Efficacy and Safety of Preoperative Intravenous Tranexamic Acid to Reduce Blood Loss During and After Elective Lower-Segment Cesarean Delivery

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ABSTRACT

Aim: This work aimed to study the efficacy and safety of preoperative intravenous tranexamic acid to reduce blood loss during and after elective lower-segment cesarean delivery.

Materials and Methods: A double-blind, randomized placebo-controlled study was undertaken of women undergoing elective lower-segment cesarean delivery of a full-term singleton pregnancy at a center in tertiary referral hospital, Egypt, between December, 2019 and March, 2020. Patients were randomly assigned (1:1) using computer-generated random numbers to receive either 1 g tranexamic acid (TXA) or 5% glucose 15 minutes before surgery. Preoperative and postoperative complete blood count, hematocrit values, and maternal weight were used to calculate the estimated blood loss (EBL) during cesarean section, which was the primary outcome. Analyses included women who received their assigned treatment, whose surgery was 90 minutes or less, and who completed follow-up.

Results: Eighty women in each group. There was no statistical difference found between women subjected to TXA and those subjected to placebo regarding maternal age, weight, gestational age or mode of previous delivery. Mean EBL was significantly higher in the placebo group (896.81 ± 519.6 mL) than in the tranexamic acid group (583.23 ± 379.62 mL; \( P < 0.001 \)).

Conclusion: Preoperative administration of tranexamic acid safely reduces blood loss during elective lower-segment cesarean delivery.

Key Words: Blood loss, cesarean delivery, tranexamic acid

INTRODUCTION

Every year over five million women die worldwide due to causes related to pregnancy and delivery. Postpartum Hemorrhage (PPH) accounts for the major part of the mortality as well as morbidity like severe anemia needing blood transfusion, hospital stay and infection\(^1\).

Millennium development goal 5 targets for reduction of maternal mortality rate by 75% by 2017, which means 5.5% reduction per year is required. People at high risk of PPH account for only small percent of all maternal deaths. Majority of morbidity and mortality happen in those with no risk factors and cannot be predicted. In an analysis of 1620 women in rural India, it was found that 9.2% experienced PPH. No maternal or socio-demographic factors differed between women with PPH and those without\(^2\).

Intraoperative and postoperative maternal hemorrhage are the main operative complications associated with high-risk cesarean delivery\(^3\). Anterior placenta previa, multiple pregnancies, and severe preeclampsia are all associated with a high risk of major PPH requiring immediate blood transfusion. Many uterotonics as oxytocin, ergometrine and prostaglandins especially misoprostol were tested to minimize both intraoperative and postoperative Blood loss during and after cesarean delivery (CD)\(^4\).

Antifibrinolytic agents as tranexamic acid (TXA) were effective in prevention of bleeding complications with few side effects in various conditions. Woman trial collaborators study proved that the use of TXA in women with postpartum hemorrhage had a large survival benefit TXA could decrease blood loss during surgery by almost one-third when compared to placebo. TXA is a synthetic derivative of lysine with antifibrinolytic action. It blocks lysine binding sites on plasminogen molecules, preventing its interaction with formed plasmin and fibrin resulting in prevention of plasminogen activation with subsequent stabilization of the preformed fibrin meshwork produced by secondary hemostasis\(^5\).

TXA was included in WHO Model List of Essential Medicines\(^6\) after confirmation of its ability to reduce
mortality in trauma patients suffering from bleeding when administered early[12]. The use of TXA to reduce intraoperative and postoperative blood loss is routine nowadays in many surgical procedures, including coronary artery bypass, orthopedic and urological surgeries[13]. In obstetrics, TXA is used to treat pregnancy-associated bleeding as threatened abortion, placenta previa and postpartum hemorrhage[14,15]. Some studies proved the effectiveness of TXA in reducing blood loss during and after CD[16,17]. However, none of them targeted high risk CD.

