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Efficacy of tranexamic acid in reducing blood loss, blood and blood products requirements in Cesarian sections for patients with placenta accreta

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Abstract

Background: Placenta accreta is an obstetric emergency and the main cause of maternal morbidity and mortality due to the associated bleeding and coagulopathy. Tranexamic acid has been widely used to decrease blood loss in trauma patients and patients with postpartum hemorrhage. We aimed at studying the effect of tranexamic acid in reducing blood loss and blood transfusion in patients with placenta accreta.

Methods: In a double-blinded randomized controlled study, 46 patients were recruited and divided into two groups, Group A is the tranexamic group where patients received 10 mg/kg tranexamic acid after cord clamping and continued on tranexamic infusion 10 mg/kg/h till the end of the surgery. Group B is the placebo where patients received normal saline instead. Primary outcome was the amount of intraoperative blood loss, and other outcomes included the number of blood and blood products transfused intraoperative and in the first 24 h postoperative, the immediate postoperative Hb level, platelet count, and coagulation profile. Data were collected, coded, tabulated, and then analyzed using Minitab® 16.1.0 statistics software package. Variables were presented as mean and standard deviation and analyzed using unpaired *t* test. Any difference with p value < 0.05 was considered statistically significant.

Results: Amount of intraoperative blood loss was significantly less in the tranexamic group 2232 ± 1204 ml compared to the placebo group 3405 ± 1193 ml (p value 0.002), and patients in the tranexamic group received less units of packed red blood cells, fresh frozen plasma, and platelets compared to those in the placebo group (4.2 ± 1.9 vs 6.1 ± 2.2 with p value 0.003, 3.4 ± 1.3 vs 4.2 ± 1.2 with P value 0.036 and 4.8 ± 2.1 vs 6.2 ± 2.4 with p value 0.041, respectively). There was no statistically significant difference in the first postoperative Hb level, platelet count, and coagulation profile between the two groups; however, the amount of blood and products transfused in the first 24 h postoperative were significantly less in the tranexamic group

Conclusion: Tranexamic acid infusion was effective in reducing intraoperative blood loss and intraoperative and postoperative blood and blood products' transfusion.

Keywords: Placenta accreta, Tranexamic acid, Cesarean section

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Introduction

Placenta accreta (PA) is the clinical condition of abnormal adherence of the entire or a part of the placenta to the uterine wall. It is divided into three categories based on the extent of penetration of the abnormal placenta: placenta accreta, where the invasion is limited to the myometrium and the decidual layer is not well-defined; placenta increta when full penetration of the myometrium is achieved; and placenta percreta in which the villi invade the uterine serosa and sometimes the adjacent organs like bladder (Khong 2008).

There is an increase in the uterine artery blood flow from 100 to 350 ml/min in normal pregnancy (Thaler et al. 1990) which is further increased in patients with PA, as in these patients uterine blood vessels are not only larger in diameter with increased blood flow compared to normal pregnancy, but have less muscular tissue and thin elastic layer [3]. As a result, they become a source of uncontrolled hemorrhage when torn during delivery due to their inability to undergo vasospasm (Khong and Robertson 1987).

PA and its variant is an obstetric emergency and needs to have planned resuscitation strategies. The medical caregivers should be ready to deal with uncontrolled hemorrhage, associated hemorrhagic shock, massive transfusion, and its associated complications like disseminated intravascular coagulopathy. Studies have shown an average blood loss of 3 L with mean transfusion volume of 10 units RBCs (range of 3–29 units) (Rosen 2008). The rate of complications like hemorrhagic shock is found to be 50% and 25% for complications like coagulopathy or disseminated intravascular coagulation (DIC) (Zelop et al. 1993).

Maternal mortality with placenta accreta has been reported to be as high as 7% (O'Brien et al. 1996). Maternal death may occur despite optimal planning, transfusion management, and surgical care. From a cohort of 39,244 women who underwent Cesarean delivery, researchers identified 186 that had a Cesarean hysterectomy performed. The most common indication was placenta accreta (38%) (Shellhaas et al. 2009).

