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Original Research Article

A clinical trial to assess the blood loss in women predisposed to postpartum hemorrhage with the use of prophylactic intravenous tranexamic acid

K. Satyasri[1]*, Chandana C.[2]

[1]Department of Obstetrics and Gynecology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India
[2]Department of Obstetrics and Gynecology, Oxford Medical College Hospital and Research Centre Bangalore, Karnataka, India

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***Correspondence:**
Dr. K. Satyasri,
E-mail: satyasrikoya@gmail.com

ABSTRACT

Background: Postpartum hemorrhage (PPH), a complication encountered during third stage of labour, contributes to 25% of maternal death worldwide. Despite various measures for prevention and management of PPH, burden of PPH still looms.
Methods: Prospective randomized controlled clinical trial (RCT) was conducted in Vydehi Institute of Medical Sciences, among 128 patients predisposed to PPH, over 18 months. After meeting the inclusion and exclusion criteria, participants were randomized to receive tranexamic acid (TXA) intravenously 10 mg/kg along with 10 IU of oxytocin following the delivery. Patients were analysed for, blood loss, need for medical or surgical interventions.
Results: Parameters like age, mean gestational age at haemoglobin estimation, and at delivery were similar among groups. The need or parenteral iron, blood transfusions, uterine artery ligation and compression suture were higher in controls group, but not statistically significant. Among the cesarean section (CS) group, most significant pre-disposing factors for PPH were previous CS (p value=0.012) and anaemia (p value =0.01). Incidence of PPH 0.69% (p value =0.031) and use of additional uterotonics were statistically significant (p value <0.05). Among the vaginal delivery (VD) group, most significant pre-disposing factors were anaemia (p value =0.002), thrombocytopenia (p value =0.045), and fetal-macrosomia (p value =0.020). Incidence of PPH 0.25% (p value <0.001) and use of additional uterotonics and hospital stay were statistically significant.
Conclusions: We conclude that, anemic patients were at higher risk of PPH irrespective of the mode of delivery. Prophylactic TXA lowers incidence of PPH, blood loss, use of additional uterotonics and hospital stay even in the presence of pre-disposing factors. Quantification of blood loss is better estimated by drop in haemoglobin after 24 hours.

Keywords: Indirect method of quantification of blood loss, Postpartum hemorrhage, Tranexamic acid

INTRODUCTION

Though labour is a physiological process, it is not devoid of complications, most common being hemorrhage, which is almost always underestimated, which in turn results in delayed decision-making, delaying resuscitative measures, gravely influencing maternal outcome.

Obstetric hemorrhage is defined as hemorrhage which may manifest before, during or even after delivery, about 80% it is during postpartum. Hence, postpartum hemorrhage (PPH) is more common in occurrence and dreaded complication of pregnancy.[1] It is due to failed obstetrical, surgical, or systemic hemostasis. In the postpartum period, after the separation and expulsion of the placenta, if the

uterus fails to contract adequately, or trauma to genital tract and implausibly from disorders of coagulation.

PPH was traditionally defined as estimated blood loss more than 500mL for vaginal delivery (VD) and more than 1000 ml for cesarean section (CS).[5] Redefined in 2017 by ACOG as "a cumulative blood loss greater than 1000 ml with signs of hypovolemia within 24 hours of the birth process, regardless of route of delivery". Most common cause of PPH is uterine atonicity, followed by trauma. PPH is a life-threatening outcome of both CS and VD.

PPH accounts for 1 out of 4 maternal deaths globally, and risk of PPH mounts with increasing age.[3] However, in developing countries it can be as high as 60%, while in developed countries PPH is largely preventable and manageable.[4]

Several pharmacological agents have used for the management of PPH. As obstetrician our foremost shield against PPH is active management of third stage of labour (AMTSL). Nevertheless, there are many uterotonics to our rescue. I) Oxytocin, a naturally occurring hormone, causes uterine contractions, with no contraindications and minimal side effects. II) Misoprostol, a PGE1 analogue with delayed onset of action. III) Methergine, an ergot alkaloid, aids in sustained uterine contractions. IV) Carboprost, a synthetic analogue of PGF. V) Carbetocin. VI) Recombinant factor VIIa.

