Efficacy of Oxytocin Infusion Versus Tranexamic Acid Infusion in Controlling Blood Loss During Elective Lower Segment Caesarean Section

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ABSTRACT

Background: Caesarean section represents a risk factor for intrapartum and postpartum hemorrhages and a burden of ongoing anemia. Therefore, methods of controlling blood loss during caesarean section decrease maternal morbidity and mortality and enhance the quality of mother's life during puerperium.

Objective: to compare efficacy of oxytocin infusion after oxytocin bolus and efficacy of tranexamic acid infusion after oxytocin bolus in controlling blood loss during elective lower segment caesarean section.

Patients and methods: The study included 138 legally adult pregnant women (18 – 38 years old) with singleton pregnancies at term (37 – 42 weeks) who were recruited from Ain Shams University Maternity Hospital where and booked for primary elective caesarean section. They were randomly divided into three groups. Group (A) was given an intravenous slow bolus of oxytocin 10 IU over 1 minute and 40 IU oxytocin in 500 l of 0.9% saline solution over 4 hours after delivery of baby. Group (B) was given an intravenous slow bolus of oxytocin 10 IU over 1 minute and 1 gm tranexamic acid in 200 ml of 0.9% saline solution over 5 minutes after delivery of baby. Group (C) was given only an intravenous slow bolus of oxytocin 10 IU over 1 minute after delivery of baby. The three groups would be compared regarding to gravimetric assessment of “measured” blood loss and mathematical estimation of “calculated” blood loss.

Results: The estimated and calculated blood loses in group (A) were statistically insignificant less than those in group (B). But those loses in group (C) were statistically significant more than the loses in other groups.

Conclusion: The tranexamic acid infusion after oxytocin bolus is effective as oxytocin infusion after oxytocin bolus in controlling blood loss during elective lower segment caesarean section. It can help against postpartum hemorrhage with no considerable side effects.

Keywords: oxytocin, tranexamic acid, postpartum hemorrhage, caesarean section.

INTRODUCTION

Postpartum hemorrhage (PPH) is an obstetrical emergency. It is a major cause of maternal morbidity, and one of the top three causes of maternal mortality in both high and low per capita income countries (1). In the developing world about 1.2%of deliveries are associated with PPH and when PPH occurred about 3% of women died (2). PPH remains a major cause of both maternal mortality and morbidity worldwide more so in developing countries with an estimated mortality rate of 140,000 per year or one maternal death every four minutes. PPH occur in 5% of all deliveries, majorities of death occur within four hours of delivery indicating that it is a consequence of third stage of labour (3).The major four causes for PPH related to four —Ts: Tone, Tissue, Trauma, and Thrombin (4). Their incidences are: 70% for uterine atony, 20% for genital trauma, 10% for retained tissue and 1% for coagulation defects (5).

Tranexamic acid is a synthetic analog of the amino acid lysine. It serves as an antifibrinolytic by reversibly binding four to five lysine receptor sites on plasminogen or plasmin. This prevents plasmin from binding to and degrading fibrin and preserves the framework of 48 fibrin's matrix structure. It has roughly eight times the antifibrinolytic activity of an older analogue, e-aminocaproic acid (6). So, TXA has been widely used to reduce blood loss in elective surgery where it reduces blood transfusion by about one-Third (7). It was found by Chandrakala and Venkateswarlu (8) that tranexamic acid significantly reduced bleeding form placental delivery to 2 hours post partum in study group (given slow IV tranexamic acid 1 gm in 20ml 5% dextrose 10 minute before skin incision with oxytocin 20 units IV Drip after delivery of baby) compared with control group (given only oxytocin 20 units IV Drip after delivery of baby). In the study group total blood loss was reduced by 76.8ml as compared with that of the control group. There was significant increase in the difference of postoperative and preoperative value of the Hb % and PCV in the study group compared with the control group.

PATIENTS AND METHODS

The study group included 138 pregnant women who admitted at Ain Shams University Maternity Hospital to be delivered through elective primary caesarean section. The study included all legally adult pregnant women (18 – 38 years old), primigravida or multigravida without history of previous caesarean section, at term (37 – 42...
weeks), with singleton pregnancies, booked for elective caesarean section and without medical and obstetric disorders. All pregnant were subjected to careful and detailed history and examination and were investigated for complete blood count, prothrombin time, activated partial thromboplastin time, liver function tests (AST and ALT) and kidney function tests (blood urea and serum creatinine). The study was double-blinded randomized clinical trial in which an intravenous slow bolus of oxytocin 10 IU over 1 minute and 40 IU oxytocin in 500 ml of 0.9% saline solution over 4 hours after delivery of baby were given to group (A). An intravenous slow bolus of oxytocin 10 IU over 1 minute and 1 gm tranexamic acid in 200 ml of 0.9% saline solution over 5 minutes after delivery of baby were given to group (B). Only an intravenous slow bolus of oxytocin 10 IU over 1 minute after delivery of baby was given to the control group (C).

