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A comparative study between misoprostol combined with oxytocin versus oxytocin alone in reducing postpartum blood loss

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Abstract

Background: Oxytocin remains as the first line utero-tonic drug used in the management of postpartum hemorrhage (PPH). Because of its certain disadvantages, another cost effective uterotonic drug which can be used orally or vaginally with good absorption is misoprostol, which is a prostaglandin E1 analogue. The study aimed to compare and evaluate the effectiveness of oxytocin versus oxytocin plus misoprostol in the prevention of PPH.

Materials and methods: A prospective randomized interventional study was conducted on 160 term pregnant women from February 2019 to August 2019. The study subjects were randomized into two groups of 80 each. During the active management of third stage of labour, all patients in the study group were administered with standard drug treatment of 10 IU of oxytocin through intramuscular route along with 600µg of misoprostol given sublingually, whereas the patients in the control group were given only 10IU of oxytocin alone.

Results: The average postpartum blood loss and the need for blood transfusion were significantly higher among the control group compared to the study group. The overall incidence of PPH was found to be 28.5% among the control group and it was 6.4% among the study group. Adverse events such as fever, shivering, nausea, vomiting and diarrhoea were more among the study group than that of the control.

Conclusion: A single dose of 600µg of sublingual misoprostol as an adjunct to standard 10 units of intramuscular oxytocin was found to be more effective in reducing blood loss than using 10 units of intramuscular oxytocin alone in the Active Management of Third Stage of Labour.

Keywords: post partum haemorrhage; oxytocin; misoprostol; labor

Introduction

According to the World Health Organization (WHO) report, worldwide the maternal mortality rate had fallen significantly over the past 10 years, MMR which was 342 in the year 2000 has come down to 211 in 2017, thereby reducing the global maternal deaths from 451 000 to 295 000 during this period [1]. The report further stated that about 40% of this absolute decline was contributed from fewer maternal deaths that had reported in India. In India the current MMR as per 2022 SRS data was 97 per lakh live births and we are now progressing towards the target of <70 as given by sustainable development goals which is to be achieved by 2030 [2, 3].

The most common cause for MMR in India is haemorrhage during the time of delivery, it could either antepartum or

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postpartum haemorrhage [4]. Postpartum hemorrhage (PPH) is often considered as a life-threatening obstetric emergency that usually occurs within 24 hrs after delivery. The criterion for PPH is blood loss of more than 500ml after a normal vaginal delivery or more than 1000ml after a cesarean section. Targeting PPH would have a major impact in reducing the MMR and so to curb PPH-related maternal mortality there are medical treatments in the form of drugs, mechanical or non-pharmacological measures, uterus preserving surgeries or hysterectomy [5]. Among all these available measures medical management was found to be more effective with lesser side effects. Medical management with the use of uterotonic drugs such as oxytocin remains an important integral part of the first line management of PPH [6]. The major disadvantages of using oxytocin are it should be administered parenterally and therefore it requires skillful health personnel for administration and it is more heat sensitive, oxytocin gets inactivated when exposed to high temperature and so it should be refrigerated and more so the drug is costlier [7].

Another cost effective utero-tonic drug which can be used orally or vaginally with good absorption is misoprostol, which is a prostaglandin E1 analog [8, 9]. Adverse effects such as nausea, vomiting, shivering and fever which are considered as the most common adverse effects of misoprostol are generally mild and self-limited and more over it does not necessarily requires skilled personnel for its administration [10, 11]. Furthermore, its stability at ambient temperatures, longer half-life, wider availability at low cost are some of the added advantages of misoprostol [12, 13]. Research studies have shown that usage of 600 mcg dose of oral misoprostol was safe and effective in preventing PPH [14].

