Efficacy of Intravenous Tranexamic Acid before Cesarean Section in Preventing Post Partum hemorrhage- a Prospective Randomised Double Blind Placebo Controlled Study

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A B S T R A C T

The incidence of severe post partum hemorrhage (PPH) has been found to be 10.5% of all live births globally which is come to be around 14 million. This not only results in a case fatality rate of 1% (1, 40,000 yearly), nearly 12% women (1.6 million each year) survive with severe anemia and its debilitating consequences. [1] The incidence of cesarean delivery is increasing and the average blood loss during cesarean delivery is almost double the amount lost in vaginal delivery. [2] The hematocrit falls by 10% and blood transfusion is required in 6% of women undergoing cesarean delivery compared with 4% of women who gave vaginal birth. [3] Although many obstetric units use intravenous bolus or infusion of oxytocin to prevent uterine atony during and after cesarean delivery, 10%-40% of women receiving oxytocin require additional uterotonic agents. [4, 5] Tranexamic acid is an antifibrinolytic agent which is safe, easy to use and in a number of studies has been found to be a cost-effective drug in decreasing bleeding during different surgical procedures [6-12]. Studies have proved that it is effective in reducing PPH during both vaginal and cesarean delivery [13-17] The aim of the present study was to evaluate the efficacy and safety of intravenous tranexamic acid administered immediately before cesarean section to reduce postpartum blood loss.

Introduction

This was a prospective, randomized, double blind, placebo controlled study conducted in the department of Gynecology and Obstetrics, College of Medicine and Sagore Dutta Hospital and Nil Ratan Sircar Medical College and Hospital from March 2013 to February 2014.

Inclusion criteria were women aged 20-40 years with 38-40 weeks of gestation who underwent elective cesarean section.

Exclusion criteria were women having risk factors for post partum hemorrhage, such as, multiple pregnancy, polyhydramnios, fetal macrosomia, antepartum hemorrhage, obstructed labor; hemoglobin <8 gm%, severe pre eclampsia and coagulopathy; previous history of cesarean delivery or intra abdominal surgery; active thromboembolic disease, eg., deep vein thrombosis, pulmonary embolism, cerebral thrombosis; history of thrombosis or thromboembolism; intrinsic risk for thrombosis, eg., thrombogenic valvular disease, thrombogenic cardiac rhythm disease, hypercoagulopathy, thrombophilia; cardiovascular, renal or liver disorders and hypersensitivity to tranexamic acid.

The participants who fulfilled the eligibility criteria were explained in simple language about the study with special reference to the beneficial and possible adverse effects of intravenous tranexamic acid. Informed consent was obtained from the willing participants. The study was approved by the Independent Ethics Committee of the Institution.

Participants were randomly assigned to tranexamic acid group or group A (n=70) and placebo group or group B (n=70). Randomization was done by residents using computer generated random numbers. Allocation concealment was done by sequentially numbered opaque sealed envelope (SNOSE).

Group A received 1 gram (10 ml) of intravenous bolus dose of tranexamic acid just before skin incision, group B received 10 ml of sterile water for injection intravenously at the same time.

Both the patients and the investigators remained blinded to the group assignment. All patients also received 20 units of oxytocin during the first 8 hours post operatively. Additional uterotonics in the form of oxytocin infusion, Inj methyl ergometrine, Inj. carboprost and Tab misoprostol 600 mcg per rectally were given as and when needed.
All the operations were performed under spinal anesthesia. The standard technique of transperitoneal lower segment cesarean section was adopted. To avoid bias related to surgical skill, a group of 4 surgeons from a particular obstetric unit performed all the surgeries. Transfusion was performed if a patient's hemoglobin level was ≤7 g/dL.

Primary outcome measures were

1. Blood loss from delivery of the placenta to the end of the cesarean section which was measured by adding the volume of the contents of the suction bottle which was changed after delivery of placenta to avoid being mixed with amniotic fluid and blood from parities and the difference in weight (in grams) between the dry and the soaked operation sheets, gauze pieces and mops (1 gram is equivalent to 1 ml).

2. Blood loss from the end of cesarean section to 2 hours post partum which was measured by weighing the soaked pads (in grams) and subtracting the weight of dry pads (in grams) from it (1 gram is equivalent to 1 ml).

