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Original research article

A Double Blinded Randomised Clinical Trial to Compare the Effect of Intravenous Tranexamic Acid and Misoprostol for Postpartum Haemorrhage

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Abstract

Aim: Comparison effect of intravenous tranexamic acid and misoprostol for postpartum haemorrhage.

Methods: This double blinded randomised clinical trial study was done the Department of Obstetrics and Gynaecology, Hi-Tech Medical College, Rourkela, Odisha, India from February 2021 to November 2021. 80 women with PPH (500-1500 ml) diagnosis after caesarean or normal delivery, according to their haemorrhage level after usual therapies for controlling haemorrhage, after getting consent were included in the study. They were divided into two equal intervention and control groups randomly. Patients in group A were treated with intravenous TXA and patients in group B with rectal Misoprostol. Intervention group (group A) which were receiving intravenous TXA (1gr) and if there was relieve in haemorrhage, next TXA dose was repeated after 30 minutes and in patients of control group (group B) after usual therapies, 5 rectal 200 micrograms Misoprostol pills were used. The bladder was emptied before therapy in both groups.

Results: Mean age of all studied patients was 27.7 ± 5.5 years which ranged from 15 to 41 years. As distinct groups mean age of women in group A, was 28.1 ± 5.3 years and in group B it was 27.7 ± 5.8 years. Mean age difference between two groups of under study patients was not statistically significant (P = 0.87). Based on sonography mean gestational age in group A, was 37.8 ± 3.5 and in group B, was 37.5 ± 3.4 weeks. Difference of two groups in terms of gestational age and amount of haemorrhage, was not statistically significant (P = 0.34 and P = 0.47 respectively). In group A, natural vaginal delivery (NVD) was performed, while in group B there in 38 patients (95%) NVD and in 2 patients (5%) caesarean delivery was performed. According to analysis, the difference between two groups was not statistically significant considering mentioned aspects. NVD in 30 cases (75%) in group A and in 36 patients (90%) in group B, was together with episiotomy or laceration and its difference was statistically significant (P = 0.003). Mean massaging time for patients in group A was 25 ± 17.9 minutes and in group B, was 25.5 ± 13.6 minutes. In terms of clinical consequence, 37 patients (92.5%) in group A and 36 patients in group B were discharged without any specific problem.

Conclusions: It is possible to state that misoprostol has no specific preference over TXA, but it is better to investigate its effect with other studies with more sample size and associated with misoprostol.

Keywords: tranexamic acid, misoprostol, postpartum haemorrhage

Introduction

Obstetric hemorrhage is the leading cause of maternal mortality worldwide, irrespective of mode of delivery. Cesarean section is one of the most commonly performed major operations in women throughout the world, escalating to between 20 and 30% in most developed countries over the past four decades.[1] India is representative of the magnitude of this problem. The increasing incidence of cesarean section has contributed to postpartum hemorrhage (PPH), as the average blood loss during cesarean section is twice that during vaginal delivery.[2] Although the value of routine oxytocin to reduce PPH after vaginal birth has been well established, their value in cesarean section has received little attention. It has been assumed that the benefits of oxytocin are observed at vaginal birth also apply to cesarean section. However, 10 to 42% of women receiving oxytocin were found to require additional oxytocin agents, such as ergot alkaloids and prostaglandins.[3] Moreover, oxytocin may not be the ideal agent for prevention of PPH in patients with preeclampsia, prolonged labor, or cardiac disease.[4,5] In addition, oxytocin is both light and heat sensitive, and requires cold storage, which limits its use in developing countries. Misoprostol has been proposed as an alternative to injectable uterotonic agents for preventing PPH following vaginal or cesarean delivery. Misoprostol is a prostaglandin E1 analogue, which has strong uterotonic activity through selectively binding E-series prostanoid receptors (Ep2/Ep3) and is also relatively inexpensive and is stable at room temperature with a long shelf-life. As a consequence, the World Health Organization has enlisted it as an essential medicine for primary PPH in 2011, especially for resource-poor countries.[6] It is well absorbed when administered by oral, buccal, sublingual, vaginal, or rectal routes.[7] A pharmacokinetic study found that sublingual misoprostol has the shortest time to peak concentration, the highest peak concentration, and the greatest bioavailability when compared with other routes. The peak concentration is achieved about 30 minutes after sublingual and oral administration, whereas following vaginal administration, it takes 75 minutes. This is due to rapid absorption through the sublingual mucosa as well as the avoidance of the first-pass metabolism via the liver. The abundant blood supply under the tongue and the relatively neutral pH in the buccal cavity may be contributing factors. However, sublingual administration, which gives the highest Cmax is also associated with the highest incidence of side effects when compared with other routes.[8] Another popular approach is to minimize perioperative bleeding through the prophylactic use of the antifibrinolytic agent, tranexamic acid (TXA). The TXA is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of the lysine-binding sites on plasminogen molecules. There have been studies that showed that TXA injection significantly reduced the blood loss from the placental delivery to 2 hours postpartum without complications of thrombosis.[9-11]

