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Assessing the Safety and Efficacy of Tranexamic Acid Usage in Osteogenesis Imperfecta Patients

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Background: Osteogenesis Imperfecta (OI) usually causes an increased fracture burden and bone deformity, with subsequent operations common. In addition to skeletal manifestations, there is a potential increase in bleeding susceptibility due to the increased frequency of orthopedic procedures, warranting investigation into methods to mitigate this risk. This study aims to evaluate the safety and efficacy of tranexamic acid (TXA) usage to reduce intraoperative blood loss in children with OI. We want to assess the potential benefits, risks, and complications involved with TXA use in this patient population.

Methods: TXA-receiving patients (cases) were matched 1:1 with non-TXA-receiving controls on the following criteria: age within 2 years, bone category, and OI Type. Descriptive statistics were used to summarize the data. Fisher Exact Test was performed to compare transfusion status between groups. A Wilcoxon Rank Sum test was performed to assess differences between the groups in days of stay, length of surgery, and estimated blood loss (EBL). All analyses were conducted using SAS version 9.4. $P < 0.05$ was considered statistically significant.

Results: Our TXA-receiving population of 30 patients consisted of 11 females and 19 males. One patient was OI type I, 13 were OI type III, 14 were OI type IV, and 2 were categorized as Other (not Type I through Type IV). We found a significant difference in transfusion status ($P = 0.02$), with zero TXA patients requiring a transfusion compared with 20% of the control cases. There is also a significant difference in median EBL ($P = 0.0004$) between groups, with TXA patients having decreased intraoperative EBL (20 vs. 62.5 mL). There was also a difference in median days of postoperative stay between TXA-receiving and non–TXA-receiving patients ($P = 0.001$; 2.6 vs. 4 d).

Conclusions: Our study concluded that TXA use in OI patients is associated with lower perioperative transfusions and intraoperative blood loss rates. These results support the standard usage of TXA in these patients to reduce intraoperative blood loss.

Level of Evidence: Level III

Key Words: pediatric orthopedics, metabolic management, brittle bone disease, blood loss

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Osteogenesis imperfecta (OI) is a genetic disorder characterized by impaired bone formation, strength, and substantial growth deficiency. Bone fragility and susceptibility to fractures is a hallmark of OI; however, physical phenotypes and the degree of severity vary widely. Multiple clinical or phenotypic forms of OI have been characterized, the most common being an autosomal dominant mutation in one of 2 genes encoding type I collagen.[1–5] Autosomal recessive forms are rare and believed to be due to defects in genes relating to the formation or regulation of the collagen prolyl 3-hydroxyl complex.[1–5]

There is currently no definitive cure for OI. Furthermore, these patients commonly experience extraosseous manifestations such as respiratory dysfunction, poor dentition, cardiac involvement, and susceptibility to infection.[4,6,7] As such, treatments focus on improving quality of life and managing associated comorbidities, such as bisphosphonate usage, which are often a first-line pharmacological therapy to improve bone density.[1–6] OI patients often undergo multiple surgeries aimed at correcting deformities, strengthening extremities, and preventing future fractures. The skeletal deformities and low bone mineral density in OI patients present a unique surgical challenge.[5] While most OI patients tolerate surgery well, operations commonly involve highly vascular bone and occur in small patients; thus, OI patients are uniquely susceptible to increased blood loss, with multiple reports of intraoperative coagulopathy and fatal hemorrhage.[6–10] This risk may be a consequence of abnormal collagen disrupting primary hemostasis and increasing vascular fragility; however, there exists no widespread consensus on the etiology of increased bleeding in this population. Given the unique surgical risks in the OI patient population, investigation of antifibrinolytic agent use to minimize bleeding is of great clinical and therapeutic importance.