3. Hemoglobin estimation was done in all patients pre operatively and 24 hours post operatively and the change in concentration was noted.

Secondary outcome measures were:

1. Need for additional uterotonics
2. Use of additional surgical interventions to control post partum hemorrhage
3. The amount of fluid infused
4. Need for blood transfusion
5. Mild side effects such as nausea, vomiting, headache, skin reactions
6. Maternal death or severe maternal morbidity such as seizure, thromboembolic events, need for intensive care unit admission, hysterectomy.

Sample size calculation- It was estimated that 70 patients in each group would be needed with an alpha error of 5% and beta error of 10% to detect 62 ml blood loss difference. Two tailed P<0.05 was considered significant.

RESULTS

Initially 150 women were enrolled for the study. Eight did not meet the inclusion criteria and two refused to participate. One hundred and forty women were randomized into study and placebo groups (n=70 for each group). Analysis was by intention to treat.

The study and the control groups were similar with respect to their age, BMI, gestational age and gravidity. (Table 1). Blood losses from both placental deliveries to the end of cesarean section and from end of cesarean section to 2 hours postpartum were significantly lower in the study group. (p < 0.0001). (Table 2).

Change in hemoglobin concentration in study group was also significantly less than in the control group. (p<0.0001). (Table 2).

Total amount of oxytocin required was significantly less in tranexamic acid group

(p< 0.0001). Also the number of women requiring other oxytocics (Inj. methyl ergometrine, Inj. carboprost and Tab misoprostol per rectally) was significantly less in tranexamic acid group (p= 0.0078).

Neither group required any additional surgical intervention to control PPH.

The amount of intra-operative fluid required were significantly less in tranexamic acid group (p< 0.0001). However post-operative fluid requirement was comparable in both the groups (p= 0.0943).

Minor side effects in the form of nausea and vomiting were comparable in both the groups. (Table 2).

No major side effect was observed in either group. Three mothers of the control group were given blood transfusion post operatively for post partum hemorrhage.
Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules. [18]

A number of studies have been performed to find out the pre operative application of intravenous tranexamic acid to prevent post partum hemorrhage in cesarean section. All of them found significantly less bleeding from the end of cesarean section to 2 hours postpartum in pre operative tranexamic acid treated group. [14, 15, 17]. Bleeding from the placental delivery to 2 hours postpartum was also found to be less in study group [16, 17]. Tranexamic acid was found to be beneficial not only to prevent PPH, but also for its management. [17]

**Table 1: Demographic variables in study and control groups**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study group (mean± SD) n=70</th>
<th>Placebo group (mean± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age(years)</td>
<td>25.94± 3.78</td>
<td>26.04± 3.39</td>
<td>0.8694</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.5± 5.65</td>
<td>67.72± 4.14</td>
<td>0.3531</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.62± 0.779</td>
<td>38.72± 0.671</td>
<td>0.4172</td>
</tr>
<tr>
<td>Gravidity</td>
<td>2.12± 1.0028</td>
<td>1.94± 0.998</td>
<td>0.2890</td>
</tr>
</tbody>
</table>

**Post operative Hb% was also found to be significantly greater in tranexamic acid treated group. [15].**

During placental separation, fibrinogen and fibrin degrade rapidly. The products of plasminogen and fibrin degradation increase due to activation of the fibrinolytic system, which can last 6–10 hours, causing more bleeding. Blocking this activation of fibrinolytic system, according to Ali and associates, is the mechanism of action of the drug to prevent post partum hemorrhage. [19]

No study, like us found any adverse effect of the drug. However an article by Peitsidis et al where the use, efficacy and safety of tranexamic acid in the prevention and treatment of postpartum hemorrhage were reviewed, have found two cases of pulmonary embolism in tranexamic acid treated group [20]. They have not however concluded about the causal relationship of tranexamic acid forthis adverse effect.

**CONCLUSION**

Intravenous bolus administration of tranexamic acid 1 gram before skin incision was found to be effective and safe in preventing post partum hemorrhage in cesarean delivery. In a developing country like ours where PPH is a major threat to the life of the mothers, it seems to be a promising option.

**REFERENCES**


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