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A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROL TRIAL TO ASSESS WHETHER TRANEXAMIC ACID AS PROPHYLAXIS LOWERS THE RISK OF PPH IN WOMEN DELIVERING VAGINALLY

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ABSTRACT **Aim –** To assess whether tranexamic acid as prophylaxis lowers the risk of PPH in women delivering vaginally. **Objective –** To compare the amount of blood loss, incidence of PPH, need for blood transfusion and proportion of women requiring other oxytocics or emergency surgery for PPH in both the groups. **Background –** Maternal mortality is an indicator of women's health. Primary cause of maternal death is PPH. The phrase "Prevention is better than cure" stands most appropriate in context of PPH. It is a preventable condition, hence early timely intervention can prevent development of such dreadful condition. One such intervention is Active management of third stage of labor. It includes administration of uterotonic (preferably oxytocin) soon after delivery of baby, controlled cord traction and uterine massage after delivery of placenta.Use of an anti-fibrinolytic drug (like tranexamic acid) along with uterotonic creats an add-on effect in reduction of blood loss after delivery. **Method –** It is a randomized,double blind placebo control trial carried out from February 2023 to March 2024. Total 92 antenatal women with term pregnancy are included in this study and blood loss is assessed via V-drape. **Result –** According to this study there is significant decrease in the amount of blood loss and fall in Hemoglobin in study group as compared to control group. **Conclusion –** Present study recommends the use of tranexamic acid with oxytocin for AMTSL as it leads to significant reduction in blood loss during labor and hence reduces the risk of PPH.

KEYWORDS : PPH, Tranexamic acid

INTRODUCTION

Postpartum hemorrhage (PPH) is a nightmare even to the present day obstetricians, as it is sudden, often unpredictable and the consequences may be catastrophic. PPH is the most common cause of maternal death, accounting for about 35% of all maternal deaths worldwide. The incidence of PPH is 2%–4% after vaginal delivery and 6% after a cesarean section [1]. As per the Sample Registration System (SRS) report by Registrar General of India (RGI) for the last three years, Maternal Mortality Ratio (MMR) of India is 97 per 100,000 in 2018–20 [2]. PPH is not only responsible for maternal mortality but also causes morbidity known as Severe Acute Maternal Morbidity (SAMM) [3]. Uterine atony is the most common cause of PPH (80%)[1]. Other causes include genital tract trauma, retained placental tissue or maternal coagulation disorders. PPH is a preventable condition and early, timely intervention can prevent development of this deadly condition. One such intervention that is highly recommended is active management of third stage of labour. AMTSL is a preventive measure and when practiced routinely, can reduce hemorrhage by up to 60% [12]. Main component of AMTSL is administration of a prophylactic uterotonic (Oxytocin 10 IU im) after the delivery of a baby. WHO recommends AMTSL, in all pregnant females for prevention of PPH. Oxytocin is a gold standard drug for prevention and treatment of PPH [4]. It is a uterotonic which acts on the uterine muscles and is effective in preventing atonic PPH. Sometimes there is associated traumatic PPH also which is not taken care by oxytocin alone. Besides, uterus is a very vascular organ which bleeds tremendously from its sinuses if the three components of myotamponade, thrombosis or living ligature are anywhere faulty. Tranexamic acid is a synthetic analogue of lysine and acts by blocking lysine binding sites on plasminogen molecules, which prevents conversion of plasminogen to plasmin, thereby inhibits fibrinolysis. Its efficacy and safety in reducing hemorrhage and lowering transfusion requirements have been well established in various elective surgeries [5-7]. Also, TA has been reported to reduce blood loss in gynecological diseases such as menorrhagia, hysterectomy, and myomectomy [8-10]. Recently, in 2020 a multicenter, double-blind RCT was conducted in which TA was given intravenously just after cesarean section, and it significantly reduced blood loss postpartum and risk of PPH [11]. Thus, the study was conducted to assess the efficacy of tranexamic acid with oxytocin as prophylaxis for PPH.

MATERIALS AND METHODS

It is a prospective Randomized, Double blind, Placebo control Trial conducted between March 2023 to February 2024 involving 92 pregnant women expected for normal vaginal delivery at term in the labour ward of Pt. J.N.M. Medical College and associated Dr. B.R. Ambedkar Memorial Hospital, Raipur, Chhattisgarh, India. All the participants, expected for normal vaginal delivery were randomized in two groups (Group A – Study group and Group B – Control group) in 1:1 ratio by simple random sampling. Each group will be having 46 cases. Detailed medical and obstetric history was taken. Vital parameters were checked and basic investigations were done. Detailed general and obstetric examination was done. All the patients were counseled well and informed consent was obtained. The study group (Group A) received inj. Tranexamic acid 1 gm (10 ml) slowly intravenously over 3 min after delivery of baby with prophylactic inj. Oxytocin 10 IU intramuscularly during third stage of labour, while control group (Group B) received 10 ml normal saline as placebo along with prophylactic oxytocin. In order to conceal the medicine allocation and to maintain double-blinding, pre-prepared 10 ml syringes are kept in two boxes labeled as box-A and box-B, containing 1gm TA and NS respectively. These syringes are prepared by a nursing staff in the delivery room who had no involvement in any aspect of the study. In this way both the investigator and the patient, are unaware about the trial medication.