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Tranexamic acid (TXA) is one such antifibrinolytic agent. TXA is a lysine analog that reduces bleeding by competitively binding to plasminogen. The landmark CRASH-2 trial confirmed the efficacy of TXA in reducing mortality in hemorrhagic trauma compared with placebo without apparent safety issues.[11–13] A systemic meta-analysis of 129 randomized control trials found that TXA reduced blood loss by ~one-third.[14] Consequently, TXA has gained widespread use and has shown to be efficacious in a variety of domains, ranging from elective surgery to acute traumatic blood loss in postpartum hemorrhage, cardiac surgery, theaters of war, and orthopedics.[11–19] Studies of pediatric cerebral palsy (CP) patients (who also exhibit susceptibility to bleeding) found that TXA use decreased intraoperative blood loss and transfusion rates without associated risk of complications.[20–22]

Few prior studies have investigated the clinical use of TXA in the pediatric OI population. Only 1 study from 2015 could be identified, with Hancock et al finding that TXA decreased the hemoglobin drop in OI patients undergoing intermedullary rodding.[23] The aim of this study was to further investigate the efficacy and safety of intraoperative TXA use in pediatric OI patients.

METHODS

We conducted an IRB-approved retrospective chart review of OI patients who had their first intramedullary rod insertion surgery between 2003 and 2020 at a single institution. Variables collected include the type of OI, gender, age, height, weight, BMI at time of surgery, length of surgery, estimated blood loss (EBL) during surgery, preoperative and postoperative hemoglobin and hematocrit, perioperative transfusion status, presence of thromboembolic events and other complications perioperatively, length of stay in hospital postoperatively, TXA administration, medication use history, past medical history, family history, and prior history of a bleeding disorder or related comorbidity.

Our initial sample was comprised 60 OI patients undergoing long-bone surgery. Of the 60 patients, 30 patients received TXA intraoperatively during surgery and 30 patients served as a control group and did not receive TXA during their surgery. Surgeries were classified on the basis of which bone was operated on during each procedure and were organized as follows: unilateral femur; unilateral femur + any other bone (arms and tibias); bilateral femurs; and bilateral femurs + any other bone (arms and tibias). This categorization schema was used to clearly delineate operations on the femur and tibia primary sites as they commonly cause different amounts of blood loss. This primary site schema enabled us to create 2 cohorts of 30 patients which were evenly matched 1:1 with respect to bone primary site, patient age at date of surgery (+/−2 y), and OI type.

Blood loss was measured by consensus between the anesthesiologist and orthopedist on all cases, as is the current protocol for estimating blood loss in our hospital. We did not have a standard objective mechanism for measuring postoperative blood loss. Unfortunately, we also did not have preoperative hemoglobin measurements on enough patients to allow us to compare to the postoperative hemoglobin that we routinely draw to allow us to quantify blood loss more objectively.

The indication for each surgery was intramedullary rod fixation to correct the bowing of long bones or repair fractures. Tourniquets were used for surgeries of the tibia but not for operations involving the femur. Our data did not include the exact number of osteotomies performed in each case. Furthermore, we were unable to assess the number of surgeries that were potentially revisions for patients who underwent prior surgeries at outside institutions.

Descriptive statistics such as means, medians, minimums, standard deviations, maximums for all continuous variables/counts, and percentages for categorical responses were used to summarize the data. Fisher Exact test was used to compare transfusion status between cases and controls. A Mann-Whitney (Wilcoxon Rank Sum) test was performed to assess for differences between groups in days of stay, length of surgery, and EBL. All analyses were conducted using SAS version 9.4. $P < 0.05$ was considered statistically significant.

RESULTS

The TXA group consisted of 30 patients with a sex distribution of 11 females and 19 males with an average age of 4.7 years old. These patients had a median height of 78.4 cm and a median weight of 12.4 kg. The control (non-TXA) group consisted of 30 patients with a sex distribution of 16 females and 14 males with an average age of 4.5 years old. These patients have a median height of 77.6 cm and a median weight of 15.7 kg. Full descriptive data can be found in Table 1.

In our initial sample of 60 patients, zero had a past medical history outside of their OI diagnosis. There was no history of bleeding problems. In addition, we did not identify any contributory family history in our patients. However, 2 patients had an unknown family history. Neither the TXA nor the control group experienced intraoperative complications, intraoperative fractures, or intraoperative thromboembolic events.

