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Comparative study between uterotonics and tranexamic acid for the treatment of postpartum hemorrhage

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Abstract
Postpartum haemorrhage (PPH) is a major cause of maternal mortality, accounting for one-quarter of all maternal deaths worldwide. Uterotonics after birth are the only medical intervention that has been shown to be effective for PPH prevention and management. Tranexamic acid (TXA), an antifibrinolytic agent, has been investigated as a potentially useful complement to this for both prevention and treatment because its hypothesized mechanism of action in PPH supplements that of uterotonics and because it has been proved to reduce blood loss in normal delivery and caesarean section. This is a prospective observational study done during Dec 2018 to Dec 2020. 200 pregnant women who were booked in this hospital and delivered vaginally and clinically diagnosed with postpartum hemorrhage were taken for the study. 100 patients received standard protocol with placebo and 100 received standard protocol with Tranexamic acid 1 gm iv. Mean blood loss was 750 ml +/- 100 ml in standard protocol, whereas in Tranexamic acid it was 650ml +/- 100 ml. 2 patients required surgical intervention in standard protocol group, whereas no patients required surgical intervention in Tranexamic acid group. TXA is not a new drug and is generally well tolerated without any thrombogenic side effects.

Keywords: Postpartum Hemorrhage [PPH] Tranexamic acid Uterotonics Blood loss vaginal delivery

Introduction
Post-Partum Haemorrhage is commonly defined as blood loss more than or equal to 500 ml after vaginal delivery or more than or equal to 1000ml after caesarean section[1].However these thresholds do not take into account pre-existing health status, and blood loss of as little as 200ml can be life threatening for a woman with severe anaemia or cardiac disease.
Primary Postpartum Haemorrhage (PPH) is classically defined as blood loss of > or equal to 500ml in the first 24 hours after delivery. Prevalence estimates for PPH in the literature vary widely from 3-15% of deliveries. PPH remains a leading cause of maternal death accounting for about 3lakhs to 4lakhs death every year [2]. PPH is poorly predictable, but its direct causes are uterine atony, trauma to genital tract and retained placenta. Some guidelines have been issued for optimal use of obstetric intervention and uterotonic drugs [3]. In contrast haemostatic abnormalities in this setting have long been considered consequences of uncontrolled bleeding, not deserving early specific treatment thus haemostatic drugs are not routinely used as first line treatment in PPH [3].

Tranexamic acid and its effects on bleeding
In the haemostatic process, coagulation occurs rapidly at the site of a damaged vessel building a tight net of fibrin while, the fibrinolytic system removes the fibrin deposits that could cause permanent vascular occlusion once vascular repair has taken place[4]. The coagulation and fibrinolytic system are believed to be in a state of dynamic balance which maintains an intact vascular system. Tranexamic acid is a potent antifibrinolytic agent that exerts its effect by blocking lysine binding sites on plasminogen molecules and has the potential to enhance the effectiveness of the patient's own haemostatic mechanism. Consequently, clot break down (fibrinolysis) is inhibited and excessive or recurrent bleeding is reduced. As TXA inhibits the breakdown of fibrin deposits already formed, it might theoretically increase the risk of thromboembolism. During delivery, when the placenta separates from the uterine wall, a sequence of physiologic and hemostatic changes occur that reduce bleeding, increase myometrial contraction, increase platelet activity, release of massive coagulant factors and a parallel increase in the fibrinolytic activity [5].

As a result, there is theoretical rationale for the use of antifibrinolytic agents in the treatment of PPH [6].

Methods

This is a prospective observational study done during Dec 2018 to Dec 2020. 200 pregnant women who were booked in this hospital and delivered vaginally and clinically diagnosed with postpartum hemorrhage were taken for the study. 100 patients received standard protocol with placebo and 100 received standard protocol with Tranexamic acid 1 gm IV.

Diagnosis of PPH was made by the following clinical observation

1. Estimated blood loss after delivery >500 ml
2. Estimated blood loss which compromise the haemodynamic status of the mother

Inclusion criteria

1. Singleton pregnancy
2. Term gestation

Exclusion criteria

1. Multiple pregnancy
2. History of previous thrombo-embolic events
3. Intrauterine fetal demise
4. Medical and surgical complications involving systems like cardiac, liver/kidney/blood disorders
5. Anaemic patients (<7g/dl), severe anaemia
6. Previous PPH

The blood loss following delivery was calculated using BRASS V DRAPE.