AIM OF THE WORK

The aim of our study is to investigate the safety and efficacy of preoperative TXA for reduction of blood loss during and after elective lower-segment cesarean delivery to reduce intraoperative blood loss in high risk lower segment cesarean sections

MATERIALS AND METHOD

This study is a prospective, double-blinded, randomized placebo-controlled one that was conducted between December, 2019 and March, 2020 at a tertiary referral hospital. All participating women have signed an informed written consent after explaining the risks and benefits of the study. Eligible criteria

All participants were scheduled for elective lower segment Cesarean section with their age ranged between 20 and 40 years old and gestational age between completed 37 and 41 weeks. All participants had one or more high risk for increased intraoperative blood loss. The risk factors included women with overdistended uterus (e.g. multiple gestations, macrocosmic fetus > 4500 gm or polyhydramnios with amniotic fluid index > 24), placenta previa, anemia and those who received intraoperative blood transfusion during prior CS.

Exclusion criteria included women with previous history of thromboembolic events, allergy to tranexamic acid and those with morbidity adherent placenta.

Women who encountered intraoperative complications as uterine artery or visceral injuries were also excluded from the study. Randomization and Intervention

All participants were carefully evaluated through full history, general and abdominal examination to evaluate the risk factors properly and ensure adherence to our inclusion and exclusion criteria.

Obstetric ultrasound was done before surgery to assess the fetal age and maturity, placental location and amniotic fluid volume. Routine laboratory investigations were done including complete blood count and coagulation profile.

At the same day of surgery, women were equally randomized using computer-generated random numbers to one of the 2 groups. The anesthesiologist, obstetric surgeon, participants and outcome assessor were all blinded.

Fifteen minutes before surgery, women in the active group received 1 gram (10 ml) of tranexamic acid (Kapron, Amoun, Egypt; diluted in 20 mL of glucose 5% while women in the control group received 30 mL of glucose 5%. Tranexamic acid ampoules were stored at 15 – 20 °C temperature in a dry container. Both solutions were injected slowly over a period of 5 minutes.

All CD were done under regional anesthesia by obstetric surgeon with 5 or more years’ experience in obstetric management. The same technique was used in all women. Pfannenstiel incision, transverse lower segment uterine incision, Cord clamping immediately after fetal extraction, uterine exteriorization, two layers closure of the uterine incision and closure of the abdominal wall in layers were done in all women. All women were followed up for 48 hours.

After fetal extraction, all participants received a combination of intravenous 5 IU oxytocin (Syntocinon, Novartis, Basel, Switzerland) and intramuscular 0.2 mg ergometrine (Methergin, Novartis, Basel, Switzerland) followed by intravenous drip of 20 IU oxytocin diluted in 500 mL lactated Ringer’s solution with a rate of 125 mL/h).

All women have instructed to report any manifestations of thromboembolism. Reexamination for all participants was done after 1 and 4 weeks after discharge.

We calculated the intraoperative blood loss by taking the mean of the 2 famous methods of estimation. The first one was done through the formula Blood loss=estimated blood volume (EBV)×preoperative hematocrit–postoperative hematocrit/preoperative hematocrit. While the second one was through the weight difference of the towels and dressings before and after the operation added to the volume of fluid inside the suction apparatus.

Intraoperative blood loss was the primary outcome parameter in our study. Other outcomes included the need for further ecobic, the need of intraoperative blood transfusion and occurrence of any side effects as thromboembolism.

Sample size

Sample size calculation was done using estimated intraoperative blood loss as the primary outcome. Shakur et al[18] reported the Mean ± SD blood loss as 324 ± 167 mL. Eighty women in experimental group and 80 in the control one were needed to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.9. The Type I error probability associated with this test of this null hypothesis is 0.05. Sample size calculation was done using G*Power software version 3.1.2.11

STATISTICAL ANALYSIS

Data were coded and entered using SPSS version 25 (IBM, Armonk, NY, USA). Data were described using
mean ± SD, median, range for numerical data, and number and percentage for categorical data. Kruskal-Wallis and Mann-Whitney tests were used to compare numerical variables and χ² test was used to compare categorical data. P value less than 0.05 was considered statistically significant.

RESULTS

We assessed 410 women evaluated, 160 were randomized to one of the 2 groups (Figure 1).

No statistical difference was found between women subjected to TXA and those subjected to placebo regarding maternal age, weight, gestational age or mode of previous delivery (Table 1).

