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CASE REPORT

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Utility of topical tranexamic acid for adult patients with spinal deformity and contraindications to systemic tranexamic acid: initial experience and report of 2 cases

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Tranexamic acid (TXA) is an antifibrinolytic agent with demonstrated efficacy in reducing blood loss when administered systemically. However, in patients with contraindications to systemic or intravenous TXA, topical TXA (tTXA) has been shown to reduce perioperative blood loss, with some studies suggesting equivalence compared to systemic TXA. However, these studies have been conducted in healthy cohorts without contraindications to systemic TXA. In the surgical management of adult spinal deformity (ASD), comorbid disease is commonly encountered and may preclude use of systemic TXA. In this subset of patients with ASD who have contraindications for systemic TXA, use of tTXA has not been reported.

The primary objective of this study was to conduct a systematic review on the use of tTXA in spine surgery and to present the authors' initial experience with tTXA as a novel hemostatic technique for 2 patients with medically complex ASD. Both patients had contraindications to systemic TXA use and underwent high-risk, long-segment fusion operations for correction of ASD. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to obtain studies related to spine surgery and tTXA from the National Institutes of Health PubMed (www.pubmed.gov) database. Criteria for final selection included a demonstration of quantitative data regarding operative or postoperative blood loss with the use of tTXA, and selection criteria were met by 6 articles.

Topical TXA may offer a potential therapeutic role in reducing intra- and postoperative blood loss following long-segment spinal fusion surgeries, particularly for medically complex patients with contraindications to systemic TXA. It is reasonable to consider the use of tTXA as a salvage technique in complex high-risk patients with contraindications to systemic TXA, although further research is needed to delineate safety, magnitude of benefit, and optimization of dosing.

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KEYWORDS topical; tranexamic acid; spine; spinal; fusion; TXA; deformity

Surgical treatments for adult spinal deformity (ASD) are typically complex procedures associated with significant blood loss and the potential risk for perioperative coagulopathy, as well as requisite blood product administration, volume resuscitation, and their associated risks.[28,29] Acute intraoperative blood loss can be managed with allogeneic transfusions; however, the risks include transfusion-related acute lung injury, hemolytic transfusion reactions, and transfusion-associated sepsis.[31] Reducing perioperative blood loss in complex spine surgery is correlated with improving patient outcomes by decreasing postoperative hemorrhagic complications, associated coagulopathies, and anemias.[37] Currently, there are limited techniques to decrease intraoperative surgical site bleeding.[3,10,21,22,26,37] Tranexamic acid (TXA), a synthetic antifibrinolytic agent, has been shown to reduce surgical site bleeding in orthopedic and cardiac procedures as well as several short-segment spine series.[6,11,13,25,35,36] However, contraindications to systemic TXA (through either oral or intravenous [IV] routes) exist due to increased risk for prothrombotic, renal, or neurotoxic complications. Prior studies have evaluated the efficacy of topical TXA (tTXA) compared to systemic TXA in healthy patients without contraindications to systemic TXA. Although they demonstrate equivalence in surgical site bleeding, the safety of tTXA in patients with systemic contraindications has yet to be reported.[5,14,17,26,27] Here, we present our initial experience with tTXA as a salvage hemostatic technique that we

ABBREVIATIONS AP = anterior-posterior; ASD = adult spinal deformity; DVT = deep venous thrombosis; IV = intravenous; PE = pulmonary embolism; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PSIF = posterior spinal instrumentation and fusion; tTXA = topical tranexamic acid; TXA = tranexamic acid.

