Systematic review and meta-analysis of topical tranexamic acid in spine surgery

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OBJECTIVE Tranexamic acid (TXA) is an antifibrinolytic drug associated with reduced blood loss in a range of surgical specialties, including neurosurgery, orthopedic surgery, and cardiac surgery. Concerns about venous thromboembolism and seizures from intravenous (IV) TXA have led to increased use of topical TXA. Given the relative scarcity of the literature on topical TXA compared with that on IV TXA within neurosurgery, the authors aimed to conduct a systematic review and meta-analysis on the safety, efficacy, and optimal administration of topical TXA in a wide range of spinal procedures and pathologies.

METHODS The PRISMA guidelines, Cochrane risk of bias tool, and Newcastle-Ottawa Scale were used to extract randomized controlled trials and high-quality case-control and cross-sectional/cohort studies (adult studies only) from PubMed, Web of Science, Cochrane Library, and Embase published between 2016 and 2023. Studies were analyzed by two independent reviewers for variables including dosage, TXA administration route, type of spine procedure, blood loss, adverse events including thromboembolism and infection, postoperative hemoglobin level, and hospitalization length. Pooled analysis comparing intraoperative and postoperative blood loss, postoperative hemoglobin levels, and hospitalization length of stay on the basis of route of TXA administration was conducted.

RESULTS Four cohort studies, 1 cross-sectional study, 1 case-control study, and 12 randomized controlled trials, together involving 2045 patients, were included. The most common route of topical TXA administration was via TXA in saline solution. Other routes of topical TXA included retrograde injection and TXA-soaked Gelfoam. In pooled analysis, topical TXA significantly reduced visible blood loss (standardized mean difference [SMD] −0.22, 95% CI −0.45 to −0.00001), postoperative blood loss (SMD −1.63, 95% CI −2.03 to −1.22), and length of hospital stay (SMD −1.02, 95% CI −1.42 to −0.81), as well as higher postoperative hemoglobin (SMD 0.59, 95% CI 0.34–0.83), compared with non-TXA controls. No significant differences in outcomes were found between topical and IV TXA or between combined (topical and IV) and IV TXA. Thromboembolism and infection rates did not significantly differ between any TXA administration group and non-TXA controls.

CONCLUSIONS In pooled analyses, topical TXA was associated with decreased perioperative blood loss in a wide range of scenarios, including cervical spine surgery and thoracolumbar trauma, as well as in patients with a thromboembolic history.

https://thejns.org/doi/abs/10.3171/2023.7.FOCUS23363

KEYWORDS antifibrinolytic; hemostasis; neurosurgery; spine surgery; tranexamic acid; topical; TXA

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loss when administered orally, intravenously, topically, or as a combination of the latter two routes.\textsuperscript{6,8,9} 

In neurosurgery, intravenous (IV) TXA is the most studied TXA administration route.\textsuperscript{6,8,9} Nonetheless, there remain concerns regarding postoperative seizures and thromboembolic events after IV TXA administration, with the highest reported incidence of seizure being 3.5%.\textsuperscript{10,11} Topical TXA limits systemic exposure, expanding the clinical indications of TXA.\textsuperscript{12} Although recent reviews have emphasized the efficacy of topical TXA for reducing blood loss, the literature on topical TXA, including randomized controlled trials (RCTs), is not as robust compared with that on IV TXA.\textsuperscript{13–16} There have been limited investigations into the safety and efficacy of topical TXA in the wider clinical context of spinal oncology, cervical spine disorders, and thoracolumbar trauma.

Applying the keywords “topical tranexamic acid and spine surgery” within Cochrane Library, Embase, Web of Science, and PubMed, we noted that approximately 70% of the search items were published between 2019 and 2023. Prior meta-analyses have focused on articles published before 2019; hence, an update on topical TXA may be timely.\textsuperscript{15,17–19} Here, we used RCTs, cohort studies, and cross-sectional studies from 2016 through 2022 to conduct a quantitative review of the safety and efficacy of topical TXA for various spinal procedures. To the best of our knowledge, this review includes the most recent articles regarding topical TXA.

Methods

Literature Search

We followed the PRISMA guidelines to optimize reporting quality.\textsuperscript{20} An expansive search of electronic databases was conducted, including PubMed, Embase, Cochrane Library, and Web of Science, for studies published from January 1, 2016, to January 1, 2023. The following keywords were used in the database search: “local infiltration/topical tranexamic acid” AND “neurosurgery,” “spine surgery,” “interbody fusion,” “spinal fusion,” “spinal tumor,” “trauma,” and “thoracolumbar fracture.”

Study Selection and Quality Assessment

Two researchers independently assessed the studies, reaching a consensus on their relevance. Disagreements were resolved via a third party (A.K.C.). The full texts of the RCTs and cross-sectional, cohort, and case-control studies were read and included if they met at least three of the following criteria: 1) inclusion of adult patients (age ≥18 years) who underwent spinal surgery; 2) comparison of combined or topical TXA versus controls or IV TXA; 3) published in English; and 4) evaluation of dosage, safety, and efficacy of topical TXA using at least 1 of the following variables of PBL, VBL, postoperative hemoglobin, length of hospital stay (LOS), or complications (including infections and thrombosis). Studies regarding topical TXA that did not meet these criteria were evaluated and included in the Discussion only.

