ORIGINAL RESEARCH PAPER | Medical Science | Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

Randomized Controlled Trial of Tranexamic Acid Among Parturients At Increased Risk for Postpartum Hemorrhage Undergoing Cesarean Delivery in A Tertiary Care Teaching Hospital At Rims Kadapa

KEYWORDS: Cesarean Delivery, High-Risk Pregnancy, Post Partum Hemorrhage, Tranexamic Acid.

*** Dr. T. Lakshmi Suseela**
Associate Professor, Department of Obstetrics & Gynaecology, Rajiv Gandhi Institute of Medical Sciences, Kadapa, Andhra Pradesh.
* Corresponding author

Dr. S. Jaya Jyothi
Pharm D Post Baccalaureate, P. Rami Reddy Memorial College of Pharmacy, Kadapa, Andhra Pradesh.

Dr. P. Rabbani
Assistant Professor, Department of Obstetrics & Gynaecology, RIMS, Kadapa. Andhra Pradesh.

Dr.Chb. Jhonsi
Assistant Professor, Department of Obstetrics & Gynaecology, RIMS, Kadapa. Andhra Pradesh.

ABSTRACT *Objective: To assess the effects of tranexamic acid among patients undergoing cesarean delivery who were at high risk of postpartum hemorrhage for Obstetrics and Gynaecology department in RIMS Kadapa.* ***Methods:*** *Between August 1, 2014, and April 30, 2015, a randomized controlled trial was performed at a tertiary care teaching hospital at kadapa. Women undergoing an elective or emergency cesarean delivery who were at high risk for postpartum hemorrhage were enrolled. They were randomly assigned using sealed, opaque envelopes to receive 10 mg/kg tranexamic acid or normal saline 10 min before skin incision. Anesthesiologists were not masked to group assignment, but patients and obstetricians were. The primary outcome was need for additional uterotonic drugs within 24 h after delivery. Analyses were by intention to treat.* ***Results:*** *Thirty patients were assigned to each group. Additional uterotonic drugs were required in 7 (23%) patients assigned to tranexamic acid and 25 (83%) patients in the control group (P < 0.001).* ***Conclusion:*** *Intravenous tranexamic acid, administered before skin incision, significantly reduced the requirement for additional uterotonics among women at increased risk for postpartum hemorrhage.*

INTRODUCTION

Postpartum hemorrhage (PPH) is the leading cause of maternal morbidity and mortality worldwide [1, 2] and there is an urgent need for more aggressive measures for its prevention and control. The most common etiology for PPH is uterine atony, which responds to uterotonic drugs, including Oxytocin, Methyl Ergometrine, and Prostaglandins [3]. However, several adverse effects are associated with these drugs [3–6], and oxytocin-receptor down regulation and desensitization following exposure to oxytocin leads to a lack of further improvement in uterine contractions irrespective of dose increases [7]. Oxytocin induced desensitization is dependent on the duration of oxytocin exposure and occurs over a clinically relevant time frame of 4.2 h [4]. Thus, prolonged oxytocin labor augmentation makes the uterus refractory to its effects. Another cause of PPH is genital-tract trauma, for which the management is surgical. In cases of abnormal placentation and retained placenta, the lower uterine segment fails to contract [3]; these cases do not respond well to uterotonic drugs because the lower uterine segment is poor in oxytocin receptors [8]. Uterine bleeding due to other etiologies e.g. hypertensive disorders and cholestasis of pregnancy [9] is caused by poor platelet quality or low plasma levels of coagulation factor, and therefore does not respond well to incremental doses of uterotonics. Thus, pharmacological interventions to prevent and control PPH have to go beyond the sole use of uterotonic drugs [6]. Tranexamic acid is an inexpensive, antifibrinolytic drug long used to control bleeding due to surgery, menorrhagia [10], or trauma [11]. Additionally, tranexamic acid has been shown to reduce bleeding during cesarean delivery [12] as well as the need for additional uterotonic agents [13], albeit to a minimal degree. However, previous studies have been performed only in women with a standard risk for PPH and have not focused on assessing the effects of tranexamic acid in high-risk women. The main aim of the present study was to assess the effects of tranexamic acid in women at high risk of PPH following cesarean delivery. The need for additional uterotonic drugs during the first 24 h was the primary endpoint.

