INTRAVENTOUS VERSUS TOPICAL TRANEXAMIC ACID ADDING TO INTERNAL ILIAC ARTERY LIGATION IN THE CONSERVATIVE MANAGEMENT OF PLACENTA ACCRETA: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Objective: The aim of this study was to investigate the effect of adjunctive IV versus topical tranexamic acid (TA)on measured blood loss during and after caesarian section in patient undergone internal iliac artery ligation due to placenta previa accreta with the aim of conservative management. Methods: In this double-blind randomized controlled trial, 110 women were undergoing cesarean delivery for placenta accreta. were randomly allocated to managed conservatively with internal iliac artery ligation to control post-partum hemorrhage between June 2014 to June 2015. Placenta previa – accreta was diagnosed according to gray-scale, and color Doppler ultrasonography in addition to the intraoperative findings based on fragmentary or difficult separation of the placenta. In the case of conservative treatment protocol failure, cesarean hysterectomy was performed. Results: 93 women were enrolled (n=31 in each group). Both groups of women received IV tranexamic acid (group II) and topical tranexamic acid (Group III) showed great reduction in blood loss either intraoperative or post-operative (post operative vaginal bleeding and blood in intraabdominal drain) compared with (Group I) which received internal iliac artery ligation without tranexamic acid (P=0.0001, 0.0001, 0.015, 0.0001), so the overall estimated blood loss in group II and III showed highly reduction compared with group I (P=0.0001, 0.0001). Conclusion: Preemptive use of adjunctive IV and topical tranexamic acid (TA) in patient undergone internal iliac artery ligation due to placenta previa accreta, is associated with decrease blood loss during and after caesarian section, lower hysterectomy rate compared with internal iliac ligation alone.

Keywords: placenta accreta, internal iliac artery ligation, tranexamic acid

INTRODUCTION

Obstetric hemorrhage is estimated to be responsible for about one fourth of all maternal deaths and is the leading direct etiology of maternal mortality worldwide. (1) The United Nations Millennium Development Fifth Goal, to reduce 75 percent of maternal mortality by 2015 that not reached yet, cannot be hold without significant improvements in PPH-related mortality. (2)

Abnormally invasive placentas describe an abnormality in the adherence of the placenta to the myometrium. Placenta accreta is an obstetric condition that is closely linked with massive obstetric hemorrhage. Is not only associated with a 40% chance of requiring massive transfusion (>4 units of packed red blood cells) but also it is now the leading etiology of cesarean hysterectomy. The incidence has progressively risen worldwide from one in 2500 pregnancies to approximately one in 500, mainly due to the increasing rates of cesarean section. (3)

The optimal management of placenta accreta remains inconclusive. The extirpative approach involves manual removal of the placenta is associated with massive hemorrhage and emergency hysterectomy trying to stop the bleeding. (4) Even with advanced pre-surgical preparation, life-threatening hemorrhage often occurs in cases of placenta previa accreta during cesarean hysterectomy. Treatment, various conservative measures have been developed to avoid hysterectomy and preserve fertility. A multidisciplinary approach with surgical expertise, availability of transfusion facilities and further interventions including interventional radiology is essential and may result in reduced maternal morbidity and mortality. Also, various conservative surgical techniques such as myometrial compression sutures with uterine balloon tamponade may be used to decrease blood loss. (3)

Intentional retention of the placenta (IRP) is an option in view of a require for future fertility. Unfortunately, it may lead to serious maternal morbidity and mortality including septic shock and secondary hemorrhage. (11)

A new conservative surgical technique called the ‘Triple-P Procedure’ involves peri-operative placental localization and delivery of the fetus via transverse uterine incision above the upper border of the placenta, pelvic devascularization and placental non-separation
with myometrial excision and reconstruction of the uterine wall. It has been described as a safe and effective alternative to intentional retention of the placenta or peripartum hysterectomy. (5)

For several decades, internal iliac artery ligation (IIAL) has been used as an effective means of controlling intractable intraoperative or postpartum hemorrhage and contributing to the improvement of maternal outcome. (6) The aim is to reduce the blood supply to the uterus and to prevent or help to arrest postpartum hemorrhage

TXA is a lysine analogue which acts as an antifibrinolytic via competitive inhibition of the binding of plasmin and plasminogen to fibrin (7). There is a clear theoretical rationale for the use of antifibrinolytic agents to reduce post- partum blood loss. In fact, both the coagulation and fibrinolysis processes are implicated in the control of postpartum blood loss, supporting the hypothesis that TXA might be effective in PPH prevention (8).

