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Original Article

Bilateral uterine artery ligation plus intravenous tranexamic acid during cesarean delivery for placenta previa: a randomized double-blind controlled trial

Ahmed M. Abbas[1,*], Nahla W. Shady[2], Hany F. Sallam[2]

[1] Department of Obstetrics & Gynecology, Faculty of Medicine, Assiut University, Egypt
[2] Department of Obstetrics & Gynecology, Faculty of Medicine, Aswan University, Egypt

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ABSTRACT

Objective: To investigate the effect of adjunctive intravenous tranexamic acid (TA) on blood loss during cesarean section (CS) in patients with placenta previa undergone bilateral uterine arteryligation (BUAL).
Methods: The study was double-blind randomized controlled trial carried out in a tertiary University Hospital between June 2016 to October 2017. We includedpatients scheduled for CS due to placenta previa. They were randomly allocated to group (I) managed by BUAL alone and group (II) managed by intravenous TA plus BUAL. The primary outcome was the amount of totalestimatedblood loss both intra- and post-operative.
Results: Sixty-two patients were enrolled (n = 31 in each group). Patients received intravenous TA showed great reduction in total estimated blood loss compared with BUAL alone (p = .001). Additionally, the post-operative pulse was significantly higher in group (I) compared with group (II) ($p = .002$) and post-operative hemoglobin concentration was significantly lower in the same group compared with the other group ($p = .034$). More additional uterotonics was needed in group (I) than group (II) (29% vs. 3.2%, $p = .006$). Blood transfusion ≥4 units was required in 17 (54.8%) patients in group (I) versus 4 patients in group (II) (12.9%) ($p = .0001$). No difference between the study groups regarding the rate of cesarean hysterectomy ($p = .27$).
Conclusion: The adjunctive use of intravenousTA in patients undergone BUAL due to placenta previa is associated with decrease blood loss, need for additional uterotonics and blood transfusion during CS compared with BUAL alone.

Introduction

Obstetric hemorrhage is estimated to beresponsible 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 % of maternal mortality by 2015 that not reached yet, cannot be hold without significant improvements in postpartum hemorrhage (PPH) related mortality [2].

Placenta previa (PP) is an obstetric condition that is closely linked with massive obstetric hemorrhage with varied incidence about once in every 150–250 live births [3]. It is considered one of the causes of increased need for blood transfusion and cesarean hysterectomy [4]. PPH due to PP typically starts during cesarean section (CS) in the placental bed, at the lower uterine segment mostly after placental separation. Proceeding for cesarean hysterectomy can be the only effective line of management in spite of the associated high morbidity rate [4].

Various conservative measures have been developed to avoid hysterectomy and preserve fertility in patients with PP. Bilateral Uterine artery ligation (BUAL) is one of the reported surgical procedures carried out in these cases as it is easy and quick. It can be used alone or with adjunctive measures with a fair success rate [5]. The aim is to reduce the blood supply to the uterus and to prevent PPH.

TA is a lysine analogue which acts as an antifibrinolytic via competitive inhibition of the binding of plasmin and plasminogen to fibrin [6].The rationale for its use in reduction of blood loss depending on the implication of the coagulation and fibrinolysis processes implicated in the control of PPH [7]. However, concerns about possible thromboembolic events with parenteral administration of TA have stimulated increasing interest in its topical use [8,9].

* Corresponding author at: Woman's Health Hospital, Assiut University, Assiut, Egypt.
E-mail address: bmr90@hotmail.com (A.M. Abbas).

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Therefore, the aim of our study was to assess the role of adjunctive use of IV-TA plus BUAL to reduce the blood loss as well as to preserve the fertility and avoid hysterectomy in patients with PP.

Materials and Methods

The current study was a double-blind randomized controlled trial conducted at a tertiary University Hospital in the period between the 1st of June 2016 and the 31st of October 2017. The Institutional Ethical review Board approved the study. Informed written consent was obtained from all patients prior to their enrollment in this study.