MATERIALS AND METHODS

A randomized controlled trial was conducted at RIMS Hospital, Kadapa, India, between August 1, 2014, and April 30, 2015. Pregnant women who had at least one risk factor for PPH and who were to undergo elective or emergency cesarean delivery were eligible for inclusion in the study. The risk factors considered were pregnancy-induced hypertension, use of oxytocin augmention for at least 4 h, more than two previous cesarean deliveries, chorioamnionitis (oral temperature > 38.5 °C with a high leukocyte count, after ruling out other sources of infection), general anesthesia, placenta previa, polyhydramnios (amniotic fluid index >95th percentile for the length of pregnancy as reported on prenatal ultrasonography), fibroids, multiparity (parity >4),multiple pregnancy, cholestasis, acrosomia (estimated birth weight >4 kg), and genital-tract injury. Patients were enrolled once the decision to undertake cesarean delivery (elective or emergency) was taken. Patients who had gone undergo a category-1 emergency cesarean delivery (urgent threat to the life or the health of them other or fetus) were not enrolled because informed consent could not be obtained. Other exclusion criteria were a history of ischemic cardiac disease, hemodynamic instability, bleeding disorders, and known allergy to tranexamic acid, history of any thrombogenic episodes, anticoagulant use, and a history of kidney disease, and an operating surgeon with fewer than 10 years of experience. Ethical approval was provided by the RIMS Hospital Ethics Committee. All participants provided written informed consent. After pro-

Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

viding informed consent, participants were randomly assigned in a 1:1 ratio to receive tranexamic acid (group T) or to a control group (group C). Women were requested to randomly choose an envelope from a container of sealed, opaque envelopes. At the beginning of the study, the container was filled with opaque envelopes, each containing one sheet of paper with either a T or a C written on it. The selected envelope was opened by the anesthesiologist in charge of the case, who then prepared the appropriate drug. Patients, obstetricians, and data analysts were masked to group allocation. Demographic characteristics, the indication for cesarean delivery, and preoperative hematocrit levels within the 24 h before delivery (in the absence of significant preoperative bleeding) were recorded. According to the allocated group, patients were given 10 mg/kg intravenous tranexamic acid (500 mg cyclocapron per 5 mL ampoule) diluted to 10 mL with normal saline (group T) or 10mL normal saline (Group C) 10 min before skin incision. Standard patient monitoring, including non invasive blood pressure measurement, electrocardiography, and pulse oximetry, was performed using an Intellivue MP 20 G5-M1019A monitor. Anesthesia was administered according to the anesthesiologist's instructions. Any hypotension likely to be due to the anesthetic agents was treated by intravenous ephedrine as required. As soon as the umbilical cord was clamped after delivery, all patients received 5 IU intravenous oxytocin diluted to 5 mL with normal saline over 30 s (timed by stopwatch). All patients also received an infusion of 20 IU oxytocin in 450 mL normal saline over 3 h, followed by 10 IU oxytocin in 500 mL normal saline over the next 5 h. Following placental delivery by controlled cord traction, the uterus was exteriorized and massaged. Five minutes after the bolus administration of oxytocin, the obstetrician was allowed to request additional uterotonic drugs at any time during the surgery (in case of increased capillary ooze or unsatisfactory uterine tone towards the end of uterine closure) or within the first 24 h after delivery (in case of increased postoperative vaginal bleeding, defined as a change of more than three fully soaked pads in any one hour). In case of increased bleeding, additional oxytocin doses were administered according to the PPH protocol followed at RIMS Hospital (Table 1). The endpoint for uterotonic drug administration was determined by the surgeon's clinical judgment. The requirement for additional uterotonics was recorded from the time of delivery for 24 h.