Blood loss will be assessed in all cases by using calibrated V – drape. This drape was kept pre-prepared in the delivery room by using plastic apron supplied in disposable delivery kit. The lower edge of the plastic apron is sealed using a tape, converting it into a cone which is then calibrated using a scale which has already been standardized and marked denoting different volumes at various measurements on it. The calibrations are done every 50ml starting from 50 ml up to 500 ml and then at 1L. The drape was placed under the buttocks of the women after the delivery of baby, after clamping and cutting the cord till 1 hour post delivery. The belt of the plastic apron was tied in front of her abdomen firmly to avoid slipping of drape and to prevent spillage of blood, which ensures siphoning of all the blood into the cone for direct assessment of blood loss. The collected blood was then transferred to calibrated flask to get the exact measurement up to 10 ml.

Inclusion Criteria

- All antenatal females of age > 18 years with > 37 weeks of gestation with singleton pregnancy in labour.

Exclusion Criteria

- Women with any risk factor of PPH ie. anemia, multiple gestation, antepartum hemorrhage
- Women already in DIC, history of thromboembolism or arterial thrombosis

- Severe anemia (Hb <7 gm%)
- Known case of coagulopathy
- Active Liver disease
- Antepartum hemorrhage
- Seizure disorder (including eclampsia)
- Cases of morbidly adherent placenta
- Cases of obstructed labor, prolonged labor
- Allergy to Tranexamic acid

Primary outcomes include blood loss after delivery, need for additional uterotonics, need for blood transfusion, need for surgical methods for management of PPH.

Secondary outcome includes hemoglobin levels 24 hours after delivery, hemodynamic instability within 24 hours of delivery (BP, Pulse rate, Urine output, Respiratory rate), adverse drug effect including fever, chills, severe throbbing headache, stomach pain or discomfort, nausea, vomiting, diarrhoea, hypotension, dizziness, muscle pain or stiffness, runny or stuffy nose.

RESULT

Total 92 antenatal women were randomized equally into study and control groups (46 participants in each group). Both the groups were comparable regarding socio-demographic characteristics. The majority of the participants in this study belong to age group 21 – 30 years (mean age 24.80 & 25.33 years in study & control group respectively). 52.2% patients in study group & 56.5% in control group were primigravida. 33 patients in study group and 35 patients in control group were having gestational age >/= 37 weeks, but < 40 weeks (mean gestational age of 39.12 weeks in study group & 39.22 weeks in control group). 81.5% participants were from rural region. Out of total patients, only 13% were booked.

Table-1: Socio-demographic profile

CHARACTERISTICS	GROUP – A STUDY GROUP (n = 46)	GROUP – B CONTROL GROUP (n = 46)	P VALUE
Mean age (years)	24.80	25.33	0.973
Parity			
• **Primi**	52.2 %	56.5 %	0.675
• **Multi**	47.8 %	43.5 %	
Mean gestational age (weeks)	39.12	39.22	0.671
Region			
• **Rural**	80.4 %	82.6 %	0.788
• **Urban**	19.6 %	17.4 %	
Booking status			
• **Booked**	15.2 %	10.9 %	0.536
• **Unbooked**	84.8 %	89.1 %	
Occupation			
• **Employed**	6.52 %	10.9 %	0.459
• **Unemployed**	93.5 %	89.1 %	
Socioeconomic status			
• **Low**	89.1 %	97.8 %	0.091
• **Middle**	10.9 %	2.2 %	

In this study, 21.7% patients in study group and 13% patients in control group had induction of labour. As Tranexamic acid is an anti-fibrinolytic agent and has no role on uterine contractility, no significant difference was observed in duration of labour between both the groups. Total 72.3% patients in study group & 86.9% patients in control group received episiotomy. Mean birth weight of babies delivered was 2.66 kg in study group & 2.80 kg in control group.

Table-2: Obstetric characteristics

CHARACTERISTICS	GROUP – A STUDY GROUP (n = 46)	GROUP – B CONTROL GROUP (n = 46)	P VALUE
Onset of labour			
• **Induced**	21.7 %	13.0 %	0.271
• **Spontaneous**	78.2 %	86.9 %	
Duration of labour (min)			
• **1st stage**	854.35	908.70	0.141
• **2nd stage**	46.72	47.28	0.637
• **3rd stage**	5.11	4.96	0.412
Total duration (min)	906.17	1014.72	0.140
Episiotomy			
• **Yes**	72.3 %	86.9 %	0.271
• **No**	21.7 %	13.0 %	
Mean birth weight of baby (kg)	2.66	2.80	0.137

The mean blood loss in study group was 63.04 ml, while in control group it was 178.04 ml. Tranexamic acid when given prophylactically causes significant reduction in post-partum blood loss. Also none of the patients landed in PPH (i.e. blood loss > 500 ml), which indicates that Inj. Oxytocin given during AMTSL is itself very much effective in reducing the risk of PPH. The maximum blood loss observed was 300 ml in control group. As none of the patients observed blood loss of > 500 ml, there was no need for additional uterotonics to be given in both the groups.