We included all pregnant women with a single term fetus scheduled for elective CS for PP and invited them to participate in the study. PP was defined as a placenta partially or completely coveringthe cervical os in ultrasound examination [4]. Patients with cardiac, hepatic, renal or thromboembolic disease were excluded. Additionally, patients known coagulopathy and those presented with severe antepartum hemorrhage were excluded. Moreover, we excluded allergic patients to TA and those declined participation in the study. Patients with high possibility of morbid adherent placenta by two-dimensional and color Doppler sonographic signs carried out by an expert sonographer were also excluded.

Data were collected regarding the age, parity, weight, gestational age at delivery and history of previous CS of all recruited women. Clinical examination was performed included pulse and blood pressure measurement. Finally, hemoglobin concentration was measured before CS.

The required sample size was calculated based on previous study assessing the mean blood loss with conservative surgical management of PPH due to PP. Maher and his colleague reported that the mean blood loss in their study was 1705 ± 446.61 ml [10]. We assumed that a 20 % decrease in blood loss with addition of TA will be clinically significant. Using an 80% power with α error of 0.05, a sample size of 31 women was needed in each group(Epi-info: Centers for Disease Control and Prevention, Atlanta, GA, USA).

Patients were randomized to two groups according to a two-blocked randomization list which was coded (a) or (b) at 1:1 ratio. The two parallel groups were prepared using a computer-generated randomization system. The allocated groups were concealed in serially numbered sealed opaque envelopes that were opened only after recruitment. Patient allocation was performed prior to the induction of anesthesia by an independent researcher, who was not otherwise being involved in this study. The trial was appropriately double-blind as both the participants and the managing surgeons were blinded to the procedure performed.

Eligible participants were allocated to one of two groups. **Group (I):** patients managed by bilateral uterine artery ligation (BUAL) after delivery of the fetus.**Group (II):** patients received 1 gm TA (2 ampoules of Capron® 500 mg /5 ml; Amoun, Cairo, Egypt) intravenous just before skin incision plus BUAL. In group I, patients received single injection of intravenous saline before skin incision prepared in a syringe and coded by a pharmacist in the pharmacy of the hospital. Neither the surgeon nor the anesthetist known the nature of the IV administered drug before CS.

In all eligible participants, CS was performed under general anesthesia by the same operative and anesthesia team.A dose of 1 g of first-generation cephalosporin (Cefazolin®; Bristol Mayers Squibb, Cairo, Egypt) was administered intravenously immediately prior to skin incision.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.

After delivery of the fetus, all participants received an IV infusion of oxytocin (Syntocinon®; Novartis Pharma, Berne, Switzerland) 20 IU dissolves into 500 mL of normal 0.9% sodium chloride solution and infused at a rate of 125 mL/hour started after clamping of the umbilical cord to prevent premature separation of placenta.

BUAL started immediately through blunt dissection downwards and laterally of the peritoneum covering the uterine isthmus and cervix. The peritoneum is mobilized freely at the uterine angles to expose both uterine arteries and avoid inclusion of the ureters in the ligation. The uterine artery pulsations were palpated digitally at the level of the internal os. Then, we passed a 1.0 chromic catgut suture posteriorly to anteriorly through the cervical tissues and the ligature consisted of a simple stitch. A second stitch was performed below the first, at a distance of 1 cm. The placenta was delivered out of the uterus afterwards.

Any additional surgical procedures, uterotonics or cesarean hysterectomy required for management of blood loss were recorded. Finally, the uterus was closed in two layers and pelvic drain was inserted in Douglas pouch in all patients followed by standard repair of the abdominal wall.

Intra-operative 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 estimated total blood loss was calculated by the addition of intra-operative and post-operative blood loss.

The duration of surgery and immediate post-operative vital signs were recorded. The hemoglobin level was measured 24 hours after CS. Any additional intra-operative uterotonics or blood transfusion given was recorded.The duration of hospital stay was also recorded.

