Original Article

Comparison of Intravenous (IV) Oxytocin with (IV) Oxytocin plus Sublingual Misoprostol for Active Management of Third Stage of Labor in Vaginal Birth among Primigravida with Singleton Pregnancy

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Abstract

Objective: To compare intravenous (IV) oxytocin with IV oxytocin plus sublingual misoprostol for active management of third stage of labor in vaginal birth among primigravida with singleton pregnancy.

Methodology: This randomized controlled trial study was conducted in MCH Center, Unit I, Pakistan Institute of Medical Sciences, Islamabad after the approval of synopsis from Dec 2017 to Jun, 2018. A total of 65 patients each were enrolled in each study group. Women presenting to MCH Center at term, who were primigravida, had singleton gestation at term (37 to 41 weeks) and were in spontaneous labor were included in the study. Patients with instrumental vaginal deliveries, AVBD, APH and with any medical disorders including PIH were excluded. Group A received IV oxytocin 10 IU + misoprostol 400 mg sublingually whereas group B patients received IV oxytocin 10 IU. The primary study outcome was measured in terms of comparison of mean blood loss between the study groups.

Results: Overall most of the women were between 26 and 30 years. Average age of patients was 27.4 ± 2.6 years in oxytocin + misoprostol group compared to 27.5 ± 2.2 years in the oxytocin alone group. The frequency of blood loss > 500 ml was 13.8% in oxytocin alone group compared to 4.6% in oxytocin + misoprostol group. The mean blood loss was 363.1 ml in oxytocin + misoprostol compared to 406.9 ml in the oxytocin alone group (p-value, <0.001). In the combination group 4 (6.0%) cases were found to have shivering compared to 1 (1.5%) in oxytocin alone group.

Conclusion: Combination of IV oxytocin + sublingual misoprostol is better than IV oxytocin alone in the management of blood loss in the third stage of labour. The mean blood loss was significantly lower in the combination group when compared with IV oxytocin alone group.

Keywords: Postpartum hemorrhage, prevention, oxytocin, Misoprostol.

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Introduction

Post-partum hemorrhage (PPH) is still the commonest direct cause of maternal mortality among developing countries. However, active management of third stage of labor can prevent its occurrence. Blood loss of 500 ml or more in the first 24 hours after delivery from the genital tract is defined as postpartum hemorrhage.[1] According to the most recent large-scale WHO multi-country study, across middle- and low-income countries, 1.2% of mothers who gave birth to 275,000 children reported having PPH, and the total PPH mortality rate was 38 per 100,000 live births. Furthermore, 18% of those with a PPH experienced a severe maternal outcome, and 3% died.[2] Despite medical, surgical innovations, PPH rates remain high in several countries. In the UK, deaths from PPH still occur (0.39/100,000 maternities in 2006-2008). According to a statistical analysis done in 2007 in Pakistan, the maternal mortality ratio is 320 per 100,000 live births, out of which 70% is due to PPH, the leading

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cause of maternal deaths.[2,3] Primary postpartum hemorrhage is uterine atony, accounting for 80 to 90% of cases; therefore, early assessment of blood loss is important to prevent delay in the management of this critical and life-threatening condition.[4,5]

Uterotonic agents are used for the prevention of atonic postpartum haemorrhage. These agents include Oxytocin, Carbetocin, Methylergometrine, and Misoprostol. Several studies have confirmed that oxytocin is the gold standard heat labile agent for prevention of blood loss.

Misoprostol is a prostaglandin E1 analogue which is a heat stable agent. It is recommended for the treatment of the third stage of labour since it is rapidly absorbed from the mucosa when orally administered, vaginally, or rectal. The sublingual route has been preferred for the management of PPH as it has longer half-life and hence prolongs uterine contraction which controls bleeding, however, it has some side effects like fever, nausea and shivering. [5-8]

Regarding the use of oxytocin and misoprostol there is still controversy regarding the ideal dose, infusion rates and mode of therapy, and so far the literature reports variable outcomes.[7,8] A study by El-Moneim A reported that sublingual misoprostol was better in controlling blood loss (227.5 ml) than rectal misoprostol (310.7 ml) and IV ergometrine (331.2 ml).[9] Another study by Sheldon et al reported that patients who were managed with oxytocin alone were found to have greater mean blood loss (277.0 ml) than those given combination therapy (235.0 ml).[2] We could not locate any study directly comparing the combination of oxytocin and misoprostol with oxytocin alone in the management of PPH. This increases the curiosity behind our hypothesis that the combination of oxytocin and misoprostol would be better than oxytocin alone and provides the basis to assess these interventions. In this study, we aimed to compare a standard 10 IU bolus of oxytocin with additional misoprostol 400 gm sublingually to determine whether use of an inexpensive and widely used drug can further improve prevention of hemorrhage in addition to routine use of bolus oxytocin.