However, concerns about possible thromboembolic events with parenteral administration of TXA have stimulated increasing interest in its topical use. The direct application of TXA to the bleeding surface has the potential to reduce bleeding with minimal systemic effects. The evidence in the literature for the use of topical TXA for bleeding highlight that local application of TXA reduces bleeding after surgery (cardiac, knee, head and neck surgery spinal or thoracic). (9) In most of the trials, TXA was administered in saline solution directly onto the bleeding site, either by pouring or spraying into the surgical wound. (10) To the best of our knowledge, local use of TXA has not been investigated for PPH prevention during cesarean section due to placenta accreta.

Till now there is a controversy about the best conservative management strategies of placenta previa accreta, although primary objective in placenta accreta is to prevent bleeding, the ideal treatment of abnormal placentation should restore the uterine anatomy and ensure a new pregnancy with minimal risk of complications. The ideal treatment of placenta accreta still illusive and debatable. With the rising incidence of abnormal placentation, it is important to define management strategies with a focus on reducing maternal morbidity and mortality mainly decrease PPH. (11)

So, the aims of our study to assess the adjunctive role of IV versus topical tranexamic acid (TA) added to (IIAL) to reduce intraoperative and post-operative hemorrhage as well as to preserve fertility and avoid hysterectomy.

**MATERIALS AND METHODS**

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local departmental Ethics Committee. Informed written consent was obtained from all patients prior to their enrollment in this study.

This study was a double blinded randomized controlled study conducted at Aswan University Hospitals, Egypt from June 2014 to June 2015. Study inclusion criteria were women undergoing elective cesarean delivery for placenta accreta. Diagnosis of placenta accreta based on ultrasound in which one or more of ultra-sonographic features were present: 1- loss of the retroplacental clear space. 2- Thinning of the myometrium overlying the placenta- 3-multiple irregular placental lacunae with a “moth-eaten” or “Swiss cheese” appearance of placenta. 4- turbulent blood flow through the lacunae on Doppler velocimetry. Exclusion criteria were: 1-Patients with cardiac, hepatic, renal or thromboembolic disease. 2- patients with placenta percreta (ultrasound features showed invasion of the placenta into the bladder or increased vascularity of the uterine serosa–bladder interface). 3-patients had allergy to tranexamic acid.

**Eligible participants**

There were 110 patients who were asked to participate, 17 patients were excluded, 13 patients not meeting inclusion criteria and 4 patients refuse to participate. Therefor the remaining 93 patients were included in the study. All participants underwent detailed history, general examination, abdominal examination and both abdominal and vaginal ultrasound examinations. The participants who fulfilled the eligibility criteria were explained about the study with the beneficial and possible adverse effects of tranexamic acid. Informed consent was obtained from them, after those participants were randomized to 3 groups: group 1 [31 patients received 20 IU oxytocin (syntocinon. Novartis company) IV infusion plus bilateral internal iliac artery ligation after fetus delivery], group 2 [31 patients received 1 gm tranexamic acid (2 ampoules of Capron 500 mg 5 ml Amoun company) IV just before skin incision plus 20 IU oxytocin IV infusion and
bilateral internal iliac artery ligation after fetus delivery] and group 3 [31 patients received 20 IU oxytocin IV infusion and bilateral internal iliac artery ligation after fetus delivery plus 2gm topical tranexamic acid (4 ampoules of Capron 500mg 5 ml ) applied on placental bed after placental delivery.

Randomization

Patients were randomized to three groups, each comprised of 31 patients according to a three-blocked randomization list which was coded (a or b or c) at 1:1:1 ratio. The three parallel groups were prepared using a Computer-generated randomization system. The allocated groups will be concealed in serially numbered sealed opaque envelopes that will only be opened after recruitment. Patient allocation will be performed prior to the induction of anesthesia by an independent person, who will not otherwise be involved in this study. The trial will be appropriately blinded; the participants, outcome assessors and the surgeon performing the procedure will be blinded to the medication type, which will be used.