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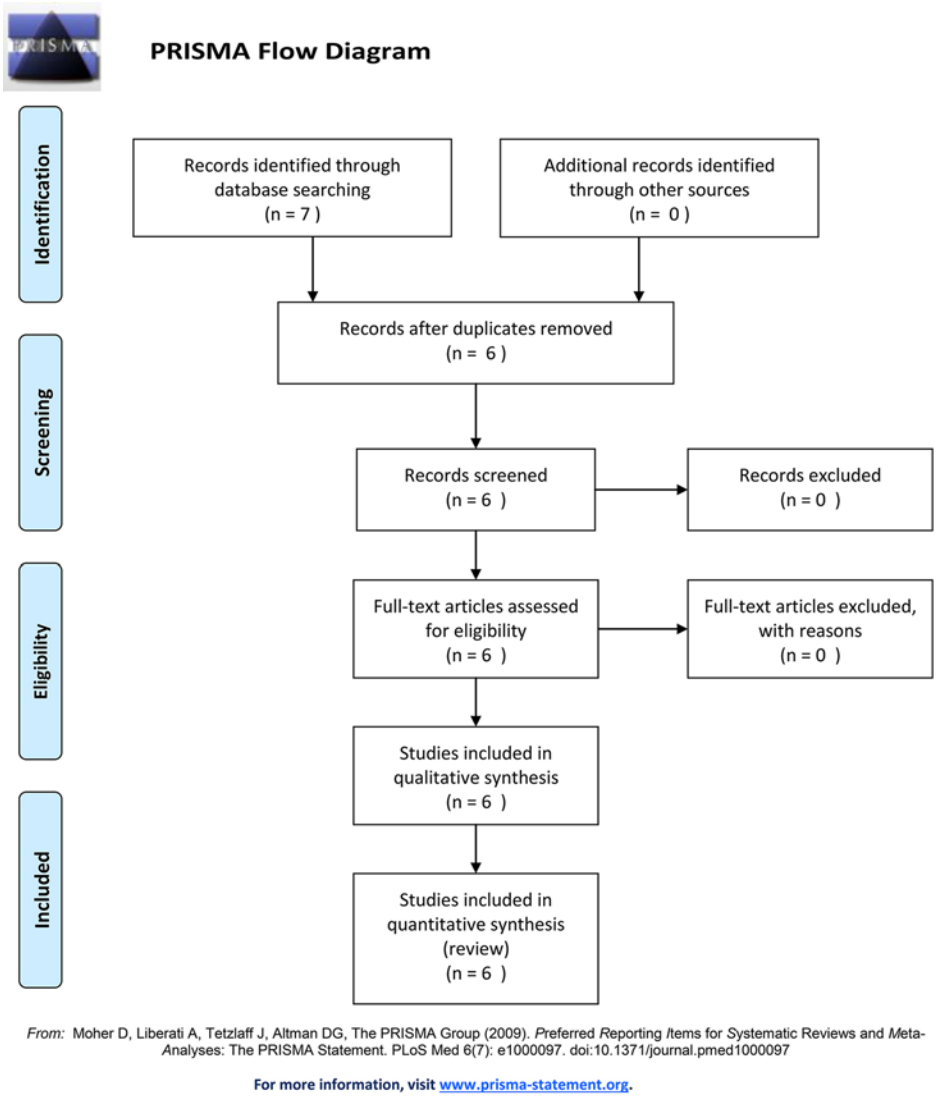

FIG. 1. PRISMA flowchart for literature review. Figure is available in color online only.

used in similar fashion to its use in cardiac and orthopedic surgery. The 2 patients with ASD in our report had contraindications to systemic administration of TXA, and thus tTXA was used as an alternative hemostatic method during high-risk, long-segment fusion for correction of ASD.

Methods

For preparation of the tTXA, we independently first mixed 3 g of TXA into 200 ml of normal saline to create the concentrated mixture. Numerous sterile sponges were then soaked in this mixture. During the intraoperative period, we used freshly soaked sponges and packed them into the operative cavity we were not actively working in for 5- to 10-minute intervals. This occurred at multiple time points throughout the surgery—during the surgical exposure, during instrumentation, and prior to wound closure. We noted subjective hemostasis from the surgical site through use of this technique. We always used fresh sponges when repacking the wound site. The used sponges were discarded. Typically, repacking the wound was done 3 times on each side. Dosing used for the tTXA mixture is directly in line with dosing used by orthopedic surgeons in joint replacement as well as the few papers on tTXA in small-segment spinal fusion procedures.[18,20,33]