Methodology

It was a randomized control trial conducted in the Gynecology and Obstetrics Department, MCH Unit 1, PIMS Hospital, Islamabad. The study duration was 6 months onwards from the date of approval of the synopsis December 2017 to June 2018. A total of 130 patients (65 cases in each group) were included in the study. Using the WHO sample size calculator with the following assumptions, alpha error= 5%, Confidence level = 95%, and anticipated mean blood loss in oxytocin + misoprostol group and oxytocin alone group was 227.5 ml[9] vs 277.0 ml[1], standard deviation = 100.0. Random allocation using lottery method was used as sampling technique. The inclusion criteria were singleton gestation, gestational age at term (37 to 41 weeks), and spontaneous labor, whereas instrumental vaginal deliveries, AVBD, APH, and any medical disorders, including PIH, were considered exclusion criteria.

After receiving permission from the institutional ethics committee, the study was initiated. Following informed verbal permission, all patients reporting to the labour room of MCH Unit-1 and fulfilling the inclusion criteria were enrolled. Patients who were recruited in the study had a detailed obstetric and menstrual history collected, and then they underwent a general, systemic, and obstetrical examination along with all routine tests. The patients allocated to group A received IV oxytocin 10 IU + misoprostol 400 mg sublingually, whereas those allocated to group B received IV oxytocin 10 IU. The patients were allocated to each study group using the lottery method, where any patient had equal chance of being randomized to either of the two study interventions. Patients were vigilantly monitored during third stage of labor. The woman were kept under observation after delivery and bleeding per vagina was noted every 15 minutes for the first hour and every 30 minutes for the next two hours through blood collected in soiled pads. The loss of blood after delivery was noted. All the study-related information was recorded on a specially designed proforma. The study procedures and data collection were done by the researcher herself to reduce the chances of selection bias as well as to maintain data continuity and quality. The primary study outcome was measured in terms of a comparison of mean blood loss between the study groups.

Data was entered into SPSS version 21.0 for analysis Mean and standard deviations were calculated for quantitative variables like age, blood loss. Frequencies and percentages were calculated for qualitative variables like side effects, i.e. shivering, fever, hyperpyrexia, nausea, vomiting, and diarrhea. The mean blood loss (mls) was compared among the two study groups using a student's t-test. A significance level of <0.05 was considered significant. The results were described and also presented as tables and graphs, whichever was found suitable.

Results

In this study, a total of 130 cases were enrolled and assigned to oxytocin + misoprostol (n=65) and oxytocin alone (n=65). Overall, most of the women were between 26 and 30 years. In oxytocin + misoprostol group, 28 (43.1%) patients were aged younger than 25 years, 33 (50.8%) were between 26 and 30 years. Similarly, in oxytocin alone group 10 (15.4%) patients were up to 25 years of age, 50 (76.9%) were between 26 to 30 years. The gestational age of patients was found to be up to 40 weeks in 35 (53.8%) of combination group cases compared to 37 (56.9%) in oxytocin alone. Similarly, 30 (46.2%) patients were 41 week or above gestational age in combination group compared to 28 (43.1%) in oxytocin alone group. The average age of patients was 27.4±2.6 years in oxytocin + misoprostol group compared to 27.5±2.2 years in the oxytocin alone group. Similarly, the mean gestational age was 39.5±2.6 weeks in combination group and 38.8±2.2 weeks in oxytocin alone group. (Table I)

Greater than 500-mL blood loss was found to be more common in the oxytocin alone group than in the oxytocin + misoprostol combination group (13.8% versus 4.6%). However, this proportionate difference was not proven statistically significant (p-value, 0.120).

