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Full Length Research Paper

Efficacy of intravenous tranexamic acid at reducing blood loss during elective caesarean section in Abakaliki: A double blind randomized placebo controlled trial

Obi V. O.*, Umeora O. U. J., Dimejesi I. B. O., Asiegbu O., Mgbafulu C. C., Ifemelumma C. C. and Obi C. N.

Department of Obstetrics and Gynaecology, Faculty of Medicine, Federal Teaching Hospital Abakaliki, Nigeria.

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Increasing caesarean section rate is a source of concern to obstetricians due to the attendant increased health risk, its commonest complication is bleeding, which occasionally may be life threatening. Tranexamic acid has recently been investigated as a potentially useful adjunct for the prevention of maternal morbidity. The research aim to evaluate the efficacy of tranexamic acid at reducing blood loss during elective caesarean section. The method used was a double blind randomized placebo controlled trial among women who had elective caesarean section at the Federal Teaching Hospital Abakaliki (FETHA) and Mile 4 Hospital Abakaliki. Data analysis was done using statistical Package for Social Science (IBM SPSS) software (version 20, Chicago II, USA). The results from the finding show that mean estimated blood loss was significantly lower in the tranexamic acid group (566.78±267.42 ml versus 819.09±348.36 ml, p<0.001). Blood loss >1000 ml was also significantly lower in the study group compared with the control group 5(8.8%) versus 16(27.6%); alternatively, 0.25; 95% CI 0.09 to 0.74; p=0.012. Tranexamic acid significantly reduced the need for additional uterotonics. However, the number of patients that had blood transfusion between had no difference and the maternal side effect profile was similar. Intravenous tranexamic acid significantly reduced blood loss at elective caesarean sections. It also reduced the risk of blood loss greater than 1000 ml and the need for additional uterotonics without increasing maternal risks.

Key words: Tranexamic acid, blood loss, elective caesarean section.

INTRODUCTION

Caesarean section (CS) or caesarean delivery refers to the delivery of a fetus, placenta, and membranes through an abdominal and uterine incisions (Ugwu et al., 2011) after the age of viability (Incerpi, 2013; Nwobodo et al., 2011). One of the most worrisome aspects of modern obstetrics is the relentless increase in the caesare an

*Corresponding author. E-mail: obivitus04@gmail.com.

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section rate (Ugwu et al., 2011; Incerpi, 2013; Nwobodo et al., 2011; Arulkumaram, 2012; Geidam et al., 2009).

Despite the safety in carrying out caesarean section, increasing caesarean section rate is a major challenge to obstetricians because of the attendant increased health risk for mothers and their babies as well as the increased cost of health care (Ugwu et al., 2011; Curtin et al., 2015). Delivery by CS can cause more complications than normal vaginal delivery and one of the most common complications is excessive blood loss, which often can be life threatening (Curtin et al., 2015; Magann et al., 2005).

Estimated blood loss, greater than 1000 ml, was recorded in 9.2% of caesarean births in an observational study in Demark (Bergholt et al., 2003). In a similar study reported by Magann et al. (2005). PPH was reported in 6.75% of emergency caesarean section; while 4.84% of elective caesarean sections were complicated by PPH (Magann et al., 2005). About one in five of these hemorrhage progresses to a severe form that may endanger the mother's life or at least her future fertility and exposes her to the risks of blood transfusion, further surgery and intensive care (Bateman et al., 2010; Guerriero et al., 2010).

The uterine blood flow reaches up to 750 ml/min at term (Kliman, 2000). When the placenta separates from the uterine wall during delivery, strong myometrial contractions occur along with increased platelet activity and a release of pro-coagulant factors. Fibrinolytic activity also increases during placental delivery (Hellgren, 2003). Other tissue injuries encountered during CS can shift the haemodynamic equilibrium towards fibrinolysis, contributing to more coagulopathy and bleeding (Hellgren, 2003; Levy et al., 2010). Hence, placental expulsion is a critical window for the prevention of PPH, and various preventive interventions during this stage have been proposed (Hellgren, 2003). Active management of the third stage of labour (AMTSL) has displayed effectiveness in reducing postpartum haemorrhage (Levy et al., 2010). Administration of uterotonics, in particular oxytocin, is the major component of AMTSL that has shown effectiveness in preventing PPH (Sadler et al., 2000). However, AMTSL may only prevent about 60% of postpartum haemorrhage (Cotter et al., 2001). Therefore, additional biochemical haemostatic effects obtained from the use of pro-haemostatic drugs such as tranexamic acid may go a long way in complementing the effects of oxytocics in the prevention of PPH (Guerriero et al., 2010).