Material and methods

This double blinded randomised clinical trial study was done the Department of Obstetrics and Gynaecology, Hi-Tech Medical College, Rourkela, Odisha, India from February 2021 to November 2021, after taking the approval of the protocol review committee and institutional ethics committee.

Methodology

80 women with PPH (500-1500 ml) diagnosis after caesarean or normal delivery, according to their haemorrhage level after usual therapies for controlling haemorrhage, after getting the consent were included in the study. Collecting bag method of sponges was used for measuring amount of haemorrhage. They were divided into two equal intervention and control groups randomly. Patients in group A were treated with intravenous TXA and patients in group B with rectal Misoprostol.

Intervention group (group A) which were receiving intravenous TXA (1gr) and if there was relieve in haemorrhage, next TXA dose was repeated after 30 minutes and in patients of control group (group B) after usual therapies, 5 rectal 200 micrograms Misoprostol pills were used. The bladder was emptied before therapy in both groups.

The routine therapy protocol to control haemorrhage in our hospital is prescribing 20 IU syntocinon in one litre of Ringer serum, which its infusion takes half an hour. This therapy was implemented immediately after removal of placenta if this therapy failed to control haemorrhage, birth canal was investigated in terms of cervical and vaginal lacerations to determine origin of haemorrhage. Then retraction of uterus was investigated and if uterus was not retracted, monomanual uterine compression and then bimanual uterine compression was performed, and in case of lack of haemorrhage by these methods, patients were included into the study.

In each group of patients, in case of Misoprostol or TXA therapy failure, F2-alpha prostaglandin injection was used. Finally in case of F2-alpha prostaglandin injection failure, surgery methods such as artery ligation, uterine compression sutures, balloon tamponade, selective arterial embolisation and finally hysterectomy were available options to control haemorrhage. Before starting therapy with TXA, we assured that usual therapies for PPH has been conducted and then determined haemorrhage level was more than normal level or patient's haemodynamic was yet unstable. After starting therapy with TXA and Misoprostol, next evaluation was compared for determining effect of TXA and Misoprostol on PPH and its complications. Any side effects due to misoprostol and TXA were investigated in both groups. Women with medical diseases or severe surgery including diseases of heart, liver, kidney and blood disorders, allergies to TXA, thromboembolic disorders and high-risk pregnancy complications such as severe preeclampsia were excluded from the study.

Statistical analysis
Analyzing data collected from the study was done by descriptive statistic methods (frequency, percentage, mean ± standard deviation) and by SPSSTM statistical software version 24.0 using Chi-square test or Fisher's exact test and Independence samples t-test. P-value less than 0.05 were considered as statistically significant.

Results
Mean age of all studied patients was 27.7 ± 5.5 years which ranged from 15 to 41 years. As distinct groups mean age of women in group A, was 28.1 ± 5.3 years and in group B it was 27.7 ± 5.8 years. Mean age difference between two groups of under study patients was not statistically significant (P = 0.87). Based on sonography mean gestational age in group A, was 37.8 ± 3.5 and in group B, was 37.5 ± 3.4 weeks. Difference of two groups in terms of gestational age and amount of haemorrhage, was not statistically significant (P = 0.34 and P = 0.47 respectively).