In spite of the promising results from various trials on misoprostol's therapeutic efficacy for the treatment of PPH, Misoprostol still today in most of the hospitals is not being routinely used neither as an isolated regimen nor as an add on treatment in the prevention of postpartum haemorrhage. It is only considered as a last treatment option. With this available background the present study was conducted to evaluate the effectiveness of oxytocin versus oxytocin plus misoprostol in the prevention of PPH.

Materials and methods

A prospective randomized interventional study was conducted on 160 term pregnant women in Government Coimbatore Medical College and Hospital in the department of Obstetrics and Gynaecology for a period of 6 months from February 2019 to August 2019. The study was started after getting approval from the institutional ethics committee. A total of 200 patients were recruited for our study. Term pregnant women in the age group between 20 and 30 years without any risk factors, undergoing uncomplicated normal vaginal delivery were included as our study subjects.

Out of 200 study subjects after making necessary exclusions based on the inclusion and exclusion criteria of our study a total of 160 term pregnant women were taken as our study sample. The study subjects were randomized into two groups of 80 each by following a simple random technique using a computer generated random number table. Single blinded technique was followed, were the study subjects were not aware of the group which they were allotted. Written informed consent was obtained from all the study participants involved in the study. Three patients in each group were excluded from the study due to non-progression of labour and ending in assisted vaginal delivery or cesarean section and so finally 77 patients in each group were involved in the study. Basic demographic details and obstetric history was obtained from the study subjects. All relevant blood investigations were conducted and the foetal heart rate was monitored regularly. During the active management of third stage of labour, all patients in the study group were administered with standard drug treatment of 10 IU of oxytocin through intramuscular route along with 600µg of misoprostol (treatment arm) given sublingually, whereas the patients in the control group were given only 10IU of oxytocin alone.

Measurement of blood loss was done soon after delivery of the baby. Blood collecting drape (BRASS-V Drape) was tied to the waist of the patient. Blood loss was measured till one hour after delivery and in case if the bleeding continued after one hour, it was measured till the active bleeding was stopped. When active bleeding had stopped, calibrated blood collecting portion of the drape was examined and the volume of blood loss was quantified. Vital parameters such pulse rate, respiratory rate, blood pressure, temperature were monitored throughout the period. Number of patients requiring blood transfusion and additional utero-tonic agents in both the groups were monitored and recorded. Patients developing pyrexia and shivering were noted and treated appropriately. For all patients haemoglobin and haematocrit levels were measured prior to active labour and approximately 24hrs post-delivery. All patients were monitored upto 24hrs after delivery, general examination, systemic examination, abdominal examination and per-vaginal examination were conducted at the end of 24 hrs.

Statistical analysis

All data were entered and analyzed using SPSS version 24. Mean and SD were calculated for all parametric variables and percentage for all frequency variables. Student "t" test and chi-square test were used to derive the statistical inferences.

Results

The demographic and the clinical characteristics among the study subjects along with their obstetric profile were shown in table 1. All these parameters were compared between the study and control group and no statistical significant difference was observed between the two groups for all these parameters. Pre-delivery haemoglobin and haematocrit levels were also almost similar in both the study and control group and so all the baseline characteristics are well comparable between the two groups and both the groups were equally matched (Table 1).

Table 1: Demographic and clinical characteristics of the study subjects.

Demographic characteristics	*Control group (n=77)*	*Study group (n=77)*	*p value*
Age (in years)	22.90 ± 03.70	23.10 ± 03.60	0.707*
Mother's weight (in kg)	66.20 ± 12.60	69.50 ± 12.00	0.098*
Birth weight (in Kg)	02.80 ± 00.40	02.90 ± 00.40	0.428*
Contraceptive usage			
Used (Multi)	16 (20.5%)/35	15 (19.5%)/35	0.711#
Not used	61 (79.2%)	62 (80.5%)	
Parity			
Primiparous	43 (55.1%)	42 (54.5%)	0.192#
Multiparous	35 (44.9%)	37 (45.5%)	
Clinical parameters			
Pulse rate	80.43 ± 5.22	80.36 ± 6.10	0.813*
Blood sugar level	78.60 ± 5.64	77.86 ± 5.58	0.747*
Pre-delivery Hb %	11.6 ± 0.7	11.5 ± 1.0	0.849*
Pre-delivery HCT	34.7 ± 3.1	35 ± 3.3	0.818*

Abbreviations: *: p value derived using student T test; # : P value derived using chi-square test.