The main outcome measures were gravimetric assessment of “calculated” blood loss and mathematical estimation of “calculated” blood loss with determination of percentage of major obstetric haemorrhage which is defined as calculated blood loss > 1000 ml.

The cases that fulfilled the criteria were randomly distributed into three groups. Group (A) contained 46 women assigned to receive an intravenous slow bolus of oxytocin 10 IU over 1 minute after delivery of baby followed by 40 IU oxytocin in 500 ml of 0.9% saline solution over 4 hours, Group (B) contained 46 women assigned to receive an intravenous slow bolus of oxytocin 10 IU over 1 minute and 1 gm tranexamic acid in 200 ml of 0.9% saline solution over 5 minutes after delivery of baby, and Group (C) contained 46 women assigned to receive only an intravenous slow bolus of oxytocin 10 IU over 1 minute after delivery of baby. It represented a control group.

All pregnant that fulfilled the criteria underwent LSCS which was done by senior doctor and all were exposed to spinal anesthesia.

The estimation of blood loss was done through two ways:

1. Measuring blood loss: The amount of blood loss (ml)
   = [(weight of the used towels – weight of the towel prior to the surgery) + the volume sucked in the suction bottle after placental delivery in ml] provided that conversion of weight of towels by (gm) to volume by (ml) by equation (1000 gm = 962 ml) \(^9\). Measuring blood loss was done after delivery of placenta and four hours postpartum after completion of LSCS and all pads were included in the estimation.

2. Calculating blood loss: The amount of blood loss (ml)
   = [estimated blood volume \times (preoperative PCV – postoperative PCV)/preoperative PCV] (where estimated blood volume = booking weight (kg) \times 85) \(^10\). Major obstetric haemorrhage is defined as calculated blood loss > 1000 ml.

Also, heart rate, respiratory rate and blood pressure were checked before the surgery, immediately after placental delivery and one and four hours after birth, respectively. Hemoglobin and hematocrite values were noted 24 hours after operation for all groups.

The secondary outcomes included the usage of an additional uterotonic agent, the need of blood transfusion and maternal and neonatal side effects of oxytocin and tranexamic acid.

**Ethical approval:**

The study would be approved by Ethical committee of the Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University.

**Statistical analysis**

Data Management and Analysis: The collected data was revised, coded, tabulated and introduced to a PC using statistical package for social sciences (IBM SPSS 20.0). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

**I-**

**II- Descriptive Statistics:**

1. Mean, Standard deviation (± SD) and range for parametric numerical data, while Median and Interquartile range (IQR) for non-parametric data.
2. Frequency and percentage of non-numerical data.

**III- Analytical Statistics:**

1. **ANOVA** was used to assess the statistical significance of the difference of a parametric variable between means of more than two study groups.
2. **Chi square test** was used to examine the relationship between two qualitative variables but when the expected count is less than 5 in more than 20% of the cells; Fisher’s Exact Test was used.
3. **Paired t-test** was used to compare two means Before-and-after observations on the same subjects.

**P-value: Level of significance:**

P>0.05: Non-significant (NS) - P<0.05: Significant (S) - P<0.01: Highly significant (HS)

**RESULTS**

Demographic data of the pregnant under the study in groups A , B and C showed no statistically significant difference as regard to age (means equal 26.30 , 27.24 , 26.92 years respectively), weight (means equal 74.76 , 73.50 , 75.10kg respectively) and gestational age (means equal 38.54, 38.04, 38.42 weeks respectively. Group (A) contained 10 primigravidae and 36 multigravidae. Group (B) contained 19 primigravidae
and 27 multigravidae. Group (C) contained 18 primigravidae and 28 multigravidae. This division depended on randomization. The most common causes for cesarean section were breech (46 cases), cephalopelvic disproportion (39 cases) and IUGR (35 cases). The duration of cesarean section showed no statistically significant variation between the three groups (means: 39.48 min, 38.22 min, 40.8 min respectively).