The main finding of this study was that TXA resulted in a statistically significant decrease in median EBL per case. Patients receiving TXA experienced a lower median EBL compared with those who did not receive TXA [(20 vs. 62.5 mL); ($P = 0.0004$; Table 2)]. In addition, the incidence of postoperative transfusion in any form was significantly lower in the TXA group than in the non-TXA controls. [(0%, 0/30) vs. (20%; 6/30); $P = 0.02$; Table 2)]. Transfusions were indicated by hemoglobin <7 g/dL and were administered either intraoperatively or during the perioperative period, whenever deemed medically necessary by the medical team. In addition, the TXA cohort experienced a significant decrease in median days of hospitalization following surgery compared with the non-TXA control group. [(2.65 vs. 4 d); ($P = 0.001$;

TABLE 1. This Figure Shows the Demographics and Other Descriptive Information of Our Patient Population

	Group			
	TXA case (N = 30)	Non-TXA control (N = 30)	Total (N = 60)	*P*
Sex, n (%)	—	—	—	0.19*
Female	11 (36.7)	16 (53.3)	27 (45.0)	—
Male	19 (63.3)	14 (46.7)	33 (55.0)	—
OI type, n (%)	—	—	—	1.00†
I	1 (3.3)	1 (3.3)	2 (3.3)	—
III	13 (43.3)	13 (43.3)	26 (43.3)	—
IV	14 (46.7)	14 (46.7)	28 (46.7)	—
Other	2 (6.7)	2 (6.7)	4 (6.7)	—
Number of bones operated on, n (%)	—	—	—	0.95†
1	9 (30.0)	9 (30.0)	18 (30.0)	—
2	13 (43.3)	11 (36.7)	24 (40.0)	—
3	3 (10.0)	3 (10.0)	6 (10.0)	—
4	5 (16.7)	7 (23.3)	12 (20.0)	—
Bone category n (%)	—	—	—	1.00†
Bilateral femurs	10 (33.3)	10 (33.3)	20 (33.3)	—
Bilateral femurs + any other bone (arms and tibias)	8 (26.7)	8 (26.7)	16 (26.7)	—
Unilateral femur	9 (30.0)	9 (30.0)	18 (30.0)	—
Unilateral femur + any other bone (arms and tibias)	3 (10.0)	3 (10.0)	6 (10.0)	—
Age	—	—	—	0.92‡
N (Missing)	30 (0)	30 (0)	60 (0)	—
Mean (SD)	4.7 (4.04)	4.5 (3.70)	4.6 (3.85)	—
Median (IQR)	4.5 (1.0, 7.0)	3.0 (1.0, 7.0)	4.0 (1.0, 7.0)	—
Range	0.0, 15.0	1.0, 13.0	0.0, 15.0	—
Height at Surgery (cm)	—	—	—	0.86‡
N (Missing)	25 (5)	30 (0)	55 (5)	—
Mean (SD)	83.5 (16.63)	88.1 (25.06)	86.0 (21.58)	—
Median (IQR)	78.4 (69.5, 94.1)	77.6 (68.0, 105.3)	78.0 (68.8, 100.0)	—
Range	62.0, 124.0	63.5, 144.0	62.0, 144.0	—
Weight at surgery (kg)	—	—	—	0.78‡
N (Missing)	30 (0)	30 (0)	60 (0)	—
Mean (SD)	15.8 (11.71)	15.7 (12.54)	15.8 (12.03)	—
Median (IQR)	12.3 (8.7, 15.3)	10.6 (8.3, 17.2)	11.4 (8.4, 16.4)	—
Range	6.7, 57.5	6.1, 57.0	6.1, 57.5	—

*χ^2 *P*-value.
†Fisher Exact *P*-value.
‡Wilcoxon rank sum *P*-value.

Table 2)]. There was no significant difference in the length of surgery between TXA and non-TXA patients [(175.5 vs. 166.5 min); ($P = 0.22$; Table 2)].

DISCUSSION

Existing evidence suggests that patients with OI may be at an elevated risk for increased bleeding.[6–10] Given that OI patients are often small individuals and commonly undergo multiple orthopedic procedures of highly vascular bones throughout their lifetimes, excessive intraoperative blood loss poses a potentially serious problem for this patient population. Despite this elevated risk, few prior studies have investigated ways to mitigate the risks of excessive blood loss in these patients.[23] Therefore, the purpose of this study was to assess the efficacy of TXA in decreasing intraoperative blood loss and transfusion risk for OI patients undergoing intramedullary rodding of the lower extremities.

