the operating room before the skin incision was made. After the operation, all of the assessments were performed by 2 orthopedic residents blinded to TXA injection status.

Two orthopedic surgeons (SGB and SC) performed all of the surgeries with the patients under spinal anesthesia and without a tourniquet. TXA (10 mg/kg IV bolus) was administered to group A patients 30 minutes before the surgery. A longitudinal incision (ca. 5 cm in length) was created through the midline of the patellar tendon. A nail entry point was fashioned in the midline using a curved awl. A guidewire was inserted through the hole and passed into the distal fragment, with reduction. The medullary cavity was reamed to be 1 mm greater than the nail diameter. Two proximal and 2 distal static locking screws were positioned (Trigen; Smith & Nephew, Memphis, TN, USA). Absorbable sutures were used for closure. No cast or brace was applied for immobilization. Isometric quadriceps and active ankle dorsiflexion-plantar flexion exercises were initiated immediately after surgery. A standard antibiotic regimen was prescribed. Cefazolin sodium (1g IV bolus) was administered to all of the patients 30 minutes before the operation and applied 3 times in 24 hours. Subcutaneous injection of enoxaparin sodium [1×40 mg (0.4 mL)] on each of 30 days after surgery was used to prevent the development of deep vein thrombosis (DVT). All of the patients were advised to use 2 crutches and to employ touch-down weight bearing for 2 to 3 weeks, to be followed by full weight-bearing as tolerated.

At the 1-month follow-up evaluation, the patients were advised to use 1 crutch on the contralateral side, and were told to stop using assistive walking devices whenever they felt that they were unnecessary. Patient data regarding age, gender, weight, length of time until surgery, preoperative hemoglobin (Hb) and hematocrit (Hct) levels, and the postoperative 1-hour, and 24-hour, and 48-hour Hb and Hct levels were recorded. Any need for an erythrocyte suspension was noted. Patients were examined 2, 4, 6, and 12 weeks postoperatively. Radiological fracture healing was recorded using the Radiologic Union Scale for Tibia Fractures (RUST) criteria.[7] DVT status was evaluated in the inpatient clinic with Doppler ultrasonography (US) at the 4-week follow-up. Patients with open fractures were prescribed triple antibiotics (cefazolin, gentamycin, and metronidazole) after wound debridement.

**Statistical Analysis**

The statistical analysis was performed using SPSS for Windows, Version 11.0 (SPSS, Inc., Chicago, IL, USA). Data satisfying the conditions are expressed as the mean±SD, and intergroup comparisons were performed using Student’s t-test. Data not satisfying the conditions were presented as the median and interquartile range. Intergroup comparisons were performed using the Mann-Whitney U test.

**RESULTS**

In this study group, 47 patients were male and 23 were female. The mean age of Group A patients was 36.51±11.91 years (range: 17–56 years) and that of Group B was 35.03±14.49 years (range: 16–64 years). The age distribution did not differ

![Figure 1](image-url)

*Figure 1. The fracture type distribution in Group A and Group B patients, derived using the AO Classification.*
significantly between the groups (p=0.6409). Seven Group A and 5 Group B patients had type 1 Gustilo/Anderson open fractures. In Group A, the distribution of fractures according to the AO/OTA classification was AO 42A1: n=9; 42A2: n=4; 42A3: n=10; 42B2: n=9; and 42C1: n=3; in Group B, the figures were AO 42A1: n=14; 42A2: n=6; 42A3: n=10; 42B2: n=2; 42B3: n=2; and 42C2: n=1 (Fig. 1).

The pre- and postoperative 1-hour Hb and Hct levels did not differ significantly between the groups, but differences were evident in the 24- and 48-hour levels (Table 1). No Group A patient required an allogeneic blood transfusion (ABT), but 1 unit of an erythrocyte suspension was given to 2 Group B patients because the Hct value fell below 27%. No DVT or embolism was noted in any patient. Two Group A patients exhibited wound detachment, 2 Group B patients developed superficial infections, and 1 Group B patient developed a hematoma.

No significant between-group difference was observed in terms of the length of hospital stay. All of the fractures healed; however, the fracture healing time of patients given TXA was significantly shorter than that of the other group (Table 2).