This review follows the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and by the Cochrane Handbook for Systematic Reviews of Interventions. Please see Fig. 1 (the PRISMA flowchart for literature review) for more details. Studies pertaining to spine surgery and tTXA were identified from the National Institutes of Health PubMed (www.pubmed.gov) database. Initial search terms used included "spine surgery," "spine," "topical tranexamic acid," and "topical TXA." The search was conducted in January 2018. Article reference lists were also used to identify additional pertinent studies, leading to a total of 7 identified articles. Two of the articles were published by the same authors with the same data, so one

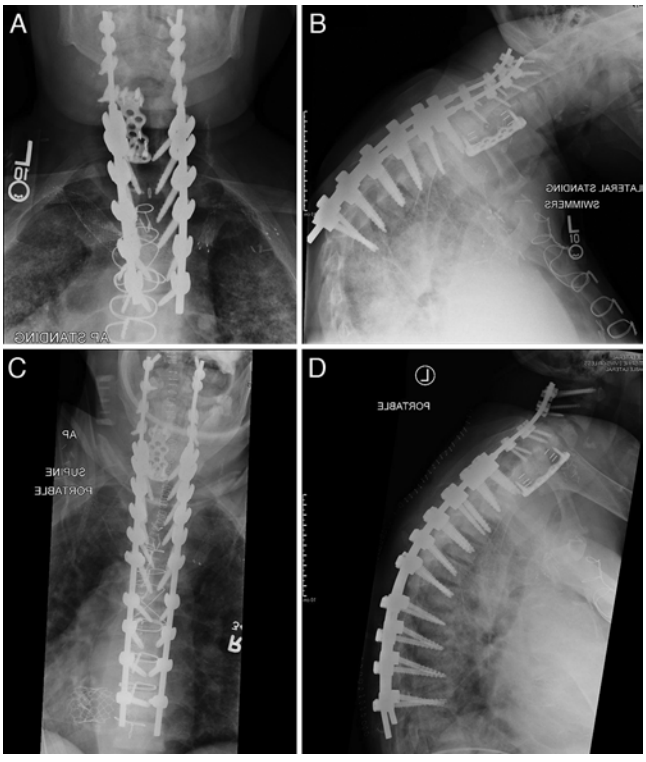

FIG. 2. Case 1. Extension of cervical thoracic spinal fusion to C1–T10. **A:** Preoperative anterior-posterior (AP) view. **B:** Preoperative lateral view. **C:** Postoperative AP view. **D:** Postoperative lateral view.

of them was excluded. Criteria for final selection included a demonstration of quantitative data regarding operative or postoperative blood loss with the use of tTXA. These selection criteria were met by 6 articles. Each study was assessed for the number of patients, year of publication, study design, number of levels of the spinal procedure, intervention, outcomes, and thrombotic complications.

Case Reports

Case 1

History and Examination

A 47-year-old man presented to our clinic with progressive thoracic kyphosis and worsening myelopathy following a prior C2–T6 instrumented spinal fusion complicated by pseudarthrosis. His medical history was complex and significant for stage V chronic kidney disease requiring dialysis, superior vena cava syndrome, endocarditis status after mitral valve replacement on warfarin, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, renal osteodystrophy, chronic femoral vein deep venous thrombosis (DVT), and a history of prior pulmonary embolism (PE). The patient's poor overall health required multidisciplinary preoperative clearance. Despite the potential high risks of surgery, the patient wished to proceed with elective operative intervention due to the substantial pain and disability resulting from his spinal deformity and progressive myelopathy. The patient was bridged with a therapeutic heparin infusion, which was paused before surgery.