The primary outcome of the study was the mean total estimated blood loss.The secondary outcome measures included the intra-operative blood loss, post-operative blood loss, the post-operative vital signs, the post-operative hemoglobin concentration, the need for additional uterotonics,the need for blood transfusion $\geq$4 units, the duration of surgery, the duration of hospital stay and the rate of cesarean hysterectomy

Data were entered and statistically analyzed using the Statistical Package for Social Sciences (SPSS) version 22. Qualitative data were described as numbers and percentages. Chi-square test, Fisher's Exact 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, Student's T-testwas used for comparison between groups. In the non-normally distributed variables, Mann Whitney test was used for comparison between groups. P-value < 0.05 was considered to be statistically significant.

Results

Seventy nine women were approached to participate in the study. We excluded 13 cases (eight patients scheduled for emergency CS due to severe antepartum hemorrhage and five patients were highly suspected to have morbidly adherent

placenta preoperatively). Additionally, four women refused to participate in the study as shown in the study flowchart (Fig. 1).

There was no significant difference regarding the participants' age, weight, parity, number of previous CS, gestational age, pre-operative pulse, systolic blood pressure (SBP), diastolic blood pressure (DBP) and initial hemoglobin concentration (Table1).

Patients who received TA showed significant lower intra-operative and post-operative blood loss compared with the other group. Hence, the total estimated blood loss in group (II) was significantly lower ($p = .001$) (Table 2).

There was a significant higher post-operative pulse and lower SBP and DBP in group (I) compared with Group (II). The post-operative hemoglobin concentration was significantly lower in group (I) ($p = .034$) (Table 3).

More additional uterotonics were used in group (I) (29% vs. 3.2%) than group (II) ($p = .006$). Moreover, Blood transfusion ≥ 4 units was required in 17 (54.8%) patients in group (I) versus 4 patients in group (II) (12.9%) ($p = .0001$) (Table 3).

Post-operative hospital stay was significantly longer in group (I) (4.9 ± 1.5) days compared with group (II) (3.9 ± 0.9) ($p = .001$). Finally, no difference between the study groups regarding the duration of surgery ($p = .33$) and the rate of cesarean hysterectomy ($p = .27$) (Table 3).

Discussion

In the current study, the adjuvant use of either intravenous TA plus BUAL during CS for patients with PP effectively reduce the intra-operative, post-operative blood loss, blood transfusion needs as well as the additional use of uterotonics than BUAL alone. Up to our knowledge, this is the first study evaluates the effect of TA as an adjunctive measure to BUAL in prevention of blood loss in patients undergone CS for placenta previa.

Placenta previa is a potential life threatening obstetric condition that may cause serious adverse maternal outcomes as excessive hemorrhage, massive blood transfusions and the need for adjunctive surgical procedures to control the bleeding [11]. The incidence of PP has been recently increased over the past few years correlated with the elevated CS rates [5]. The amount of blood loss and the rate of blood transfusion during CS are significantly higher in cases of PP than in normal placental presentation [4].

Therefore, different prophylactic approaches had been evaluated to stop bleeding including uterine packing, uterotonics administration, balloon tamponade and vascular ligation, but which one of them could be suitable for all cases is still lacking in the literature [4]. Uterovarian or hypogastric vascular ligations are technically difficult and need expert surgeons for performance. On the other hand, BUAL is simple, rapid and easily done by most of obstetricians. Also, it considers ligation of the main source of bleeding in CS which is effective in most of cases of atonic PPH as reported in the literature. Hysterectomy should be a life-saving procedure in cases of PP; however, this approach has serious psychological consequences especially in young women who wish to preserve their fertility[12].

There are many trials published before to evaluate the efficacy of TA in prevention of PPH during CS [13–16] however, no one specifically asses the role of TA in CS for placenta previa.TA concentration reach its peak in the plasma immediately after administration and its antifibrinolytic effect lasts up to 7–8 hours. The half-life of TA is 2 hours [7].