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that exerts its anti-fibrinolytic effect through the reversible blockade of the lysine binding sites on the plasminogen molecules (Product monograph prCyclokapron, 2018). Intravenous administration of the tranexamic acid has been shown to reduce the need for transfusion and risk of death in trauma patients (Shakur et al., 2010). Its efficacy in the treatment of postpartum et al., 2010). Its efficacy in the treatment of postpartum haemorrhage has been validated in a large global multicentre randomized control trial (Shakur et al., 2010). Compared with placebo, some randomized control trials have shown that it is effective in reducing blood loss at caesarean section (Gai et al., 2004; Gohel et al., 2007; Gungorduk et al., 2011). However, a systematic review has recommended that further trials are required to confirm its efficacy and safety (Novikova and Hofmeyr, 2010). Tranexamic acid is associated with a good safety profile; however, some adverse effects (nausea, vomiting and diarrhea, dizziness and hypotension) have been reported, the most dreaded being venous thromboembolism (Product monograph prCyclokapron, 2018).

MATERIALS AND METHODS

This was a double blind randomized placebo controlled trial on the efficacy and safety of intravenous tranexamic acid at reducing blood loss in women undergoing elective caesarean section at the Federal Teaching Hospital Abakaliki (FETHA) and Mile 4 Hospital Abakaliki. The study lasted for a period of six months; participants for this study included parturients with singleton pregnancy at 37-42 weeks' gestational age, admitted for elective caesarean section in both facilities after obtaining an informed consent. The following women were excluded- women who have known allergy to tranexamic acid, prior history of thromboembolism or bleeding disorders. Parturients with medical disorders in pregnancy; renal disease, liver pathology, hypertensive disorders in pregnancy, antepartum hemorrhage, and women who did not consent to the study were also excluded. The minimum sample size was determined using the formula for comparison between two groups when the end is a quantitative data. Using an effect size of 30% reduction in blood loss, with a standard deviation of 0.485[23] and setting the power at 80%, with two-sided confidence level at 95% and 10% patients drop rate the sample size needed to produce a statistically acceptable data was 60 for each group.

Both drug and placebo were heat stable and were stored at room temperature. The company label on the drug and those on the placebo were carefully removed and replaced using a plane paper by a pharmacist and each was coded before blinding was done, hence the drug and the placebo were similar in appearance except for the number code on each bottle. The key to the code was at the custody of the pharmacist until the end of the study.

The participants were randomized by means of a computer-generated random-number using the software Research Randomizer®. Using this software, sixty numbers were randomly generated from a pool of one hundred and twenty numbers (1-120) and these numbers were assigned to Group A (tranexamic acid group) while the remaining sixty numbers were automatically assigned to Group B (the placebo group).

Group A received 1 g tranexamic acid (Exacyl®; Sanofi Aventis Paris France) at the rate of 1 ml/min over 10 min starting 20 min before the skin incision.

Group B received 10mls of water for injection (Biofem®; JuhelAnambra Nigeria) at the rate of 1 ml/min over 10 min starting 20 min before the skin incision.

Concealment was done in sequentially numbered opaque sealed envelopes. These numbers (1-120) were inscribed on brown envelopes and on a piece of paper, on which a code and the corresponding drug or placebo, was inserted and sealed. A statistician did the randomization, while a hospital pharmacist did the concealment without revealing the outcome to the researcher.