As regard to the main primary outcome which was the blood loss, it was interpreted by Kruskal Wallis test and interquartile (Q3 – Q1) as the data showed skewness from the normal distribution. However it could be expressed in mean and standard deviation even if the data were not normally distributed because there were more than double dozen of patients i.e. 24 in each group as we couldn’t follow the central limit theorem in this case. The study results showed that there was statistically significant difference as regard the blood loss between the three groups. The estimated blood loss which was representative for the actual bleeding shows p value = 0.021 and ANOVA = 4.933 meaning that it was statistically significant with 2.1% to obtain the same result by chance (table (1)). Also this parameter showed statistically significant difference between Group (A) and Group (C) with p value = 0.039 and statistically significant difference between Group (B) and Group (C) with p value = 0.045. But there was no statistically significant difference in comparison between Group (A) and Group (B) (p value = 0.345). With regard to the calculated blood loss depending on preoperative and postoperative hematocrite values and booking weight, the result showed statistically high significance difference between the three groups with p value = 0.009 and ANOVA = 7.870 (table (1)). Also there was statistically high significant difference between Group (A) and Group (C) with p value = 0.006 and statistically high significant difference between Group (B) and Group (C) with p value = 0.008. And there was no statistically significant difference between Group (A) and Group (B) with p value = 0.561. This meant that tranexamic acid infusion was as effective as oxytocin infusion in controlling blood loss during cesarean section as shown statistically with regard to estimated and calculated blood loss.

Table (1): Comparison between groups (A), (B) and (C) regarding estimated blood loss and calculated blood loss using ANOVA

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>ANOVA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>+ SD</td>
<td>Mean</td>
<td>+ SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Estimated Blood Loss</td>
<td>625.77</td>
<td>170.02</td>
<td>686.71</td>
<td>134.23</td>
<td>751.38</td>
</tr>
<tr>
<td>Calculated Blood Loss</td>
<td>590.93</td>
<td>205.89</td>
<td>594.03</td>
<td>135.81</td>
<td>688.18</td>
</tr>
</tbody>
</table>

(*** Highly statistically significant at P < 0.01) (**) Statistically significant at P < 0.05

The same result is obtained when the data was expressed nonparametrically by using Kruskal Wallis test and interquartile (Q3 – Q1). There was statistically significant difference as regard the blood loss between the three groups, the p values for estimated and calculated blood loss are 0.021 and 0.034 respectively table (2). Also, there was a statistically significant difference between Group (A) and Group (C) as regard to estimated blood loss with p value = 0.011 (table (22)) and statistically high significant difference as regard to calculated blood loss with p value = 0.009. Similarly, there was a statistically significant difference between Group (B) and Group (C) with p value = 0.015 for estimated blood loss and 0.019 for calculated blood loss. But no statistically significant difference was present between Group (A) and Group (B) (p value = 0.056 for estimated blood loss and 0.061 for calculated blood loss.

Table (2): Comparison between groups (A), (B) and (C) regarding estimated blood loss and calculated blood loss using interquartile range and median

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Kruskal Wallis test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Media n</td>
<td>IQR</td>
<td>Media n</td>
<td>IQR</td>
<td></td>
</tr>
<tr>
<td>Estimated Blood Loss</td>
<td>595.52</td>
<td>70.47</td>
<td>618.56</td>
<td>81.15</td>
<td>38.181</td>
</tr>
<tr>
<td>Calculated Blood Loss</td>
<td>550.20</td>
<td>85.28</td>
<td>570.66</td>
<td>99.81</td>
<td>16.960</td>
</tr>
</tbody>
</table>
The amount of bleeding during the period from placental delivery till the operation end was statistically significant among the three groups (p value = 0.012) and was statistically high significant among them during the four hours after the operation end (p value = 0.003) as shown in table (3). The comparison between Group (A) and Group (C) showed statistically significant difference during the period from placental delivery till the operation end (p value = 0.031) and statistically high significant difference during the four hours after the operation end (p value = 0.007). And comparison between Group (A) and Group (B) showed statistically significant difference during the period from placental delivery till the operation end (p value = 0.048) and statistically insignificant difference during the four hours after the operation end (p value = 0.325). This meant statistically that tranexamic acid infusion was effective in controlling blood loss during the period from placental delivery till the operation end and the four hours after the operation as comparison with the control group oxytocin bolus only (Group C).

The same statistical result was obtained with oxytocin bolus and infusion (Group A) in comparison with the control group oxytocin bolus only (Group C). Also the statistical results showed that the tranexamic acid infusion (Group B) is as effective as oxytocin bolus and infusion (Group A) in controlling the blood loss the four hours after the operation but it was less effective than oxytocin bolus and infusion in controlling blood loss during the period from placental delivery till the operation end.