The research quality of the nonrandomized studies was assessed independently by two trained researchers using the Newcastle-Ottawa Scale, with studies scoring 7–9 considered to have low bias.\textsuperscript{21} Studies with scores less than 7 were excluded. For RCTs, the Cochrane risk of bias tool for randomized trials was used to assess the risks of bias in randomization, intended interventions, missing outcome data, measurement outcomes, and reporting of results.\textsuperscript{22}

Data Extraction and Analysis

Extracted data included the study and treatment groups, sample size, and mean ± standard deviation (SD) PBL, VBL, hemoglobin level, transfusion rates, and LOS. Mean differences without standard deviations were considered in the systematic review, not the pooled analysis. Hemoglobin values obtained immediately after the procedure were used. Meta-analysis was performed using the meta package in RStudio version 4.3.0. The metacont function was used to perform a random-effects model meta-analysis. Hedges’ g method was applied to calculate standardized mean difference (SMD), the Hartung and Knapp method was used to estimate variance, and the restricted maximum likelihood method was used to assess heterogeneity. Forest plots were generated using the forest.meta function.

Results

Database searches in Embase, Web of Science, Cochrane, and PubMed between January 1, 2016, and January 1, 2023, yielded 264, 267, 80, and 110 papers, respectively (Fig. 1). After removal of duplicates, 128 papers remained, with 78 involving topical TXA in adult spine surgery. After exclusion of meta-analyses, reviews, letters to the editor, and cohort studies scoring less than 7 on the Newcastle-Ottawa Scale, 18 studies remained. Table 1 lists the PBL, VBL, hemoglobin level, and LOS, complications, and dosages for each of the 18 papers. Complications were reported in half the included studies, with no significant differences reported between TXA and controls. Transfusion rates were not reported with standard deviations, preventing pooled analyses.

Topical TXA Compared With No TXA

Visual Blood Loss

Mallepally et al. found significantly lower VBL (410.57 ± 189.72 ml vs 783.33 ± 332.71 ml) in the topical TXA group compared with the saline control group during single-level open transfaminal lumbar interbody fusion (p < 0.001).\textsuperscript{23} Farzaneegan et al. (lumbar laminectomy and discectomy) and Khadivi et al. (cervical laminectomy and fusion) also reported significantly reduced VBL with topical TXA (p < 0.05).\textsuperscript{24,25} Other studies showed no significant difference in VBL between groups.\textsuperscript{6,12,26–34} This discrepancy may be because topical TXA was applied throughout the procedure in two of the studies that displayed significance rather than immediately before closure, as was the case in many of the other studies.\textsuperscript{23–25} Pooled analysis showed a significant decrease in VBL (SMD −0.22, 95% CI −0.45 to −0.00001) (Fig. 2A).

Postoperative Blood Loss

All studies demonstrated a significant reduction in PBL with topical TXA compared with no TXA.\textsuperscript{6,12,23,25–35} For
example, 1 study (that included patients with degenerative grade 1 or 2 spondylolisthesis treated with single-level interbody fusion) reported PBL of 67.3 ± 32.6 ml with topical TXA compared with 316.3 ± 110.1 ml in the non-TXA group (p < 0.00001). Pooled analysis demonstrated a significant decrease in PBL (SMD −1.63, 95% CI −2.03 to −1.22) (Fig. 2B).

Postoperative Hemoglobin

Most papers that reported hemoglobin levels also reported reduced blood loss and higher hemoglobin levels with topical TXA compared with no TXA (SMD 0.59, 95% CI 0.34–0.83) (Fig. 2C).

Length of Stay

LOS was reduced in nearly all studies. Shen et al. reported the greatest decrease in LOS (6.08 ± 0.77 days) with topical TXA compared with no TXA (9.78 ± 2.03 days) (p < 0.001). Two studies that did not report significant differences in LOS investigated procedures traditionally associated with shorter LOS (cervical surgery, lumbar laminectomy). Pooled analysis showed a significant decrease in LOS after topical TXA (SMD −1.02, 95% CI −1.42 to −0.61) (Fig. 2D).

Topical TXA Compared With IV TXA

Visual Blood Loss

Four of five studies demonstrated a significant increase in visual blood loss with topical TXA compared with IV TXA (p < 0.0001). Pooled analysis showed a significant increase in visual blood loss with topical TXA compared with IV TXA (SMD 0.29, 95% CI 0.09–0.49) (Fig. 2E).