Latter are recent drugs, with limited feasibility, storage, or availability.

During PPH, hemostatic abnormalities are considered as consequences of bleeding rather than cause for bleeding. Hence, hemostatic drugs are not considered as first-line drugs. However, recent studies have suggested otherwise, there is a demonstrable relation between decreased fibrinogen and hemorrhage. Antifibrinolytic agents like TXA and aprotinin, have been used widely to achieve hemostasis and significantly contributing to reduce morbidity and mortality associated with hemorrhage in many surgical fields, but its use in Obstetrics is less explored.[5]

Aims and objectives

To compare blood losses in women receiving prophylactic intravenous TXA to those receiving oxytocin alone, after delivery. To assess the role of prophylactic intravenous TXA in reducing the blood loss postpartum, thereby the need for blood transfusions or hematinics. To assess the need for medical or surgical Intervention for the management of PPH.

METHODS

A prospective randomised controlled trial was carried out among the pregnant women visiting antenatal and labour wards of Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India, over a period of 18 months (September 2020 to February 2022).

A total of 128 pregnant women satisfying inclusion and exclusion criteria, admitted to the antenatal/labour ward of the institute were included, after duly administering and obtaining a wilful and valid consent. 64 patients were randomised to receive prophylactic TXA along with AMTSL and 64 others received AMTSL alone. Furthermore, subgroups of 32 each were made based on mode of delivery, for VD and CS.

The Inclusion criteria was laid down, to include most of the known risk factors for PPH such as: age of the pregnant women (19-40 years), type of onset of labour spontaneous or induced, parity nullipara or multipara (3 or more), anaemia, multiple gestations, polyhydramnios, abnormal placentation, hypertensive disorders in pregnancy- PIH, prolonged labour, instrumental vaginal delivery, second stage cesarean section, previous cesarean section, thrombocytopenia and abruptio placenta.

Similarly, patients were also excluded from the study based on certain parameters such as, prior history of seizure disorder, known hypersensitivity to TXA, patients with renal impairment and prior history of thrombo-embolic events. All of which were known or suspected adverse reactions of TXA.

After approval from Institutional Ethics Committee, the patient fulfilling the inclusion and exclusion criteria with valid consent were recruited. All the patients were subjected to clinical evaluation at the time admission and data was collected in a predesigned proforma.

Study patients were randomized by block randomization. patients were randomly allocated to intervention and control group. Allocation sequence was concealed and double blinding was followed.

Pre-partum haemoglobin and hematocrit were noted, and labour was stringently monitored. Prior to the anticipated delivery, a set of pre-weighed mops and gauzes were given to each patient, which were later collected to estimate the blood loss. AMTSL (injection oxytocin 10 IU) was followed for all patients. In intervention group, AMTSL and injection TXA 10 mg/kg intravenously was given. While, among the control group AMTSL alone was followed. Immediately after the baby delivery, care was taken not to soak the mops or gauze with liquor during vaginal delivery. Among the CS group care was taken to minimise the suctioning of liquor. Although, VEBL was practised among all groups.

The blood loss during delivery was quantified by following ways: pre-weighed set of mops were used, following delivery, soaked mops were weighed to determine the blood loss. In case of CS, blood loss calculated by suction drain volume. In case of VD, VEBL was used. Post-natal or postoperative haemoglobin which

was sent after 24 hours of the delivery. Post-natal or postoperative haematocrit, which was sent after 24 hours of the delivery.

Total blood loss (ml) = (weight of soaked mops - weight of unsoaked mops) + blood loss quantified by VEBL (+ blood collected in suction system - in case of CS)

During intra-partum period, patients were evaluated for the need of interventions, like additional uterotonics, uterine artery ligation or compression sutures. Patients were monitored for a period of 48 hours for any drug-related reactions in the post-partum period.