All the envelopes were kept in a locker that was accessible to all

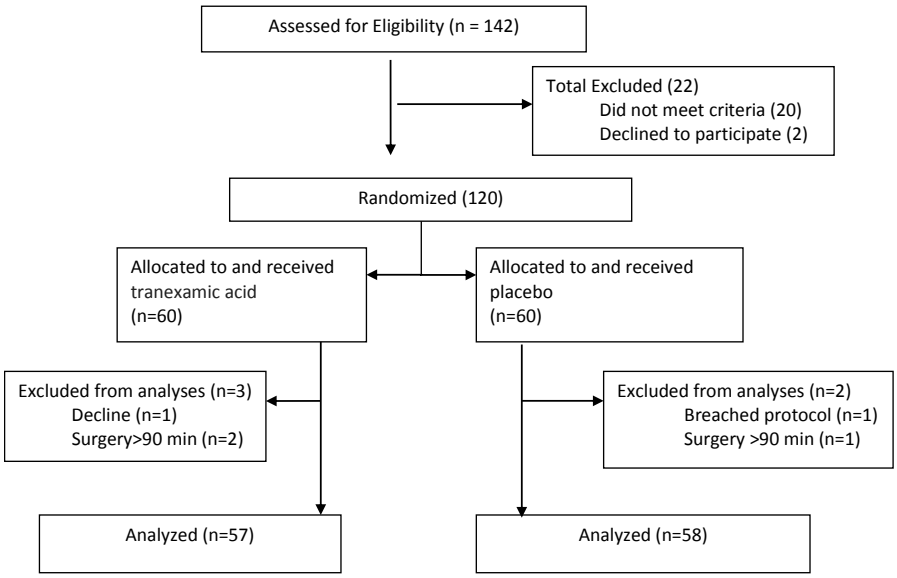

Figure 1. The flow of patients through the study.

the members of the research team.

Participants that met the inclusion criteria having signed the informed consent form were given sequential study number and the corresponding numbered opaque sealed envelope were then allocated to the patient.

The allotted sealed envelope was taken to the theatre and handed over to the anesthetist who administered the drug or the placebo over 10 min (starting 20 min before the skin incision) to the patient without telling neither the researcher nor the patient the content of the envelope. All the surgery was lower segment caesarean section, carried out under spinal anaesthesia by consultants and senior registrars. The operations were carried out according to standard protocol. Patients whose operations lasted for more than 90min were excluded from the study to reduce the risk of drug clearance from maternal circulation. Following delivery of the placenta, all patients recruited for this study received intravenous oxytocin 10IU bolus (Oxytocine®, RotexMedica GmbH Germany). Infusions of 40IU oxytocin (Oxytocine®, RotexMedica GmbH Germany) in 1 L of 5% Dextrose water were used when indicated. Others oxytocics and surgical interventions required to control excessive bleeding were used as indicated. Patients who needed blood transfusion intra-operatively received same as indicated, otherwise if the post operation haematocrit was less than 48 hs post operation. These interventions were noted.

The maternal vital signs (pulse, blood pressure and respiratory rates) were taken at various times: on admission, at the delivery of the placenta, at the end of the surgery, 1 h after the surgery and 2 h after the surgery. All oxytocics were stored at 4°C in a refrigerator inside the hospital theater.

The estimated blood loss was measured using the difference in haematocrit value taken before the surgery and 48 h after the caesarean section using the formula below (Novikova and Hofmeyr, 2010; Yehia et al., 2014):

$$EBL = \frac{EBV \times \text{Preoperative Haematocrit} - \text{Post-operative haematocrit}}{\text{Preoperative Haematocrit}}$$

Where EBL: Estimated blood loss

EBV: Estimated blood volume (maternal weight in Kg × 85 ml)

Blood loss greater than >1000 ml would be regarded as excessive bleeding.

Primary Outcome Measure was the estimated blood loss at elective caesarean section. Secondary Outcome Measures were; excessive blood at caesarean section loss defined as blood loss > 1000mL, change in haematocrit after caesarean section, the need for additional uterotonics to control bleeding, the need for blood transfusion during or after the surgery and maternal side effects (nausea, vomiting, headache, skin rash, thromboembolism, and maternal death). Data was collated, tabulated then statistically analyzed using statistical Package for Social Science (IBM SPSS) software (version 20, Chicago II, USA). Continuous variables were presented as mean and standard deviation (Mean ± 2SD), while categorical variables were presented as numbers and percentages. Chi-square test (X^2) was used for comparison between groups for qualitative variables, while student t-test was used for comparison between groups for quantitative variables. A difference with a P value <0.05 was considered statistically significant. Analysis was done using intention to treat.