TABLE 1. Operative details in 2 patients with ASD and contraindications for systemic TXA who underwent high-risk spine surgery

Variable	Case 1	Case 2
No. of levels	16	13
Op time (mins)	346	512
Blood loss (ml)	4000	7000
Transfusion		
Crystalloid (ml)	2000	7000
Colloid (ml)	1850	2000
Blood (ml)	1162	4305
Fresh-frozen plasma (ml)	0	937
Platelet (no. of units)	1	2
Cryoprecipitate (no. of units)	1	4
Blood transfused 48 hrs postop (ml)	583	1296
Drain output 24 hrs postop (ml)	610	1030
Total drain output (ml)	780	1705
Total drain duration (hrs)	96	96

Operation

For correction of the deformity, the patient underwent a C1–T10 posterior spinal instrumentation and fusion (PSIF) with Smith-Petersen osteotomies at the T4–5, T5–6, T6–7, T7–8, and T8–9 levels (Fig. 2). Operative and hematological details are summarized in Table 1. Due to the patient's aforementioned prothrombotic risk, systemic TXA was contraindicated and tTXA was used during surgery. Topical TXA was prepared as a concentrated mixture of 3 g of TXA per 200 ml of saline.[18,20,33] Sterile sponges were soaked in this mixture. These sponges were then placed in the operative cavity for 5-minute intervals at multiple time points throughout the surgery—during the surgical exposure, instrumentation, and prior to wound closure. Bleeding from the surgical site was subjectively improved through use of this technique. Please see the *Methods* section for additional details on technique and dosing.

Postoperative Course

Following the surgery, the patient was transported to the ICU in stable condition with planned early extubation. Ten hours after surgery, the patient developed a decline in lower-extremity strength. The patient's neurological examination demonstrated pressure-dependent weakness, and postoperative imaging demonstrated a medial T10 pedicle screw for which the patient was taken back to the operating room for repositioning of the screw. The patient remained stable and did not have any other complications during the postoperative period. Of note, the patient did not suffer any thrombotic events during the postoperative course.

Case 2

History and Examination

A 67-year-old woman presented to our clinic for further evaluation of sagittal malalignment and neurogenic claudication in the setting of prior spinal decompression

including Smith-Petersen osteotomies at the L1–2, L2–3, and L3–4 levels and a T9–L4 PSIF. The patient demonstrated positive sagittal spinopelvic malalignment and associated increased back pain and lower-extremity radicular complaints. Past medical history was significant for stroke, morbid obesity, and coronary artery disease status after placement of a drug-eluting stent on dual-antiplatelet therapy. The patient's stent was placed 7 months prior to this procedure, and the patient was instructed to suspend both clopidogrel and aspirin use 3 days prior to surgery.

Operation and Postoperative Course

For correction of the patient's sagittal malalignment, we performed T4 to the pelvis PSIF with an extended pedicle subtraction osteotomy at the L4 level and L3–4 transforaminal lumbar interbody fusion (Fig. 3).[2] Due to her recent drug-eluting stent placement and prior stroke history, systemic TXA was contraindicated, and tTXA was used as a salvage hemostatic technique. Similar to the patient in case 1, surgical sponges soaked in 3 g TXA with 200 ml of normal saline were packed in the surgical wound intermittently throughout the surgical exposure, instrumentation, and prior to wound closure.[18,20,33] Local hemostasis was achieved and could be appreciated during the surgery by the surgical team. Operative details are summarized in Table 1. The patient did not suffer any complications perioperatively and had no thrombotic events during the postoperative course.