Statistical analysis

Data was analysed using SPSS 22 version software. Chi-square test, ANOVA and Independent t-test were used in the analysis. Data was comprehended to arrive at the following outcomes:

Primary outcome

Amount of blood loss in both groups, and changes in haemoglobin and haematocrit

Secondary outcome

Need for blood transfusions and postpartum iron preparations; need for medical/surgical aids to control PPH, and adverse reactions to TXA.

RESULTS

Of 128 recruited pregnant women, the incidence of PPH was 84.3% among controls while it was 39% among cases, with a p value of 0.003, which is statistically significant, thus justifying our criteria for predisposed population to PPH.

Table 1: Characteristics of the study population.

Characteristics		VD		P value	CS		P value
		Control	Case		Control	Case	
Age		24.91	24.06	0.390	27.41	26.88	0.655
Rural population		17 (53.13%)	14 (43.75%)	0.453	13 (40.63%)	12 (37.50%)	0.798
Urban population		18 (56.25%)	15 (46.88%)		19 (59.38%)	20 (62.50%)	
Parity	1	21 (62.6%)	17 (53.12%)	0.403	9 (28.12%)	15 (46.87%)	0.351
	2	8 (25%)	10 (31.25%)		20 (62.5%)	16 (50%)	
	3	2 (6.25%)	5 (15. 62%)		2 (6.25%)	1 (3.12%)	
	4	0%	0%		1 (3.12%)	0%	
	5	1 (3.12%)	0%		0%	0%	
Gestational age at Hb estimation		38.3	37.9	-	37.5	37.3	-
Gestational age at delivery		38.8	39	-	38.4	38.1	-
Prepartum Hb		11.25	10.02	0.008	11.82	10.79	0.007
Prepartum haematocrit		34.45	31.22	0.011	35.99	22.78	0.003

Table 2: Predisposing factors in the study population.

Predisposing factor	VD		P value	CS		P value
	Control	Case		Control	Case	
Previous CS	1 (3.13%)	2 (6.25%)	0.554	10 (31.25%)	20 (62.50%)	0.012
Anemia	12 (37.50%)	24 (75.00%)	0.002	7 (21.88%)	17 (53.13%)	0.010
Abruption placenta	1 (3.13%)	0.00%	0.313	0.00%	1 (3.13%)	0.313
Thrombocytopenia	6 (18.75%)	1 (3.13%)	0.045	4 (12.50%)	1 (3.13%)	0.162
Prolonged labour	0.00%	0.00%	-	3 (9.38%)	1 (3.13%)	0.302
Prolonged second stage	9 (28.13%)	8 (25.00%)	0.777	5 (15.63%)	1 (3.13%)	0.086
Fetal macrosomia	5 (15.63%)	0.00%	0.020	-	-	-
Placenta previa	0.00%	1 (3.13%)	0.313	0.00%	3 (9.38%)	0.076
Multiple gestation	0.00%	1 (3.13%)	0.313	2 (6.25%)	0.00%	0.151
Hypertensive disorders of pregnancy	0.00%	1 (3.13%)	0.313	-	-	-
Deranged coagulation profile- COVID	1 (3.13%)	1 (3.13%)	1.000	-	-	-
Polyhydramnios	0.00%	0.00%	-	2 (6.25%)	0.00%	0.151
HELLP	1 (3.13%)	0.00%	0.313	-	-	-
Deranged coagulation profile	1 (3.13%)	0.00%	0.313	-	-	-
Beta-thalassemia	0.00%	1 (3.13%)	0.313	-	-	-
Second stage CS	-	-	-	3 (9.38%)	1 (3.13%)	0.302

Table 3: Blood loss parameters and medical management of PPH.