Ethical clearance was sought and obtained from the Health Research and Ethics committee of the Federal Teaching Hospital with a REC No: FETHA/REC/Vol 1/2016/349

RESULTS

Over the study duration, 142 patients were assessed for randomization into the study; 22 patients were excluded while 120 were allocated to receive either the tranexamic acid or the placebo. Only 57 patients in the study (tranexamic acid) group and 58 in the control (placebo) group were available for the final analysis Figure 1. The characteristics of the women in the two groups were matched and there was no significant difference in the maternal demographics characteristics; maternal age, weight, height, body mass index (BMI) on admission, gestational age and parity ($p>0.05$). There was also no

Table 1. Demographic characteristics of the patients and some surgery determinant.

Variable	Study group (mean ± SD)	Placebo group (mean ± SD)	P value
Maternal age (years)	29.5±4.8	28.2±3.7	0.1062
Weight (kg)	77.4±13.6	75.4±12.9	0.4201
Height (m)	1.58±0.07	1.60±0.06	0.1025
Maternal BMI (kg/m^2)	28.8±4.7	29.2±4.1	0.6275
Gestational age (weeks)	39.6±1.5	39.3±1.4	0.2698
Parity	1.9±1.7	1.5±1.6	0.1964
Mean duration of surgery (min)	42.4±5.6	40.6±7.5	0.1481
Fetal birth weight	3.21±0.58	3.18±0.62	0.7893
APGAR score			
First minute	7.8±1.2	7.7±1.4	0.6819
Fifth minute	9.6±0.8	9.7±0.6	0.4493
Mean platelet count	213.6±47.3	217.4±49.5	0.6737

Table 2. some surgery determinants.

Variable	Study group (n=57)	Placebo group (n=58)	Chi square	P value
No of previous scar				
0	20	18		
1	12	15	0.0875	0.891
2	16	18		
≥3	9	7		
Cadre of surgeon				
Senior registrar	48	46	0.4625	0.4964
Consultant	9	12		
Years of experience				
≤2 years	18	23	0.8173	0.3659
>2 years	39	35		

statistically significant difference in the mean duration of the surgery, the birth weight and APGAR scores in the first and fifth minutes (p>0.05). The mean platelet count was also not different between both groups; Table 1.

Table 2 shows some surgery determinants. The number of primary caesarean section and repeat caesarean sections were similar between the groups. There was also no significant difference in the cadre of surgeon and the level of experience of the surgeon between the groups, p value >0.05. The indication for the surgery was also similar between the two groups, as seen in Table 3. The mean estimated blood loss was significantly lower in the tranexamic acid group compared with the placebo group (566.78±267.42 ml versus 819.09±348.36 ml, respectively; p<0.001). More so, blood loss > 1000 ml was also significantly lower in the study group compared with the control group with 5(8.8%) versus 16(27.6%) respectively giving an Odd Ratio (OR) 0.25; 95% Confidence interval (CI) 0.09 to 0.74; p=0.012. There was no significant difference in the pre-operative haemoglobin and pre-operative haematocrit values between both group p >0.05. However, the mean post-operative haematocrit was significantly higher in the tranexamic acid group compared with the control (29.5±2.1 versus 28.0±2.4; p=0.005). In addition, the mean post operative haemoglobin was significantly higher in the study group compared to the control group (9.8±0.7 mg/dL versus 9.3±0.9 mg/dL, p=0.001). The mean change in haematocrit and change in haemoglobin value were significantly less in the tranexamic acid group compared with the control group p<0.001.

There was no statistical difference in the number of

Table 3. Indication for the surgery.

Indication	Study group	Control group	Chi square	P value
Two previous scar	16	18		
≥3 previous scar	9	7		
1 previous scar with another indication	12	15		
Breech in a primigravida	4	5	0.6198	0.4311
Transverse lie at term	5	3		
Fetal macrosomia	6	8		
IUGR, short preg. interval, others	5	2		

Table 4. Intraoperative and postoperative variables in the study group and in the control group.