Placenta previa was the commonest risk factor in both groups followed by fetal macrosomia and anemia (Table 1).

The duration of the operation, neonatal birth weight, parameters of neonatal outcomes named Apgar 1 minute, Apgar 5 minutes and neonatal ICU admission were statistically not different between the 2 study groups (Table 1).

The estimated blood loss was significantly higher in the placebo group when compared to TXA group ($P < 0.001$) (Table 2).

Both postoperative hemoglobin and hematocrit were lower and their change percentages were higher in the placebo group when compared to TXA one (Table 2).

The need for further ecbolic was higher in placebo group when compared to TXA group ($P < 0.001$) (Table 2).

The need for intraoperative blood transfusion was more in placebo group compared to TXA one. However, that difference didn’t reach statistical significance ($P 0.071$) (Table 2).

Fig. 1: Prisma flow chart
Table 1: Demographic and clinical characteristics.\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid group (n=80)</th>
<th>Placebo group (n=80)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.4 ± 4.46</td>
<td>29.5 ± 4.45</td>
<td>0.758</td>
</tr>
<tr>
<td>Weight (kilogram)</td>
<td>88.7 ± 7.8</td>
<td>94.1 ± 8.84</td>
<td>0.121</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.1 ± 1.1</td>
<td>37.9± 1.1</td>
<td>0.729</td>
</tr>
<tr>
<td>Mode of previous deliveries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>10 (12.5%)</td>
<td>12 (15%)</td>
<td></td>
</tr>
<tr>
<td>VD</td>
<td>16 (20%)</td>
<td>19 (23.75%)</td>
<td></td>
</tr>
<tr>
<td>1 previous CS</td>
<td>34 (42.5%)</td>
<td>34 (42.5%)</td>
<td>0.521</td>
</tr>
<tr>
<td>2 previous CS</td>
<td>11 (13.75%)</td>
<td>10 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>(&gt; 2) previous CS</td>
<td>9 (11.25%)</td>
<td>5 (6.25%)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>11 (13.75%)</td>
<td>13 (16.25%)</td>
<td></td>
</tr>
<tr>
<td>Polyhydramnios</td>
<td>8 (10%)</td>
<td>5 (6.25%)</td>
<td></td>
</tr>
<tr>
<td>Fetal macrosomia</td>
<td>15 (18.75%)</td>
<td>17 (21.25%)</td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twin pregnancy</td>
<td>6 (7.5%)</td>
<td>9 (11.25%)</td>
<td>0.623</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>31 (38.75%)</td>
<td>25 (31.25%)</td>
<td></td>
</tr>
<tr>
<td>Received blood transfusion during previous CS</td>
<td>9 (11.25%)</td>
<td>11 (13.75%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Duration of operation (minutes)</td>
<td>49.9± 19.7</td>
<td>47.8± 19.1</td>
<td>0.341</td>
</tr>
<tr>
<td>Neonatal birth weight (grams)</td>
<td>3888.4± 712.8</td>
<td>3912.1± 761.9</td>
<td>0.824</td>
</tr>
<tr>
<td>Neonatal outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apgar 1 min</td>
<td>7.1 ± 0.9</td>
<td>7.0 ± 0.9</td>
<td>0.885</td>
</tr>
<tr>
<td>Apgar 5 min</td>
<td>8.9 ± 1.1</td>
<td>8.9 ± 1.0</td>
<td>0.619</td>
</tr>
<tr>
<td>NICU admission</td>
<td>8 (10%)</td>
<td>9 (11.25%)</td>
<td>0.662</td>
</tr>
</tbody>
</table>

\(^a\) Values given as mean ± SD or number (percentage).