Tranexamic acid (TXA) is a potent antifibrinolytic agent that exerts its effects by blocking lysine-binding sites on plasminogen molecules and has the potential to enhance the effectiveness of the patient's own hemostatic mechanisms. Consequently, clot breakdown (fibrinolysis) is inhibited and bleeding is reduced (Novikova and Hofmeyr 2010).

During delivery, when the placenta separates from the uterine wall, physiologic and hemostatic changes occur sequentially to reduce bleeding: strong myometrial contractions, increased platelet activity, massive release of coagulation factors, and consequently a parallel increase in fibrinolytic activity (Hellgren 2003). While oxytocin administration enhances the first mechanism, TXA administration might be able to counter the latter and thus facilitate the hemostatic process. Finally, the association between the extent of the initial decrease in plasma fibrinogen and the subsequent severity of blood loss reported in women with early postpartum hemorrhage (PPH) (Cortet et al. 2012) suggests that both coagulation and fibrinolysis processes are implicated in the control of postpartum blood loss and further supports the hypothesis that TXA might be effective in PPH prevention. Accordingly, there is a clear theoretical rationale for the use of antifibrinolytic agents to reduce postpartum blood loss (Ducloy-Bouthors et al. 2011; Peitsidis and Kadir 2011).

Methods

A double-blinded prospective randomized controlled study which was conducted at King Faisal Specialist Hospital and Research Center in Jeddah, Saudi Arabia, and approved by the Hospital Institutional Review Board. Written informed consent was obtained from patients who were randomized using block randomization technique and a research randomizer program.

Assuming that the standard deviation of blood loss in patients with placenta accreta is around 1000 ml, the sample size was calculated that at least 23 patients is needed in each group to detect a significant difference of at least 1000 ml of blood loss with a power of 0.9 and a significance level of 0.05.

All patients admitted for elective Cesarian section with placenta accreta were included. Patients were excluded if they were admitted for emergency Cesarean section, admitted with bleeding, known to have coagulation disorders, with preoperative anemia (defined as hemoglobin (HB) less than 8 gm/dl), thrombocytopenia, or any other medical diseases with pregnancy as pre-eclampsia or gestational diabetes, and also, patients were excluded if hysterectomy was performed. Patients were consented for the need of major packed red blood cells and blood product transfusion and for possible hysterectomy. Baseline CBC and coagulation profile were recorded in all patients.

Patients were divided into two groups and randomized using a block randomization technique and a research randomizer program; group A the TXA group included 23 patients who received TXA acid started as a loading dose after cord clamping and continued as infusion till the end of surgery and group B the placebo group included 23 patients who did not receive TXA and received placebo normal saline instead.

Before induction, wide bore intravenous and radial artery catheters were inserted under local anesthesia then patients were attached to the regular monitors plus invasive blood pressure monitoring, and then, general anesthesia was induced. Baseline arterial blood gases (ABG) was extracted.

After delivery of the baby and cord clamping, TXA bolus was given to group A patients as a loading dose of 10 mg/Kg over 10 min followed by infusion of 10 mg/Kg/h which was stopped after skin closure while for group B patients, normal saline was infused instead of TXA. Syringes containing normal saline or TXA were prepared by an anesthesiologist who was aware about the randomization list and was not involved in the intraoperative or postoperative management. Blood loss was closely monitored, and Hb level was frequently measured from ABG. Blood transfusion was started once the Hb level dropped to 8 gm/dl, and massive transfusion protocol (MTP) was initiated when blood loss exceeded 1000 ml where one unit of fresh frozen plasma and one unit of platelets were transfused with every unit of packed red blood cells. In addition, cryoprecipitate transfusion was initiated if blood loss exceeded 2.5 L or if more than 4 units of fresh frozen plasma were transfused.

