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Misoprostol versus oxytocin in reducing postpartum hemorrhage after labor induction

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Abstract
Introduction: Postpartum haemorrhage is the most serious complication in obstetric practice. The greatest number of maternal deaths from haemorrhage is due to PPH, which is almost entirely a preventable condition. WHO defines PPH as blood loss of 500 ml or more in first 24 hours post-partum. PPH is one of the most common obstetric maternal complications and is among the three most common etiologies of maternal death worldwide.
Objective: To compare misoprostol versus oxytocin in reducing postpartum hemorrhage after labor induction.
Methods: The study was a randomized clinical trial carried out at the Department of Gynaecology & Obstetrics, Institute Of Child And Mother Health, Matuail, and Dhaka, Bangladesh June 2021 to July 2022. One hundred (110) patients were included. Women with term pregnancy were randomized to receive either 200 µg misoprostol sublingually or 10 IU oxytocin intramuscularly after vaginal delivery. Primary outcome measured was mean blood loss and incidence of primary postpartum hemorrhage (PPH). Secondary outcome measured included duration of third stage of labor, side effects of drugs and need for additional oxytocics to treat life-threatening hemorrhage.
Results: Total 110 women with term pregnancy in two groups of 55 each were studied. The mean blood loss with sublingual misoprostol and oxytocin groups was 320.58±244.12 vs. 253.27±171.74 ml; (P= 0.11). The mean duration of third stage of labor was similar and the difference was not statistically significant (6.65±3.47 vs. 6.08±3.07 minutes) (P=0.38), as well as need for additional oxytocics (14.5% vs. 7.2% P=0.18) misoprostol and oxytocin, respectively. In misoprostol group, side effects were shivering, fever, nausea and abdominal pains, while the oxytocin group abdominal pains, headaches and shivering.
Conclusion: Sublingual misoprostol has similar efficacy to standard intramuscular oxytocin in the active management of third stage of labor. This study also revealed that a 200 µg tablet may be as effective as the previously investigated higher doses. Thus, misoprostol at 200 µg with its thermo stability may be an effective alternative to intramuscular oxytocin in active management of third stage of labor.

Keywords: ICMH, oxytocin, misoprostol, postpartum hemorrhage

Introduction

Postpartum haemorrhage is the most serious complication in obstetric practice. The greatest number of maternal deaths from haemorrhage is due to PPH, which is almost entirely a preventable condition. WHO defines PPH as blood loss of 500 ml or more in first 24 hours post-partum [1]. PPH is still the leading cause of maternal mortality despite some decline in the overall mortality, an estimated 303,000 maternal deaths occurred in 2015, a decline of 43% from levels in 1990 [1]. Uterine agony accounts for greater 70% of the primary PPH [1]. In the developing world, several countries have maternal mortality rates in excess of 240 maternal deaths per 100,000 live births. [2] The World Health Organization statistics reported that 27% of maternal deaths are due to PPH, accounting for more than 650,000 maternal deaths between the years 2003 and 2009 [3]. In spite of the improvements in the management of PPH, it remains one of the most challenging complications that an obstetrician encounters. Thus prevention, early recognition and prompt appropriate intervention are the keys to minimizing its impact. The most ideal uterotonic agent for the active management of third stage of labor has been the subject of research. However, intramuscular 10 IU of oxytocin remains the standard of care by the World Health Organization (WHO) recommendation [4, 5]. Postpartum blood loss is difficult to evaluate especially in developing countries where most of the women are anaemic with poor reserve and these conditions are further aggravated by increased demand during pregnancy and blood loss during 3rd stage of labour [6]. PPH is the leading cause of maternal death worldwide, with an estimated mortality rate of 1,40,000 per year, or 1 maternal death every 4 minutes [7]. PPH occurs in 5% of all deliveries and is responsible for a major part of maternal mortality [8].