FIG. 1. PRISMA model used for the systematic review of the literature. Data added to the PRISMA template (from Page MJ, McKenzie JE, Bossuyt PM, Bouthinon I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71) under the terms of the Creative Commons Attribution (CC BY 4.0) License (https://creativecommons.org/licenses/by/4.0/).
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study &amp; Year</th>
<th>Study Size</th>
<th>Study Design</th>
<th>Type of Surgery</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Complications</th>
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<tbody>
<tr>
<td>Arain et al., 2021</td>
<td>Prospective RCT at a single tertiary academic center</td>
<td>28</td>
<td>Expanding decompressive lumbar laminectomy of 1-4 levels</td>
<td>Group 1: Surgical site bathed in saline immediately prior to wound closure Group 2: Initiation dose of 10 mg/kg IV TXA prior to incision and 2nd dose after 3 hrs Group 3: Topical TXA (3 g TXA diluted in 250 ml saline) immediately prior to wound closure</td>
<td>Group 1: PBL 172 ± 98.2 ml; VBL 211.2 ± 152.5 ml; HGB NA; LOS* Group 2: PBL 72.8 ± 52.9 ml†; VBL 157.1 ± 119.2 ml; HGB NA; LOS* Group 3: PBL 52.0 ± 50.0 ml†; VBL 175.6 ± 153 ml; HGB NA; LOS*</td>
<td>No statistically significant differences in postop complications between groups</td>
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<tr>
<td>Arun-Kumar &amp; Naresh-Babu, 2021</td>
<td>Single-center RCT</td>
<td>78</td>
<td>Degenerative grade 1 or 2 spondylolisthesis treated with single-level interbody fusion</td>
<td>Group 1: 10 ml 2% lidocaine with adrenaline prior to incision Group 2: IV TXA (single dose of 1 g) prior to incision Group 3: Topical TXA (1 g in 100 ml saline) immediately prior to wound closure</td>
<td>Group 1: PBL 316.3 ± 110.1 ml; VBL 344.0 ± 88.4 ml; HGB 9.05 ± 0.48 g/dl; LOS 4.4 ± 1.6 days Group 2: PBL 190 ± 112.7 ml†; VBL 223.6 ± 40.1 ml†; HGB 11.04 ± 0.33 g/dl†; LOS 3.1 ± 0.5 days† Group 3: PBL 67.3 ± 32.6 ml†‡; VBL 311.3 ± 84.7 ml†‡; HGB 9.09 ± 0.73 g/dl‡; LOS 3.0 ± 0.6 days†</td>
<td>No complications reported</td>
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<tr>
<td>Chen et al., 2022</td>
<td>Single-center RCT</td>
<td>133</td>
<td>Cervical expansive open-door laminoplasty</td>
<td>Group 1: No intervention Group 2: TXA administered through Gelfoam soaked with 1 g in 20 ml saline prior to wound closure Group 3: 1 g TXA in 20 ml saline administered through retrograde injection in the wound drain postop &amp; clamped for 1 hr</td>
<td>Group 1: PBL 275.45 ± 75.27 ml; VBL 125.20 ± 45.44 ml; HGB 11.28 ± 1.76 g/dl; LOS 7.50 ± 1.25 days Group 2: PBL 156.60 ± 38.63 ml†; VBL 138.60 ± 52.76 ml; HGB 12.14 ± 1.53 g/dl†; LOS 5.64 ± 0.96 days† Group 3: PBL 126.60 ± 31.27 ml†‡; VBL 123.30 ± 35.83 ml; HGB 12.58 ± 1.67 g/dl‡; LOS 5.31 ± 1.18 days‡</td>
<td>No complications reported</td>
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<tr>
<td>Emrah et al., 2021</td>
<td>Single-center cross-sectional study</td>
<td>60</td>
<td>Thoracicolumbar fusion surgery</td>
<td>Group 1: No intervention Group 2: Topical TXA (1 g) immediately prior to wound closure</td>
<td>Group 1: PBL 241.6 ± 51.8 ml; VBL 125.20 ± 45.44 ml; HGB 11.28 ± 1.76 g/dl; LOS 5.53 ± 1.25 days Group 2: PBL 136.0 ± 53.5 ml; VBL 650.0 (487.5–812.5) ml; HGB NA; LOS 5.53 ± 1.25 days</td>
<td>No complications reported</td>
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<td>Erdogan et al., 2022</td>
<td>Retrospective observational study</td>
<td>112</td>
<td>Retropsoic thoracic/lumbar spine fusion surgery</td>
<td>Group 1: Saline Group 2: 10 mg/kg IV TXA prior to incision, w/ saline &gt; 10 mg/kg/hr of isotonic solution during surgery Group 3: 1–2 g local administration of TXA immediately prior to wound closure</td>
<td>Group 1: PBL 588.4 ± 232.2 ml; VBL 813.4 ± 451.9 ml; HGB 12.16 ± 1.55 g/dl; LOS NA Group 2: PBL 383.0 ± 166.9 ml; VBL 581.3 ± 294.4 ml; HGB 12.77 ± 1.61 g/dl; LOS NA</td>
<td>1 patient in the TXA group had pulmonary embolism; another patient in the TXA group had paraparesis due to spinal epidural hematoma</td>
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<tr>
<td>Farzanegan et al., 2022</td>
<td>Single-center RCT</td>
<td>104</td>
<td>Posterior lumbar spine surgery w/ diagnosis of disc herniation, spinal canal stenosis, or both</td>
<td>Group 1: Saline Group 2: Topical TXA (3 g in 100 ml saline) immediately prior to wound closure</td>
<td>Group 1: PBL NA; VBL 407.20 ± 165.77 ml; HGB NA; LOS 1.34 ± 0.59 days Group 2: PBL NA; VBL 230 ± 323.58 ml†; HGB NA; LOS 1.24 ± 0.55 days</td>
<td>Nonsignificant difference in complications: Group 1 (13/50 patients) vs Group 2 (9/54 patients)</td>
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<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
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<tr>
<td>Khadivi et al., 2023&lt;sup&gt;25&lt;/sup&gt;</td>
