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The relative efficacy of antifibrinolytics in adolescent idiopathic scoliosis: a prospective randomized trial.

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The Relative Efficacy of Antifibrinolytics in Adolescent Idiopathic Scoliosis
A Prospective Randomized Trial

Kushagra Verma, MD, MS, Thomas Errico, MD, Chris Diefenbach, MD, MS, Christian Hoelscher, BS, Austin Peters, BS, Joseph Dryer, MD, Tessa Huncke, MD, Kirstin Boenigk, MD, and Baron S. Lonner, MD

Investigation performed at the Spine Center, Department of Orthopaedics, Hospital for Joint Diseases, New York University, New York, NY

Background: Antifibrinolytics can reduce intraoperative blood loss. The primary aim of this study was to determine the efficacy of intraoperative tranexamic acid, epsilon-aminocaproic acid, and placebo at reducing perioperative blood loss and the transfusion rate in patients with adolescent idiopathic scoliosis undergoing posterior spinal arthrodesis.

Methods: This is a prospective, randomized, double-blind comparison of tranexamic acid, epsilon-aminocaproic acid, and placebo used intraoperatively in patients with adolescent idiopathic scoliosis. One hundred and twenty-five patients with adolescent idiopathic scoliosis were randomly assigned to the tranexamic acid, epsilon-aminocaproic acid, or control groups. Parameters recorded included estimated blood loss, hematocrit, blood product usage, drain output, and total blood losses. The primary outcomes were intraoperative blood loss and postoperative drainage. Secondary outcomes were transfusion requirements and hematocrit changes both intraoperatively and postoperatively.

Results: One hundred and twenty-five patients (ninety-seven female and twenty-eight male, with a mean age of fifteen years) were randomized to receive tranexamic acid (thirty-six patients), epsilon-aminocaproic acid (forty-two patients), or saline solution (forty-seven patients). The groups were similar at baseline, with one exception: the saline solution group had a higher estimated blood volume at baseline than the tranexamic acid group. Both tranexamic acid and epsilon-aminocaproic acid reduced the estimated blood loss per degree and estimated blood loss per pedicle screw. Epsilon-aminocaproic acid, but not tranexamic acid, reduced estimated blood loss and estimated blood loss per level. Tranexamic acid also reduced total blood losses compared with epsilon-aminocaproic acid or saline solution. In an analysis controlling for level, degree, and number of anchors, tranexamic acid reduced drain output and total blood losses. Tranexamic acid or epsilon-aminocaproic acid had a smaller decrease in hematocrit postoperatively. In an analysis controlling for the mean arterial pressure during surgical exposure, tranexamic acid reduced estimated blood loss and total blood losses. Overall, antifibrinolytics (tranexamic acid or epsilon-aminocaproic acid) reduced estimated blood loss, total blood losses, and the decline in hematocrit postoperatively compared with saline solution. There was no difference among the groups with respect to the transfusion rate, duration of surgery, levels fused, or pedicle screws placed.

Conclusions: Tranexamic acid and epsilon-aminocaproic acid reduced operative blood loss but not transfusion rate. Tranexamic acid is more effective at reducing postoperative drainage and total blood losses compared with epsilon-aminocaproic acid. Maintenance of the mean arterial pressure at <75 mm Hg during surgical exposure appears to be critical for maximizing antifibrinolytic benefit.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.
The relative efficacy of antifibrinolytics in adolescent idiopathic scoliosis

Materials and Methods

Study Design

This is a prospective, randomized, double-blinded placebo-controlled trial conducted at a single institution. This clinical trial was registered at ClinicalTrials.gov (“Tranexamic Acid [TXA] Versus Epsilon Aminocaproic Acid [EACA] Versus Placebo for Spine Surgery,” NCT00958581). The protocol was also reported in a previous study11.

Patient Selection

Following institutional review board approval, 125 patients with adolescent idiopathic scoliosis undergoing posterior spinal arthrodesis were recruited for the study. Informed consent was obtained from adult patients. For minors, a parent or guardian provided consent while assent was obtained from the minor.