Table (3): Comparison between groups (A), (B) and (C) regarding blood amount from placental delivery till end of operation and 4 hour after operation

<table>
<thead>
<tr>
<th>blood amount</th>
<th>Group</th>
<th>ANOVA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A Mean</td>
<td>Group B Mean</td>
<td>Group C Mean</td>
</tr>
<tr>
<td>From placental delivery till end of operation</td>
<td>457.35</td>
<td>73.00</td>
<td>483.89</td>
</tr>
<tr>
<td>4 hour after operation</td>
<td>60.43</td>
<td>7.92</td>
<td>66.33</td>
</tr>
</tbody>
</table>

(**) Highly statistically significant at P<0.01 \ (*) Statistically significant at P<0.0

The comparison among the three groups showed a statistically significant difference as regard to the major obstetric hemorrhage (more than 1000 ml) with p value = 0.042 as shown in table (4). Also this statistically significant difference was present in comparison between Group (A) and Group (C) with p value = 0.017 and comparison between Group (B) and Group (C) with p value = 0.032 . But there was no statistically significant difference between Group (A) and Group (B) (p value = 0.678). The number needed to treat (NNT) to prevent major obstetric hemorrhage when compared group (A) with the control group (C) was 7.67. It was 9.2 when compared group (B) with the control group (C). This meant that 7 patients needed to prevent PPH for one of them in case of oxytocin infusion and 9 patients needed to prevent PPH for one of them in case of tranexamic acid infusion.

Table (4): Comparison between groups (A), (B) and (C) regarding major obstetric hemorrhage

<table>
<thead>
<tr>
<th>Group</th>
<th>Chi square test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A No.</td>
<td>%</td>
<td>Group B No.</td>
</tr>
<tr>
<td>No</td>
<td>45</td>
<td>97.83%</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>2.17%</td>
</tr>
</tbody>
</table>

As regard blood hemoglobin level and hematocrite value, there was only a statistical
significance in hematocrite value 24 hour postoperative although there was no statistically significant difference between the three groups in preoperative blood hemoglobin level and hematocrite value. The comparison between Group (A) and Group (C) showed no any statistic insignificance except in hematocrite value 24 hour postoperative (p value = 0.034). The same result between Group (B) and Group (C) was obtained (p value = 0.044). But there was no statistic significance in comparison between Group (A) and Group (B) as regard as hematocrite value 24 hour postoperative (p value = 0.055).

Although the preoperative vital signs like pulse rate, blood pressure and respiratory rate showed no statistical significance between the three groups (p value = 0.495, 0.848, 0.105 and 0.194 for HR, RR, SBP and DBP respectively) and there was a statistically insignificant difference between Group A, Group B & Group C as regard HR, RR, Systolic and Diastolic B.P. after Placental Delivery (P > 0.05), there was a statistically significant difference between Group A, Group B & Group C as regard Systolic and Diastolic B.P. 1 Hr after birth (P < 0.05). However; there was a statistically insignificant difference between Group A, Group B & Group C as regard HR, RR 1 Hr after birth (P > 0.05). Comparison of group (A) and Group (B) with Group (C) as control showed statistical significance as regard systolic and diastolic blood pressure 1 hour postoperative (p values equal 0.035 for SBP and 0.020 for DBP in case of Group (A) and 0.038 for SBP and 0.024 for DBP in case of Group (B)). But the comparison between Group (A) and Group (B) showed only statistical significance in systolic blood pressure 1 hour after operation. SBP one hour after the operation was lower in case of tranexamic acid infusion than in case of oxytocin infusion. There was a statistically insignificant difference between Group A, Group B & Group C as regard Systolic B.P. 4 Hr after birth (P > 0.05) but there was a statistically significant difference between each of both Group A and Group B in comparison with Group C as regard DBP and HR four hour after operation (P > 0.05). Also the comparison between Group (A) and Group (B) shows statistical significance in HR and DPB.

As regard to the usage of uterotic agents, the results show that there was a statistically significant difference between Group A, Group B and Group C (p value = 0.043). Also there was a statistically significant difference when comparison between Group (A) and Group (C) (p value = 0.039) and comparison between Group (B) and Group (C) (p value = 0.040), but there was no statistically significant difference between Group (A) and Group (B) (p value = 0.621). This statistically meant similar effectiveness between tranexamic acid infusion (Group B) and oxytocin bolus and infusion (Group A) with comparison of each other and comparison each of them with the control oxytocin bolus only (Group C) as regard to the management of bleeding by uterotic agents e.g. methyrgine and syntocinon.