Variable	Study group (mean ± SD)	Placebo group (mean ± SD)	P value
		(A)	
Blood loss at the Caesarean Section	566.8±267.4	819.1±348.4	<0.001
Maternal haematocrit			
Preoperative	32.3±2.5	32.2±1.8	0.5951
Post operative	29.5±2.1	28.0±2.4	0.005
Change in haematocrit	2.8±1.4	3.8±1.8	0.0012
Maternal haemoglobin			
Preoperative	10.7±0.9	10.8±1.1	0.5951
Post operative	9.8±0.7	9.2±0.9	0.0012
Change in haemoglobin	0.9±0.5	1.5±0.9	<0.001

		(B)		
	Study group N (%)	**Placebo group N (%)**	**P value**	**OR 95% CI**
Blood loss ≥ 1000 ml	5(8.8%)	16(27.6%)	0.01	0.25 (0.09 to 0.74)
Patients requiring additional oxytocics	13(22.8%)	25(43.1%)	0.02	0.39 (0.17 to 0.87)
Patients requiring blood transfusion	2(3.5%)	5(8.6%)	0.2668	0.38 (0.07 to 2.07)
Patients with minor side effects	11	8	0.4286	1.49 (0.5 to 4.04)
Nausea/vomiting	46	50		
Nil				
Patients with major side effects	0	0		
Thromboembolism	0	0		
Maternal deaths				

patients that had blood transfusion between both groups 2 (3.5%) versus 5 (8.6%) respectively OR 0.38; 95% CI 0.07 to 2.07; p=0.2668. Significantly less women in the tranexamic acid group needed additional uterotonics agents than those in the control group 13 (22.8%) versus 25 (43.1%) alternatively, 0.39; 95% CI 0.17 to 0.87; p=0.021. No patient needed a surgical procedure, such as a brace suture, uterine artery ligation, or caesarean hysterectomy. There was no thromboembolism reported in either of the tranexamic acid group or in the control group. There was also no maternal death. However, the cases of gastrointestinal side effects (nausea and vomiting) were more in the tranexamic acid group but the difference was not statistically significant; 11(19.3%) versus 8(13.8%) alternatively, 1.49 95% CI; 0.5 to 4.04; p=0.4286), as displayed in Table 4a, b.

Table 5 shows the vital signs of the patients at specific times from admission through 2 h post operation. There was no statistically significant difference in the mean vital signs (respiratory rate, pulse rate, systolic and diastolic blood pressure) on admission, pre-operatively, immediately after placental delivery, or 1 h and 2 h after

Table 5. maternal vital signs at different times during and post caesarean section.

Maternal vital signs	Study group	Placebo	P value
On admission			
Respiratory rate	21.9±2.5	21.5±2.2	0.3641
Pulse rate	79.9±6.6	81.5±6.4	0.1896
Systolic blood pressure	123.4±16.7	121.7±14.4	0.5597
Diastolic blood pressure	75.1±11.33	72.0±12.9	0.1734
Preoperative			
Respiratory rate	21.4±1.8	21.4±2.7	0.9511
Pulse	80.3±8.0	80.8±8.0	0.7382
Systolic blood pressure	118.3±12.11	116.9±10.8	0.5139
Diastolic blood pressure	75.9±10.1	74.9±7.9	0.555
At placental delivery			
Respiratory rate	22.4±1.5	22.3±2.2	0.7767
Pulse	83.6±7.2	82.2±8.6	0.7382
Systolic blood pressure	117.9±13.7	118.4±11.0	0.8294
Diastolic blood pressure	76.9±11.0	75.6±9.5	0.4988
1 h after surgery			
Respiratory rate	22.6±1.9	22.8±1.7	0.3739
Pulse	78.6±15.4	82.0±8.4	0.1435
Systolic blood pressure	115.8±9.3	116.7±11.2	0.6404
Diastolic blood pressure	72.9±8.4	74.1±9.9	0.4852
2 h after surgery			
Respiratory rate	22.8±1.6	22.7±2.0	0.768
Pulse	80.2±5.4	80.6±7.9	0.7522
Systolic blood pressure	114±9.8	115.1±10.7	0.7153
Diastolic blood pressure	74.3±7.5	75.4±6.3	0.3959

CS between both groups.