Patient Randomization and Blinding

Prior to the operative procedure, patient deidentified identification numbers were randomly assigned to the tranexamic acid (TXA; thirty-six patients), epsilon-aminocaproic acid (EACA; forty-two patients), or placebo (forty-seven patients) groups using computer-generated random assignment (Fig. 1). The randomization was performed in 2009 after institutional review board approval. Allocation assignments were blinded from all persons, except the pharmacist, and were reused so as to prevent potential bias. Allocation assignments favored the saline solution group over the treatment groups when the allocation assignments were revealed.

Medication Dosage

For tranexamic acid, the loading dose was 10 mg/kg infused over fifteen minutes, while the maintenance dose was 1 mg/kg/hr. For epsilon-aminocaproic acid, the

**TABLE I Demographics and Baseline Characteristics of Enrolled Patients**

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>TXA†</th>
<th>EACA†</th>
<th>Saline Solution</th>
<th>P Value</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>36</td>
<td>42</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>4:32</td>
<td>8:34</td>
<td>16:31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age† (yr)</td>
<td>15.30 (2.37)</td>
<td>14.61 (1.89)</td>
<td>15.01 (2.37)</td>
<td>0.390</td>
<td>Overall</td>
</tr>
<tr>
<td>BMI‡</td>
<td>21.19 (5.62)</td>
<td>21.92 (4.50)</td>
<td>22.69 (5.22)</td>
<td>0.423</td>
<td>Overall</td>
</tr>
<tr>
<td>No. of levels arthrodesed‡</td>
<td>8.8 (2.3)</td>
<td>9.5 (2.8)</td>
<td>9.0 (2.0)</td>
<td>0.369</td>
<td>Overall</td>
</tr>
<tr>
<td>Coronal Cobb angle‡ (deg)</td>
<td>54.6 (10.1)</td>
<td>53.4 (10.8)</td>
<td>54.1 (9.2)</td>
<td>0.871</td>
<td>Overall</td>
</tr>
<tr>
<td>No. of anchors placed‡</td>
<td>16.3 (3.7)</td>
<td>16.6 (3.6)</td>
<td>16.1 (3.2)</td>
<td>0.775</td>
<td>Overall</td>
</tr>
<tr>
<td>Estimated blood volume‡ (mL)</td>
<td>3672 (949)</td>
<td>3996 (1129)</td>
<td>4273 (1131)</td>
<td>0.035§</td>
<td>TXA vs. saline solution</td>
</tr>
</tbody>
</table>

*BMI = body mass index. †TXA = tranexamic acid, and EACA = epsilon-aminocaproic acid. ‡Values are given as the mean, with the standard deviation in parentheses. §Significance achieved at p < 0.05.
loading dose was 100 mg/kg infused over fifteen minutes, while the maintenance
dose was 10 mg/kg/hr. Since tranexamic acid is reported to be ten times more
potent than epsilon-aminocaproic acid, the dose is adjusted in accordance
with existing guidelines.[12-15] The net volume of medication administered
was identical for either treatment option. The literature has also noted the
asfeus etranaexmic acid oadidose of100m g/kgfollowed by
maintenance dose of10 mg/kg/hr. However, improved efficacy at this higher
dose of tranexamic acid has not been proven. Additionally, as reported in a
2008 review by Eaton[16], the acquisition cost of these drugs is comparably low: $1
to $2 for a 5-g vial of epsilon-aminocaproic acid, and $20 to $25 for a 1 g vial of
tranexamic acid.

Surgical Correction of the Spine
Intraoperative exposure of the posterior vertebral elements was achieved by
careful dissection of the paraspinal musculature from the spinous process, lamina,
and facet. Soft-tissue releases and osseous osteotomies were performed to in-
crease flexibility followed by pedicle screw fixation. Local autologous and al-
lograft bone graft was used to achieve osseous fusion. Subfascial drains (Hemovac;
Zimmer, Warsaw, Indiana) were routinely placed at the wound site during closure
and were uniformly removed postoperatively when wound drainage was <40 mL
per eight-hour shift.