Table 1
Order of drugs to be given in case of increased bleeding

Step	Drug/intervention	Time
1	Doubling the rate of oxytocin infusion	5 min after oxytocin bolus
2	Methylergometrine (200 µg, intravenous)	10 min after step 1
3	Carboprost (250 µg, intramuscular)	10 min after step 2
4	Carboprost (250 µg, intramuscular)	15 min after step 3
5	Carboprost (250 µg, intramuscular)	15 min after step 4
6	Misoprostol (800 µg, sublingual)	15 min after step 5

Blood loss was estimated by the difference in hemoglobin values assessed before delivery and 48 h after delivery according to the following formula [14]:

$$\{[(Hb^{pre} - Hb^{48}) / Hb^{pre}] \times [(0.3669\ H^3) + (0.03219 \times W) + 0.6041]\} + \{(V \times 18) / Hb^{pre}\},$$

Where Hb^{pre} is the preoperative hemoglobin in g/dL, Hb^{48} is the postoperative hemoglobin at 48 h in g/dL, W is the patient's weight in kilograms, H is the height in meters, V is the total volume of blood transfused, and 18 is the hemoglobin concentration of the packed red blood cell units available at RIMS Hospital.

The need for perioperative blood transfusion (after excessive perioperative bleeding or postoperative hemoglobin < 8 g/dL), postoperative hemoglobin at 48 h, or any neonatal adverse events or thrombogenic events in the mother were also noted.

The primary outcome was the need for additional uterotonic drugs within the first 24 h after delivery. The secondary objectives were the estimated blood loss, blood transfusion requirements, and any neonatal adverse events or thrombogenic episodes in the mother.

Two previous studies involving normal obstetric populations showed that the incidence of additional uterotonic drug use in conjunction with [13] or without [15] tranexamic acid was 8.5% and 40%, respectively. Therefore, 60 patients were recruited to the present study to ensure an 80% power to detect a decrease in the primary outcome measure from 40% in the control group to 8.5% in the experimental group at a 5% level of significance.

An intention-to-treat analysis was performed using the SPSS version 17.0 program for Windows. A Shapiro–Wilk test was conducted to verify the distribution of the data. Data with a normal distribution were summarized as mean ± standard deviation, whereas those with a skewed distribution were described as median (interquartile range). The $\chi 2$ test was used to compare the differences in variables between the two groups. The Student t test was used for continuous, normally distributed variables. The Mann Whitney test was used to test independent relationships between the variables that did not demonstrate normality. A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Both groups contained 30 participants (Fig. 1). The two groups were similar in terms of the risk factors for PPH (Table 2), patient demographics (Table 3), and the indications for cesarean delivery (Table 4). One patient in group C received tranexamic acid on the first postoperative day because of continued bleeding. Nevertheless, because an intention-to-treat analysis was used, she was not excluded from the study and was analyzed in the group to which she was originally assigned (group C). Additional uterotonic drugs were required in significantly more patients group C than in group T ($P < 0.001$) (Table 5). Each type of uterotonic drug was used significantly more in group C than in group T (Table 6). Hemoglobin and hematocrit levels 48 h after delivery were significantly lower in group C than in group T ($P = 0.001$ and $P = 0.011$, respectively) (Table 5). The estimated blood loss at 48 h was lower in group T than in group C ($P < 0.001$) (Table 5).Whereas no patients in group T had an estimated blood loss of more than 1000 mL, more than one-fifth in group C bled more than 1000 mL in the perioperative period ($P = 0.011$) (Table 5). There was no significant difference in the proportion of patients who required a blood transfusion (Table 5). One of the patients in group C—who had a postoperative hemoglobin level of 69 g/L—refused the blood transfusion.

Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

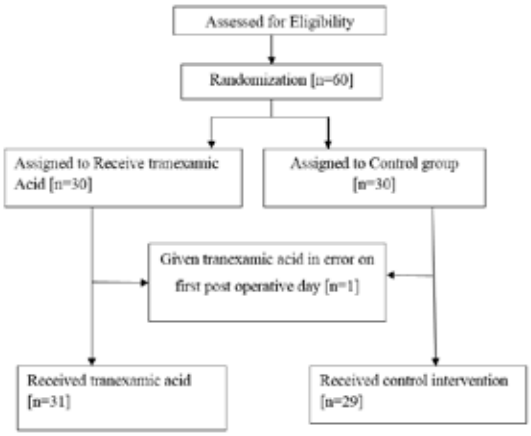

Fig. 1 flow of patients through the study

There was one case of intrauterine fetal death in group C. One neonate in group T developed seizures within the first 24 h due to maternal chorioamnionitis and was diagnosed with early neonatal sepsis.