<td>88</td>
<td>Single-center retrospective study</td>
<td>Posterior cervical laminectomy &amp; fusion surgery</td>
<td>Group 1: No intervention</td>
<td>Group 1: PBL 113.7 ± 75.4 ml; VBL 292.2 ± 155.8 ml; HGB NA; LOS 1.45 ± 0.55 days</td>
<td>No complications reported</td>
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<td>Group 2: Irrigation of surgical field w/ topical TXA (3 g in 100 ml saline) throughout procedure</td>
<td>Group 2: PBL 70.8 ± 64.9 ml†; VBL 215.9 ± 167.2 ml†; HGB NA; LOS 1.5 ± 0.65 days</td>
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<td>Li et al., 2020&lt;sup&gt;23&lt;/sup&gt;</td>
<td>280</td>
<td>Single-center RCT</td>
<td>2-level posterior lumbar fusion</td>
<td>Group 1: 100 ml IV saline</td>
<td>Group 1: PBL 180.42 ± 42.54 ml; VBL 270.15 ± 90.64 ml; HGB 7.84 ± 1.44 g/dl; LOS*</td>
<td>No statistically significant differences in postop complications btwn groups</td>
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<td>Group 2: Single-dose of 15 mg/kg IV TXA administered 1 hr prior to incision</td>
<td>Group 2: PBL 124.63 ± 31.12 ml†; VBL 226.60 ± 50.53 ml†; HGB 8.80 ± 1.01 g/dl†; LOS*</td>
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<td>Group 3: Topical TXA (2 g in 20 ml saline) administered w/ retrograde injection through wound drain postop &amp; clamped for 6 hrs</td>
<td>Group 3: PBL 134.48 ± 40.45 ml‡; VBL 259.40 ± 40.34 ml‡; HGB 8.74 ± 1.17 g/dl‡; LOS*</td>
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<td>Group 4: IV TXA prior to incision plus retrograde injection of topical TXA postop &amp; clamped for 6 hrs</td>
<td>Group 4: PBL 87.24 ± 13.28 ml†‡; VBL 150.10 ± 30.90 ml†‡; HGB 9.74 ± 1.13 g/dl†‡; LOS*</td>
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<td>Liang et al., 2016&lt;sup&gt;34&lt;/sup&gt;</td>
<td>90</td>
<td>RCT</td>
<td>Lumbar spondylosis w/ or w/o disc herniation undergoing posterior lumbar decompression &amp; fusion of ≥2 levels</td>
<td>Group 1: No TXA or Gelfoam</td>
<td>Group 1: PBL 96.08 ± 34.59 ml; VBL 320.33 ± 184.21 ml; HGB 11.50 ± 1.91 g/dl; LOS 6.90 ± 3.45 days</td>
<td>Group 1: 2 complications w/ wound oozing &amp; 1 complication w/ dressing reinforcement 30 days postop</td>
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<td>Group 2: TXA administered through Gelfoam soaked with 2 g in 20 ml saline prior to wound closure</td>
<td>Group 2: PBL 30.03 ± 23.99 ml†; VBL 376.67 ± 249.39 ml; HGB 12.03 ± 1.69 g/dl†; LOS 5.00 ± 2.26 days*</td>
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<td>Liang et al., 2020&lt;sup&gt;27&lt;/sup&gt;</td>
<td>40</td>
<td>Retrospective observational study</td>
<td>Degenerative lumbar scoliosis undergoing posterior lumbar decompression &amp; fusion of ≥3 levels</td>
<td>Group 1: No TXA</td>
<td>Group 1: PBL 605.50 ± 184.70 ml; VBL 516.50 ± 241.25 ml; HGB 10.57 ± 1.45 g/dl; LOS 9.80 ± 2.44 days</td>
<td>Group 1: 1 complication w/ wound oozing 1 wk postop</td>
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<td>Group 2: TXA retrograde injection (10% Transamin [10 ml, 1000 mg], Daiichi Sankyo) postop &amp; clamped for 1 hr</td>
<td>Group 2: PBL 80.02 ± 41.00 ml†‡; VBL 456.20 ± 210.10 ml; HGB 11.24 ± 1.43 g/dl; LOS 7.50 ± 0.95 days†</td>
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<tr>
<td>Maethungkul et al., 2022&lt;sup&gt;30&lt;/sup&gt;</td>
<td>65</td>
<td>Single-center RCT</td>
<td>Palliative decompressive thoracolumbar spinal metastasis</td>
<td>Group 1: 1 g IV TXA prior to incision followed by saline-soaked gelatin sponge immediately prior to wound closure</td>
<td>Group 1: PBL 670 ± 527 ml; VBL 648 ± 465 ml; HGB NA; LOS NA</td>
<td>No complications reported</td>
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<td>Group 2: Preop IV TXA + gelatin sponge soaked in 1 g of TXA in 20 ml saline immediately prior to wound closure</td>
<td>Group 2: PBL 790 ± 493 ml; VBL 589 ± 381 ml; HGB NA; LOS NA</td>
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<tr>
<td>Mallepally et al., 2020&lt;sup&gt;23&lt;/sup&gt;</td>
<td>250</td>
<td>Prospective case-controlled study</td>
<td>Single-level transforaminal lumbar interbody fusion</td>
<td>Group 1: Wound surface soaked w/ 100 ml saline solution for 3 mins throughout the procedure</td>
<td>Group 1: PBL 167.10 ± 53.83 ml; VBL 783.33 ± 332.71 ml; HGB NA; LOS 7.0 ± 2.3 days</td>
<td>No statistically significant differences in postop complications btwn groups</td>
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<td>Group 2: Wound surface soaked w/ 1 g topical TXA for 3 mins throughout the procedure</td>
<td>Group 2: PBL 99.33 ± 37.5 ml‡; VBL 410.57 ± 189.72 ml‡; HGB NA; LOS 4.8 ± 1.1 days†</td>
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### TABLE 1. Systematic review of studies published between January 1, 2016, and January 1, 2023, and evaluated on the basis of the PRISMA method