Data Collection
The preoperative, operative, and postoperative data gathered are outlined in the
Appendix. Estimated blood volume, or the preoperative total volume of blood,
was calculated as the weight of the patient (in kilograms) × 70 mL/kg. Estimated
blood loss was estimated to be three times the volume in the Cell Saver (Haemonetics,
Braintree, Massachusetts) for almost all patients. For patients in whom estimated
blood loss was ≤300 mL, intraoperative approximations were used. A transfu-
sion threshold was utilized. During surgery, the team was advised to transfuse
only for a hematocrit of ≤25 in patients with ongoing bleeding. Postoperatively,
a symptomatic patient with a hematocrit of ≤22 received a transfusion. Blood urea
nitrogen and creatinine levels were followed daily to monitor renal function.
Anesthesiologists were asked to maintain a mean arterial pressure of 60
to 80 mm Hg during the surgical exposure and anchor placement and a mean
arterial pressure of 70 to 90 during the surgical correction[17,18]. The so-called
average mean arterial pressure was estimated by measuring systolic and diastolic
blood pressure at fifteen-minute intervals during the procedure as described

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Fig. 1

CONSORT (Consolidated Standards of Reporting Trials) flowchart.
All information was recorded onto a deidentified data collection sheet by the researchers and then entered onto a protected electronic database.

### Outcomes
The primary study end points were intraoperative blood loss and postoperative drainage. Secondary end points were transfusion requirements and hematocrit changes both intraoperatively and postoperatively. The outcomes remained unchanged during the study.

### Statistical Methods
Descriptive analysis (mean, range, and standard deviation) was performed for each parameter. Comparisons within, and between, groups were assessed using analysis of variance with least significant difference post hoc tests and the t test; the level of significance was set at p < 0.05. The initial power analysis required pooling of data from several studies as no study directly compared tranexamic acid and epsilon-aminocaproic acid. The estimated sample size was between thirty-four and eighty patients per group, which was dependent on the variable of interest (estimated blood loss, drain output, or transfusion rate).

### Source of Funding
Funding for this study was provided exclusively by departmental funds.

### Results

#### Preliminary Data and Power Analysis
After sixty patients were enrolled (thirteen in the TXA group, seventeen in the EACA group, and thirty in the saline solution group), a power analysis was repeated. Estimated blood loss for each treatment arm was a mean (and standard deviation) of 783 ± 514 mL for the TXA group, 493 ± 120 mL for the EACA group, and 960 ± 175 mL for the saline solution group. Drain output was a mean of 391 ± 113 mL for the TXA group, 538 ± 131 mL for the EACA group, and 568 ± 514 for the saline solution group. The transfusion rate was more variable, with a