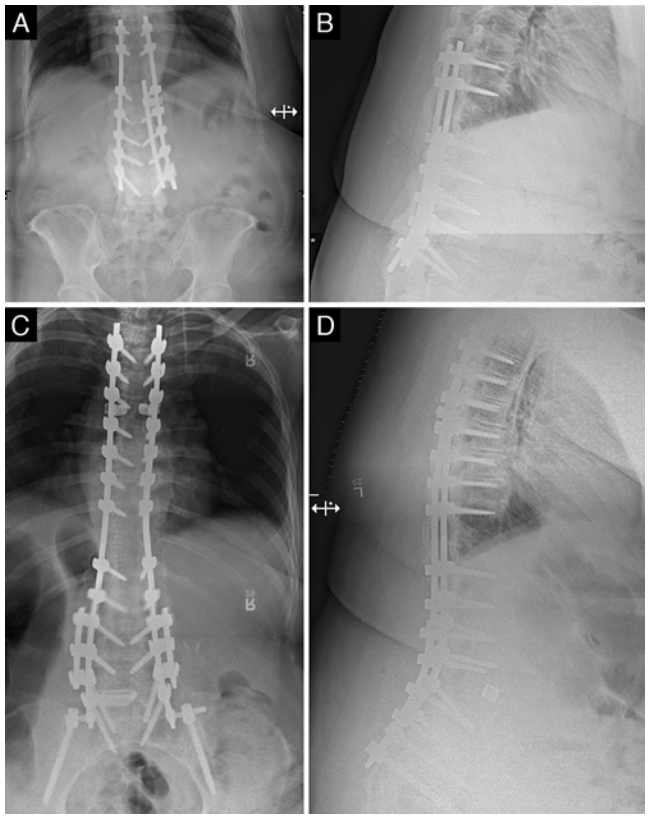

FIG. 3. Case 2. Extension of T9–L4 posterior fusion to T4–iliac posterior fusion. **A:** Preoperative AP view. **B:** Preoperative lateral view. **C:** Postoperative AP view. **D:** Postoperative lateral view.

Results

Among spine patients, several studies have demonstrated a benefit of tTXA usage in reducing perioperative blood loss. Six studies met inclusion criteria for our review, and the findings are summarized in Table 2.[6,11,13,25,35,36] Generally, each of these studies found a significant reduction in perioperative blood loss or postoperative drain output among patients receiving tTXA. Of note, the patient populations of these study groups included patients undergoing short-segment procedures and excluded patients with complex medical conditions (including comorbid conditions that might preclude systemic TXA). In addition, the goal of these studies was to determine efficacy or noninferiority of tTXA, and often did not comment on the prothrombotic risk associated with its use. In addition, there were no thrombotic complications reported among 303 patients.

Discussion

Tranexamic acid is a synthetic antifibrinolytic agent that competitively inhibits lysine-binding sites on plasminogen molecules and noncompetitively inhibits the binding of plasmin to fibrin.[30] Systemic TXA has been shown to decrease perioperative blood loss among patients undergoing spine surgery.[4,16] Adverse events with systemic TXA administration have been reported, however, and include neurotoxicity, acute renal cortical necrosis, toxic epidermal necrolysis, DVT, and PE.[15,16,23,32] As such, systemic TXA is relatively contraindicated in patients at risk of thrombotic complications, and current reviews recommend prudence in IV administration of TXA for high-risk patients.[7,8,19] Furthermore, despite the demonstrated efficacy of tTXA in patients undergoing spine and orthopedic joint replacement surgery, prior studies have selectively excluded medically complex patients with high thrombotic risks.[19] Consequently, the safety and efficacy of tTXA in patients with relative contraindications to systemic TXA has not yet been rigorously investigated. Although definitive conclusions cannot be drawn from our case report, we report a novel technique for TXA administration.

Previous studies suggest that tTXA may provide equivalent surgical site benefits with regard to bleeding and transfusion rates while attenuating the thrombotic complication risks of systemic TXA.[1,9,24,26,33] Our systematic review cites 6 studies that have found clinical efficacy of tTXA in reducing perioperative blood loss in short-segment spine procedures. More significantly, the findings suggest that the overall risk of adverse events is quite low, with no associated adverse events reported among 303 patients. Given these findings, it is possible that tTXA may provide additional benefits to local hemostasis while attenuating the risks of adverse events, especially as a salvage technique for patients with contraindications to systemic TXA. Orthopedic studies have reported minimal postoperative tTXA absorption based on systemic concentrations of TXA following topical administration.[12,33] Furthermore, because TXA is an antifibrinolytic agent, it has significant properties in preventing clot breakdown. Two recent randomized controlled trials demonstrated that TXA-soaked