Table 1 compares some demographic information of patients in two groups. In group A, natural vaginal delivery (NVD) was performed, while in group B there in 38 patients (95%) NVD and in 2 patients (5%) caesarean delivery was performed. According to analysis, the difference between two groups was not statistically significant considering mentioned aspects. NVD in 30 cases (75%) in group A and in 36 patients (90%) in group B, was together with episiotomy or laceration and its difference was statistically significant (P = 0.003). Estimating the amount of haemorrhage during delivery, Hb at hospitalisation time, during haemorrhage, 6-12 hours

after delivery and during discharge were investigated and its description in women and their comparison are presented in detail in Table 2

Table 1: Basic information of patients in study groups

Groups variable	Group receiving Tranexamic Acid (N = 40)	Group receiving Misoprostol (N = 40)	P-value
Weight (kg)	69.4±5	69±6.2	0.61
Height (m)	1.61±0.02	1.62±0.02	0.052
Body mass index (Kg/m^2)	27.6±2.1	27±2.5	0.14
Gravidity	2.2±1.3	1.8±1.3	0.37
Parity	1±0.3	1±0.3	0.26
Abortion	0.3±0.1	0.3±0.1	0.71
Alive	0.9±0.1	0.8±0.1	0.22
Hospitalisation duration (h)	9.5±2.9	14.5±4.8	0.01
Hospitalisation duration after delivery (h)	39.2±18.8	46.5±41.2	0.12

Table 2: Haemodynamic Status and Administered Products of Study Groups

Groups variable	Group receiving Tranexamic Acid (N = 40)	Group receiving Misoprostol (N = 40)	P-value
Haemorrhage (litres)	1.21±0.33	1.19±0.46	0.71
Hb during hospitalisation (g/dl)	11.5±0.7	11.7±0.7	0.12
Hb during haemorrhage (g/dl)	10.2±0.9	10.5±0.9	0.03
Hb 6-12 hours after delivery (g/dl)	8.8±0.9	9±0.9	0.27
Hb during discharge(g/dl)	9.1±0.7	9.3±0.7	0.25
Administered serum(lit)	1.1±0.7	0.8±0.7	0.26
Administered pack Cell (UI)	0.7±0.2	0.8±0.2	0.61
Administered fresh frozen plasma (UI)	0.3±0.1	0.4±0.1	0.59

Before drug administration, uterine massage to control haemorrhage was performed. In 39 cases (97.5%) of patients in group A, one-handed massage and two-handed massage was performed and only in 1 case (2.5%) just one-handed massage had been given. Also in group B in all cases one-handed and two-handed massage was given, Difference between two groups was not significant (P = 0.41). Mean massaging time for patients in group A was 25 ± 17.9 minutes and in group B, was 25.5 ± 13.6 minutes. In conducted statistical analysis the difference between two groups in terms of massage duration was not statistically significant (P = 0.72). In terms of clinical consequence, 37 patients (92.5%) in group A and 36 patients in group B, were discharged without any specific problem.

No side effects such as nausea, vomiting, diarrhea or hypotention were detected due to TXA administration was not detected in group A. No side was detected due to rectal misoprostol administration was not detected in group B, except one case of disseminated intravascular

coagulation which was due to preeclampsia. In group A, ICU admission frequency was 2 cases and in group B it was 3. The difference between two groups was not significant (P = 0.51).

Discussion

Mean age of all studied patients was 27.7 ± 5.5 years which ranged from 15 to 41 years. As distinct groups mean age of women in group A, was 28.1 ± 5.3 years and in group B it was 27.7 ± 5.8 years. Mean age difference between two groups of under study patients was not statistically significant (P = 0.87). Based on sonography mean gestational age in group A, was 37.8 ± 3.5 and in group B, was 37.5 ± 3.4 weeks. Difference of two groups in terms of gestational age and amount of haemorrhage, was not statistically significant (P = 0.34 and P = 0.47 respectively).