#### TABLE II Postoperative and Overall Blood Loss for Individual Groups

<table>
<thead>
<tr>
<th>Individual Groups*</th>
<th>TXA</th>
<th>EACA</th>
<th>Saline Solution</th>
<th>P Value</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drain total (mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>789 (449)</td>
<td>1016 (422)</td>
<td>1034 (559)</td>
<td>0.027†</td>
<td>TXA vs. saline solution</td>
</tr>
<tr>
<td></td>
<td>0.867</td>
<td>0.043†</td>
<td></td>
<td></td>
<td>EACA vs. saline solution</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TXA vs. EACA</td>
</tr>
<tr>
<td>Per level</td>
<td>90.5 (42.9)</td>
<td>111.0 (43.5)</td>
<td>117.9 (61.0)</td>
<td>0.038†</td>
<td>TXA vs. saline solution</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EACA vs. saline solution</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TXA vs. EACA</td>
</tr>
<tr>
<td>Per degree</td>
<td>14.9 (7.6)</td>
<td>18.7 (7.3)</td>
<td>19.9 (11.1)</td>
<td>0.031†</td>
<td>TXA vs. saline solution</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EACA vs. saline solution</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>TXA vs. EACA</td>
</tr>
<tr>
<td>Per anchor</td>
<td>48.6 (26.0)</td>
<td>62.9 (26.5)</td>
<td>67.2 (37.9)</td>
<td>0.020†</td>
<td>TXA vs. saline solution</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>EACA vs. saline solution</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>TXA vs. EACA</td>
</tr>
<tr>
<td>Total losses‡ (mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1531 (911)</td>
<td>1775 (853)</td>
<td>2116 (1201)</td>
<td>0.015†</td>
<td>TXA vs. saline solution</td>
</tr>
<tr>
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<td></td>
<td>EACA vs. saline solution</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TXA vs. EACA</td>
</tr>
<tr>
<td>Per level</td>
<td>177.0 (95.3)</td>
<td>189.7 (79.9)</td>
<td>234.6 (111.6)</td>
<td>0.014†</td>
<td>TXA vs. saline solution</td>
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<tr>
<td></td>
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<td>EACA vs. saline solution</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TXA vs. EACA</td>
</tr>
<tr>
<td>Per degree</td>
<td>29.0 (16.2)</td>
<td>32.7 (14.9)</td>
<td>40.3 (22.9)</td>
<td>0.013†</td>
<td>TXA vs. saline solution</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>EACA vs. saline solution</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TXA vs. EACA</td>
</tr>
<tr>
<td>Per anchor</td>
<td>94.9 (53.6)</td>
<td>107.6 (46.0)</td>
<td>136.3 (92.1)</td>
<td>0.011†</td>
<td>TXA vs. saline solution</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td>EACA vs. saline solution</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>TXA vs. EACA</td>
</tr>
</tbody>
</table>

*The values are given as the mean, with the standard deviation in parentheses. Tranexamic acid (TXA) significantly reduced overall drainage versus epsilon-aminocaproic acid (EACA), as well as all drainage parameters versus saline solution. TXA also significantly reduced all total losses parameters versus saline solution. For the combined treatment group, total losses were significantly reduced versus saline solution. †Significance achieved at p < 0.05. ‡Total losses consist of the estimated blood loss and the drain total.
mean of 38% ± 51% for the TXA group, 6% ± 24% for the EACA group, and 20% ± 41% for the saline solution group. To detect a significant difference with 80% power between tranexamic acid and saline solution would require thirty-one, fourteen, and 128 patients per treatment arm for estimated blood loss, drain output, and transfusion rate, respectively.

### Patient Demographics and Surgical Strategy (Table I)

One hundred and twenty-five patients with adolescent idiopathic scoliosis (ninety-seven female and twenty-eight male patients) were randomly assigned to receive tranexamic acid (thirty-six patients), epsilon-aminocaproic acid (forty-two patients), or saline solution (forty-seven patients). There was no significant difference between the three groups with respect to age (mean, 15 ± 2.2 years; range, ten to twenty-one years), body mass index (mean, 22 ± 5 kg/m²), preoperative coronal Cobb angle (mean, 54° ± 10°), number of vertebral levels arthrodesed (mean, 9.1 ± 2.4), or number of pedicle screws placed (16.3 ± 3.5). Patients who received saline solution had a larger estimated blood volume compared with patients who had tranexamic acid (p = 0.035). No patients were excluded after enrollment.

### Intraoperative Blood Loss (See Appendix)

#### Individual Groups (Fig. 2)

Tranexamic acid reduced estimated blood loss per degree of Cobb angle (p = 0.042) and estimated blood loss per pedicle screw (p = 0.042) compared with saline solution. There was a trend toward lower estimated blood loss (p = 0.058) and estimated blood loss per level (p = 0.066) as well. Epsilon-aminocaproic acid decreased estimated blood loss (p = 0.037), estimated blood loss per level (p = 0.022), estimated blood loss per degree (p = 0.036), and estimated blood loss per
pedicle screw ($p = 0.029$) compared with the patients who received saline solution.

