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PILOT STUDY OF TRANEXAMIC ACID IN CASES OF PPH IN BANARAS HINDU UNIVERSITY

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Abstract

Aims and Objectives: *To rationalize the use of Tranexamic Acid in postpartum haemorrhage through prospective randomised trial. To know the mechanistic aspect of Tranexamic Acid in PPH and mechanism of action of Tranexamic Acid in myometrium as the experimental part of the study.*

It is due to this hypothesis (myometrial action of TXA) we are looking at the mechanistic aspect of TXA in cases of PPH. PPH is best controlled by uterine contraction, coagulation has a little role to play. Then the postulated hypothesis is TXA effective in PPH due to it's action on the myometrium due to some inflammatory mediators or action on the receptors (direct/indirect)? If it acts on the myometrium then it is a drug of choice for PPH.

Methods: *We decided to a do a pilot study in both the clinical arm and experimental arm till we got the support from ICMR. In the study group of clinical arm (case group) 1gram (10ml) of Tranexamic Acid was given slowly intravenously over 5 minutes (30 minutes before the LSCS).In the control group Oxytocin bolus and Oxytocin infusion was administered but TXA was not given, 10ml of Normal Saline will be injected instead. The quantity of blood loss (ml) was estimated. Haemoglobin was estimated before the operation and 48hrs after the Caesarean section.*

Results: *In this pilot study a total of 25 patients were included. The age range of the participants was 22-29 years. 13 pregnant mothers were primigravida and 12 were multigravida. The estimated blood loss was approximately 350ml in the maximum range among 25 patients (abdominal swabs 211 ml + suction apparatus 139 ml). This is far below the allowed blood loss in Caesarean section (1000 ml). Only two patients (2/25) needed administration of Prostaglandin F2 alpha to achieve haemostasis. Duration of surgery was between 45 minutes-60 minutes with no major complications. Postoperative Haemoglobin estimation was not below 10 grams in any of the patients. In these preliminary experiments we were able to record the uterine contractions in these non-pregnant human uterine tissues. We observed spontaneous uterine contractions with a frequency of 0.3 to 0.5/min and developed force in the range of 10-50 mg/g tissue (mean = 25 ± 5.8 mg/g). We aim to record stimulated and unstipulated pregnant myometrial contractions in the same way.*

Conclusions: *Obstetric haemorrhage is a dire emergency which challenges almost every Obstetrician. There are constant efforts to manage it better by developing newer Medical, Surgical or Radiological methods. Existing drugs (Oxytocin, Methyl Ergometrine, Prostaglandin and Misoprostol are quite effective but they have their side-effects/cost/storage requirements/half-life. There are situations when PPH does not respond to any medication. Preliminary clinical study shows encouraging results of role of TXA in Postpartum haemorrhage. The estimated blood loss is relatively low and Haemoglobin level are also within reasonable limit. Once funded, we will complete the study with larger sample size and will have better data to formulate a guideline which will help community at a large.*

Keywords: *Postpartum Haemorrhage, Tranexamic Acid, Lower segment caesarean section, Acetylcholine, Prostaglandin and Oxytocin*

Introduction: The rate of maternal mortality is still very high [1]. Nearly 530,000 women die each year due to complications of child bearing and childbirth. 99% of these deaths are in low and middle income countries. The target India was supposed to achieve for MDG (Millennium Development Goals) by 2015, we have to achieve it yet. India, the country with second

largest population on the planet at 1.2 billion, accounts for an estimated 68,000 maternal deaths per year.[2] The high rate of maternal mortality in India are not evenly spread across the country with Uttar Pradesh (360) reporting the second maximum number of deaths (after Assam 390) and Kerala the least 81. Moreover, in India one woman dies of complications related to childbirth every seven minutes. MMR varies in East and West UP as well: Jhansi Mandal (241): FaizabadMandal (451). MMR in 2005 was 1992, with a gradual reduction to 230 in 2008, the target for 2015 is 109/100,000 live births. MMR has declined to 212 in 2007-2009 (Sample registration system). Leading causes of maternal deaths in India are Haemorrhage 37%, Sepsis 11%, Complications of Abortion 8%, Hypertensive disorder 5% and Obstructed Labour 5%. Hemorrhage, which usually occurs in the postpartum period, is responsible for approximately one third of maternal deaths. [3,4,5]Postpartum Haemorrhage is one of the leading causes of maternal mortality in our country. There are plenty of medications available along with surgical methods to control PPH. In spite of that there is heavy proportion of maternal mortality due to PPH in India.

