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EFFECT OF MISOPROSTOL VERSUS OXYTOCIN IN REDUCING POSTPARTUM HEMORRHAGE AFTER LABOR INDUCTION

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ABSTRACT

Introduction: Postpartum hemorrhage (PPH) is a life-threatening obstetric emergency that occurs after caesarean section (CS) or normal vaginal delivery (NVD). It may be defined as ≥500 mL hemorrhage after vaginal or ≥1000 mL hemorrhage after CS delivery. 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 low dose sublingual misoprostol with the standard 10 IU of intramuscular oxytocin in active management of third stage of labor. **Materials and Methods:** The study was a randomized clinical trial carried out at the Department of Gynaecology & Obstetrics, 250 Bedded General Hospital, Noakhali, Bangladesh from July to December 2021. One hundred (100) 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 100 women with term pregnancy in two groups of 50 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 (14.0% vs. 6.0% 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 (20.0% vs. 14.0% respectively; P=0.43). Among the women who were recruited (safety population), the frequencies of the expected side effects did not differ significantly between the two groups. In misoprostol group, side effects were shivering, fever, nausea and abdominal pains, while the oxytocin group abdominal pains, headaches and shivering. **Conclusion:** Misoprostol administered in the third stage of labor after labor induction by Oxytocin showed a trend towards significantly reducing postpartum blood loss and incidence of postpartum hemorrhage. Sublingual misoprostol has similar efficacy to standard intramuscular oxytocin in preventing PPH following vaginal birth. Misoprostol at 200 µg with its thermostability may be an effective alternative to intramuscular oxytocin in active management of third stage of labor.

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INTRODUCTION

Postpartum hemorrhage (PPH) is a life-threatening obstetric emergency that occurs after caesarean section (CS) or normal vaginal delivery (NVD). It may be defined as ≥500 mL hemorrhage after vaginal or ≥1000 mL hemorrhage after CS delivery [1,2]. PPH is one of the most common obstetric maternal complications and is among the three most common etiologies of maternal death worldwide [3]. The direct pregnancy-related maternal mortality rate in the United States is approximately 17 women per 100,000 live births. National U.S. statistics suggest that approximately 11% of these deaths are caused by postpartum hemorrhage (PPH) [4]. In industrialized countries, PPH usually ranks in the top 3 causes of maternal mortality, followed by hypertension and embolism [5]. In the developing world, several countries have maternal mortality rates in excess of 240 maternal deaths per 100,000 live births [6]. 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 [7]. 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. Up till now there is no single, universal definition of PPH. An estimated blood loss of more than 500ml following vaginal birth and 1000 ml following cesarean delivery has often been used for the diagnosis [8]. Another definition of PPH is a decline in hemoglobin levels (between ante and postpartum) of 10% [9]. In the third stage of labor, contraction of the myometrium is the primary mechanism by which the placenta separates and hemostasis is achieved as the blood vessels are constricted [10]. Primary PPH is caused by uterine atony in 80% or more of cases [11,12]. Active management of the third stage of labor has been shown to reduce total blood loss, and studies have not demonstrated any increased risk of placental entrapment [13,14]. Misoprostol, a synthetic

prostaglandin E1 analogue, is used for induction of labor. It stimulates uterine contractions which is an important mechanism in controlling PPH [15]. It has few side effects, stable at room temperature and is inexpensive. On the other hand, Oxytocin acts on its specific receptors present in the myometrium causing uterine contractions. Use of Oxytocin for labor induction in the first stage of labor may cause its receptors to be exhausted thus rendering its use to control PPH less effective. 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 [16]. Despite the preference for oxytocin, it is not always feasible to administer oxytocin in economically challenged environment, given its requirement for cool storage [17]. Carbetocin room temperature stable (RTS) is a new development by WHO to address the challenge of cold chain transport and storage with oxytocin; however, it also requires skilled personnel for parenteral administration and sterile equipment like oxytocin [18].