**Combined Groups (Fig. 3)**

Both antifibrinolytic medications together (tranexamic acid or epsilon-aminocaproic acid; seventy-eight patients) reduced estimated blood loss ($p = 0.019$), estimated blood loss per level ($p = 0.015$), estimated blood loss per degree ($p = 0.015$), and estimated blood loss per pedicle screw ($p = 0.013$) compared with saline solution.

**Postoperative and Total Losses (Tables II and III)**

**Individual Groups (Figs. 4 and 5)**

Drain output was lower for tranexamic acid compared with epsilon-aminocaproic acid ($p = 0.043$) or saline solution ($p = 0.027$). Compared with saline solution, tranexamic acid also lowered drain output per level arthrodesed ($p = 0.038$), per degree of curve ($p = 0.031$), and per pedicle screw placed ($p = 0.020$). Tranexamic acid also reduced total blood losses (total blood loss = drain output + estimated blood loss) ($p = 0.015$), total blood loss per level ($0.014$), total blood loss per degree ($0.013$), and total blood loss per anchor ($p = 0.011$) compared with saline solution.

**Combined Groups**

The combined antifibrinolytic group decreased total blood loss ($p = 0.019$), total blood loss per level ($p = 0.007$), total blood loss per degree ($p = 0.008$), and total blood loss per pedicle screw ($p = 0.010$) compared with saline solution.

**Changes in Hematocrit (See Appendix)**

**Intraoperative Findings**

For individual groups, hematocrit was measured at the time of incision, start of pedicle screw placement, correction, and closure. At incision, the hematocrit was lower for tranexamic acid ($p = 0.010$) and epsilon-aminocaproic acid ($p = 0.008$) compared with saline solution. Hematocrit at pedicle screw placement was also lower for tranexamic acid than for saline solution ($p = 0.005$). Epsilon-aminocaproic acid had a smaller change in hematocrit from incision to closure than saline solution ($p = 0.031$).

The combined antifibrinolytic group had a smaller hematocrit at incision ($p = 0.002$) and at pedicle screw placement ($p = 0.021$) than saline solution.

**Postoperative Findings**

For individual groups, the change in hematocrit from the time in the postanesthesia care unit to postoperative day 1 was similar between groups. From postoperative day 1 to day 2 and from the time in the postanesthesia care unit to postoperative day 2, the change in hematocrit was significantly reduced with epsilon-aminocaproic acid, but not tranexamic acid, compared with saline solution ($p < 0.001$ and $p = 0.011$, respectively).
Comparison of the three test substances with regard to postoperative drainage. Tranexamic acid (TXA) significantly reduced drainage compared with epsilon-aminocaproic acid (EACA) and compared with saline solution. Epsilon-aminocaproic acid did not significantly reduce drainage versus saline solution. The values are given as the mean, with the standard deviation represented by the error bars.

Comparison of the three test substances with regard to total losses (estimated blood loss [EBL] + postoperative drainage). Tranexamic acid (TXA) significantly reduced total blood losses compared with saline solution. Total blood losses were not significantly reduced between epsilon-aminocaproic acid (EACA) and saline solution as well as between tranexamic acid and epsilon-aminocaproic acid. The values are given as the mean, with the standard deviation represented by the error bars.
The combined antifibrinolytic group had a smaller decrease in hematocrit from postoperative day 1 to day 2 \((p = 0.002)\) and from the time in the postanesthesia care unit to postoperative day 2 \((p = 0.012)\) than did the saline solution group (see Appendix).

**Variations with Average Exposure Mean Arterial Pressure (See Appendix)**

There was no difference in the average mean arterial pressure between the three treatment groups. Within each group, patients were stratified according to "high mean arterial pressure" \((≥75 \text{ mm Hg})\) and "low mean arterial pressure" \(<75 \text{ mm Hg}\).