Characteristics	VD		P value	CS		P value
	Control	Case		Control	Case	
Quantified blood loss	934.37	369.35	<0.001	1356.25	603.12	<0.001
Drop in Hb	1.478	0.831	<0.001	1.918	0.86	<0.001
Incidence of PPH	28 (87.5%)	7 (21.87%)	<0.001	26 (81.25%)	18 (56.25%)	0.031
use of oxytocin	16 (50%)	1 (3.13%)	<0.001	11 (34.37%)	1 (3.13%)	0.001
use of methergine	10 (31.25%)	1 (3.13%)	0.003	10 (31.25%)	0.00%	0.0005
Use of carboprost	12 (37.5%)	2 (6.25%)	0.0024	8 (25%)	0.00%	0.002
Use of repeated TXA	0.00%	2 (6.25%)	0.1509	0.00%	6 (18.75%)	0.01
Need for parenteral iron	7 (21.87%)	4 (12.5%)	0.320	7 (21.87%)	3 (9.37%)	0.168
Need for blood transfusion	3 (9.37%)	1 (3.13%)	0.302	3 (9.37%)	2 (6.25%)	0.641
Hospital stay	4.78	3.25	0.004	4.88	4.78	0.849

Demographic factors like age, type of population, and parameters like gestational age at estimation of haemoglobin and delivery, prepartum haemoglobin and haematocrit were comparable among all groups. While the percentage of second gravida were higher among CS group while primigravida predominated the VD group were comparable in both cases and intervention groups, as depicted in Table 1.

Predisposing factors for PPH among, were studied among the patients. Anemia was the leading cause of PPH irrespective of mode of delivery. Among the VD group, anemia, thrombocytopenia and fetal macrosomia were the significant causes of PPH, while previous CS and anemia were the significant cause of PPH among the CS group, which were statistically significant, other factors are listed in Table 2, though not significant.

The post-partum parameters, such as blood loss, drop in haemoglobin, incidence of PPH, and use of additional uterotonics, like oxytocin, methergine and carboprost were statistically significant in both vaginal delivery and cesarean section groups. Hospital Stay was comparable among CS group, but significant in the VD group, 4 to 5 days in controls as compared to 3 days in intervention group.

Parameters like need for repeated tranexamic acid, parenteral iron therapy and blood transfusions were not statistically not significant though they were elevated in controls as compared to intervention group, as seen in Table 3.

Table 4: Surgical management of PPH.

Surgical intervention	Controls	Cases	P value
Uterine artery ligation	3 (4.68%)	1 (1.56%)	0.309
Compression sutures	2 (3.12%)	1 (1.56%)	0.559

Since the study population were predisposed to PPH, the need for surgical management was also warranted in certain cases. The need for surgical management of PPH such as uterine artery embolization and compression sutures predominated in the LSCS group, but not statistically significant, as illustrated in Table 4.

DISCUSSION

Hemorrhage, is a leading cause of mortality, accounting for nearly quarter of maternal death globally, in low-income countries and 17.7% in developed countries.[6] Majority of these death occur within 24hours of the delivery, most of which are preventable. AMTSL, set of guidelines was first introduced in 2003, as a response to PPH which was the leading cause of maternal mortality in Ghana, and worldwide in 2003, later modified in 2012 by WHO, adapted worldwide currently.[7] It was reported that about 14 million women experience PPH annually, which roughly translates to 70,000 maternal death globally.[8] Most of these women reside in Low-income or the developing countries. It is also noted that PPH contributes significantly to hospital stay and cost of hospital care especially in Low and middle-income countries (LMICs).[9] Thus mandating us to step up our defences against PPH.[10]

Although over the years, MMR has significantly come down, nevertheless prevention holds the key to tackle PPH. While both medical and surgical management of PPH are well studied and practiced. Moreover, risk factors for PPH are also well documented, hence we should aim interventions at modifiable risk factors and improve them antenatally. Anaemia, being the major pre-disposing factor for PPH, irrespective of the mode of delivery, to be tackled throughout the pregnancy, delivery, and puerperium.