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<tr>
<th>Authors &amp; Year</th>
<th>Study Size</th>
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<tr>
<td>Mu et al., 2019</td>
<td>126</td>
<td>Single-center randomized placebo-controlled trial</td>
<td>PLIF for lumbar degenerative disease</td>
<td>Group 1: Gelatin sponge soaked in 100 ml saline administered immediately prior to wound closure&lt;br&gt;Group 2: IV TXA (15 mg/kg in 100 ml saline) prior to incision &amp; maintained at a dose of 1 mg/kg&lt;br&gt;Group 3: Topical TXA (1 g of TXA in 50 ml saline) &amp; gelatin sponge soaked for 5 mins immediately prior to wound closure</td>
<td>Group 1: PBL 291.78 ± 42.91 ml; VBL 476.31 ± 77.23 ml; HGB 9.30 ± 1.375 g/dl; LOS 8.00 ± 1.13 days&lt;br&gt;Group 2: PBL 187.89 ± 42.61 ml; VBL 301.78 ± 34.66 ml; HGB 10.716 ± 1.477 g/dl; LOS 6.27 ± 1.76 days†&lt;br&gt;Group 3: PBL 193.59 ± 65.36 ml; VBL 461.03 ± 65.36 ml‡; HGB 10.077 ± 1.185 g/dl‡; LOS 6.67 ± 1.03 days†</td>
<td>Group 1: 2 postop wound infections&lt;br&gt;Group 2: 1 postop wound infection&lt;br&gt;Group 3: 2 postop wound infections</td>
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<tr>
<td>Shen et al., 2021</td>
<td>35</td>
<td>Single-center RCT</td>
<td>Acute thoracolumbar burst fracture requiring early decompression</td>
<td>Group 1: Saline administration after sacrospinal muscle was stripped&lt;br&gt;Group 2: Topical TXA (1 g in 100 ml saline) soaked for 5 mins after sacrospinal muscle exposure</td>
<td>Group 1: PBL 144.05 ± 30.04 ml; VBL NA; HGB 10.600 ± 0.864 g/dl; LOS 9.78 ± 2.03 days&lt;br&gt;Group 2: PBL 101.28 ± 14.45 ml†; VBL NA; HGB 11.546 ± 0.808 g/dl†; LOS 6.08 ± 0.77 days†</td>
<td>No complications reported</td>
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<tr>
<td>Shi et al., 2021</td>
<td>120</td>
<td>Single-center retrospective cohort study</td>
<td>Previous history of embolism diagnosed w/ lumbar degenerative disease &amp; received a single-level PLIF surgery</td>
<td>Group 1: 100 ml saline immediately prior to wound closure&lt;br&gt;Group 2: Topical TXA (1 g in 100 ml saline) immediately prior to wound closure</td>
<td>Group 1: PBL 385.17 ± 184.86 ml; VBL 313.83 ± 111.39 ml; HGB*; LOS 8.00 ± 1.54 days&lt;br&gt;Group 2: PBL 238.83 ± 140.49 ml†; VBL 218.00 ± 79.67 ml; HGB*; LOS 7.17 ± 1.22 days†</td>
<td>Group 1: 5% DVT, 3.3% infection&lt;br&gt;Group 2: 3.3% DVT, 3.3% infection</td>
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<td>Sudprasert et al., 2019</td>
<td>57</td>
<td>Prospective RCT</td>
<td>Thoracolumbar spine trauma treated w/ long-segment instrumented posterior spinal fusion</td>
<td>Group 1: 20 ml normal saline administered through retrograde injection in wound drain postop &amp; clamped for 2 hrs&lt;br&gt;Group 2: 1 g TXA in 20 ml saline administered through retrograde injection in wound drain postop &amp; clamped for 2 hrs</td>
<td>Group 1: PBL 488.8 ± 223.5 ml; VBL 260.3 ± 160.0 ml; HGB 11.399 ml; HGB NA; LOS 17.3 ± 6.5 days&lt;br&gt;Group 2: PBL 279 ± 135.2 ml†; VBL 285.0 ± 146.6 ml; HGB NA; LOS 12.9 ± 5.1 days†</td>
<td>No adverse events or complications were recorded in any patient during treatment over a mean follow-up period of 27.5 mos</td>
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<td>Wang et al., 2019</td>
<td>181</td>
<td>Single-center RCT</td>
<td>Thoracolumbar fracture treated w/ percutaneous pedicle screw fixation</td>
<td>Group 1: 15 mg/kg IV TXA administered 30 mins before op &amp; saline before wound closure&lt;br&gt;Group 2: Preop IV saline and 3 g topical TXA immediately prior to wound closure&lt;br&gt;Group 3: 15 mg/kg IV TXA administration prior to incision followed by 3 g topical TXA immediately prior to wound closure</td>
<td>Group 1: PBL 354.13 ± 117.46 ml; VBL 103.44 ± 71.92 ml; HGB NA; LOS NA&lt;br&gt;Group 2: PBL 453.56 ± 223.77 ml†; VBL 139.34 ± 63.32 ml†; HGB NA; LOS NA&lt;br&gt;Group 3: PBL 302.03 ± 154.88 ml; VBL 92.03 ± 60.74 ml; HGB NA; LOS NA</td>
<td>No complications reported</td>
</tr>
<tr>
<td>Xu et al., 2020</td>
<td>60</td>
<td>Single-center RCT</td>
<td>PLIF</td>
<td>Group 1: Wound soaked in normal saline for 5 mins immediately prior to wound closure&lt;br&gt;Group 2: Wound soaked in 1 g TXA in 100 ml saline immediately prior to wound closure</td>
<td>Group 1: PBL 249.0 ± 103.4 ml; VBL 324.5 ± 184.6 ml; HGB NA; LOS 6.9 ± 1.8 days&lt;br&gt;Group 2: PBL 183.6 ± 102.6 ml; VBL 314.9 ± 203.6 ml; HGB NA; LOS 5.1 ± 2.3 days</td>
<td>No complications reported</td>
</tr>
</tbody>
</table>