DISCUSSION

We conducted a prospective, randomized, double-blinded study of the utility of preoperative IV TXA in patients with tibia diaphysis fractures treated via IMN. This is the first published study to evaluate TXA efficacy and safety in this context. It is common to use tourniquets during plate placement in trauma patients with tibial fractures. However, the use of tourniquets during IMN can cause friction burns, especially in patients with narrow medullae.[8] Hemorrhage, hematoma, and ecchymosis developing after tibial IMN can trigger wound site complications. Peripheral soft tissue damage, hematomas, and ecchymoses forming in the fracture region or under the skin may predispose the site to infection by creating microenvironments that encourage bacterial colonization; this is detrimental to the patient, as infection retards healing.[9]

TXA is a synthetic lysine derivative that blocks lysine-binding sites on plasminogen and thus prevents plasmin activation. Plasmin breaks fibrin clots; TXA thus prevents clot breakup but does not contribute to clot formation. Further, TXA may exert an anti-inflammatory effect because the pathways of coagulation and inflammation overlap.[10,11] TXA has long been used for epistatic prophylaxis in patients with dysfunctional uterine bleeding and to treat hereditary hemorrhagic telangiectasia.[12,13]

ABT after orthopedic surgery is risky in terms of surgical wound infection.[14] In addition, ABT is associated with various side effects, including febrile reactions, hemolysis, allergic reactions, circulatory overload, and infectious disease, as well
as a high cost. Husted et al. showed that blood transfusion after total knee prosthesis (TKP) placement increased the length of the hospital stay. Many efforts have been made to reduce postoperative bleeding after TKP placement, to reduce the need for ABT, and to prevent side effects. These include preoperative erythropoietin, iron, and adrenaline therapy; fibrin glue placement; and local and systemic TXA. The need for blood transfusion is reduced in patients given TXA.

TXA is now administered to patients with orthopedic trauma; those requiring major procedures such as spinal and pelvic fixation, and those with less serious trauma, such as calcaneus fractures. We found that TXA reduced postoperative blood loss after tibial IMN. The preoperative Hgb and Hct values were compared with the early and later postoperative values and TXA prevented significant decreases in the Hgb and Hct levels.

We used Doppler US to evaluate DVT status at postoperative week 4. No DVT was noted in any patient of either group. The effect of TXA was not what we predicted. The fracture-healing time of the TXA-treated group was shorter than that of the control group. We suggest that TXA may stabilize hematomas in the fracture region. TXA is supposed to exert anti-inflammatory activity, but its effect on fracture-healing should be evaluated in future studies with larger numbers of patients.

Johansson et al. compared a total hip reconstruction (THR) group given 15 mg/kg TXA IV preoperatively with a placebo group and observed that TXA significantly reduced bleeding. Reduced bleeding and less need for postoperative ABT have been reported in THR patients to whom TXA was given systemically. When TXA was administered at 10 mg/kg IV preoperatively and 3 times daily perorally postoperatively for 5 days (250 mg in capsules), it was reported to reduce postoperative blood loss and the need for transfusion without increasing the risk of thromboembolism. In addition, Singh et al. gave IV TXA to half of a group of patients undergoing primary THR (the other half served as a control group). Blood loss did not differ between the groups, but ABT was not required for any TXA patient. Hourlier and Fnemma compared patients given 2 mg/kg TXA IV for 20 hours and found no significant difference (compared to a control group) in terms of total bleeding. Our results are similar to those of studies on patients given single TXA doses systemically. We believe that TXA is useful when given as an IV bolus.

TXA can theoretically trigger intravascular thrombosis, cerebrovascular events, myocardial infarction, DVT, and pulmonary embolism (PE). However, such complications have not, in fact, been reported. TXA has not been associated with the complications of DVT or PE when given after major arthroplasty procedures. In a meta-analysis of 19 clinical trials, Alshryda et al. found that TXA significantly reduced the need for blood transfusion and did not increase the risk of DVT or PE. Another meta-analysis found that TXA reduced bleeding without increasing the thromboembolism rate. We performed DVT scans (using Doppler US) on all patients 1 month postoperatively. No DVT or embolism was evident, either clinically or radiologically, in any patient of either group. This may be attributable to postoperative enoxaparin prophylaxis and early patient mobilization.