Intervention

Eligible participants were allocated to one of three groups after induction of general anesthesia and immediately prior to the operation and just before skin incision. they received 1-gram tranexamic acid (10 ml) in 100 ml saline infusion or placebo (110 normal saline) by slow intravenous injection at an approximate rate of 1 mL per min. The abdomen was exposed through Pfannensteil incision, after skin incision, the subcutaneous fat and abdominal fascia were opened crosswise, and the rectus muscle was opened on the midline, the parietal peritoneum was opened longitudinally, the visceral peritoneum was opened transversely and dissected downwards with the bladder and kept against symphysis pubis by a Doyen retractor, followed by transverse incision of the uterus at the upper border of the placenta to avoid transplacental incision which provoke severe bleeding (Figure3). The fetus was delivered. Bilateral internal iliac artery ligation (IIAL) was done before placental delivery by Transabdominal/Trans peritoneal Approach. First Viscera were packed away to the contralateral side of the pelvis. Identification of the bifurcation of the iliac artery was done by palpation then the peritoneum over the iliac bifurcation was incised longitudinally and extended proximally and distally for a few centimeters (Figure4). The medial peritoneal flap and medial pelvic contents were retracted medially, and the lateral flap retracted laterally. Blunt dissection was then performed around the vessels and the areola tissue was opened. Once the bifurcation exposed, the internal iliac artery was confirmed as the branch coming off at right angles and coursing medially and inferiorly. The external iliac artery was confirmed as traversing laterally and superiorly over the psoas muscles. Careful and meticulous dissection was performed to separate the internal iliac artery from the veins.

Some right-angle forceps were used to separate the plane between artery and vein and then artery was ligated with suture ties on both sides. 20 IU oxytocin was given IV infusion after IIAL to prevent premature separation of placenta which provoked severe bleeding then placenta delivery was done. Finally, a towel soaked with 2g tranexamic acid (20 ml) diluted in 100 ml of sodium chloride 0.9% or placebo (120ml of sodium chloride 0.9%). used to compress the placental bed for 5 minutes (Figure5). To ensure a sufficiently high concentration, the tranexamic acid was diluted only to a volume sufficient to moisten a large wound surface32: 20 ml moistens at least 1500 cm2. The uterus was closed in three layers and pelvic drain was inserted in Douglas pouch in all patients followed by standard repair of abdominal wall.

Blood loss estimation

Intraoperative blood loss was measured by adding the volume of the contents of the suction bottle and the difference in weight (in grams) between the dry and the soaked operation sheets and towels (1 gram = 1 ml.). Post-operative blood loss was measured by adding the volume of the contents of the pelvic drain which measured every 12 hours and on removing the drain and the difference in weight (in grams) between the dry and the soaked vaginal pads after 4 hours post-operative (1 gram = 1 ml). After that the total blood loss was calculated by the addition of intraoperative and postoperative blood loss.

Study outcome

The primary outcome was estimation of intraoperative, postoperative and total blood loss (ml).

The secondary outcome measures included pulse rate, blood pressure and temperature which recorded continuously intraoperative, then every 30 minutes after operation therefor the mean were calculated.
Also measures included the need for blood transfusion≥4 units, operative time, period for hospitalization, cesarean hysterectomy, bladder injury, 24 hours postoperative hemoglobin concentration and any side effects such as nausea, vomiting and diarrhea.

After collecting all the data, the data were tabulated and analyzed.

**Statistically analysis:**

Data were entered and statistically analyzed using the Statistical Package for Social Sciences (SPSS) version 16. Qualitative data were described as numbers and percentages. Chi-square test, Fisher's exact test, and Monte Carlo test were used for comparison between groups, as appropriate. Quantitative data were described as means (SD) or medians, as appropriate. They were tested for normality by Kolmogorov-Smirnov test.

In the normally distributed variables, one-way ANOVA test with LSD post-hoc multiple comparisons were used for comparison between groups, as appropriate. In the non-normally distributed variables, Mann Whitney test and Kruskal-Wallis test were used for comparison between groups, as appropriate. Odds ratios and their 95% confidence interval were calculated. "p value ≤0.05" was considered to be statistically significant.