When the mean blood loss was compared between the two groups, it was found that it was significantly different between the two groups. The mean blood loss was 363.1 ml in oxytocin + misoprostol compared to 406.9 ml in the oxytocin alone group, and this difference in the two means was statistically found significant (p-value, <0.001). (Table II) The overall prevalence of postpartum Haemorrhage (PPH) in this study was found to be 9%, out of the total 130 cases. There were a few cases of minor side effects in the two groups, otherwise both interventions were found safe. In the combination group 4 (6.0%) cases were found to have shivering compared to 1 (1.5%) in oxytocin alone group. Few cases were found to have nausea as well (4.6% versus 1.5%) in oxytocin alone and combination groups respectively. Similarly, vomiting was found in (3.0%) cases in combination group and (1.5%) in oxytocin alone group and no significant differences were noted in the occurrence of side effects between the two groups. There were no other side effects noted in the study patients in both groups. (Table III)

Table I: Demographic Variables among both the groups.

	Oxytocin + Misoprostol (n=65)	Oxytocin alone (n=65)	Total (n=130)
Age (years)	27.4+2.6	27.5+2.2	-
Up to 25	28 (43.1%)	10 (15.4%)	38 (29.2%)
26 to 30	33 (50.8%)	50 (76.9%)	83 (63.8%)
31 or above	4 (6.2%)	5 (7.7%)	9 (6.9%)
Gestational age (wks)	39.5+2.6	38.8+2.2	-
Up to 40	35 (53.8%)	37 (56.9%)	72 (55.4%)
41 or above	30 (46.2%)	28 (43.1%)	58 (44.6%)

Table II: Comparison of Blood Loss (ml) between the two study groups.

	Oxytocin + Misoprostol (n=65)	Oxytocin alone (n=65)	p-value
Blood loss (≥ 500 ml)	363.1 ± 50.3	406.9 ± 52.1	<0.001
Yes	3 (4.6%)	9 (13.8%)	0.120
No	62 (95.4%)	56 (86.2%)	

Table III: Comparison of side effects between the two groups.

	Oxytocin + Misoprostol (n=65)	Oxytocin alone (n=65)	Total (n=130)
Fever	0 (0.0%)	0 (0.0%)	-
Shivering	4 (6.1%)	1 (1.5%)	5
Vomiting	2 (3.0%)	1 (1.5%)	3
Nausea	1 (1.5%)	3 (4.6%)	4
Diarrhea	0 (0.0%)	0 (0.0%)	-
Hyperpyrexia	0 (0.0%)	0 (0.0%)	-

Discussion

In this study, we compared a combination of intravenous oxytocin + sublingual misoprostol with intravenous oxytocin alone in the management of PPH. Overall age was found to be comparable between the two groups, however, majority of the study cases were found between 26 and 30 years of age and the mean age was 27.45 ± 2.4 years. A similar average age 25.8 ± 5.7 years was reported by a previous study on the safety and efficacy of misoprostol and oxytocin in the prevention of postpartum hemorrhage by Rajei M and colleagues.[10] Another study by Gohil et al also witnessed a similar average age in the misoprostol group 25.7 years and oxytocin group 24.1 years in their study.[11] Age of women, usually in the reproductive age who are primigravida means recently married are mostly seen

between 20 and 30 years in developing regions like Pakistan.

Rejei M et al also reported that there was no difference in the average gestational age between misoprostol and oxytocin groups.[10] The gestational age of patients was found out to be 39.5 week and 38.8 weeks between the combination group and oxytocin alone group in this study. Gohil et al also reported a similar gestational age in their study in both misoprostol and oxytocin groups.[11]

Since gestational age has not been implicated as any role in the significance of PPH, it is usually otherwise full term pregnancies. In the current study the combination of IV oxytocin + sublingual misoprostol significantly decreased blood loss postpartum than IV oxytocin alone (363.1 ml versus 406.9 ml, p-value, <0.001), respectively. Many previous studies have also proven this effect. Rajei M and colleagues also found that misoprostol significantly reduced average hemorrhage size that intravenous oxytocin.[10] The effects of misoprostol and oxytocin in high risk patients were examined by Chaudhuri et al. Participants received 400 µg of sublingual misoprostol or matched placebo following delivery. All participants received 20 IU of oxytocin. In comparison to the placebo group, the mean intraoperative blood loss was considerably lower in the misoprostol group. They were able to conclude that misoprostol, used in conjunction with oxytocin, appeared to reduce blood loss more efficiently than oxytocin by itself.[12] Bellad et al. used 10 IU of intramuscular (IM) oxytocin to compare the effects of sublingual misoprostol to conventional treatment. The mean blood loss was 192±124 mL among sublingual misoprostol group compared to 366 ± 136 mL among IM oxytocin. No woman lost >1000 mL of blood.[13] In another study Favole et al reported that women who received Although misoprostol and routine uterotonics decreased postpartum blood loss, the impact was not statistically significant for blood losses of at least 500 mL or at least 1000 mL. Misoprostol also reduced the need for non-routine oxytocin.[14]