In developing countries most of the pregnant women start pregnancy on low reserve of Iron and with lower levels of Haemoglobin compared to the women in developed world. It is because of this reason that these women suffer greater cardiovascular compromise. Therefore even a lesser amount of blood loss in anaemic women should be taken seriously.

In low resource countries deaths not only occur in hospital but also at home, as good proportion of pregnant women are unable to access the hospital services. Postpartum haemorrhage is a major killer among parturient women even if properly managed due to gravity of the situation.

Blood borne infection can occur in women who receive blood transfusion in spite of the fact that blood is thoroughly screened for viral infection. [6]The chance of that happening is higher in developing world as the screening procedures may not be that stringent. Therefore it should be our utmost effort to avoid blood transfusion by getting effective control of PPH.

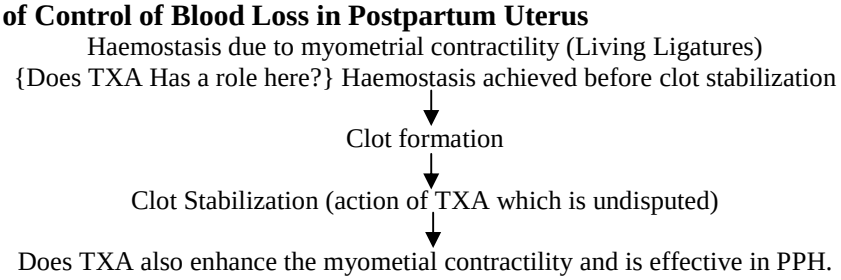
Postpartum Haemorrhage (PPH) is commonly defined as a blood loss of 500ml or more within 24 hours after normal birth, while in case of Caesarean section it is 1000ml. Postpartum Haemorrhage (37%) is one of the leading causes of maternal mortality in our country. There are plenty of medications available along with surgical methods to control PPH. In spite of that there is heavy proportion of maternal mortality due to PPH in India.

Tranexamic Acid (TXA) is an antifibrinolytic agent which is readily used for control of haemorrhage in surgical, gynaecological and traumatic bleeding. [7,8,9,10]Postpartum haemorrhage (PPH) is controlled not only due to coagulation factors but also due to contraction of uterine muscles, in fact the major contribution is due to uterine muscle contraction. It was our intention to know whether Tranexamic acid is actually useful in patients of postpartum haemorrhage? We are planning to do both clinical and experimental study.

The clinical study was done as a part of pilot project and while we are waiting to start the full project. TXA was administered before the lower segment caesarean section and its effect was observed.

In the experimental arm we will be looking at the mechanistic aspect of TXA in cases of PPH. PPH is best controlled by uterine contraction, coagulation has a little role to play. Then the postulated hypothesis is that TXA effective in PPH due to it's action on the myometrium due to some inflammatory mediators or action on the receptors (Oxytocin, Acetylcholine or Prostaglandin; direct/indirect action)? If the study confirms that it acts on the myometrium (through receptors or through inflammatory mediators) then it would become the drug of choice for PPH, because it is very cheap, needs no refrigeration and readily available in the developing countries.

Natural Steps of Control of Blood Loss in Postpartum Uterus



Aims & Objectives: To rationalize the use of Tranexamic Acid in postpartum haemorrhage through prospective randomised trial in 250 patients and 250 control subjects in the clinical arm. To know the mechanistic aspect of Tranexamic Acid in PPH and mechanism of action of Tranexamic Acid in myometrium as the experimental part of the study.But as a part of preliminary work we decided to a do a pilot project in the clinical arm and laboratory work.

- Rationalize the use of Tranexamic Acid in postpartum haemorrhage through prospective randomised trial in 250 patients and 250 control subjects.
- Mechanistic aspect of Tranexamic Acid in PPH.
- Mechanism of action of Tranexamic Acid in myometrium as the experimental part of the study.