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### Allocation

**Assessed for the study**  
(n = 110)

- Excluded (n = 17)
  - not meeting inclusion criteria (n = 13)
  - Refuse to participate (n = 4)

**Randomized (n = 93)**

- 31 Women received standard regimen + internal iliac artery ligation
- 31 Women received standard regimen + internal iliac artery ligation + 1 Gm. IV Tranexamic acid before skin incision
- 31 Women received standard regimen + internal iliac artery ligation + 2 Gm. topical Tranexamic acid placental bed after placental delivery

**Estimation of total blood loss**  
(intraoperative + postoperative)

- Analyzed (n=31)
- Discontinued (n=0)

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### Table (1): preoperative Characteristics of pregnant women in study groups:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I (n = 31)</th>
<th>Group II (n = 31)</th>
<th>Group III (n = 31)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>30.71 ± 2.84</td>
<td>30.68 ± 2.53</td>
<td>31.13 ± 2.91</td>
<td>0.774</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.68 ± 5.48</td>
<td>77.13 ± 4.92</td>
<td>77.13 ± 5.16</td>
<td>0.891</td>
</tr>
<tr>
<td>Parity</td>
<td>3 (2–5)</td>
<td>3 (2–5)</td>
<td>3 (2–6)</td>
<td>0.707</td>
</tr>
<tr>
<td>Height</td>
<td>162.03 ± 3.89</td>
<td>163.52 ± 4.55</td>
<td>162.61 ± 4.06</td>
<td>0.375</td>
</tr>
<tr>
<td>Pulse</td>
<td>80.19 ± 5.03</td>
<td>79.65 ± 5.3</td>
<td>79.32 ± 5.0</td>
<td>0.795</td>
</tr>
<tr>
<td>Temperature</td>
<td>37.0 ± 0.14</td>
<td>36.97 ± 0.18</td>
<td>36.97 ± 0.13</td>
<td>0.709</td>
</tr>
<tr>
<td>SBP</td>
<td>120.1 ± 2.52</td>
<td>120.13 ± 2.7</td>
<td>119.8 ± 2.53</td>
<td>0.889</td>
</tr>
<tr>
<td>DBP</td>
<td>78.74 ± 3.14</td>
<td>78.26 ± 3.23</td>
<td>78.06 ± 3.08</td>
<td>0.685</td>
</tr>
<tr>
<td>Initial Hemoglobin (%)</td>
<td>9.88 ± 0.67</td>
<td>9.91 ± 0.7</td>
<td>9.96 ± 0.65</td>
<td>0.874</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>36.58 ± 0.62</td>
<td>36.55 ± 0.77</td>
<td>36.55 ± 0.62</td>
<td>0.977</td>
</tr>
<tr>
<td>Previous cesarean section (CS)</td>
<td>2.97 ± 0.84</td>
<td>2.87 ± 0.85</td>
<td>2.94 ± 0.93</td>
<td>0.906</td>
</tr>
</tbody>
</table>

SBP (Systolic Blood Pressure), DBP (Diastolic Blood Pressure), CS (Cesarean Section)

# Variables are presented as mean and standard deviation, median (minimum – maximum) and number (percentage).

Statistical significance if p value ≤0.05

### Table (2): primary outcome in the study groups:

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (n = 31)</th>
<th>Group II (n = 31)</th>
<th>Group III (n = 31)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative</td>
<td>1383.55 ± 315.36</td>
<td>913.23 ± 194.07</td>
<td>914.84 ± 234.99</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Postoperative vaginal bleeding</td>
<td>210(60-280)</td>
<td>150(80-110)</td>
<td>140(80-250)</td>
<td>0.018*</td>
</tr>
<tr>
<td>Blood in drains</td>
<td>110(60-280)</td>
<td>80(50-300)</td>
<td>80(50-300)</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Total blood loss</td>
<td>1800 ± 980</td>
<td>1151.61 ± 246.38</td>
<td>1153.87 ± 293.49</td>
<td>0.0001*</td>
</tr>
</tbody>
</table>

* Statistical Significant Difference (Group I versus Group II / Group I versus Group III / Group II versus Group III)

# Variables are presented as mean and standard deviation, median (minimum–maximum) and number (percentage).
Table (3): secondary outcome in the study groups:

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (n = 31)</th>
<th>Group II (n = 31)</th>
<th>Group III (n = 31)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse</td>
<td>92.52 ± 10.05</td>
<td>87.0 ± 6.38</td>
<td>85.77 ± 6.29</td>
<td>0.002* 0.006* / 0.001* / 0.536</td>
</tr>
<tr>
<td>Temperature</td>
<td>36.95 ± 0.16</td>
<td>36.95 ± 0.16</td>
<td>36.94 ± 0.14</td>
<td>0.918</td>
</tr>
<tr>
<td>SBP</td>
<td>112.23 ± 7.71</td>
<td>118.52 ± 2.54</td>
<td>118.45 ± 2.53</td>
<td>0.0001* 0.0001* / 0.959</td>
</tr>
<tr>
<td>DBP</td>
<td>73.87 ± 5.58</td>
<td>77.26 ± 3.38</td>
<td>77.1 ± 3.36</td>
<td>0.003* 0.002* / 0.004* / 0.881</td>
</tr>
<tr>
<td>Post op Hemoglobin (%)</td>
<td>9.16 ± 0.56</td>
<td>9.37 ± 0.61</td>
<td>9.56 ± 0.6</td>
<td>0.034* 0.159 / 0.01* / 0.223</td>
</tr>
<tr>
<td>NO of ICU admission</td>
<td>9 (29.0)</td>
<td>1 (3.2)</td>
<td>2 (6.5)</td>
<td>0.007* 0.006* / 0.02* / 1.00</td>
</tr>
<tr>
<td>Bladder injury</td>
<td>3 (9.7)</td>
<td>2 (6.5)</td>
<td>2 (6.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Need Blood Transfusion &gt;4 unit</td>
<td>17(54.8)</td>
<td>4 (12.9)</td>
<td>5 (16.1)</td>
<td>0.0001* 0.0001*/ 0.001*/ 1.00</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (9.7)</td>
<td>6 (19.4)</td>
<td>4 (12.9)</td>
<td>0.652</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (3.2)</td>
<td>2 (6.5)</td>
<td>1 (3.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (3.2)</td>
<td>2 (6.5)</td>
<td>1 (3.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Operative times</td>
<td>101.94 ± 11.6</td>
<td>98.16 ± 9.83</td>
<td>100.97 ± 9.35</td>
<td>0.001* 0.0001*/ 0.001*/ 0.824</td>
</tr>
<tr>
<td>Hospital stays</td>
<td>4.9 ± 1.5</td>
<td>3.87 ± 0.85</td>
<td>3.94 ± 0.93</td>
<td>0.269</td>
</tr>
<tr>
<td>No of cesarean hysterectomy (%)</td>
<td>5(16.1)</td>
<td>1(3.2)</td>
<td>2(6.5)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

SBP (Systolic Blood Pressure), DBP (Diastolic Blood Pressure).

*Statistical Significant Difference (GroupI versus GroupII / GroupI versus GroupIII / GroupII versus GroupIII)

# Variables are presented either mean and standard deviation &Number (percentage).

Figure 2: placenta accreta
Figure 3: Uterine incision above the upper edge of the placenta.

Figure 4: Identification of the bifurcation of the iliac artery.

Figure 5: Application of topical TA on placental bed.
RESULTS

Our study started with 110 patients who were asked to participate. 17 patients were excluded, 13 patients not meeting inclusion criteria and 4 patients refuse to participate. Therefore, the remaining 93 patients were randomized to 3 groups each group comprised of 31 patients: group I (31 patients received 20 IU oxytocin IV plus bilateral internal iliac artery ligation after delivery), group II (31 patients received 1 gm tranexamic acid IV just before skin incision plus 20 IU oxytocin IV and bilateral internal iliac artery ligation after delivery) and group III (31 patients received 20 IU oxytocin IV and bilateral internal iliac artery ligation after delivery plus 2gm topical tranexamic acid applied on placental bed after placental delivery).

There was no significant difference with respect to their age, weight, height, parity, gestational age, pre-operative pulse, systolic blood pressure (SBP), diastolic blood pressure (DBP), temperature, initial hemoglobin and number of previous cesarean sections (CS). (Table 1)

Both Group II and Group III showed a great reduction in intraoperative blood loss compared with Group I, (P=0.0001 and 0.0001). Also, the post-operative bleeding in form of vaginal bleeding and blood in intraabdominal drain were significant reduction in group II than group I (p=0.015 and 0.0001 respectively) and group III than group I (p=0.015 and 0.0001 respectively). Hence the total estimated blood loss in group II and III showed a highly reduction compared with group I (P=0.0001 and 0.0001).