Patients in the study group were administered with standard drug treatment of 10IU of oxytocin through intramuscular route along with 600µg of misoprostol given sublingually, whereas the patients in the control group were given only 10IU of oxytocin alone. Towards the end of the 3rd stage of labour the outcome parameters were measured and compared between the two groups. The average postpartum blood loss and the need for blood transfusion were significantly higher among the control group compared to the study group. The overall incidence of PPH was found to be 28.5% among the control group and it was 6.4% among the study group. Similarly the use of additional utero-tonic agents was also significantly more among the control group, whereas number of patients developing fever and shivering were more among the study group compared to the control group and the difference was found to be statistically significant (p<.001) (Table 2).

The pre-delivery haemoglobin and haematocrit values were almost similar among both the study and control groups, whereas the post delivery, Hb and HCt levels were significantly lower in the study group compared to the control group (p<.05). Adverse events such as nausea, vomiting and diarrhoea were more among study group than that of the control group and the difference was found to be statistically significant (p<.05) (Table 3).

Discussion

PPH is the most common and serious obstetric risk factor resulting in increased morbidity and mortality among women in developing and under developed countries. Though many protocols and guidelines were framed for the prevention of PPH but still the incidence of PPH found to be on the raise. Active Management of Third Stage of Labour (AMTSL) using appropriate medications is the major factor in reducing the incidence of PPH. Though oxytocin have certain limitations related to the route of administration, storage at a very low temperature and the cost of the drug still it is being considered as the gold standard utero-tonic drug used in the prevention and treatment for PPH [15]. On the other hand another utero-tonic drug which is currently being used is misoprostol, a prostaglandin analogue which can be administered orally, stored at normal

Table 2: Analysis of efficacy parameters (Outcome parameters).

Efficacy parameter	*Control group (n=77)*	*Study group (n=77)*	*p value*
Average postpartum blood loss	237.4 ± 138.3 ml	187.5 ± 102.4ml	<.0001*
No. of patients with blood loss of >500ml but <1000ml	17 (22.1%)	04 (05.2%)	<.001#
No. of patients with blood loss of > 1000ml	05 (06.5%)	01 (01.2%)	<.001#
Need of blood transfusion	29 (37.1%)	07 (09.1%)	<.0001#
Need of additional uterotonic agents	28 (36.36%)	9 (11.68%)	<.0001#
No.of patients developed shivering	3 (3.9%)	26 (33.7%)	<.0001#
No.of patients developed pyrexia	2 (2.6%)	24 (31.16%)	<.0001#

Abbreviations: *: p value derived using student T test; #: P value derived using chi-square test.

Table 3: Comparison of the blood parameters and the incidence of adverse events between the two groups.

Parameter	*Control group (n=77)*	*Study group (n=77)*	*p value*
Haemoglobin (mean ± SD)	9.2 ± 1.8	10.6 ± 1.0	0.031*
Haematocrit (mean ± SD)	29.3 ± 4.3	31.7 ± 3.1	0.016*
Nausea	12 (15.5%)	23 (29.8%)	<.0001#
Vomiting	2 (2.5%)	17 (22%)	<.0001#
Diarrhoea	0	9 (11.6%)	<.01#

Abbreviations: *: P value derived using student T test; #: P value derived using chi-square test.

room temperature and comparatively cost effective. As of today misoprostol is not being used as an alternate for oxytocin in the prevention or treatment of PPH it is only considered as a add on treatment along with oxytocin. Our study was aimed to assess the effectiveness between oxytocin vs oxytocin with misoprostol in the reduction of postpartum blood loss [16].