The majority of these deaths occur within 4 hours of delivery, which indicates that they are a consequence of the third stage of labour [9,10]. Despite the preference for oxytocin, it is not always feasible to administer oxytocin in economically challenged environment, given its requirement for cool storage.[5] The Oxytocin receptor belongs to a class of receptors that is susceptible to decreasing responsiveness as exposure to its complementary hormone increases in amount or duration. The receptor is thought to be desensitized after prolonged or repeated stimulation [11]. Despite the preference for oxytocin, it is not always feasible to administer oxytocin in economically challenged environment, given its requirement for cool storage [12]. The use of oxytocin and other parenteral uterotonics is often restricted to urban centers. Ease of administration and storage with the background of its effectiveness, favours the use of misoprostol in communities of resource poor settings [13]. The most recent Cochrane database review of misoprostol for third stage recognized the paucity of published work on lower dose of misoprostol for active management of third stage of labour and suggested the need for further research on low dose misoprostol [2, 3]. This study was a prospective randomized controlled comparison of a low dose 200 µg sublingual misoprostol with the standard 10 IU of intramuscular oxytocin for the active management of third stage of labour. The effect of this low dose regimen on postpartum blood loss and the side effects was compared with the standard treatment of intramuscular oxytocin. In low-resource settings, synthetic prostaglandins such as misoprostol, which also have uterotonic properties, have become popular as they are not only less expensive as compared to oxytocin and carboprost but also their storage and administration do not require maintenance at any specific temperature or need for syringes, needles, or skilled paramedics [14]. It has also gained acceptance as a new and underutilized technology to reduce maternal mortality [15].

Materials and Methods

The study was a randomized clinical trial carried out at the Department of Gynaecology & Obstetrics, Institute of Child and Mother Health, Matuail, and Dhaka, Bangladesh June 2021 to July 2022. One hundred (110) patients were included. The targeted population was booked women admitted into the labor room anticipating vaginal delivery and who had a singleton pregnancy with cervical dilatation of 6 cm or less and packed cell volume of at least 30%. Women in advanced stage of labor (cervical dilatation >6cm), known allergies to prostaglandins, oxytocin homologues or excipients, had a serious cardiovascular disorder, serious hepatic or renal disease, or epilepsy were not eligible. All the participants gave a written informed consent. The sample size was determined using statistical formula for comparing two proportions with accepting a study power of 80%, confidence interval of 95%, study/control of 1:1 and an acceptable dropout rate of 10%. Women underwent randomization when vaginal birth was imminent.

The envelopes were drawn to know the group into which a subject falls only when delivery is imminent. Women were randomly assigned to receive a single intramuscular injection oxytocin at a dose of 10 IU or 200 µg sublingual misoprostol immediately after the birth of the baby, the drug was administered and the management of the third stage of labor was conducted as recommended in the WHO guidelines [16]. Blood was collected for 1 hour but careful surveillance for further bleeding was put in place till 24 hours after delivery. Additional oxytocics were used when subsequent blood loss was adjudged excessive. The blood collected in the receptacle was visually noted and also transferred to a measuring jar and volume noted. Dry weight of all swabs that were used during the third stage were measured and noted. Blood soaked swabs were weighed and the dry weight of the swabs was subtracted in grams. Assuming an equivalence of 1 g to 1 ml, this volume was added to the volume of blood from the BRASSS-V drape. Participation in the study ended at discharge from the facility, transfer of the woman to a higher care unit or death. Primary outcomes were quantity of blood loss and incidence of PPH. Secondary outcomes included duration of the third stage, need for adjunctive uterotonics to treat life-threatening hemorrhage and side effects of drugs used.

Data Analysis

Data statistical analysed using the SPSS version 23. Descriptive statistics were presented using charts, graphs and tables as appropriate. Quantitative variables were described using measures of central tendencies like mean and median as appropriate. Association between qualitative variables were tested using Chi-square test, while associations between various quantitative variables were determined using the Student's t-test and other tests as found appropriate. The level of significance was set at 5%.

Results

Total 110 women with term pregnancy in two groups of 55 each were studied. Demographic and base line characteristics of the two groups were comparable (Tables 1, 2). The mean gestational age of women was 39.43±1.17 in the misoprostol group and 39.32±1.17 weeks in the oxytocin group. The mean blood loss with sublingual misoprostol and oxytocin groups was 320.58±244.12 vs. 253.27±171.74 ml; (p=0.11) (Table 3). The mean duration of third stage of labor was similar and the difference was not statistically significant (6.65±3.47 vs. 6.08±3.07 minutes) (P=0.38), as well as need for additional oxytocics (14.5% vs. 7.2% p=0.18) misoprostol and oxytocin, respectively. There were no differences at the 5% level of significance between groups with regard to the incidence of PPH (20.8% vs. 14.5% respectively; p=0.43) (Table 4). Among the women who were recruited (safety population), the frequencies of the expected side effects did not differ significantly between the two groups (Table 5). In misoprostol group, side effects were shivering, fever, nausea and abdominal pains, while the oxytocin group abdominal pains, headaches and shivering.