However, no significant difference between group II and group III in relation to the total estimated blood loss (p=0.977) either intraoperative (p=0.980) or post-operative both vaginal bleeding (p=0.571) and blood in intraabdominal drain (p=0.920). (Table 2)

The number of patients need blood transfusion ≤ 4 bags were significant increase in group I (17 patients (54.8%)) versus 4 patients in group II (12.9%) and 5 patients in group III (16.1%). P=0.0001 and 0.0001 respectively. Also, the number of patients need admission to ICU were significant increase in group I (9 patients (29%)) versus 1 patient in group II (3.2%) and 2 patients in group III (6.5%). P=0.006 and 0.02 respectively. However, there was no significant difference between group II and III in the incidence of blood transfusion ≥ 4 bags and admission to ICU. (p= 1.00 and 1.00).

There was significant increase in postoperative hospital stay in group I (4.9±1.5) compared with group II (3.87±0.85) and group III (3.94±0.93) p=0.001and 0. 001. But no significant difference between group II and III p=0.824.

There was a significant increase in postoperative pulse in group I compared with Group II and III (P= 0.006 and 0.001 respectively). Also, there was significant decrease in both post-operative SBP and DBP in group I compared with group II (P=0.0001 and 0.002 respectively) and group III (P= 0.0001 and 0.004 respectively). However no significant difference with respect to post-operative pulse, SBP, DBP, between group II and III (P=0.536 ,0.959 and 0.881 respectively).

There was significant decrease in postoperative hemoglobin in group I compared with group III (p=0.01). However, no significant difference between group I and II. (p=0.159) and between group II and III. (p=0.223)

There was no significant difference between the three groups with respect to postoperative temperature, incidence of cesarean hysterectomy, incidence of urinary bladder injury, operation time, incidence of nausea, vomiting and diarrhea (P=0.918,0.269,1.00,0.330,0.652,1.00 and 1.00 respectively). (Table 3).

DISCUSSION

In our study in addition to prophylactic uterotonics administration, and internal iliac artery ligation for prevention of postpartum hemorrhage in patient with placenta accreta hypo sized that there is need of another agent with another mechanism of action for prevention blood loss during cesarean section due to placenta accreta.

In the best of our knowledge many trials assess the efficacy of tranexamic acid in prevention of postpartum hemorrhage during cesarean section but no trial specifically assess the role of tranexamic acid in cesarean section for placenta accreta, moreover we claim that our study was the first to evaluate the novel topical application of tranexamic acid on the placental bed and uterine scar during cesarean section adjunctive to internal iliac artery ligation for the aim of prevention of intraoperative and post-partum hemorrhage .(11)

TA is a lysine analogue which acts as an antifibrinolytic via competitive inhibition of the binding of plasmin and plasminogen to fibrin.
(7). TA concentration reach its peak in the plasma immediately after administration, antifibrinolytic effect lasts for up to 7–8 hours. The half-life of TA is 2 hours (8). A Cochrane review showed that TA significantly reduces blood transfusion in patients undergoing emergency or urgent non-obstetrical surgery (9) TA is safe in pregnancy, being FDA category B.

Placenta accreta has become one of the leading etiology of maternal mortality and is one of the leading etiology of peripartum hysterectomy. (3) The optimal management of placenta accreta remains the subject of debate. With the rising incidence of abnormal placentation, it is important to define management strategies with a focus on reducing maternal morbidity and mortality. The preferred method is cesarean hysterectomy without placental separation, but this removes the option of future pregnancy, and it is associated with severe morbidity in patients with placenta accreta. (3) Conservative management is defined as any approach that spares the uterus. (13) A recent large multicenter study reported a 78.4% uterus preservation rate, with 6% severe maternal morbidity with conservative management. (14) Worldwide, the usual treatments are administration of methotrexate, embolization of the internal iliac vessels, and resection of the affected uterine segment, use of uterine compression sutures, and oversuturing of the placental bed (12). in our study we examine a novel adding tranexamic acid as adjunctive plus IIAL to decrease blood loss during cesarean section and shown great efficacy in decrease blood loss, decrease admission rat to intensive care unit, decrease number of hysterectomy.