TA has an antifibrinolytic effect through inhibition of plasminogen activator that helps in the conversion of plasminogen to plasmin. Therefore, it has been commonly used to reduce blood loss in elective surgery where it reduces blood transfusion by about one-third of cases [17]. Moreover, the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) trial has

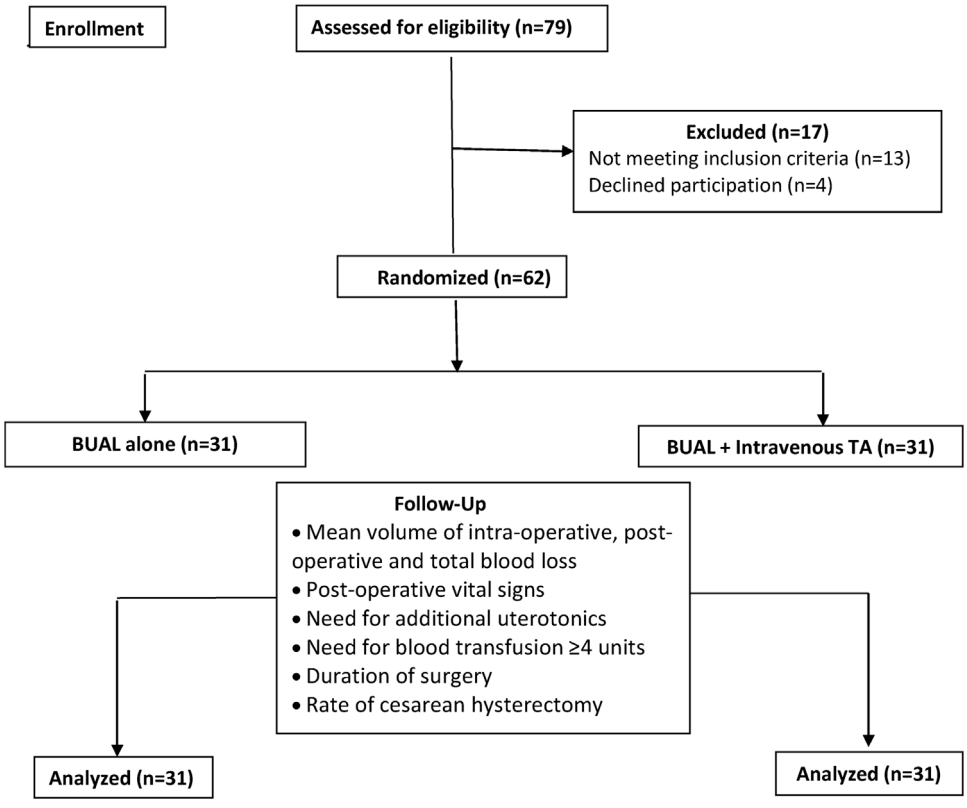

Fig. 1. The study flowchart.

Table 1
The baseline and pre-operative characteristics of the study participants.

Characteristics	Group (I) BUAL group (n = 31)	Group (II) BUAL + intravenous TA group (n = 31)	p-value
Age (years)	30.7 ± 2.8	30.6 ± 2.5	.77
BMI	28.1 ± 2.7	28.3 ± 2.4	.61
Parity[#]	3 (2 – 5)	3 (2 – 6)	.71
Previous CS	2.9 ± 0.8	2.8 ± 0.8	.90
Gestational age (weeks)	36.6 ± 0.6	36.5 ± 0.8	.87
Pulse	80.2 ± 5.0	79.6 ± 5.3	.79
SBP	120.1 ± 2.5	120.1 ± 2.7	.89
DBP	78.7 ± 3.1	78.3 ± 3.2	.68
Pre-operative Hemoglobin (gm/dl)	10.88 ± 0.67	10.91 ± 0.7	.87

BUAL (bilateral uterine artery ligation), TA (Tranexamic acid), BMI (body mass index), CS (cesarean section), SBP (Systolic Blood Pressure), DBP (Diastolic Blood Pressure).
All variables are presented as mean and standard deviation.
[#] Data are presented as median (range).

Table 2
The primary outcome among study groups

Outcomes	Group (I) BUAL group (n = 31)	Group (II) BUAL + intravenous TA group (n = 31)	p-value
Intra-operative blood loss	1383.5 ± 315.36	913.2 ± 194.07	**.001**[*]
Post-operative vaginal bleeding	208.83 ± 88.5	134.41 ± 67.3	**.015**[*]
Blood in drains	116.72 ± 81.2	80 ± 25.63	**.001**[*]
Total estimated blood loss	1800 ± 980	1151.6 ± 246.38	**.001**[*]

BUAL (bilateral uterine artery ligation), TA (Tranexamic acid).
All variables are presented as mean and standard deviation.
[*] Statistical significant difference.