DISCUSSION

The present results suggest that the use of tranexamic acid among women at high risk of PPH after cesarean delivery reduces the need for additional uterotonic drugs. Furthermore, the median estimated blood loss 48 h after delivery was considerably lower among patients assigned to receive tranexamic acid than among those in the control group.

Table 2
Risk Factors for Postpartum Hemorrhage.[a]

Risk factors	Group T (n = 30)[b]	Group C (n = 30)[c]	P value
Hypertension of pregnancy	4 (13)	10 (33)	>0.99
Oxytocin augmentation over 4 h	12 (40)	2 (7)	0.592
< 2 previous cesarean deliveries	4 (13)	1 (3)	0.671
Chorioamnionitis	0	3 (10)	>0.99
General anesthesia	3 (10)	3 (10)	>0.99
Placenta previa	2 (7)	1 (3)	>0.99
Polyhydramnios	0	1 (3)	>0.99
Fibroids	1 (3)	2 (7)	>0.99
Multiparity	0	1 (3)	0.492
Twin pregnancy	2 (7)	0	>0.99
Cholestasis of pregnancy	1 (3)	1 (3)	>0.99
Macrosomia	1 (3)	1 (3)	>0.99
Genital-tract injury	0		>0.99

[a] Values are given as number (percentage) unless indicated otherwise.
[b] Assigned to receive tranexamic acid.
[c] Control group.

Gungorduk et al. [13] performed a randomized, double-blind, placebo-controlled study to assess the efficacy of tranexamic acid in blood loss reduction following an elective cesarean delivery in 660 women, and found that the mean estimated blood loss at 48 h was significantly when compared with the lower among women treated with tranexamic acid than among those in the placebo group (499.9 ± 206.4 mL vs. 600.7 ± 215.7 mL, respectively; P < 0.001). The blood loss among patients assigned to tranexamic acid was similar in the present study, but that in group C was much higher than that recorded by ***Gungorduk et al.*** [13]. This difference is probably attributable to the fact that women at increased risk of peripartum bleeding were excluded by ***Gungorduk et al.*** [13], whereas only women at a high risk of hemorrhage were included in the present study. Additionally, ***Gungorduk et al.*** [13] observed that the proportion of women given tranexamic acid who had an estimated blood loss of more than 1000 mL was significantly lower than that of the placebo group (7 [2.1%] vs. 19 [5.8%]), but the difference was not significant.

Table 3
Demographic Characteristics.[a]

Characteristic	Group T (n = 30) [b]	Group C (n = 30) [c]	P value
Age, y	29.40 ± 4.16	30.27 ± 4.31	0.431
Weight, kg	73.16 ± 9.67	73.81 ± 12.78	0.825
Height, cm	161.27 ± 6.32	160.47 ± 6.41	0.643
Body mass index [d]	28.16 ± 3.74	28.67 ± 4.82	0.646
Preoperative hematocrit, %	34.59 ± 3.18	35.59 ± 3.72	0.269
Preoperative hemoglobin, g/L	116.2 ± 10.5	118.4 ± 13.6	0.485

[a] Values are given as mean ± SD unless indicated otherwise.

[b] Assigned to received tranexamic acid.

[c] Control group.

[d] Calculated as weight in kilograms divided by the square of height in meters.

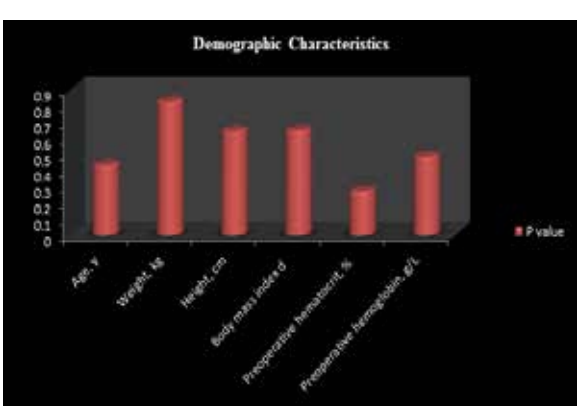

Fig. 2 Demographic Characteristics

With regard to additional uterotonic drugs, they were administered to more women in the present study than in that of ***Gungorduk et al.*** [13] (48 [14.5%] of 330 women in the control group and 28 (8.5%) of 330 in the

Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

tranexamic acid group received additional uterotonic drugs in the previous investigation), probably because only high-risk cases were included in the present study. Nevertheless, the present tranexamic acid group had a lower incidence of uterotonic use and the number of drugs used was also significantly lower than reported by ***Gungorduk et al.*** [13].