Internal iliac artery ligation (IIAL) has been known as an effective means of reducing PPH and preventing maternal morbidity. The rationale for this is based on the hemodynamic studies of Burchell,(17) which showed that IIAL reduced pelvic blood flow by 49% and pulse pressure by 85%, resulting in venous pressures in the arterial circuit thus promoting hemostasis. However, the reported success rate of IIAL varies from 40 to 100%, (17) and the procedure averts hysterectomy in only 50% of cases.

An international multicenter randomized trial of 20,211 bleeding trauma patients (the CRASH-2 trial) showed that tranexamic acid reduced death due to bleeding with no apparent increase in vascular occlusive events. (18) In 2012, WHO guidelines recommended that tranexamic acid should be used for the treatment of post-partum hemorrhage when uterotonics fail to control the bleeding or when the bleeding is thought to be due to trauma. (10)

The topical tranexamic group demonstrated that topical administration of 2gm of tranexamic acid in in 2000ml normal saline at placental bed and uterine scar at cesarean delivery reduced intra- and postoperative blood loss, as well as the amount of intraoperative oxytocin used. Hemoglobin level showed a non-significant r decrease in the control group.

There was no study in the literature address the role of topical tranexamic acid during cesarean section although Two case reports on the use of topical tranexamic acid to control postoperative local bleeding in 2 women with clotting disorders who were undergoing gynecologic procedures (18) A 51-year old woman with essential thrombocytenia underwent an uneventful total abdominal hysterectomy and salping-oophorectomy; however, the patient experienced continuous loss of blood from drains placed in the peritoneal cavity and sub rectal space. After multiple failed attempts to stop the bleeding with pressure dressings, a pressure dressing soaked in 5 mL of tranexamic acid (100 mg/mL) was applied. Bleeding decreased within a few minutes, and 2 additional applications were used over a 48-hour period, which allowed the patient to be discharged with no further complications on postoperative day 6.

In the second case, a 75-year-old female with a history of severe factor XI deficiency underwent a vaginal hysterectomy and vaginal wall repair. Postoperatively, the vaginal vault bleed which could not be controlled with vaginal packs. The bleeding was controlled once a vaginal pack soaked in 15 mL of tranexamic acid (100 mg/mL) was applied, with a reduction in bleeding observed the following day. The patient was subsequently initiated on oral tranexamic acid, given as 1 g daily for 7 days, and was discharged on postoperative day 6 with no further complications. (18)

One concern regarding use of TXA in pregnancy is the potential for thromboembolic events in a population at already high baseline risk of thrombosis (19), but in or study no case reported to complicated with DVD or pulmonary embolism post-operative in the early postoperative period.
One limitation of our study was we not used alkaline hematin method which is a validated method for accurate measurement of blood loss ,but use instate a gravimetric method to measure the amount of blood loss.(20) Marcel H et al 2004 in veterinary surgery compare gravimetric and colorimetric methods of quantifying surgical blood loss and conclude that Estimation of blood loss using a gravimetric method is accurate and μobjective tool to evaluate intraoperative blood loss (21) One of the strength of our study was that double blind randomized study provides the first evidence that a IV or topical application of TA is a simple preemptive intervention for reduced intraoperative blood loss and need of blood transfusion and may decrease number of hysterectomy during cesarean section due to placenta accreta in patient undergone IIAL. Another strength of our study as the average amount of total blood loss was the primary outcome of this research, study power was calculated online (www.dssresearch.com) using the average value of the intervention group I (1151.61 ± 246.38),group II(1153.87 ± 293.49) and that of the control group III (1800 ± 980), the sample size was 31 for each group with 95% confidence level. The study power was found to be 100%.

**IN CONCLUSION**

Preemptive use of adjunctive IV and topical tranexamic acid (TA) in patient undergone internal iliac artery ligation due to placenta previaaccreta, is associated with decrease blood loss during and after caesarian section, lower hysterectomy rate compared with internal iliac ligation alone. Tranexamic acid appears to be a safe, effective, and inexpensive option in prevention of PPH in cases with placenta previaaccreta.

**REFERENCES**

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