Table 3
The secondary outcomes among study groups

Outcomes	Group (I) BUAL group (n = 31)	Group (II) BUAL + intravenous TA group (n = 31)	p-value
Postoperative pulse[#] (beats/min)	92.5 ± 10.1	87.0 ± 6.4	**.002**[*]
Postoperative SBP[#] (mmHg)	112.2 ± 7.7	118.5 ± 2.5	**.001**[*]
Postoperative DBP[#] (mmHg)	73.9 ± 5.6	77.3 ± 3.4	**.003**[*]
Postoperative Hemoglobin (gm/dl)[#]	9.1 ± 0.6	9.4 ± 0.6	**.034**[*]
Need for additional uterotonics[$]	9 (29)	1 (3.2)	**.006**[*]
Need for blood transfusion ≥4 units[$]	17 (54.8)	4 (12.9)	**.0001**[*]
Need for hysterectomy[$]	3 (9.6)	1 (3.2)	.27
Duration of surgery[#] (minutes)	101.9 ± 11.6	98.2 ± 9.8	.33
Duration of hospital[#] stay (days)	4.9 ± 1.5	3.9 ± 0.9	**.001**[*]

BUAL (bilateral uterine artery ligation), TA (Tranexamic acid), SBP (Systolic Blood Pressure), DBP (Diastolic Blood Pressure).
[#] Variables are presented as mean and standard deviation.
[$] Variables are presented as frequency and percentage.
[*] Statistical significant difference.

shown that the early administration of TA significantly reduces the mortality in bleeding trauma patients [18,19].

Two systematic reviews, including a total of 34 randomized trials, concluded that TA administered at the time of delivery resulted in reduced blood loss and less need for blood transfusion with no increased risk of thromboembolic complications [6,20]. Li et al reported that the mean reduction of bleeding in their systematic review about prophylactic use of TA for PPH is only 145 mlwhich is not clinically significant [20]. On the other hand, our study results revealed the total blood loss in patients received TA was significantly lower than those undergone BUAL alone during CS ($p = .001$). The blood loss reduction was approximately 650 ml which is clinically significant for cases with obstetric hemorrhage. Moreover, all the previously mentioned studies as well as ours were not powered enough to evaluate the risk of thromboembolic complications.

A recent large multi-centre RCT included more than 20,000 women with PPH revealed that TA administration decreased the risk of maternal death resulting from bleeding (1.5% compared with 1.9%, p = .045). However, the incidence of hysterectomy was not reduced with TA use (3.6% versus 3.5% in the placebo group, p= ·84). Finally, adverse events did not differ significantly in the TA versus placebo group [21].

TA was proven to be safe as a treatment measure for patients with PPH, as the WOMAN trial have shown. However, it is not proven to be safe for preventing PPH with the current evidence. We believe that the routine indication of TA to prevent PPH needs evidence from large multicenter randomized placebo controlled trials with appropriate sample size to evaluate the adverse effects, before recommending its use. Therefore, we evaluated the effectiveness of topical use of TA in our study that could definitely had lower risk of adverse effects.

The study had some strength; firstly it was a randomized clinical trial providing the first evidence that IV-TA is a simple procedure for reduced intra-operative blood loss and need for blood transfusion during CS due to PP in adjunctive with BUAL. Second, the homogeneity of the selected cases (only patients with PP) could be considered another merit. The main limitation of our

study was probably related to being a single-center study with the small sample size of the included women that may limit the generalizability of the results. Further trials should be done to confirm our results. Finally, the study was not powered enough to assess the secondary outcomes as the occurrence of adverse events or the need for cesarean hysterectomy.

In conclusion, this study indicates the adjunctive use of TA in patients undergone BUAL due to PP is associated with decrease blood loss and need of blood transfusion during CS compared with BUAL alone.

Conflict of interest

The authors declare that they have no conflict of interest.

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