Patients were transferred to surgical ICU postoperatively either intubated or extubated. Our primary outcome was the amount of intraoperative blood loss, and other outcomes included the total amount of packed RBCs, plasma, platelets and cryoprecipitate transfused intraoperative and for the first 24 h postoperative, immediate postoperative Hb level, platelet count, and coagulation profile.

Statistical methodology

Data were collected, coded, tabulated, and then analyzed using Minitab® 16.1.0 statistics software package. Variables were presented as mean ± standard deviation and analyzed using unpaired *t* test. Any difference with *p* value < 0.05 was considered statistically significant.

Table 1 Demographics

	Group A 23 patients	Group B 23 patients	Significance
Age (years)	25–41 (32.3 ± 5.2)	24–38 (30.6 ± 5.7)	0.296
Weight (Kg)	78.2 ± 10.4	82.9 ± 9.6	0.118
Preop. Hb (gm/dl)	10.2 ± 2.6	9.8 ± 2.1	0.321

Results

Between September 2016 and November 2018, 46 patients were recruited to the study and were divided into two groups as previously mentioned, 3 patients were excluded (2 from the TXA group and 1 from the placebo group) for whom hysterectomies were performed to control the bleeding, and those patients were replaced by another patients.

All results are presented as mean and standard deviation

Age, weight, and preoperative Hb were non-significant between the two groups as shown in Table 1.

The intraoperative blood loss was significantly lower in the TXA group 2232 ± 1204 ml compared to the placebo group 3405 ± 1193 ml (*p* value 0.002) as shown in Fig. 1.

The amount of packed red blood cells (PRBCs) transfused intraoperative was significantly less in group A (4.2 ± 1.9 units) compared to group B (6.1 ± 2.2 units) with *p* value 0.003, also fresh frozen plasma units transfused to group A patients was lower than group B (3.4 ± 1.3 and 4.2 ± 1.2 units, respectively) with *p* value 0.036. In addition, group A patients required significantly less platelet transfusion than group B patients 4.8 ± 2.1 and 6.2 ± 2.4 units, respectively, with *p* value 0.041.

The amount of cryoprecipitate transfused were non-significant between both groups, 2.1 ± 1.1 units in group A versus 2.6 ± 0.9 units in group B, *p* value 0.099.

These data are shown in Fig. 2.