In another study, Ugwu et al compared the efficacy of sublingual misoprostol combined with intravenous oxytocin to that of oxytocin alone. They witnessed that intraoperative and postoperative blood loss was significantly lower in combination group (451.3 mL vs. 551.2 mL; 22.7 vs. 42.2 mL, respectively). Similarly, the need for additional uterotonics was also greater in the oxytocin group (66.7% vs. 27.6%). They concluded that addition of sublingual misoprostol to intravenous oxytocin reduces postpartum blood loss and the need for additional uterotonics.[15] The current study findings regarding significant control over postpartum hemorrhage intensity using IV oxytocin + sublingual misoprostol validate the previous reports on the topic. Since Misoprostol is cost effective option, keeping in mind the developing world scenario, the Pakistani healthcare settings are ideal for this option. As a result, misoprostol might be useful in healthcare settings with a shortage of resources, such as refrigerators and qualified delivery attendants.

In the present study, the frequency of blood loss $\geq$ 500 ml was greater in IV oxytocin alone group than the combination group IV oxytocin + misoprostol. Comparatively, Bellad et al also reported that the incidence of PPH was 3.1% with misoprostol and 9.1% with oxytocin (p=0.002).[13] A local study by Mobeen N and colleagues witnessed that oral misoprostol significantly reduced the occurrence of $\geq$ 500 ml of blood loss.[16] Mirteimouri and colleagues from Iran reported that the proportion of women who lost > 500 cc of blood was significantly higher in the oxytocin group (33%) compared with the misoprostol group (19%).

Additionally, the need for excessive oxytocin for management of PPH was also significantly lower in the misoprostol group in their study.[17] The addition of uterotonics during postpartum period could have significant side effects for the women, plus it can add cost of overall treatment again an additional burden for lower social class and lower middle class families. In the current study those nine patients in whom IV oxytocin could not control blood loss were all given addition of sublingual Misoprostol. Similarly, of the three cases in the combination arm who had blood loss of more than 500 ml, 1 patient was managed with ballon temponade whereas the rest of the 2 patients were given infusion synto + repeated misoprostol dose.

There were a few side effects from the combination of oxytocin + misoprostol in the form of shivering, nausea and vomiting. Shivering was slightly more prevalent in combination group compared to IV oxytocin alone group. Many other studies have also found a similar trend of side effects. Shivering, chills, and/or fever are reported as common side effects of misoprostol. Shivering is the most common complication of misoprostol which occasionally accompanies fever. In the large WHO multicenter study shivering occurred in 18% of women who were took Misoprostol.[18] Similarly, In rural India, Derman et al. administered 600 mg of misoprostol;

52.2% of the women reported shivering, while only 4.2% experienced fever.[19] The other side effects like diarrhea, vomiting are rare and occurs in less than 1% cases. The current study has many advantages; firstly, a reasonable sample of primigravida women was randomized to two interventions on the management of PPH. Secondly, this was a RCT conducted by using rigorous scientific methods and putting more authenticity to the results. Oxytocin is expensive, needs cool storage and special healthcare setting services for this intervention whereas IV oxytocin + sublingual misoprostol not only reduces blood loss but also the chances of further uterotonics and, thus, resultant additional costs. There were no any significant limitations to the study which can be brought to light.

Conclusion

The current study concludes that the combination of IV oxytocin + sublingual misoprostol is better than IV oxytocin alone in the management of blood loss in the third stage of labour. The mean blood loss was significantly lower in the combination group when compared with the IV oxytocin alone group. Before generalization of the current study results, further large scale studies using rigorous scientific methods should be conducted in other regions of the country and internationally.

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