**Mean Arterial Pressure of <75 mm Hg**

For individual groups, tranexamic acid reduced estimated blood loss \((p = 0.042)\) and estimated blood loss per degree \((p = 0.025)\) compared with saline solution (Fig. 6). Both tranexamic acid and epsilon-aminocaproic acid independently reduced estimated blood loss per level \((p = 0.008\) and \(p = 0.010\), respectively), estimated blood loss per pedicle screw \((p = 0.023\) and \(p = 0.030\)), and the change in hematocrit from the time in the postanesthesia care unit to postoperative day 2 \((p = 0.005\) for both) compared with saline solution. Tranexamic acid, but not epsilon-aminocaproic acid, lowered total blood losses compared with saline solution also \((p = 0.013)\).

The combined antifibrinolytic group had a smaller estimated blood loss \((p = 0.019)\), estimated blood loss per level \((p = 0.005)\), estimated blood loss per degree \((p = 0.017)\), estimated blood loss per pedicle screw \((p = 0.008)\), total blood losses \((p = 0.023)\), and postoperative hematocrit drop from the time in the postanesthesia care unit to postoperative day 2 \((p = 0.001)\) than saline solution.

**Mean Arterial Pressure of ≥75 mm Hg**

For individual and combined groups, when the mean arterial pressure was ≥75 mm Hg, there was no difference between treatment and control groups for any of the blood loss parameters.

**Transfusion Rates (See Appendix)**

Of the 125 patients, thirty-four (27%) required forty-four units of packed red blood cells during surgery, while nine (7%) required eleven units postoperatively. There was no difference in intraoperative or postoperative transfusion rate between treatment groups. In eleven patients, a blood transfusion was given for a hematocrit above the suggested threshold. Exclusion of these patients did not alter the result. There was also no difference in the hematocrit before the incision between the twenty-eight patients who had predonated blood \((\text{mean, } 32.8 ± 3.4)\) or the sixty-two patients who had not predonated blood \((\text{mean, } 33.8 ± 3.4)\) \((p = 0.215)\). Lastly, the transfusion rate was similar between patients receiving autologous or allogeneic blood. Predonation history was not available for thirty-five patients (28%).
Exposure Times and Lengths of Stay (See Appendix)

Individual and Combined Groups

Tranexamic acid was associated with a shorter surgical exposure (incision to pedicle screw placement) than epsilon-aminocaproic acid ($p = 0.027$). There were no other differences in operative time or hospital length of stay between treatment and control groups.

Deviations from Protocol and Complications

For one patient, concerns regarding ongoing bleeding led to so-called unblinding during rod placement (saline solution group). Ultimately, antifibrinolytic medication was not administered as the procedure was near completion. For four patients, a drain was not placed during skin closure because of unfamiliarity with the study protocol. These patients were excluded from the "drain output" analysis. One patient was readmitted for persistent wound drainage. This quickly resolved after empiric antibiotic treatment. No renal, thromboembolic, or other major complications were observed.

Discussion

The role of antifibrinolytics to manage blood loss has remained largely surgeon-dependent and is not the standard of care for many spinal deformity surgeons. The majority of orthopaedic studies have demonstrated the efficacy of tranexamic acid and epsilon-aminocaproic acid over placebo in relation to blood loss\textsuperscript{7,10-18}. However, a reduction in intraoperative blood loss has been inconsistently reported. In two recent Cochrane reviews\textsuperscript{7,14}, tranexamic acid was noted to be more efficacious than epsilon-aminocaproic acid at reducing total blood losses, but neither drug significantly reduced intraoperative bleeding. The most recent review demonstrated a reduction in transfusion volume with antifibrinolytic medications in scoliosis surgery, but could not comment on the benefit of one medication over the other\textsuperscript{7}. Of the scoliosis studies examined in the Cochrane review, only two adequately randomized patients and blinded both the surgeon and anesthesiologist to the patient's treatment. Of the three studies limited to children, only one described blood loss and transfusion rate in both the intraoperative and postoperative period\textsuperscript{9,15,20,22-25}. The cardiac surgery literature has five prospective studies directly comparing tranexamic acid and epsilon-aminocaproic acid, but none had proper patient randomization and physician blinding\textsuperscript{9,10,12,14,16}. Comparing trials in all surgical fields including cardiac surgery, tranexamic acid, but not epsilon-aminocaproic acid, reduced the transfusion rate over placebo\textsuperscript{7,14}. To our knowledge, no orthopaedic study has directly compared tranexamic acid and epsilon-aminocaproic acid.