Table 1: Maternal baseline characteristics (N=110)

Characteristics Misoprostol	N=55 (%)	Oxytocin N=55 (%)	P-Value
Age (years)			
20-29	23(41.8)	30 (54.5)	0.46
30-39	30(54.5)	24(43.6)	
40 and above	2(3.6)	1(1.8)	
Parity			
0	10(18.2)	21(38.8)	0.174
1	18(32.7)	12(21.8)	
2	21(38.2)	18(32.7)	
3	4(7.2)	2(3.6)	
4	2(3.6)	2(3.6)	
Blood group			
O-Positive	30 (54.5)	35(63.6)	0.37
A-Positive	15(27.2)	7(12.7)	
B-Positive	9(16.3)	10(18.1)	
O-Negative	2(3.6)	1(1.8)	
B-Negative	0(0)	1(1.8)	
A-Negative	0(0)	1(1.8)	

Table 2: Mean gestational age, blood pressure and packed cell volume (N=110)

Characteristics	Misoprostol (±SD)	Oxytocin (±SD)	P-Value
Gestational age (weeks)	39.43 (1.17)	39.32 (1.17)	0.66
Mean arterial blood pressure	83.53 (10.42)	81.59 (9.57)	0.33
Intrapartum packed cell volume	32.92 (2.99)	32.17(3.13)	0.94

Table 3: Mean blood loss and mean duration of third stage of labour (N=110)

Characteristics	Misoprostol n=55(±SD)	Oxytocin N=55 (±SD)	Mean difference (95%CI)	P-Value
Blood loss (ml)	320.58 (244.12)	253.27 (171.74)	67.30 (14.8,149.4)	0.11
Duration of third stage (min)	6.65 (3.47)	6.08 (3.07)	0.56 (0.71,1.84)	0.38

Table 4: Postpartum hemorrhage and need for additional oxytocics (N=110)

Characteristics	Misoprostol N=55 (%)	Oxytocin n=55 (%)	P-Value
PPH (≥500 ml)	12 (20.8)	8 (14.5)	0.43
No PPH (<500 ml)	43 (78.1)	47(85.5)	
Additional oxytocics required	8 (14.5)	4(7.2)	0.18
Additional oxytocics not required	47 (85.5)	51 (92.8)	

Table 5: Side effect profile (N=15)

Characteristics	Misoprostol N=9 (%)	Oxytocin N=6 (%)	P-Value
Nausea	1(11.1)	0(0)	
Shivering	4(44.4)	1(16.6)	0.26
Fever	2(22.2)	0(0)	
Headache	0(0)	1(16.6)	
Abdominal pain	2(22.2)	4(66.6)	