TABLE 2. Systematic review of current tTXA spine studies

Authors & Year	Study Size	Study Design	No. of Levels	Intervention	Outcomes	Thrombotic Complications
Krohn et al., 2003	30	Prospective randomized	Not documented	tTXA vs IV TXA	Significant reduction in blood loss	Not evaluated
Saberi et al., 2010	100	Prospective randomized	Unilat 1-level (n = 50) or bilat 2-level (n = 50)	tTXA irrigation vs control (saline)	Decrease in drain output & decreased LOS	Not evaluated
Liang et al., 2016	90	Prospective randomized	2.4 levels on average	TXA-soaked Gelfoam, Gelfoam alone, & control groups	Significant decrease in postop drain output, length of drain, shorter hospital stay	Not evaluated
El-Sharkawi et al., 2017	83	Prospective randomized	Not documented	tTXA, systemic TXA, or no TXA	No significant blood loss or transfusion between tTXA & IV TXA; both groups significantly decreased vs control group ("no TXA")	1 occurrence of DVT w/ IV TXA, 0 complications w/ tTXA
Ren et al., 2017	100	Retrospective case-control	1–3 levels	tTXA vs normal saline soak	tTXA: significantly lower postop blood loss, removal time of drainage tube, & LOS	0 cases of postop MI, CVA, DVT, or PE
Xu et al., 2017	120	Prospective randomized	Not documented	Control gelatin sponge, collagen hemostatic sponge, & tTXA	tTXA: significantly less drain output POD 1 & total postop drainage, no significant difference in transfusion rates or LOS	No periop DVT/PE events documented for the 3 groups

CVA = cerebrovascular accident; LOS = length of hospital stay; MI = myocardial infarction; POD = postoperative day.

absorbable gelatin sponges were efficacious in reducing postoperative blood loss for medically cleared patients undergoing posterior lumbar procedures.[17,34] All of these studies describe the use of tTXA in short-segment spinal procedures. However, given the efficacy in smaller procedures, it is possible that the application may also prove to be useful in the treatment of medically complex patients undergoing large-segment spinal procedures.

Our experience with tTXA anecdotally improved perioperative blood loss in 2 patients with severe comorbidities who were undergoing large, complex surgical procedures. Blood loss remained quite elevated in both patients (4 L and 7 L, respectively), but there was a subjective decrease in blood loss following topical application of TXA and there were no apparent adverse events associated with its use. Postoperatively, during the first 24 hours, drainage for both patients was high, but quickly dropped off thereafter. For the patient in case 1, drain output during the first 24 hours accounted for 78% of the total drain output. For the patient in case 2, drain output during the first 24 hours accounted for 60% of the total output. Importantly, despite both patients having a prothrombotic history, neither suffered a prothrombotic complication during the perioperative period. There are intrinsic limitations to this study design; we are only reporting on 2 cases with subjective intraoperative observations. Although definitive conclusions cannot be drawn from this limited case series, our findings, combined with previous literature that supports the efficacy of tTXA for reducing blood loss, suggest that further study of tTXA application for large-deformity cases in high-risk patients is warranted.

Conclusions

Topical TXA may offer a potential therapeutic role in reducing intra- and postoperative blood loss following long-segment spinal fusion surgeries, particularly for medically complex patients with contraindications to systemic TXA. Our own experience in 2 patients with complex, high-risk surgeries demonstrated subjective efficacy intraoperatively and was without significant perioperative or postoperative thrombotic complication. It is reasonable to consider the use of tTXA as a salvage technique in patients undergoing complex, high-risk surgery and with contraindications to systemic TXA, although further research is needed to further delineate safety, magnitude of benefit, and optimization of dosing.

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Disclosures

Dr. Shaffrey has direct stock ownership in NuVasive. He is also both a consultant for and a patent holder with Medtronic, NuVasive, and Zimmer-Biomet. Dr. Smith is a consultant for Zimmer-Biomet, NuVasive, K2M, AlloSource, and Cerapedics. He receives support for a non–study-related clinical or research effort that he oversees from DePuy Synthes. He receives fellowship funding from NREF and AOSpine.

Author Contributions

Conception and design: Desai, Shaffrey. Acquisition of data: Desai. Analysis and interpretation of data: Shaffrey. Drafting the article: Desai, Taylor, Chen, Smith. Critically revising the article: all authors. Reviewed submitted version of manuscript: Desai, Taylor, Buell, Mullin, Naik, Smith. Approved the final version of the manuscript on behalf of all authors: Desai. Administrative/technical/material support: Naik. Study supervision: Shaffrey.

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