DVT = deep venous thrombosis; HGB = hemoglobin; NA = not available; PE = pulmonary embolism; PLIF = posterior lumbar interbody fusion.

Values are shown as mean ± SD or median (interquartile range) unless indicated otherwise.

* Exact value was not recorded, but no significant difference was noted between groups.
† Significant difference compared with group 1 (p < 0.05).
‡ Significant difference compared with group 2 (p < 0.05).
FIG. 2. A: Forest plot diagram showing the effect of topical TXA on VBL compared with non-TXA controls. B: Forest plot diagram showing the effect of topical TXA on PBL compared with non-TXA controls. C: Forest plot diagram showing the effect of topical TXA on postoperative hemoglobin level compared with non-TXA controls. D: Forest plot diagram showing the effect of topical TXA on LOS compared with non-TXA controls. HGB = hemoglobin.
in VBL with topical TXA compared with IV TXA.\textsuperscript{5,6,26,29} For example, Mu et al. found decreased VBL with IV versus topical TXA in posterior lumbar interbody fusion for lumbar degenerative disease (301.78 ± 34.66 vs 461.03 ± 65.36 ml, \textit{p} < 0.001).\textsuperscript{6} Similarly, Li et al. found decreased VBL with IV versus topical TXA in posterior 2-level lumbar spine fusion (226.60 ± 50.53 vs 259.40 ± 40.34 ml, \textit{p} = 0.01).\textsuperscript{29} Arain et al. (1- to 4-level lumbar laminectomy) found no significant difference in VBL when comparing IV to topical TXA (157.1 ± 119.2 vs 175.6 ± 153.0 ml, \textit{p} = 0.207).\textsuperscript{29} The large variation in operated levels may have contributed to the lack of significance. Given the heterogeneity of these studies (\textit{I}^2 = 94\%), pooled analysis demonstrated no significant difference between IV and topical TXA regarding VBL (Fig. 3A).

Postoperative Blood Loss

Arun-Kumar and Naresh-Babu found that topical TXA significantly reduced PBL compared with IV TXA in patients with degenerative spondylolisthesis undergoing single-level interbody fusion (67.3 ± 32.6 ml vs 190 ± 112.7 ml, \textit{p} = 0.0001).\textsuperscript{26} Conversely, Wang et al. reported significantly higher PBL with topical compared with IV TXA in patients with thoracolumbar fracture undergoing percutaneous pedicle screw fixation (453.56 ± 223.77 ml vs 354.13 ± 117.46 ml, \textit{p} < 0.001).\textsuperscript{5} This discrepancy may be attributed to the use of topical TXA in a percutaneous procedure, which may diminish the effect of topical agents due to reduced exposed surface area. Pooled analysis showed no statistical difference in PBL between topical and IV TXA groups (Fig. 3B).
Postoperative Hemoglobin

Arun-Kumar and Naresh-Babu were the only authors to show a statistically significant reduction in hemoglobin level with topical compared with IV TXA (9.09 ± 0.73 vs 11.04 ± 0.33 g/dl, p < 0.01) (Fig. 3C).26

Length of Stay

There were no notable differences in the LOS between groups (Fig. 3D).

Combined TXA Compared With No TXA

Two studies compared combined TXA administration with no TXA, and both reported significant improvements in VBL, PBL, and postoperative hemoglobin level.29,38 The lack of significance in the pooled analyses of VBL and PBL was likely due to the large variation in the outcomes of the two studies and the limited number of studies in this analysis.

Visual Blood Loss

Li et al. found a decrease in VBL with combined TXA versus no TXA (150.10 ± 30.90 ml vs 270.15 ± 90.64 ml, p = 0.01), and Erdogan et al. also reported a decrease in VBL between groups (581.3 ± 294.4 ml vs 813.4 ± 451.9 ml, p < 0.0002).26,38 Pooled analysis showed no significant difference in VBL between groups (Fig. 4A).

Postoperative Blood Loss

Li et al. reported a decrease in PBL with combined TXA versus no TXA (87.24 ± 13.28 ml vs 180.42 ± 42.54 ml, p = 0.02), and Erdogan et al. also reported a decrease in PBL (383.0 ± 166.9 ml vs 588.4 ± 232.2 ml, p < 0.0001).29,38 Pooled analysis showed no significant difference in PBL between groups (Fig. 4B).

Postoperative Hemoglobin

Li et al. found a significantly higher hemoglobin level with combined TXA versus no TXA (9.74 ± 1.13 g/dl vs 7.84 ± 1.44 g/dl, p = 0.03). However, Erdogan et al. did not find this association.38 Pooled analysis showed no statistically significant change between groups (Fig. 4C).

Length of Stay

Pooled analysis could not be conducted, as the two studies comparing combined TXA with no TXA groups did not report LOS.29,38

Combined TXA Compared With IV TXA

Three studies compared combined TXA with IV TXA.5,29,39

Visual Blood Loss

Li et al. found a decrease in VBL with combined TXA

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versus IV TXA (150.10 ± 30.90 ml vs 226.60 ± 50.53 ml, p = 0.01).29 Other studies did not report significant differences.5,39 Pooled analysis showed no significant difference in VBL between the groups (Fig. 5A).

Postoperative Blood Loss

Li et al. found a decrease in PBL with combined TXA versus IV TXA (87.24 ± 13.28 vs 124.63 ± 31.12 ml, p = 0.02), while the remaining studies found no significant differences.5,29,39 Pooled analysis showed no statistically significant difference in PBL between groups (Fig. 5B).