Table 2: Estimated blood loss, hemoglobin, hematocrit, platelet count, and need for ecbolics.\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid group (n=80)</th>
<th>Placebo group (n=80)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated blood loss (mL)</td>
<td>583.23 ± 379.62</td>
<td>896.81 ± 519.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin concentration (g/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>10.9 ± 1.1</td>
<td>11.0 ± 1.0</td>
<td>0.852</td>
</tr>
<tr>
<td>Postoperative</td>
<td>10.1 ± 1.2</td>
<td>9.2 ± 1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage change</td>
<td>7.34 (1.4–18.34)</td>
<td>16.36 (7.5–25.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematocrit %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>32.8 ± 3.2</td>
<td>33.1 ± 3.0</td>
<td>0.662</td>
</tr>
<tr>
<td>Postoperative</td>
<td>30.1 ± 3.4</td>
<td>27.4 ± 4.1</td>
<td>0.012</td>
</tr>
<tr>
<td>Percentage change</td>
<td>7.11 (2.7–19.87)</td>
<td>15.41 (6.9–27.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Need for further ecbolics</td>
<td>11 (13.75%)</td>
<td>37 (46.25%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Need for intraoperative blood transfusion</td>
<td>1 (1.25%)</td>
<td>5 (6.25%)</td>
<td>0.071</td>
</tr>
</tbody>
</table>

\(^a\) Values are given as mean ± SD, median (range), or number (percentage).

DISCUSSION

The results of our study clearly demonstrated the ability of preoperative TXA to minimize intraoperative blood loss during high-risk CD.

Placental separation during delivery is associated with powerful myometrial contractions, enhanced platelet activity, release of coagulation factors and increase of fibrinolytic activity (which continues for 6–10 hours after delivery\(^{[16]}\)). According to these facts, TXA can reduce blood loss after delivery regardless its mode through its fibrinolytic activity.

In our study, TXA significantly decrease intraoperative blood loss from 896.81 ± 519.6 in those who didn’t receive the drug to 583.23 ± 379.62 in women who received it.

Previous studies demonstrated the ability of TXA to decrease blood loss associated with CD.

Another study\(^{[5]}\) confirmed these findings for up to 2
hours after delivery. Furthermore, tranexamic acid has been previously found to decrease the need for additional uterotonic agents[18,19]. A lower dose of 10 mg/kg has also been shown to reduce blood loss after lower‐segment cesarean section[20]. Sentürk et al[21] confirmed the efficacy of tranexamic acid in the reduction of blood loss without any associated complications of venous thromboembolism, gastrointestinal difficulties, or hypersensitivity. Additionally, Yang et al[22] found the drug to be equally safe and effective following vaginal delivery. A 2014 study confirmed these results following administration of 1 g tranexamic acid during induction of anesthesia[23].

That meta‐analysis further revealed that the magnitude of reduction differs by surgery type and timing of TXA administration, indicating that a dose of 1 g is sufficient for most adults, with no evidence to support the use of higher doses[24]. Another meta‐analysis of 34 articles (5 randomized controlled trials, 7 observational studies, and 22 case reports)[25] showed that tranexamic acid use reduced blood loss by 32.5 mL compared with placebo. Nevertheless, two cases of pulmonary embolism were identified in that meta‐analysis, although the possible involvement of tranexamic acid demonstrated that preoperative administration of 1 g tranexamic acid is a safe and effective method for the reduction of blood loss during elective lower‐segment cesarean delivery. In these thrombotic episodes could neither be confirmed nor excluded. Maged et al demonstrated the ability of TXA to decrease the need of intraoperative blood transfusion from 6.25% to 1.25%. However, this difference didn’t reach a statistical significance. We believe that a larger sample size can detect a significant difference[26].

To the best of our knowledge, our study is double blind with properly calculated sample size. We believe that larger sample size could demonstrate additional benefits as need for transfusion. We used 2 methods to evaluate blood loss both the most common and most accurate methods. The main limitation of our study was the short follow up duration as the long term maternal and neonatal effects of the drug cannot be assessed.

CONCLUSION

Tranexamic acid is a safe and effective method for reduction of blood loss during elective lower‐segment cesarean delivery. Furthermore, the drug reduced the use of ecbolic drugs during the postoperative period. Therefore, tranexamic acid could be used in women with a high risk of blood loss to decrease the likelihood of a blood transfusion or of serious postpartum hemorrhage. However, larger trials of tranexamic acid among this population should be performed.

CONFLICT OF INTERESTS

There are no conflict of interests.

REFERENCES

PREOPERATIVE INTRAVENOUS TRANEXAMIC ACID IN CS