The study was divided into 2 groups

Group 1: Control group 100 cases

Group 2: Study group 100 cases

Control Group

Standard protocol for the treatment of PPH (Oxytocin, Ergometrine, Prostaglandins) along with placebo (normal saline 10 ml) was given after the diagnosis of PPH

Study Group

Standard protocol for the study of PPH along with Tranexamic acid 1 gm IV.

Results

Table 1: Age Distribution

Age in years	Group-a control	Group B –Tranexamic Acid
19-24	60	58
26-30	24	26
31-35	16	16
36-40	0	0

The mean age of the patients in both group was between 19-25 years

Table 2: Parity Wise Distribution

Parity	Group A Control	Group B Tranexamic Acid
PRIMI	40	36
Multi	60	64
Total	100	100

Two groups are comparable with regards to parity distribution multigravidas were more in the study

Table 3: Type of Delivery

Type of delivery	Group A-control	Group B –Tranexamic acid
FTND	93	90
VBAC	07	10
TOTAL	100	100

Two groups are comparable with respect to delivery. P value is significant ($p< 0.0001$). As there is significant difference in FTND and VBAC.

Table 4: Blood Loss

Blood loss (ml)	Group A-control	Group B Tranexamic acid
500-600	06	12
600-700	20	70
700-800	60	12
800-900	10	04
900-1000	04	02
>1000	00	00
TOTAL	100	100

Mean blood loss in the control group was 750 ml +/- 100ml while that in study group was 650ml +/- 100ml. the difference between the two groups was significantly high and hence it was statistically significant ($p< 0.0001$)

Table 5: Need for Surgical Intervention or Hysterectomy

Group	Surgical intervention or hysterectomy
A Control	02
B Tranexamic Acid	Nil

In the control group two patient required surgical intervention

Table 6: Side Effects

Group	Thrombogenic S/E On Mother Or Baby
A- Control	Nil
B- Tranexamic Acid	Nil

Both the groups showed no side effects

Discussion

Tranexamic acid is a potent antifibrinolytic drug. The main action of Tranexamic acid is blocking of the lysine binding sites of the plasminogen molecule, which are of importance for the binding to fibrin. This prevents activation of plasminogen by plasminogen activator, also absorbed to fibrin. It can be given orally or intravenously. it enters tissues and fluids in various concentrations and crosses the placenta.

During placental delivery, fibrinogen and fibrin are rapidly degraded whereas plasminogen activators and FDP increase due to activation of fibrinolytic system. This activation will last upto 6-8 hour's post-partum, causing bleeding. It was because of this activation of fibrinolytic system we have used Tranexamic acid in our study.

Our study compares standard protocol with placebo and standard protocol with Tranexamic acid in PPH.

The mean age in the present study in both group was between 19-24 years. Similar study carried out by Ming-ying Gai etal (2004) [7] had mean age group of 29 years.

In our study, majority of the people were multigravidas in both the study groups.

40 in the control group and 36 in the study group were

primiparous. Similar done by Yang H *et al*. [8] had 87 primiparous in the control and 94 primiparous in the Tranexamic acid group. study done by Anne-Sophie D [9] had 50 primiparous in the control group and 46 in Tranexamic acid group and 12 multiparas in control group 16 multiparas in Tranexamic acid in the present study, out of 100 patients in each group, 93 and 90 patients had FTND in control and Tranexamic acid group respectively.

In the present study the mean blood loss was 750 +/- 100 ml in control group and 650 +/- 100 ml in study group. The difference between two groups is statistically significant (P value <0.0001). Similar study carried out by Ming-ying Gai, Liang-fang Wu, Qi-feng Su, Karin Tatsumoto [10] (2004) showed that Tranexamic acid significantly reduces bleeding.

In the present study, 2 patients required surgical intervention in the control group.

Study done by Anne-Sophie Ducloy-Bouthors *et al*. at France [11] (2011) surgical intervention was done for 2 women in control group.

Conclusion

Tranexamic acid significantly reduces bleeding in post-partum haemorrhage. TXA is not a new drug and is generally well tolerated without any thrombogenic side effects. This data strongly supports the need for double blind study to investigate the potential effects of Tranexamic acid to reduce incidence of PPH and related maternal morbidity and mortality.

Conflict of interest: The authors declare that there is no conflict of interest.

Acknowledgment

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