There was no statistically significant difference between Group A, Group B and Group C as regard types of uterogenic drugs (P > 0.05). There were no reported cases who had a blood transfusion among the three groups. As regard to accidental intraoperative events (e.g. uterine artery avulsion, broad ligament hematoma, uterine atony and oozing suture line), there is was statistically significant difference among the three groups (p value = 0.300).

DISCUSSION

The comparison between oxytocin bolus and infusion (Group A) and oxytocin bolus (Group C) matches a study done in five maternity hospitals in the Republic of Ireland and involved 2069 women booked for elective caesarean section at term with a singleton pregnancy. They were given randomly intravenous slow 5 IU oxytocin bolus over 1 minute and additional 40 IU oxytocin infusion in 500 mL of 0.9% saline solution over 4 hours (Intervention group: bolus and infusion) and 5 IU oxytocin bolus over 1 minute and 500 mL of 0.9% saline placebo solution over 4 hours (Placebo group: bolus only). Almost one in six women in the study had a major obstetric haemorrhage, with a similar proportion requiring an additional uterotic agent. There was no difference in major obstetric haemorrhage between the groups. Women in the bolus and infusion group were less likely to require an additional uterotic agent than those in the bolus only group. A known oxytocin infusion was the most commonly chosen additional uterotic agent used (11).

Another trial done by Gungorduk (12) who compared the use of oxytocin bolus and placebo infusion with oxytocin bolus and 30 IU oxytocin infusion. Blood loss was estimated based on the haematocrit values before and 48 h after delivery. The primary outcome was the incidence of excessive bleeding (estimated blood loss of > 1000 mL), while secondary outcomes included use of additional uterotics, estimated blood loss, need for blood transfusion, duration of hospital stay and the incidence of adverse effects. Data showed reductions in both the use of additional uterotic agents and major obstetric haemorrhage. Mean estimated blood loss (P < 0.001) and the proportion of women with blood loss estimated to be greater than 1000 mL were significantly less for group B than for group A. In addition, more women in the group A required additional uterotic agents and blood transfusion.

Regarding comparison between Tranexamic acid
infusion (Group B) with oxytocin bolus (Group C) a similar results were obtained by Chandrakala and his colleagues through a prospective randomized study consisting of 200 patients undergoing caesarean section. This included 100 patients given tranexamic acid 1 gm diluted with 20ml 5% dextrose and infused IV Slowly over 5 minute 10 minute before skin incision with oxytocin 20 units IV Drip after delivery of baby (study group) and 100 patients given only oxytocin 20 units IV Drip after delivery of baby (control group). Both primigravida and primipara previous one caesarean section were included. While there was no statistical difference in the quantity of blood loss from the time of placental delivery to the end of caesarean section between the two groups, the total quantity of blood loss from the end of caesarean section to 2 hours post partum was significantly decreased in the study group compared with the control group. The total quantity of blood loss from placental delivery to 2 hour postpartum was also reduced in the study group with a statistical difference between the two groups. (8).

Similar study carried out in India by Mayur (13). It was conducted on 100 patients underwent to LSCS showed comparable results reducing the blood loss in the study group, Blood loss was collected and measured during two periods. The first period was from placental delivery to end of LSCS and second from the end of LSCS to 2 hours postpartum.

Use of TXA in pregnant women may raise the risk of occurrence of thrombo-embolism. However, previous studies have shown the safety of this drug for use in both pregnant and non-pregnant patients (14). In our study, thrombo-embolic events were not evaluated because the sample size was too low for adequate power. However, none of the women showed any signs or symptoms of immediate thrombo-embolic events and other side effects like color vision affection, allergic reaction, nausea, vomiting and diarrhea were not statistically significant in comparison with control.

CONCLUSION AND RECOMMENDATIONS

The study shows that tranexamic acid infusion after oxytocin bolus is effective as oxytocin infusion after oxytocin bolus in controlling blood loss during elective lower segment caesarean section. It decreases blood loss after placental delivery and up till the golden four hours postoperative. It decreases major obstetric hemorrhage and the need for uterotonic agent and blood transfusions. It can replace the high doses of oxytocin with its adverse effects. It can help against postpartum hemorrhage with no considerable side effects.

Conflict of Interest: Authors declare no conflicts of interest.

REFERENCES