TXA is an antifibrinolytic agent that has been used for decades in the management of bleeding disorders, heavy menstrual bleeding, and postpartum hemorrhage. More recently, its use has expanded to include other fields, including cardiothoracic, trauma, and orthopedic surgery.[11–19] In particular, a large body of work has evaluated TXA's use in pediatric orthopedic patients with CP, the majority of which demonstrated positive effects of the drug in this patient population.[20–22]

This study identified 30 OI patients who received intraoperative TXA, making it one of the largest retrospective cohort studies involving TXA usage in OI. The main finding was that, compared with the control group, the use of TXA significantly decreased the median intraoperative and perioperative EBL in OI patients (20 vs. 62.5 mL; $P < 0 = 0.0004$). The non-TXA control group had a higher maximum EBL and SD (EBL 400 and 92.2 mL, respectively) versus the maximum EBL and standard deviation of patients that received TXA (EBL 100 and 24.3 mL, respectively). We also found that TXA decreased the rates of intraoperative transfusion for OI patients undergoing intramedullary rodding. [(0% vs. 20%); ($P = 0.02$)].

Our findings are in accordance with the only study to analyze the use of TXA in OI, a 2015 analysis conducted by Hancock et al, which investigated the effect of TXA

TABLE 2. This Figure Shows the Parameters That We Used to Measure the Safety and Efficacy of Tranexamic Acid Usage in Our Patient Population and Some of The Statistical Analysis Results.

	Group			
	TXA Case (N = 30)	Non-TXA Control (N = 30)	Total (N = 60)	*P*
Estimated blood loss during surgery (mL)	—	—	—	0.0004*
N (Missing)	30 (0)	30 (0)	60 (0)	—
Mean (SD)	28.6 (24.17)	97.2 (92.16)	62.9 (75.22)	—
Median (IQR)	20.0 (12.0, 30.0)	62.5 (25.0, 150.0)	27.5 (20.0, 87.5)	—
Range	5.0, 100.0	5.0, 400.0	5.0, 400.0	—
Transfusion during surgery, n (%)	—	—	—	0.02†
No	30 (100.0)	24 (80.0)	54 (90.0)	—
Yes	0 (0.0)	6 (20.0)	6 (10.0)	—
Days of stay	—	—	—	0.001*
N	30	282	58	—
Mean (SD)	2.7 (0.72)	3.6 (1.10)	3.2 (1.02)	—
Median (IQR)	2.7 (2.2, 3.2)	4.0 (3.0, 4.0)	3.2 (2.3, 4.0)	—
Range	1.3, 4.3	1.0, 6.4	1.0, 6.4	—
Length of surgery (min)	—	—	—	0.23*
N (Missing)	30	30	60	—
Mean (SD)	195.7 (62.43)	178.5 (95.86)	187.1 (80.67)	—
Median (IQR)	175.5 (145.0, 244.0)	166.5 (105.0, 213.0)	170.0 (136.5, 235.0)	—
Range	89.0, 319.0	43.0, 420.0	43.0, 420.0	—

*Wilcoxon rank sum *P*-value.
†Fisher Exact *P*-value.
[†]We did not have days of stay data available to us for 2 of our patients in this cohort.

usage in OI patients and used preoperative and postoperative full blood counts to assess its utility in reducing blood loss and transfusion-related complications in OI patients.[23] Similar to our study, they concluded that patients utilizing TXA experienced a significantly decreased drop in hemoglobin compared with patients who did not utilize TXA as well. However, our study used the recorded EBL to assess blood loss, while Hancock et al used decreased preoperative and postoperative hemoglobin. By analyzing specific data on intraoperative transfusions, we were able to expand on their study. Specifically, our finding that TXA usage was associated with a significant decrease in intraoperative transfusion suggests that it can be an effective form of prophylaxis to reduce the transfusion rate in OI patients.