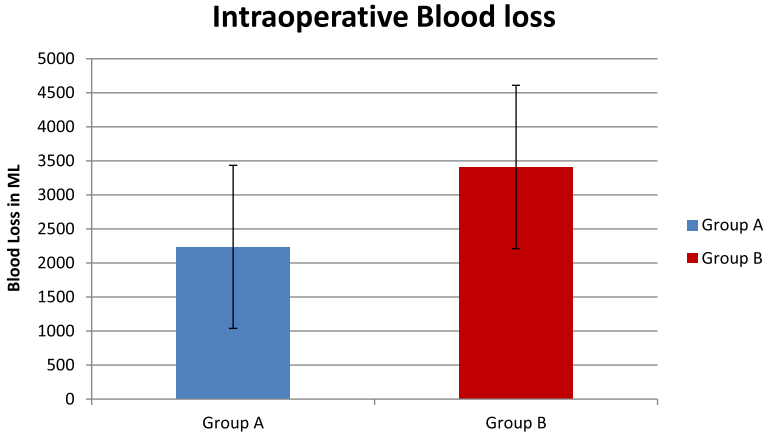

Fig. 1 The significant lower intraoperative blood loss in the TXA group

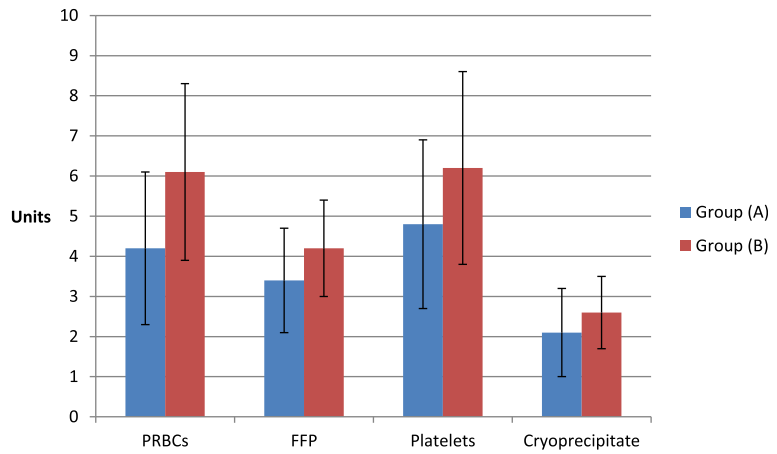

Fig. 2 The intraoperative amount of blood and products transfusion

Table 2 shows the first set of postoperative lab results done in the ICU showing a non-significant difference between the two groups

The need for packed RBCs and blood products were significantly higher in group B in the first 24 h postoperative as shown in Table 3.

Discussion

Placenta accrete spectrum (PAS) formerly known as morbidly adherent placenta is a main cause of maternal morbidity and mortality (Usta et al. 2005); it is considered a severe pregnancy complication that may be associated with massive and potentially life-threatening intrapartum and postpartum hemorrhage (Faranesh et al. 2007). Maternal morbidity had been reported to occur in up to 60% and mortality in up to 7% of women with placenta accreta. In addition, the incidence of perinatal complications is also increased mainly due to preterm birth and small for gestational age fetuses (Eller et al. 2009). PAS is becoming an increasingly common complication of pregnancy, mainly due to the increasing rate of Cesarean delivery over the past 50 years (Hamilton et al. 2005). Table 4 shows the complications associated with surgery for placenta accreta spectrum (Allen et al. 2018).

TXA has been widely used in trauma patients and in Cesarean sections to decrease the intraoperative blood loss; it is reported to be also beneficial in the management of postpartum hemorrhage. No trials have specifically examined the role of tranexamic acid in the surgical management of PAS disorders. However, the quality of the evidence on postpartum hemorrhage justifies its use in the management of women diagnosed prenatally or presenting with PAS disorders at the time of delivery (Allen et al. 2018).

We tried to examine its efficacy in reducing the intraoperative blood loss and hence the need for blood and blood products transfusion as well as the postoperative need for blood transfusion in patients with PAS being one of the main causes of maternal morbidity and mortality. We preferred to use 10 mg/Kg of tranexamic acid rather than the fixed dose of 1 gm to ensure better efficacy depending on the patient body weight, and also, to avoid any possible neonatal adverse effects, we delayed administering tranexamic till cord clamping. After the loading dose, we kept the patient on tranexamic acid infusion putting in consideration the highest volume of blood loss in patients with PAS compared to the normal Cesarean section patients and thus the highest incidence of increased fibrinolysis and coagulopathy.

The study revealed that TXA at a dose of bolus 10 mg/Kg followed by infusion of 10 mg/Kg/h till the end of the procedure was effective in reducing the intraoperative blood loss which was 2232 ± 1204 ml in patients who received TXA, and this was significantly lower than that in patients who did not receive tranexamic 3405 ± 1193 ml; this was also reflected on the amount of packed red blood cells and blood products required intraoperatively which were significantly less in the TXA group. The first set of postoperative lab results as Hb level, platelet count, and coagulation profile were statistically non-significant between the two groups; this may be due to the high volume of blood and products transfused in the placebo group which compensated the highest blood loss. However, in the first 24 h postoperative, the placebo group patients required significantly more PRBCs, platelets, and fresh frozen plasma transfusion compared to the

Table 2 Postoperative labs

	Group A 23 patients	Group B 23 patients	*p* value
Hb (gm/dl)	8.4 ± 1.7	7.9 ± 1.6	0.310
Platelet count ($\times 10^3$/mcL)	119 ± 29	132 ± 36	0.184
INR	1.3 ± 0.5	1.5 ± 0.4	0.141
PTT (seconds)	46 ± 9	51 ± 11	0.099

Table 3 Postoperative blood and product transfusion

	Group A 23 patients	Group B 23 patients	*p* value
Packed RBCs (units)	1.2 ± 0.8	3.2 ± 0.9	< 0.001
FFP (units)	1.2 ± 0.5	3 ± 1.1	< 0.001
Platelets (units)	0.8 ± 0.3	1.5 ± 0.5	< 0.001
Cryoprecipitate (units)	none	none	

TXA group, and we could not find an explanation to that as the half-life of intravenous TXA is about 3 h.