TXA is a synthetic lysine analogue, first constituted in 1962 by Japanese researchers Utako Okamoto and Shosuke.[7] TXA can inhibit the plasmin activated platelets and hence hemorrhage.[11] According to summary of product characteristics (SmPC) as given by European Medical Agency, TXA can be administered by oral, intravenous, and topical routes with a maximum dosage of 3-4.5 grams/day.[12] In a Cochrane review, the use of TXA lowered the risk of PPH, In women who were given TXA 0.5 or 1gm intravenously after AMTSL post the delivery, irrespective of mode of delivery. The patients seldom had blood loss greater than 400-500 ml. Moreover, it is known

to be chemically stable for 12 weeks when stored in temperature ranging from -20ºC to 50ºC, with convenient shelf life of 3 years. It can be conveniently stored at room temperature, easily available and can be administered by medical personnel even in the peripheral health centres.[1]

Blood loss quantification is both complex and of utmost importance. The blood loss during third stage of labour should be effectively quantified, so that the birth attendant can take necessary steps to curb the hemorrhage and improve the maternal outcome, different methods of estimating blood loss: i) visual estimation- birth attendant estimates the blood by visual inspection, ii) indirect method- the patient is placed on a shallow bedpan, which collects in the blood from the genital tract following delivery, along with the mops and gauze which have soaked in blood, during and following delivery, iii) direct method- a calibrated drape is tied to the waist of the patient, and it hangs between the legs, which will collect the blood lost, iv) novel methods like, dye dilution, radioactive techniques and formula based calculations.[13,14]

In our study we have combined multiple methods to avoid, misinterpretation of PPH.

Methods used were VEBL along with preweighted mops, suction and drop in hematocrit. Similar methods were used by Gungorduk et al in their studies in 2011 and 2013, and by Loïc Sentilhes et al in 2018.[16,17]

Since our study population were at risk of PPH, blood loss, incidence of PPH, need for interventions and hospital stay were notably high.

The blood loss quantified among cases delivering vaginally; 370 ml in our study, which is markedly high as compared to 243 ml and 260 ml in studies by Gungorduk et al, and Sentilhes et al, respectively.[17,18] Among those delivering by Cesarean section; blood loss of 603 ml was noted in our study, starkly high as compared to 499 ml in study by Gungorduk et al.[16]

Incidence of PPH was significantly high 80% among controls and 50% among the cases as compared to 6.8% and 1.8% in study by Gungorduk et al, 2013 and, 9.8% and 8.1% in study by Sentilhes et al.[17,18]

Need for additional uterotonics was significantly high among controls 40.1% as compared to 6.8% in cases, comparable results were noted by Ducloy-Bouthors, 48% in controls as compared to 43% among cases and Roy, 22% in controls as compared to 2%.[15,19]

Adverse reactions to TXA were not seen our study, however, there are documented adverse reactions like thromboembolic events, gastrointestinal disturbances, most of these are attributed to progesterone. Although drug interactions of TXA with Uterotonics are not studied, which remains an uncharted territory.[20]

Strengths of this study were the study employed multiple ways of blood loss estimation, to precisely quantify blood loss and to determine incidence of PPH. Since the population included in the study was at risk of PPH, we could also extend comparison of need for surgical management of PPH.

There were some limitations also. This was a single-centre study with small study group. We need further multi-centric studies with larger sample size to evaluate drug interactions and adverse reactions. Follow up period in this study was limited to 48 hours, but it is an undeniable fact that adverse reactions can take place as late as 6 months.

CONCLUSION

PPH is major burden among the patients delivering either by VD or CS, its incidence increases in the presence of risk factors. Prophylactic intravenous TXA in women pre-disposed to PPH along with AMTSL appeared to have significantly reduce the blood loss during delivery.

Drop in haemoglobin is a better indicator of PPH rather than VEBL and indirect method of blood quantification combined.

By effectively supporting the childbirth process, the incidence of PPH and its adverse outcomes may be prevented. Moreover, prevention of PPH is one of the steppingstones to third sustainable development goal (SDG3), ‘to reduce the global maternal mortality ratio to less than 70 per 1,00,000 live births by 2030’.

Hence, we should streamline measures to minimise hemorrhage during and after childbirth, which may be spearheaded by tranexamic acid, which has minimal complications and contraindications.

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