It is due to this hypothesis (myometrial action of TXA) we are looking at the mechanistic aspect of TXA in cases of PPH. PPH is best controlled by uterine contraction, coagulation has a little role to play. Then the postulated hypothesis is TXA effective in PPH due to it's action on the myometrium due to some inflammatory mediators or action on the receptors (direct/indirect)? If it acts on the myometrium then it is a drug of choice for PPH.

Methods

So far we have done the pilot study in the experimental arm and clinical arm. In the study group (case group) 1gram (10ml) of Tranexamic Acid was given slowly intravenously over 5 minutes (30 minutes before the LSCS). Once baby has delivered 5 units of bolus dosage of Oxytocin was given (routine management of third stage of labour was done). Mother's safety was not compromised at any stage of this study. If there was any bleeding or uterus was relaxed 20 units of Oxytocin is given as infusion (20 units in 500mls saline) over 4 hours.

In the control group Oxytocin bolus and Oxytocin infusion was administered but TXA was not given, 10ml of Normal Saline will be injected instead. If there was further bleeding Carboprost or Misoprostol or Methyl Ergometrine was given as per PPH protocol. Maternal safety was not to be compromised in any arm, only difference in the management was whether Tranexamic acid was given or not. Quantification of the blood loss was clinical as called EBL=estimated blood loss, which is the best we could do in our set up.

Very small myometrial segment (ONLY ~5mm×25mm) will be taken after the informed consent in both controls and cases (removal of such a small segment of uterine muscle segment will not affect future reproductive performance). It will be preserved in dry ice and send to the physiology lab, Institute of Medical Sciences, Banaras Hindu University. This myometrial segment will be observed for myometrial contraction (will be detailed below in the experimental arm of study).

It was done as per international obstetric standards. Patient's vitals were observed stringently. Pulse rate, respiratory rate and blood pressure were recorded before surgery, immediately after the operation and 1-2 hours after birth. Blood loss was measured following placental delivery to the end of surgery, and from the end of operation to 2 days after birth.

Estimation of blood loss: The quantity of blood loss (ml) = weight of the used materials –weight of materials prior to surgery (which would have been taken before sterilization) + Volume sucked in the suction bottle after placental delivery in ml. The mops, pads and linen was measured. The amniotic fluid will not be included in the measurement.

Swab weighing: It is a customary to practise that 1 ml. of blood weighs 1 G (so 500 Grams swab = 500 ml). The swabs must be weighed as soon as possible after contamination with blood so that the loss by evaporation is minimized. Furthermore there should be actual measurement of operative drapes as well. Preoperative weight should be actually known therefore actual weight increase can be calculated and so the estimated blood loss. This is the exact method we used.

Haemoglobin was estimated before the operation and 48hrs after the Caesarean section. The fall in the Haemoglobin was calculated and compared. Liver and renal function tests will also be done before operation and on the second post-operative day.Patients was carefully watched for postpartum haemorrhage in the postoperative period and was managed as per PPH protocol. Mothers were watched for any allergic or hypersensitivity reaction.

Inclusion criteria:	**Exclusion criteria:**
	Women with low platelet count
Age 20-35 years	Mothers with cardiac lesions
Booked pregnant mother	Mothers with renal pathology
Full term	H/o of thromboembolic disorder
Primigravida	Placenta Praevia
Singleton pregnancies	Women with coagulation factor abnormalities
Having regular antenatal check-ups	Severe pre-eclampsia
Delivered by LSCS	Twin pregnancy
	Macrosomia
	Polyhydramnios
	Severe Anaemia

Results

Institutional ethical clearance was obtained before the study took place. Informed consent was taken from all the patients. In this pilot study a total of 25 patients were included. Preoperative Haemoglobin was assessed. The Haemodynamic parameters were measured (eg pulse rate, blood pressure, respiratory rate & saturation index) during the operative procedure and after the operation.