In 2006, ***Balki et al***. [16] recommended a minimum oxytocin dose of 3 IU following cesarean delivery for labor dystocia. In the present study, however, a 5 IU dose was administered according to the center's protocol. Nevertheless, despite the higher dose, 25 patients in the control group still experienced increased bleeding. Of these 25 patients, only five responded to additional oxytocin, probably because of a down regulation and desensitization of the oxytocin receptors leading to additional doses of oxytocin being ineffective [7].

Table 4
Indication for cesarean delivery.[a]

Indication	**Group T (n = 30)**[b]	Group C (n = 30)[c]	P value
High blood pressure	3 (10)	3 (10)	>0.99
Fetal distress	2 (7)	2 (7)	>0.99
Impending uterine rupture	0	1 (3)	>0.99
Non-progress of labor	10 (3)	12 (40)	0.592
Placenta previa	2 (6)	3 (10)	>0.99
Patient request	3 (10)	2 (7)	>0.99
Failed induction	2 (7)	2 (7)	>0.99
Fibroid	1 (3)	1 (3)	>0.99
Macrosomia	1 (3)	1 (3)	>0.99
Previous cesarean delivery	4 (13)	2 (7)	0.671
Twin pregnancy	2 (7)	1 (3)	>0.99

[a] Values are given as number (percentage) unless indicated otherwise.

[b] Assigned to receive tranexamic acid.

[c] Control group.

A common mechanism underlying numerous causes of PPH is activation of the fibrinolytic system following placental delivery, leading to rapid degradation of fibrinogen and fibrin and an increase in plasminogen activators [8], which can last up to 10 h and worsen the bleeding. Tranexamic acid is a synthetic lysine analog that exerts its effect by competitively blocking the lysine binding sites on plasminogen molecules, thus inhibiting the activation of plasminogen into plasmin, and acting as a fibrinolysis inhibitor. Consequently, clot breakdown is inhibited and excessive or recurrent bleeding is controlled [8]. Thus, tranexamic acid can reduce blood loss independent of its etiology. Tranexamic acid has been deemed a category B drug by the US Food and Drug Administration, and its use is safe during breastfeeding [8].

Table 5
Surgical Outcome. [a]

Outcome	Group T (n = 30)[b]	Group C (n = 30)[c]	P value
Estimated blood loss, mL	432 (337–497)	819 (663–1001)	<0.001
Blood loss >1000 mL	0 7	(23)	0.011
Required blood transfusion	1 (3)	4 (10)	0.353
Additional Uterotonics	7 (23)	25 (83)	<0.001
Postoperative Hematocrit, %	31.30 ± 2.95	29.13 ± 3.41	0.011
Postoperative Hemoglobin, g/L	105.4 ± 9.9	95.0 ± 11.7	<0.001

[a] Values are given as median (interquartile range), number (percentage), or mean ±SD, unless indicated otherwise.

[b] Assigned to receive tranexamic acid.

[c] Control group.

The main limitation of the present study was the fact that the anesthesiologist was not masked to group allocation. However, this was considered necessary in the interest of patient safety given that tranexamic acid is known to cause hypersensitivity reactions. Furthermore, the anesthesiologist played no part in the decision to administer additional uterotonic drugs, and therefore the lack of blinding would not have affected the results. An additional limitation was the inclusion of 13 risk factors for PPH despite their varying effect on the risk for PPH. Nevertheless, because there was no difference in the distribution of risk factors between the two groups, it is unlikely that this may have led to any sampling errors. Tranexamic acid was found to be safe for the fetus and did not increase the risk for thrombogenic episodes in the mother. However, the study was not powered to test these aspects of the drug.

Table 6
Additional Uterotonic Drugs Used.[a]

Drug	**Group T (n = 30)**[b]	**Group C (n = 30)**[c]	P value
Increasing oxytocin	7 (23)	25 (83)	<0.001
Methylergometrine	3 (10)	20 (67)	<0.001
Carboprost	1 2 (7)	7 (23)	0.146
Carboprost 2	0	3 (10)	0.237
Carboprost 3	0	2 (7)	0.492
Misoprostol	0	2 (7)	0.492
Others	0	0	–

[a] Values are given as number (percentage) unless indicated otherwise.