Postoperative Hemoglobin

Li et al. found higher hemoglobin levels after combined TXA versus IV TXA (9.74 ± 1.13 g/dl vs 8.80 ± 1.01 g/dl, p = 0.03).29 Pooled analysis could not be conducted, as the other studies did not report postoperative hemoglobin levels.5,39

Length of Stay

Li et al. did not report mean and SD LOS for each cohort but indicated lack of statistically significant differences in LOS.29 Pooled analysis could not be conducted, as the other studies did not report LOS.5,39

Discussion

Many individual studies and meta-analyses have highlighted the antifibrinolytic and hemostatic properties of TXA in spine surgery patients.40-43 TXA has generally been linked to decreases in intraoperative and postoperative blood loss and may even reduce transfusion requirements.6,39,40,44-47 However, these studies largely focused solely on IV TXA.48,49 A growing body of literature has reported on the use of topical TXA.6,12,23,24,32,35 In this comprehensive review and meta-analysis, we have summarized and compared the findings of recent studies (2016–2022), exploring the effects of topical TXA on perioperative blood loss in spine surgery.

Safety and Adverse Events After Topical TXA

TXA has been touted as a low-risk treatment with a limited complication profile.40 However, the reported adverse effects—especially with systemic absorption—include potentially increased incidence of epileptic seizures and risk of clotting events such as venous thromboembolism or pulmonary embolism.40,50 The epileptogenic activity of TXA has been hypothesized to be associated with high central nervous system penetrance and potential interference with the inhibitory pathways of GABA and glycine.40,50,51 Also, the prothrombotic nature of TXA makes concerns for clotting events reasonable. However, the evidence has been inconclusive regarding such adverse events. Many studies found no link between TXA and epileptic seizures or thrombotic events.51-53 The studies that reported such associations typically administered high TXA doses (total dose 61–259 mg/kg) and were largely conducted using IV TXA.50,54,55 Therefore, topical TXA may mitigate such risks, given the reduced systemic concentrations in comparison with IV application.

Our systematic review adds to the existing body of literature that supports the overall safety profile of TXA, regardless of administration route. While some of our reviewed studies reported rare events such as venous thromboembolism, infection, and pulmonary embolism, there were no significant differences in the rates of complications among groups treated with topical TXA, IV TXA, or combined administration of TXA (Table 1).6,12,38 In fact, most studies reported no complications at all after TXA administration. Furthermore, there were no cases of post-TXA seizure in any studies reviewed (Table 1).
Although we found no association between topical TXA and adverse events, there remain concerns for its use in high-risk patients with a history of thromboembolic complications and patients in the prothrombotic, hypercoagulable states of trauma and malignancy. The individual studies included in our review may provide some insight. Shi et al. found no differences in adverse events between patients with a history of thromboembolism treated with TXA and those treated without topical TXA.12 Similarly, both Wang et al. and Maethungkul et al., studying topical TXA in patients with thoracolumbar fracture/trauma and spinal metastasis, respectively, reported no complications.5,39 Furthermore, Sudprasert et al. (studying topical TXA during thoracolumbar trauma surgery) reported no cases of seizure, deep vein thrombosis, or pulmonary embolism.33 Although these results are promising, further adequately powered studies investigating TXA treatment for high-risk patients are warranted.

**Cytoxicity and Potential Wound-Healing Complications After Topical TXA**

Although topical TXA may reduce blood loss in spine surgery, the cellular effects on the exposed chondrocytes, fibroblasts, and myocytes must be investigated. Specifically, some studies have reported mixed results regarding the cytotoxicity of topical TXA. Ambra et al. noted that topical TXA did not affect the viability of Yucatan pig chondrocytes (physiologically similar to human chondrocytes) when treated at low doses of 1–4 mg/ml.37 Marmotti et al. similarly found that human chondrocytes and synoviocytes exposed to low-dose topical TXA (7 mg/ml) conserved their structure and growth ability.58 However, increasing evidence has shown that human fibroblasts chronically exposed (> 4 hours) to > 20 mg/ml topical TXA experience a reduction in cell adhesion, motility, and viability, and an increase in apoptosis. At higher doses (> 50 mg/kg) of topical TXA, cytotoxicity is apparent after 10 minutes of exposure.59,60 These results suggest that the cytotoxicity of topical TXA may be dose and time dependent.

Application of topical TXA may expose the spinal wound environment to local excesses of TXA. Unfortunately, few studies—primarily in cardiac and orthopedic joint surgery—have quantified absorption and local concentrations after topical TXA administration (and only at a single point in time).60–63 Given the risk of cytotoxicity and impaired healing, future research is needed to study the cytotoxic and pharmacokinetic properties of topical TXA.

**Efficacy of Topical TXA Versus No TXA and IV TXA**

Although TXA has been widely reported to reduce blood loss during and after surgery, studies assessing the efficacy of topical TXA are limited. Although a few studies have yielded inconsistent results, our pooled analyses comparing topical TXA to no TXA demonstrated that topical TXA yields statistically significant benefits, including decreases in VBL, PBL, and overall hospitalization length, as well as higher postoperative hemoglobin levels (Fig. 2A–D). These findings indicate that topical TXA promotes hemostasis and may be a useful tool for limiting surgical blood loss. This is a novel pooled finding that contrasts those of prior topical TXA metaanalyses, which are limited by the inclusion of fewer RCTs and nonrandomized controlled trials, that have not clearly shown the impact of topical TXA on reducing intraoperative blood loss.15,48 However, more research into topical TXA is warranted.