Discussion

Total 110 women with term pregnancy in two groups of 55 each were studied. Demographic and base line characteristics of the two groups were comparable. The gestational age of women was 39.43±1.17 in the misoprostol group and 39.32±1.17 weeks in the oxytocin group. This study demonstrates that sublingual misoprostol is not as effective as intramuscular oxytocin for the active management of the third stage of labour. The incidence of PPH was significantly higher in the misoprostol group than in the oxytocin group. The third stage of labour was significantly longer in the misoprostol group than in the oxytocin group, with greater blood loss and lower hemoglobin levels. We also found that the need for additional uterotonics and side effects were significantly higher in the sublingual misoprostol group than in the intramuscular oxytocin group. Therefore, the results of the present study do not support the hypothesis (as suggested by several previous researchers) that misoprostol is as effective as oxytocin in managing the third stage of labor [16, 17]. Researchers highlight side effects as a limitation of the misoprostol group compared to the oxytocin group. Side effects (e.g., fever, chills) occurred in significantly more cases in the misoprostol group [18, 19, 20]. Even in studies where sublingual misoprostol was as effective as intramuscular oxytocin, a significantly higher incidence of adverse events was recorded in the misoprostol group compared to the oxytocin group [16, 17]. Although Mukta and Sahay reported that mean blood loss in the misoprostol group was higher (15.9% higher) than in the oxytocin group, they did not consider this difference to be statistically significant [16]. They also observed that the mean decrease in hemoglobin levels was greater in the misoprostol group (0.55 g/dl) than in the oxytocin group (0.48 g/dl), but this was not statistically significant could not be found. Similar results were observed in the present study, and this difference was found to be statistically significant. Additionally, the incidence of PPH in the misoprostol group was 20.8% compared to 14.5% in the oxytocin group, and the need for additional uterotonics was lower in the misoprostol group (22%) than in the oxytocin group. It was also found that the incidence was high (16%).[16] Studies with larger samples, such as the study by Atukunda *et al*. the studies conducted have highlighted the modest benefits of oxytocin compared to misoprostol, which is consistent with the observations of the present study [3]. In the above study, the risk of PPH was significantly higher in the misoprostol group compared with the oxytocin group. However, in this study he found no statistically significant difference between the two groups. The requirement of additional uterotonics, duration of the third stage of labor, and hemoglobin changes were similar in both groups. The study also reported the rate of adverse events (nausea, vomiting, fever, and shivering) to be significantly higher in the misoprostol group than in the oxytocin group. A Cochrane review evaluating the use of prostaglandins for the prevention of PPH, which included data from 72 trials involving 52,678 women, concluded that the use of misoprostol over conventional injectable uterotonics cannot be preferred as part of the management of the third stage of labour, particularly in low-risk women [6]. In the present study, we also found that sublingual misoprostol was significantly less effective in preventing PPH than the conventional uterotonic (intramuscular oxytocin) recommended for the active management of the third stage of labor. Despite encountering higher rates of blood loss, falls in hemoglobin levels, PPH, and adverse events, they termed misoprostol as effective as oxytocin. The mean blood loss with sublingual misoprostol and oxytocin groups was 320.58±244.12 ml vs. 253.27±171.74 ml; (P= 0.11). The mean duration of third stage of labor was similar and the difference was not statistically significant (6.65±3.47 vs. 6.08±3.07 minutes) (P=0.38), as well as need for additional oxytocics (14.5% vs. 7.2%; P=0.18) misoprostol and oxytocin, respectively. There was a significant difference in the side effect profile between the two groups. However, they found misoprostol to be as effective as oxytocin. In a study from Pakistan with a sample size of 70 (35 in each group) conducted by Aziz *et al*., the median blood loss in the misoprostol group was nearly 100 mL higher than in the oxytocin group. Yet, they did not find this to be statistically significant [21]. Again, this may be due to the small sample size. The frequency of side effects was also significantly higher in the misoprostol group than in the oxytocin group. Studies in other underdeveloped and developing countries have reported similar results [22, 23] but the misoprostol group showed greater blood loss, the need for additional uterotonics, and side effects has been done. They mainly focused on statistical differences in small sample size scenarios. Although fever was noted in almost all studies, Sringamwong *et al*. They found that it was dose-dependent, using different doses of misoprostol in their study, and reported lower rates of fever in the lower misoprostol dose group [24]. Therefore, the results of the present study indicate that

sublingual misoprostol is unlikely to be as effective as intramuscular oxytocin unless infrastructure deficiencies drive decision making. Most previous studies have insufficient sample sizes and their conclusions should be viewed with caution. This study has some limitations. First, our study did not evaluate neonatal safety and outcomes, which may contribute to the safety profile of misoprostol and oxytocin. Second, complicated deliveries, caesarean sections, or deliveries requiring induction of labour were not considered. Third, this study was a single-center study. Multicenter data might have allowed for a more representative analysis. Additionally, double-blind randomized controlled trials should be conducted with larger sample sizes that include pregnancy complications, delivery, and neonatal outcomes. A systematic review and meta-analysis should be conducted to evaluate the maternal and fetal outcomes of misoprostol use in the third stage of labour.

Conclusions

In this study, sublingual misoprostol was found to be less effective than intramuscular oxytocin in the active treatment of the third stage of labor. The results indicate a risk of increased blood loss, prolongation of the third stage of labor, need for additional uterotonics, increased risk of PPH, and increased incidence of side effects. The use of misoprostol is particularly important for resource-limited settings, where the availability and storage of heat-susceptible oxytocin are challenging.

Conflict of Interest: Not available

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