TXA can also be applied locally to areas of large-joint arthroplasty to reduce bleeding and the need for ABT. Konig et al. found that local application of 3 g of TXA to patients who had undergone primary THR with the placement of a total knee prosthesis significantly reduced postoperative blood loss and the need for transfusion. Yue and Kang demonstrated that the local application of 3 g of TXA significantly reduced bleeding and the need for ABT in patients who had undergone THR. In addition, both IV TXA and TXA given locally reduced bleeding after TKP. We sought to achieve hemostasis after a surgical procedure that is not amenable to the local application of agents to the wound site; therefore, we administered IV TXA to our IMN patients.

Farrokhi et al. compared patients undergoing spinal fixation surgery with 10 mg/kg IV TXA and placebo groups. Although blood loss was lower in the TXA group, there was no statistically significant difference. That may be explained by an insufficient TXA dose for spinal fixation surgery.

Xie et al. used TXA (15 mg/kg IV) preoperatively for calcaneal fracture fixation patients. No significant difference was found in peroperative blood loss, but 24 hours after the operation, the blood loss was lower in the TXA group, similar to what we observed in our study. The use of a tourniquet in calcaneal fracture surgery may have contributed to this result. Zufferey et al. used TXA (15 mg/kg IV) for hip fracture surgery and compared patients with a placebo group. The TXA group had less blood loss but a high rate of vascular complications. The nature of hip fracture surgery, the TXA dose, and patients of an older age should be considered in the large number of vascular events.

Our study had certain limitations, including the relatively small number of patients, the absence of any quantitative measure of ecchymosis, or indirect bleeding evaluation via measurement of Hgb and Hct levels. However, the fact that this is the first report of IMN to treat long bone fractures renders the work unique.

**Conclusion**

According to our results, IV TXA given preoperatively to patients with tibial fractures treated via IMN reduced postoperative bleeding, did not trigger intravascular thrombosis, and did not compromise bone healing.

Conflict of interest: None declared.
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Tibia kırklarının intramedüller çivileme ile tedavisi sırasında traneksamik asit kullanımı güvenli ve güvenilir mi?

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AMAC: Tibia diyafiz kırıklarında intramedüller çivileme yapılırken traneksamik asit kullanımının güvenli olup olmadığını, kan kaybını azaltacağını ve maliyet etkinliğini etkilemeyeceği belirlemektir.

GEREÇ VE YÖNTEM: Tibia diafiz kırığı olan 70 hasta randomize olarak iki gruba ayrıldı ve ileriye yönelik olarak kan kaybı, tromboz ve kırık iyileşmesi açısından izlendi. Birinci gruba ameliyat öncesi traneksamik asit intravenöz olarak uygulandı. İkinci grup kontrol grubu olarak belirlendi.

BULGULAR: İki grup arasında ameliyat öncesi ve sonrası birinci saat hemoglobin (Hb) ve hematokrit (Hct) değerleri arasında farklılık saptanmadı. İki grup arasında ameliyat sonrası 24–48. saat Hb ve Hct değerleri arasında anlamlı farklılık saptanmadı. Traneksamik asit uygulanan grupta (Grup A) ameliyat sonrası allojenik kan transfüzyonu gereksinimi olmadı. Traneksamik asit kullanılmayan grupta (Grup B) iki hasta Hb ve Hct değerleri düşük saptanmıştı (Hct<27) bir unite entrostos et,optionsyonu uygulandı. Hiçbir hastada derin ven trombozu ve emboli gözlenmedi.

TARTIŞMA: Intramedüller çivileme ile tibia kırıklarının tedavisinde ameliyat öncesi dönemde intravenöz traneksamik asit uygulanması ameliyat sonrası dönemde kanama miktarını azalttığı görüldü. Ameliyat sonrası dönemde hastalarda intravasküler tromboza yol açmadığı gibi kemik iyileşmesini de olumsuz etkilemediğini gözlüyoruz.

Anahtar sözcükler: Intramedüller çivileme; tibia diyafiz kırığı; traneksamit asit.