The age range of the participants was 22-29 years. 13 pregnant mothers were primigravida and 12 were multigravida. The indications of Caesarean section are given in table 1. The estimated blood loss was approximately 350ml in the maximum range among 25 patients (abdominal swabs 211 ml + suctionapparatus 139 ml). This is far below the allowed blood loss in Caesarean section (1000 ml). Only two patients (2/25) needed administration of Prostaglandin F2 alpha to achieve haemostasis. Duration of surgery was between 45 minutes-60 minutes with no major complications.

Table 1: Indications of LSCS

Indications	Numbers
Malpresentation	10
Fetal distress	3
MSAF	2
Pelvic contraction	6
Failed progress	4

Postoperative Haemoglobin estimation was not below 10 grams in any of the patients. Two patients complained of nausea. There were no cases of deep venous thrombosis. Urine output remained with normal limits in all cases.

Experimental arm: so far, we have done some preliminary experiments by transporting the non-pregnant uterine samples to the Department of Physiology, Institute of Medical Sciences, Banaras Hindu University. Uterine muscle was transported in chilled Ringer Lactate similar to the study done earlier (Deshpande et al, Cholelithiatic Human Gallbladders). In these preliminary experiments we were able to record the uterine contractions in these non-pregnant human uterine tissues. We observed spontaneous uterine contractions with a frequency of 0.3 to 0.5/min and developed force in the range of 10-50 mg/g tissue (mean = 25 ± 5.8 mg/g). We aim to record stimulated and unstipulated pregnant myometrial contractions in the same way.

Discussion & Conclusions: Tranexamic Acid is systemically is used frequently to reduce or prevent blood loss in surgery or trauma cases. A systemic review of RCTs of antifibrinolytic agents in surgical patients identified 211 randomised controlled trials including 20,781 randomised participants. The results show that TXA reduces the risk of blood transfusion by a relative 39% (RR=0.61, 95%CI 0.54 to 0.69). TXA reduced total transfused blood volume by 1.1 units (95% CI 0.64 to 1.59). The re-exploration rate (due to internal haemorrhage) also reduced (RR=0.67, 95% CI 0.41 to 1.09). So far there has not been any reported case of thrombosis.Tranexamic acid is used in case of menorrhagia and is effective in reducing the blood loss up to 50% (proven by RCTs). [11,12,13]

TXA is 'recommended for consideration' as a treatment in intractable postpartum haemorrhage in the UK. Recently WHO guideline has also given it recommendation 'the use of Tranexamic Acid is recommended for the treatment of PPH if Oxytocin and other uterotonics fail to stop bleeding or if it is thought that the bleeding may partly due to trauma (based on moderate-quality evidence, weak recommendation). [14,15,16]There is little reliable evidence from the randomized trials on the effectiveness of Tranexamic Acid in the treatment of PPH. Three trials of the prophylactic use of TXA, including a total of 460 participants were identified but the quality of trial was poor. None had adequate allocation concealment and even in aggregate the trials were too small to assess the effect of TXA on the clinically important end points i.e. maternal mortality rate, hysterectomy rate and thromboembolic side-effects. There are many trials reported but they aren't conclusive.[17,18,19]

Tranexamic acid is approved by DGC (I) for intraoperative blood loss (www.cdsco.nic.in).

Obstetric haemorrhage is a dire emergency which challenges almost every Obstetrician. There are constant efforts to manage it better by developing newer Medical, Surgical or Radiological methods. Existing drugs (Oxytocin, Methyl Ergometrine, Prostaglandin and Misoprostol are quite effective but they have their side-effects/cost/storage requirements/half-life. There are situations when PPH does not respond to any medication.[20]

PPH results in maternal mortality in far and wide areas. It happens more so in the developing world as the facilities for blood and medicines are not readily available. Therefore, this study confirming the role of TXA in both arms will be a boon to the society. The pilot study approves the role of Tranexamic acid in PPH. To add further, TranexamicAcid has been advised to be used in cases of Obstetric Haemorrhage by WHO, but London School of Hygiene and Tropical Medicine is still doing the 'WOMAN' trial and the outcome is still awaited. [21]

Preliminary clinical study shows encouraging results of role of TXA in Postpartum haemorrhage. The estimated blood loss is relatively low and Haemoglobin level are also within reasonable limit. Once funded, we will complete the study with larger sample size and will have better data to formulate a guideline which will help community at a large.

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