Our finding of significant differences in the variability and degree of EBL during surgery has important clinical implications. These findings show that the non-TXA control group experienced more variability in EBL during surgery compared with the TXA group. Therefore, given that OI patients are an inherently vulnerable patient group with great diversity in disease phenotype and surgical approach, the use of TXA may reduce the case-by-case variability in bleeding risk and lead to more predictable intraoperative and postoperative outcomes. These results support the standard usage of prophylactic administration of TXA in these patients to reduce intraoperative blood loss and risk.

The overall transfusion rate of 20% in our control non-TXA group is similar to what has been reported in prior studies (19.8% to 25.2%) analyzing the use of TXA in pediatric patients undergoing orthopedic surgeries.[24] Patients with CP are believed to have a higher bleeding risk; thus, this patient population and body of literature served as useful proxy when designing our study, outcomes, and goals. In the CP literature, studies are divided as to the utility of TXA in decreasing EBL, transfusion requirements, and length of stay.[24,25,26] A 2022 study by Compton et al analyzed the use of TXA in CP children undergoing femoral osteotomy and found TXA use decreased the overall transfusion rate compared with control [(13.8% vs. 25.2%); ($P < 0.05$)], but found no significant difference in EBL, hemoglobin decrease, or hospital length of stay.[21] Other studies found that TXA use had a significant effect on transfusion rate or EBL in CP patients undergoing hip reconstruction.[19,20] Collectively, these studies indicate that there may be similar findings of transfusion rates and bleeding risk in the pediatric orthopedic population, but the efficacy of TXA to affect these variables has yet to be elucidated.

Lastly, we showed that patients receiving TXA experienced a significant decrease in the mean days of hospital stay compared with those who did not receive TXA [(2.6 vs. 4 d); ($P = 0.0001$)]. A study done by Bower et al concluded that perioperative blood transfusions are predictive of slower and more complicated postoperative recovery.[27] While there are numerous factors that may affect the length of admission, the conclusion from the Bower study provides a possible explanation for the disparities in hospital stay observed between the TXA and non-TXA cohorts in this study. We theorize that the lower rates of transfusion and decreased intraoperative blood loss may lead to more prompt recovery times and expedited discharge from the hospital. There are certainly other variables, such as surgeon preferences, which may affect discharge time. While it is beyond the scope of the

current study to study this specific variable, all of our patients were treated at the same institution; therefore, we expect discharge protocols to be relatively similar between the TXA and non-TXA group. Furthermore, we identified no outlier cases which may have affected our results.

This study did not find any increased risk with the use of TXA. We identified no complications or ischemic/thromboembolic events (eg, deep venous thromboses or strokes) in the postoperative period for any of the patients in this study. There were no acute events that could have served as outliers to skew the aforementioned findings on transfusion rates, EBL, or average length of stay. There was also no direct evidence that may suggest increased risk posed by TXA use. These findings are similar to a recent review of 216 trials involving TXA usage and risk of thromboembolic events. The authors found that TXA is not associated with any increased risk of thromboembolic events, regardless of dosing, and therefore could be useful to prevent blood loss in surgical scenarios.[28] Prior studies have also examined the impact that transfusions have on complications and costs to patients and found that transfusions were associated with both an increase in costs and associated complications for the patients.[29] These results suggest that TXA may also be beneficial in the form of lower costs to the patient and health care system.

Some limitations include its retrospective nature, which prevents us from proactively gathering any additional data which would lend itself to more robust conclusions. For example, preoperative and postoperative hemoglobin and hematocrit were missing for a sizable portion of our patient population and were not measured extensively enough to provide any significant insight. These variables would enable us to accurately assess the impact of volumetric blood loss in each surgery and compare it to the hemoglobin drop observed in the Hancock study. In addition, the lack of long-term follow-up removed our ability to include any potential complications that occurred farther out from surgery.

Future studies can expand on ours by including other procedure types and those performed in other anatomic sites. In addition, a larger sample size with longer follow-ups can validate that these trends are more representative of the OI population would improve generalizability. A larger sample would also allow multivariate regression to elucidate TXA usage safety in this patient population in context with relevant confounders.

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