Table-3: Primary Outcomes

PARAMETERS	GROUP – A STUDY GROUP (n = 46)	GROUP – B CONTROL GROUP (n = 46)	P VALUE
Mean blood loss (ml)	63.04	178.04	**< 0.001**
Requirement of iv iron sucrose			
• **Yes**	2.2 %	26.1 %	**< 0.001**
• **No**	97.8 %	73.9 %	

The mean fall in hemoglobin level in study group was 0.4 gm/dl, while in control group it was 1.56 gm/dl. The study observed significantly less fall in hemoglobin levels 24 hours post delivery (p-value <0.001). No significant side effect was seen in women who received Tranexamic acid. Only 1 patient in study group complained of nausea and vomiting, while none of the patients observed major side effects of Tranexamic acid like thromboembolic complications (eg. Pulmonary embolism, DVT, Myocardial infarction, CVA), anaphylactic reactions or seizures.

Table-4: Secondary Outcomes

PARAMETERS	GROUP – A STUDY GROUP (n = 46)	GROUP – B CONTROL GROUP (n = 46)	P VALUE
Mean hemoglobin level (gm/dl)			
• **Pre-delivery**	10.07	10.43	0.282
• **24 hours after delivery**	9.67	8.87	
Mean fall in hemoglobin (gm/dl)	0.40	1.56	**< 0.001**
Side effects			
• **Yes**	2.17 %	00	0.315
• **No**	97.8 %	100 %	

DISCUSSION

Present study was aimed to study the efficacy of tranexamic acid - an antifibrinolytic agent in the primary prevention of PPH - the major but preventable cause of maternal mortality. The pathophysiology of PPH involves both mechanical and clotting mechanisms. For mechanical mechanism, prophylactic oxytocin administration within 1 minute of childbirth during AMTSL is practiced routinely all over the world. [12,13] Using prohemostatic drug like Tranexamic acid, can provide biochemical hemostatic effect. Before choosing the drug for adjunction, it was found that for several decades, Tranexamic acid has been used to reduce surgical bleeding in patients undergoing various types of surgeries including orthopedic, cardiac, cranial, hepatic, ENT and gynaecological operations. Also, the Clinical Randomization of an Anti-fibrinolytic in Significant Hemorrhage (CRASH-2) trial had demonstrated that, trenaxamic acid reduces mortality in bleeding trauma patients. Also, there is significant reduction in mean menstrual blood loss have been reported in menorrhagic women when treated with Trenaxamic acid. [13,14]

In this study both study and control group were comparable regarding socio-demographic characteristics, obstetric characteristics, episiotomy status and expected fetal weight. As Tranexamic acid has no effect on contractile mechanism of uterus, thus no significant effect was observed on duration of 3rd stage of labour.

Our study documented significantly lesser blood loss in women of study group (63.04 ml) as compared to control group (178.04 ml), which might be life saving in women who are already anaemic, where every drop of blood matters. Also none of the patients had blood loss of >500 ml, i.e. none of the patient had PPH, which shows that AMTSL itself is a very efficient in preventing PPH. So, there was no need of additional uterotonic drugs (eg. Misoprostol, methylergometrine, carboprost) in any of the patients. Requirement of intravenous iron sucrose transfusion was also significantly less in study group (2.2%) as compared to control group (26.1%).

The mean fall in hemoglobin levels was significantly less in study group (0.40 gm/dl) as compared to control group (1.56 gm/dl).

There was no significant major or minor side effect observed in women who received Tranexamic acid, except for 1 patient who had nausea and vomiting.

CONCLUSION

PPH is the leading cause of maternal mortality and morbidity. Treatment of PPH relies mainly on uterotonics. But in a developing country like India, where large number of females are already anaemic, even small amount of blood loss during delivery can predispose a female for PPH. Hence, adequate measures are required to prevent even minimal amount of blood loss, so as to decrease the risk of PPH in both high and low risk cases.

In present study, we practiced standard AMTSL guidelines for all women and it was observed that none of the woman landed in PPH (i.e. had blood loss of >500 ml), which proves that AMTSL itself is very effective management for prevention of PPH. This study observed significant reduction in postpartum blood loss in all females of study group. Also TXA is not having any drug interaction with oxytocin observed so far and no significant side effect was observed in other studies till now.

Hence, present study strongly recommends the prophylactic use of Inj. Tranexamic acid during active management of 3rd stage of labour in all females and specially in females of higher age, who deliver at gestational age >40 weeks and in women who deliver bigger babies to prevent the excessive blood loss during delivery to reduce the risk of development of PPH, without any additional side effect.

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