Significant international efforts have culminated in several studies investigating TXA in obstetric trauma and postpartum hemorrhage. Most recently, a large double-blind placebo-controlled trial recruited over 20 000 patients with postpartum hemorrhage between March 2010 and April 2016 to the WOMAN trial. Patients were randomly assigned to receive either 1 gm of IV TXA or placebo if they were diagnosed to have postpartum hemorrhage either after normal vaginal delivery or Cesarian section. The primary outcome was the number of deaths due to postpartum hemorrhage, and secondary outcomes were complications as thromboembolic events, organ failure, and surgical interventions as hysterectomies. The study demonstrated that, compared with placebo, tranexamic acid administration significantly reduced death due to massive obstetric hemorrhage without increasing rates of adverse events, including thromboembolism (Woman Trial Collaborative group 2017).

A recent meta-analysis of nine trials involving 2365 patients confirmed these findings, demonstrating that the administration of TXA before Cesarean delivery significantly reduces intra- and postoperative blood loss and blood transfusion with no increase in thromboembolic events (Simonazzi et al. 2016). After this analysis, three more placebo-controlled trials have shown that TXA administration immediately before Cesarean delivery significantly reduces intraoperative blood loss and postoperative declines in hemoglobin without any increase in adverse maternal or neonatal effects (Lakshmi and Abraham 2016; Ray et al. 2017; Maged et al. 2015).

Table 4 Shows the complications associated with surgery for placenta accreta spectrum (PAS) disorders (Allen et al. 2018)

Complications	
Median estimation of blood loss	2–3 L
Median units of packed red blood cells transfused	3.4–5.4 L
Large volume blood transfusions (> 10 L)	5–40%
Injury to bladder	7–40%
Injury to ureter	0–18%
Admission to intensive care unit	15–66%
Bowel injury/obstruction	2–4%
Venous thromboembolism	4%
Surgical site infection	18–32%
Reoperation	4–18%
Maternal mortality	1–7%

Another meta-analysis of 12 trials involving about 3275 patients analyzed the effect of TXA on reducing blood loss and incidence of postpartum hemorrhage after Cesarian section (10 studies) and vaginal delivery (2 studies); it also showed a significant reduction in the amount of blood loss and the incidence of postpartum hemorrhage in patients who received TXA (Sentilhes et al. 2015).

Those trials were performed on patients without abnormal placentation, and the aim was to study the effect of tranexamic acid on reducing the incidence of postpartum hemorrhage and the bleeding. Tranexamic acid was used either as a fixed intravenous dose of 1 gm IV or according to the body weight as 10 mg/Kg and infused 10 min before CS.

In this study, we did not consider the surgical and the medical complications (number of hysterectomies performed, occurrence of thromboembolism) as secondary outcomes; we focused on the blood loss and blood transfusions, and we think that carrying another study with a bigger number of cases can help in considering that.

Abbreviations

TXA: Tranexamic acidPAPlacenta accretaPPHPostpartum hemorrhagePASPlacenta accreta spectrum

Acknowledgments

Acknowledgments are not applicable.

Author's contributions

TAH performed the study, collected the data, and prepared the manuscript. The author read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author.

Ethics approval and consent to participate

The study was approved by the institutional review board of King Faisal Specialist Hospital and Research Centre in Jeddah, Saudi Arabia, and a written informed consent was obtained from every patient.

Consent for publication

Patients were consented for data publications.

Competing interests

The author declares that he has no competing interests.

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