Like topical TXA, IV TXA demonstrated reductions in VBL, PBL, and LOS compared with placebo (Fig. 6A, B, and D). However, because IV TXA is more extensively studied and used, it is important to compare these different administrations of TXA.6,8,9 Our pooled analysis demonstrated no statistically significant differences in the measured outcomes between patients treated with topical and those treated with IV TXA (Fig. 3A–D). This lack of significance may be due to the large standard deviations reported by several of the studies (Table 1, Fig. 3A).26,28

**Combined Topical and IV TXA Administration**

Topical TXA appears to be safe, even for high-risk patients. In addition, topical TXA (compared with placebo) may improve intraoperative and postoperative blood loss, resulting in higher postoperative hemoglobin levels and shorter hospitalization lengths (Fig. 2A–D). Thus, an interesting clinical question is if the combined administration of topical TXA with IV TXA would result in an additive effect for blood loss. However, our pooled analysis showed that combined topical TXA and IV TXA was not associated with significantly synergistic effects in reducing blood loss both during and after surgery (Fig. 5A and B). This is in contrast to a subset of studies that analyzed combined IV and topical TXA.5,29,38,39 Li et al. and Erdogan et al. demonstrated statistically superior VBL, PBL, and hemoglobin levels after combined TXA compared with no TXA.29,38 Furthermore, when comparing combined topical and IV TXA administration to IV TXA alone in a large RCT with 280 patients, Li et al. demonstrated statistically significant improvements in intraoperative blood loss (VBL), PBL, postoperative hemoglobin levels, and transfusion rates in the combined group compared with the IV TXA group.5 Our statistically insignificant pooled analysis results could be due to high heterogeneity (I² ≥ 94%), and our comparison may have been underpowered due to limited research that has compared combined topical and IV TXA with no TXA or IV TXA (Figs. 4A–C, 5A, and 5B).6,26,28 Further studies are required to establish if combined topical and IV TXA is superior to IV TXA alone.

**Impact of TXA Administration Route on Transfusion Rates**

Though the transfusion rates were not accompanied by standard deviations and therefore excluded from the pooled analysis, reductions in transfusion rates were reported in topical TXA and combined TXA groups when compared with non-TXA and IV TXA groups. Of 12 studies that compared topical TXA and non-TXA controls, 6 studies reported reduced transfusion rates after topical TXA. Further, 1 study, of 4 that compared transfusion rates between topical and IV TXA groups, found reduced transfusions in the topical TXA group.28 Two studies demonstrated that the transfusion rate was reduced in the combined TXA group compared with the non-TXA control.5,39,30 Three studies compared combined TXA with IV TXA, of which 1 demonstrated that the transfusion rate was reduced in the
combined TXA group compared with that of the IV TXA group.29 In the other 2 studies, 1 reported no blood transfusions in any of the patients, and the other found no significant difference in the blood transfusion rates between the combined and IV TXA groups.5,39 These findings may be clinically significant, given the transfusion-associated risks.26

Limitations
Some key limitations affected this systematic review and pooled analysis. One limitation was the diversity of studies included, with variations in prospective versus retrospective nature, patient characteristics (e.g., age, comorbidities), spine surgery types, and TXA doses. Although our pooled analyses provided promising results, most comparisons (excluding those shown in Figs. 2C, 3D, and 6D) exhibited high heterogeneity (I² > 50%). Another limitation is that similar meta-analyses were conducted previously, but they primarily focused on articles published before 2019. However, as approximately 70% of the literature on the topical administration of TXA was published after 2019, an updated analysis is warranted.15,17–19 Furthermore, prior meta-analyses from 2016 to 2021 included fewer RCTs and nonrandomized controlled trials, concentrated on the use of topical TXA for the treatment of lumbar degenerative disease, and lacked analysis of its intraoperative effects and combined administration with IV TXA. The most recent meta-analyses have discussed topical TXA, including those by Cao et al. and Xiao et al., and included more studies.48,64 However, Cao et al. included only 9 articles,
compared with 18 in this study, that investigated topical TXA specifically. Unlike Cao et al., we solely investigated topical TXA and its combined use with IV TXA in various contexts, including posterior cervical surgery, spinal oncology, and in patients with increased risk of thromboembolism. We also investigated a wider range of topical TXA administration methods, including Gelfoam, irrigation solutions, and retrograde injection via drains. The largest TXA meta-analysis to date by Xiao et al. included 21 studies published in Chinese and English. The authors conducted an analysis on several forms of TXA administration (including topical) but focused on posterior lumbar fusion surgery only. Here, we conducted a focused study on the use of topical TXA—in a variety of clinical contexts—providing novel insight into its effects on intraoperative blood loss (VBL), HGB, and LOS.

Conclusions
As an invasive procedure, spine surgery may be associated with blood loss. Topical TXA is a promising strategy to reduce overall and perioperative blood loss. Importantly, our review appreciated no cases of seizure and only rare occurrences of adverse events, such as deep vein thrombosis and pulmonary embolism, after topical TXA administration. In pooled analyses, topical TXA was associated with less intraoperative and postoperative blood loss, higher postoperative hemoglobin levels, and shorter hospitalization length compared with controls.

References


Disclosures
Dr. Chou reported personal fees from Globus and personal fees from Orthofix outside the submitted work.

Author Contributions
Conception and design: Chan, Izima, Chou. Acquisition of data: Izima, Sampath. Analysis and interpretation of data: Izima, Sampath, Tang, Ambati. Drafting the article: Chan, Izima, Sampath, Tang, Ambati. Critically revising the article: all authors. Reviewed submitted version of manuscript: Chan, Izima, Sampath, Tang, Ambati. Approved the final version of the manuscript on behalf of all authors: Chan. Statistical analysis: Izima, Tang. Study supervision: Chan.

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