Our study subjects were randomized into two groups of 77 each. One group received oxytocin alone during the active third stage of labour and the other group received oxytocin along with misoprostol and they were assessed for volume of blood loss, usage of additional utero-tonic agents, number of units of blood transfused during the time of delivery and after 24hrs of delivery, subjects were assessed for haemoglobin and haematocrit levels. All the demographic parameters such as antenatal age, BMI and parity and all the pre-delivery clinical parameters such as BP, pulse rate, Hemoglobin and haematocrit levels were matched between the two groups and no difference was observed between them. In the present study the average volume of blood loss during delivery was 237 ml in control group and 187 ml in the study group and the difference was found to be statistically significant. Our results were almost in par with the studies done earlier which had compared the efficacy between misoprotol with oxytocin versus oxytocin alone [17-19]. A study done in Uganda by Esther CA Tukunda et al., compared between oxytocin and misoprostol alone and they found no significant reduction in the blood loss between the two groups during delivery, which proves that misoprostol is more effective when used as an adjuvant along with oxytocin for the prevention of PPH [20].

In our study the number of subjects who had blood loss between 500ml -1000ml were 17 in control group and 4 in study group and similarly the number of subjects who had blood loss >1000ml were 5 in control group and 3 in study group, this proved that adding misoprostol along with oxytocin had drastically reduced the incidence of PPH. Two meta-analysis study done in 2018 quoted that the three most effective drugs for prevention of PPH were ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination. Further large number of clinical trials quotes that misoprostol is used in the dosage of 600 µgm for prevention of PPH and 800 µgm for treatment of PPH [21, 22].

In the present study less number of patients in the study group required blood transfusion and additional utero-tonics because of reduced blood loss compared to the patients in the control group, the studies done earlier and the meta-analysis report had mentioned similar type of results. Postpartum shivering and pyrexia are the common adverse events reported due to misoprostol, because of its action on central thermoregulatory mechanism and in our study these events were more among the study group and it lasted for only less than 4 hrs, the studies done earlier had also mentioned the same and the patients were treated symptomatically. The other adverse events reported in our study were

nausea, vomiting and diarrhoea which were higher among the subjects in the study group and they were treated symptomatically and there was no difference in the timing of discharge between the two groups as quoted by the studies done by Gallos et al., Leon et al., and Sheldon et al [21-24].

In the present study 2.3 gm% of haemoglobin drop was noticed in the control group compared to only 1 gm% of drop in the study group and the difference was found to be statistically significant and a similar type of fall was also seen with the heamatocrit levels. These results were almost in par with the studies done by Zuberi et al and Abdel-Aleem et al [25, 26] whereas the studies done by Widmer et al and Blum et al were contradicting to our results, in which it did not show a significant drop in Hb% and haematocrit levels between the two groups [27].

In this current study irrespective of the treatment with additional utero-tonics and blood transfusions for atonic PPH, 5 women underwent subtotal hysterectomy in control group and 1 women underwent subtotal hysterectomy in study group for uncontrolled PPH.

Few limitations of the present study were sample size was not relatively large, only antenatal mothers without risk factors were chosen for this study and in very few patients, minimal collection of amniotic fluid and patient's urine was unavoidable during postpartum collection of blood loss.

Conclusion

A single dose of 600µg of sublingual misoprostol as an adjunct to standard 10 units of intramuscular oxytocin was found to be more effective in reducing blood loss than using 10 units of intramuscular oxytocin alone in the active management of third stage of labour. Though side effects with misoprostol were common, they were found to be self-limiting and dose related, but the benefits outweigh risk with additional usage of misoprostol with oxytocin. More research studies need to be conducted in larger population group including high risk patients to further demonstrate the effectiveness of misoprostol in reducing the incidence of PPH.

Conflicts of interest

Authors declare no conflicts of interest.

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