[b] Assigned to receive tranexamic acid.

[c] Control group.

Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

CONCLUSION

In conclusion, intravenous tranexamic acid, administered at least 10 min before skin incision significantly decreased the requirement of an additional uterotonic drugs and perioperative blood loss during cesarean delivery among women at increased risk for postpartum hemorrhage.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

ACKNOWLEDGEMENTS

We sincerely would like to acknowledge **Dr. Chb. Jhonsi, Dr. P. Rabbani,** and other colleagues for their support.

FUNDING: No funding sources

REFERENCES

1. Hogan MC, Foreman KJ, Naghavi M, Ahn SY, Wang M, Makela SM, et al. Maternal mortality for 181 countries 1980–2008: a systematic analysis of progress towards Millenium Development Goal 5. Lancet 2010; 375(9726):1609–23.
2. Bouwmeester FW, Bolte AC, van Geijn HP. Pharmacologic and surgical therapy for primary postpartum haemorrhage. Curr Pharm Des 2005; 11(6):759–73.
3. Walfish M, Neuman A, Wlody D. Maternal haemorrhage. Br J Anaesth 2009; 103(Suppl1):i47–56.
4. Bhattacharya S, Ghosh S, Ray D, Malik S, Laha A. Oxytocin administration during cesarean delivery: randomised controlled trial to compare intravenous bolus with intravenous infusion regimen. J Anaesthesiol Clin Pharmacol 2013; 29(1):32–5.
5. Ibrahim SM, Mustafa E, Louon A. Postpartum severe sinus bradycardia following methylergonovine administration. J Int Med Res 2008; 36(5):1129–31.
6. Novikova N, Hofmeyr GJ, Cluver C. Tranexamic acid for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2015; 6:CD007872.
7. Sarna MC, Soni AK, Gomez M, Oriol NE. Intravenous oxytocin in patient undergoing selective cesarean section. Anesth Analg 1997; 84(4):753–6.
8. Peitsidis P, Kadir RA. Antifibrinolytic therapywith tranexamic acid in pregnancy and postpartum. Expert Opin Pharmacother 2011; 12(4):503–16.
9. Mayer DC, Smith KA. Antepartum and post partum hemorrhage. In: Chestnut DH, Polley LS, Wong CA, Tsen LC, editors. Chestnut's Obstetric Anesthesia: Principles and Practice. Philadelphia: Elsevier; 2009. p. 811–36.
10. Lethaby A, Farquhar C, Cooke I. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev 2004; 4:CD000249.
11. CRASH-2 trial collaborators Shakur H, Roberts I, Bautista R, Caballero J, Coats T, et al. Effects of tranexamic acid on death, vascular occlusive events and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomized, placebo-controlled trial. Lancet 2010; 376(9734):23–32.
12. Sekhavat L, Tabatabaii A, Dalili M, Farajkhoda T, Tafti AD. Efficacy of tranexamic acid in decreasing blood loss after cesarean section. J Maternal Fetal Neonatal Med 2009; 22(1):72–5.
13. Gungorduk K, Yildirim G, Asicioglu O, Gungorduk OC, Sudolmus S, Ark C. Efficacy of intravenous tranexamic acid in reducing blood loss after elective cesarean section: a prospective, randomized, double-blind, placebo-controlled study. Am J Peri natol 2011; 28:233– 40.
14. Stahl DL, Groeben H, Kroepf D, GautamS, Eikermann M. Development and validation of a novel tool to estimate peri-operative blood loss. Anaesthesia 2012; 67(5): 479–86.
15. Munn MB, Owen J, Vincent R, Wakefield M, Chestnut DH, Hauth JC. Comparison of Two oxytocin regimes to prevent uterine atony at cesarean section: a randomized controlled trial. Obstet Gynecol 2001; 98(3):386–90.
16. Balki M, Ronayne M, Davies S, Fallah S, Kingdom J, Windrim R, et al. Minimum oxytocin dose requirement after cesarean delivery for labor arrest. Obstet Gynecol 2006; 107:45–50.