DISCUSSION

In this study, pre-operative administration of 1g intravenous tranexamic acid was associated with a 252.3 ml (30.8%) reduction in blood loss at elective caesarean section compared with placebo; the mean blood loss in the study group was 566.78±267.42 ml while the mean blood loss in the study group was 819.09±348.36 ml. This value is similar to the 30% reduction in blood loss reported by Ahmed and coworkers in Ismaila Egypt (Ahmed et al., 2015) and the 34% reported by Maged in Cairo Egypt (Maged et al., 2015). This quantity of blood loss reduction is more than the 19.9% reported by Gai in China (Gai et al., 2004) but it is however, smaller than between 39.1- to 43.7% reduction reported in other similar studies (Gohel et al., 2007; Gungorduk et al., 2011; Movafegh et al., 2011). These differences in blood loss may be because of the different time interval employed in assessing the blood loss and the different methods used in the estimation of blood loss in the various studies. While some studies used gravimetric method and assessed blood loss after 2 h of the caesarean section (Gai et al., 2004; Gohel et al., 2007; Ahmed et al., 2015; Movafegh et al., 2011) others used change in haematocrit and assess blood loss after 48 h of the surgery (Gungorduk et al., 2011; Maged et al., 2015). More importantly, blood loss >1000 ml was significantly reduced in the study group compared to the placebo group. This reduction in the risk of primary postpartum haemorrhage had been reported in similar randomized control studies in which risk of primary postpartum haemorrhage was an assessed outcome (Gungorduk et al., 2011; Maged et al., 2015). This significant reduction in blood loss is particularly important for Abakaliki South east Nigeria where poor attitude to voluntary blood donation for obstetric use[26] and anaemia in pregnancy is prevalent (Esike et al., 2016).

This study also demonstrated that preoperative intravenous tranexamic acid reduced the need for additional uterotonics during caesarean section. This finding is consistent in most studies that compared the

efficacy of tranexamic acid to placebo in reducing blood loss at caesarean section (Gai et al., 2004; Gungorduk et al., 2011; Ahmed et al., 2015; Maged et al., 2015; Movafegh et al., 2011). No patient needed additional surgical procedure, such as a brace suture, uterine artery ligation, or caesarean hysterectomy during the procedure. There was a statistically significant difference in the mean post-operative haematocrit and mean post-operative haemoglobin between the two groups. This is also reflected in the smaller mean change in the haematocrit and haemoglobin between both groups. These findings are consistent in most similar studies (Gai et al., 2004; Gungorduk et al., 2011; Ahmed et al., 2015; Maged et al., 2015; Movafegh et al., 2011; Shahid and Khan, 2013; Yehia et al., 2014). The number of patients that received blood transfusion had no difference in both groups. This was similar to the finding in two similar studies (Gungorduk et al., 2011; Maged et al., 2015). However, Shahid and coworkers[28] and two systemic review and meta-analysis had shown that tranexamic acid reduced the need for blood transfusion in-patient who had elective caesarean section (Alam and Choi, 2015; Novikova et al., 2015).

Although tranexamic acid was not associated with change in maternal vital signs throughout the admission period, it is associated with a small increase in the risk of minor maternal side effects (majorly nausea and vomiting) although this did not attain statistical significance in this study. While some other studies did not demonstrate any difference in minor maternal gastro-intestinal side effects (Gohel et al., 2007; Gungorduk et al., 2011), others had observed significant difference (Ahmed et al., 2015; Alam and Choi, 2015; Novikova et al., 2015). This difference may be because of the dose and the rate of administration of the medication; higher doses have been associated with higher minor maternal side effects, which are not seen in smaller dose regimen. There were no major maternal side effects in this study and no maternal death occurred between the study groups. There was no difference in the neonatal APGAR scores in the first and fifth minutes between the two groups and there were no neonates in the study admitted into the newborn intensive care unit for birth asphyxia. This further suggests that tranexamic acid does not have any adverse maternal or neonatal outcome. This safety profile had been demonstrated in other similar studies (Gai et al., 2004; Gungorduk et al., 2011; Ahmed et al., 2015; Maged et al., 2015; Movafegh et al., 2011; Shahid and Khan, 2013; Yehia et al., 2014). Tranexamic acid had also been shown to reduce blood loss, following vaginal delivery and high-risk caesarean sections (Shady et al., 2017; Abbas et al., 2019).

Conclusion

This study demonstrated that pre-operative intravenous tranexamic acid significantly reduced blood loss at elective caesarean section. It also significantly reduced the risk of blood loss greater than 1000mL and it reduced the need for additional uterotonics to control blood loss. Fetal outcomes were similar in both groups. Although minor maternal side effects are slightly more, the difference was not statistically significant. There was no major maternal side effect and there was no maternal death.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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