Another important variable to consider is the efficacy of tranexamic acid (and possibly epsilon-aminocaproic acid) at different dosages. A recent study of pediatric patients undergoing craniostenosis repair demonstrated an ability to maintain blood tranexamic acid concentrations above known in vitro therapeutic levels by using loading and maintenance doses five times greater than those used in the present study\textsuperscript{7}. However, the authors of that study admit their dosage scheme may have been higher than necessary as peak plasma levels were several times above therapeutic level\textsuperscript{7}.

The change in hematocrit postoperatively was smaller for epsilon-aminocaproic acid and combined treatment groups compared with saline solution. Of note, the estimated blood volume and the hematocrit prior to incision were lower for the treatment groups compared with the saline solution group. Although unexpected, this bias favored the control group and perhaps explains why a difference was not observed intraoperatively between treatment and control groups. Lastly, we found that maintenance of the mean arterial pressure at $<75$ was important in mitigating blood losses, in accordance with previous literature\textsuperscript{7,13-15,20,22-23}. A reduced intraoperative mean arterial pressure demonstrated an improved efficacy for tranexamic acid that was greater than the improvement of epsilon-aminocaproic acid versus saline solution: all blood loss parameters, as well as total losses, were significantly reduced (Fig. 6). To our knowledge, this is the first study to describe intraoperative blood loss, the change in hematocrit during and after surgery, drain output, and transfusion rate in a direct comparison.

While transfusion rate is a sought-after outcome to assess the benefit of these medications, the decision to transfuse depends on numerous intraoperative factors—patient comorbidities, patient preference, preoperative blood donation, and clinical judgment—all of which vary substantially with institution and surgeon. These are difficult to control even with a Level-I study in a relatively healthy homogenous population of patients with adolescent idiopathic scoliosis. Tzortzopoulou et al. similarly reported being unable to find a reduction in transfusion rate when reviewing the cases of 254 prospectively randomized children with idiopathic scoliosis because of the wide confidence intervals between treatment and control groups\textsuperscript{7}. Transfusion rate, therefore, is not the ideal standard to evaluate antifibrinolytic efficacy. Rather, intraoperative estimated blood loss, drain output, total blood losses, and the change in hematocrit during and after surgery are more useful.

It may be argued that patients with adolescent idiopathic scoliosis have relatively fewer transfusion needs than adults with scoliosis or children with scoliosis secondary to a neuromuscular condition. While this is true, patients with adolescent idiopathic scoliosis were well suited for investigation because they represented a healthy homogenous group of patients free from use of anticoagulant medications. Since blood losses are generally modulated in this population, randomization to treatment or control groups was reasonable. The benefit of decreased postoperative wound drainage should also not be overlooked. These treatments may prove useful for preventing postoperative wound dehiscence and infections.

In conclusion, this study provides evidence that antifibrinolytic treatments reduce intraoperative blood loss but not transfusion rate in adolescents with idiopathic scoliosis. Tranexamic acid was about equally effective to epsilon-aminocaproic acid in reducing operative blood losses and was superior in reducing drain output and total losses compared with saline solution. Both treatment groups had a smaller decline in hematocrit postoperatively compared with placebo. Controlling the mean arterial pressure during surgery also appears to have an important role for mitigating blood losses. Physicians should consider both the intraoperative and postoperative benefits when deciding to use...
either tranexamic acid or epsilon-aminocaproic acid during surgery to manage blood losses associated with spinal deformity surgery.

### Appendix

Tables showing the preoperative, intraoperative, and postoperative data collected; intraoperative blood loss data; hematocrit data; variations with average exposure mean arterial pressure; transfusion data; and exposure times and lengths of stay are available with the online version of this article as a data supplement at jbjs.org.

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