Results of this study shows that PPH in patients undergoing therapy with Misoprostol is significantly lower than group undergoing therapy with oxytocin. Duration of the third delivery stage was also less in Misoprostol group than that of oxytocin group. Although our study was on comparing the effects of haemorrhage controlling by TXA and Misoprostol but similar to study of Beigi et al.[12]in our study haemorrhage level was lower in group receiving Misoprostol. Despite the study of Beigi et al., also the difference between two groups in terms of haemorrhage and haemoglobin level was not statistically significant. In spite of the study of Beigi et al.[12]in our study Misoprostol has been used as 5 rectal 200micrograms pills. Also in our study, in checked serial haemoglobin level, haemoglobin level was slightly higher in group receiving Misoprostol than that of group receiving TXA but two groups had no significant statistical difference except urgent Hb level during haemorrhage.

In another study, efficacy of TXA in reducing blood loss after Caesarean section was investigated; according to this study, TXA statistically reduces blood loss from end to 2hafter Caesarean and its use was not associated with any side effects or complications.[13]

Nasr et al., concluded that two groups had no difference in terms of PPH and the need for blood transfusion and loss of more than 10% in blood haemoglobin makes that study different from present study.[14]In the study of Nasr similar to the study of Beigi et al., misoprostol had been used sublingually. It has been mentioned that misoprostol has rapid mucosal absorption; especially when it is used sublingually it reaches to a high concentration in blood. So this is a very useful drug for controlling PPH especially in far suburbs and rural areas where there is no access to hospital, personnel and trained midwives. Misoprostol is cheap, light and easily transportable. It is stable at room temperature and does not need to be kept in refrigerator and to be injected, so it is a preferable drug to control PPH.[12]Abbas pouret al., studied the sensitivity and specifity of method of blood collecting with bag for evaluating PPH, according to the results in PPH, sensitivity level of collected blood bag was 80%, specifity was 95.7%, value of positive prediction was 88.9%, value of negative prediction was 95.7%, and its accuracy was 91%. Finally in this study it has been concluded that collecting bags are rapid and accurate tools for recognizing PPH. So considering the proper price, simplicity and ease of use it could be suggested to be used in labour centres of country.[15]

Zhang et al., in their study on 25381 women in 13 European countries in 2010 using collecting blood bags showed that PPH prevalence was 1.71% in intervention group (using collecting bag) and 2.06% in control group. So collecting bag could not decrease severe PPH level comparing to visual estimation, which based on the ideas of authors due to the vast extent of study, there was probability of error in way and time of using collecting blood bags.[16] So according to the results of the above study and considering numerous problems in using bags

for evaluating PPH level, we decided to estimate severity of PPH in women visually and alongside it, measure serial haemoglobin level to evaluate the effects of two used drugs and the estimation method of our study that is in contrast with the studies of Abbaspour[15] and Zhang.[16] Samimi et al.[17], studied the effect of rectal misoprostol and muscular syntometrine in preventing PPH and it was concluded that rectal suppository misoprostol is more effective and less harmful than syntometrine injection for reducing PPH. So it could be used as a selective drug for preventing PPH it was in contrast with results of present study which had PPH diagnosis.

In study of Samimi et al.[17] the mentioned drugs have been used as primary prophylaxis; which is in contrast with our study. Zafarghandi et al.[18], studied haemorrhage duration and its relationship to different factors. The results of this study showed that count of deliveries, history of abortion, weight of birth, gestational age, preoperative haemoglobin, method of placenta removal and uterine height had no statistically significant relationship with haemorrhage duration.

Some studies have mentioned that side effects of misoprostol drug are more adverse comparing to other factors which are effective for controlling PPH.[12,14] In our study, No side effects such as nausea, vomiting, diarrhea or hypotention was detected due to TXA administration was not detected in group A. No side was detected due to rectal misoprostol administration was not detected in group B, except one case of disseminated intravascular coagulation which was due to preeclampsia. In group A, ICU admission frequency was 2 cases and in group B it was 3. The difference between two groups was not significant (P = 0.51).

Conclusion

It is possible to conclude that misoprostol has no specific preference over TXA, but it is better to investigate its effect with other studies with a larger sample size and associated with misoprostol, as the current study found no significant difference between the two groups in terms of haemorrhage levels during delivery and postpartum and discharge haemoglobin levels.

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