MATERIALS AND METHODS

The study was a randomized clinical trial carried out at the Department of Gynaecology & Obstetrics, 250 Bedded General Hospital, Noakhali, Bangladesh from July to December 2021. One hundred (100) 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 >6 cm), 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 fall 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 [9]. Period taken from delivery of fetus to delivery of placenta was noted. Blood loss was measured using a plastic drape for blood collection (the BRASSS-V Drape), which was placed under the buttocks before delivery; the calibrated blood collection receptacle was however opened only after delivery of the baby, clamping and cutting of the cord and drainage of amniotic fluid. 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 statistical analysed using the SPSS version 20. 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 100 women with term pregnancy in two groups of 50 each were studied. Demographic and base line characteristics of the two groups were comparable [Tables 1, 2]. 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 (14.0% vs. 6.0% 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 (20.0% vs. 14.0% 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=100)

Characteristics Misoprostol	**n=50 (%)**	**Oxytocin n=50 (%)**	**χ2**	**p value**
Age (years)				
20-29	21(42.0)	27(54.0)	1.54	0.46
30-39	27(54.0)	22(44.0)		
40 and above	2(4.0)	1(2.0)		
Parity				
0	9(18.0)	19(38.0)	6.37	0.174
1	16(32.0)	11(22.0)		
2	19(38.0)	16(32.0)		
3	4(8.0)	2(4.0)		
4	2(4.0)	2(4.0)		
Genotype				
AA	40(80.0)	40(80.0)	2.22	0.33
AS	10(20.0)	8(16.0)		
AC	0(0)	2(4.0)		
Blood group				
O-positive	27(54.0)	31(62.0)	5.39	0.37
A-positive	13(26.0)	6(12.0)		
B-positive	8(16.0)	10(20.0)		
O-negative	2(4.0)	1(2.0)		
B-negative	0(0)	1(2.0)		
A-negative	0(0)	1(2.0)		

Table-2: Mean gestational age, blood pressure and packed cell volume (N=100)

Characteristics	**Misoprostol (±SD)**	**Oxytocin (±SD)**	**t**	**p value**
Gestational age (weeks)	39.43 (1.17)	39.32 (1.17)	0.45	0.66
Mean arterial blood pressure	83.53 (10.42)	81.59 (9.57)	0.98	0.33
Intrapartum packed cell volume	32.92 (2.99)	32.17(3.13)	0.07	0.94

Table-3: Mean blood loss and mean duration of third stage of labour (N=100)

Characteristics	**Misoprostol n=50(±SD)**	**Oxytocin n=50 (±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=100)

Characteristics	**Misoprostol n=50 (%)**	**Oxytocin n=50 (%)**	**χ2**	**p value**
PPH (≥500 ml)	10(20.0)	7(14.0)	0.63	0.43
No PPH (<500 ml)	40(80.0)	43(86.0)		
Additional oxytocics required	7(14.0)	3(6.0)	1.77	0.18
Additional oxytocics not required	43(86.0)	47(94.0)		

Table-5: Side effect profile (N=13)

Characteristics	**Misoprostol n=8 (%)**	**Oxytocin n=5 (%)**	**χ2**	**p value**
Nausea	1(12.5)	0(0)		
Shivering	3(37.5)	1(20)	5.29	0.26
Fever	2(25.0)	0(0)		
Headache	0(0)	1(20)		
Abdominal pain	2(25.0)	3(60)		

DISCUSSION

Oral Misoprostol has rapid onset of action, with some drawbacks (fever, shivering) that are dose-dependent [18]. This is mostly due to the fact that it reaches a higher peak than other routes, and lasts for a shorter period [19, 20]. However, rectal routes have slower onset of action, lower peak, and a longer duration of action and less adverse effects than the oral route. In our study total 100 women with term pregnancy in two groups of 50 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). Misoprostol use is found to be more practical alternative in low-resource settings due to the fact of its low cost, easy storage and stability at room temperature. In this randomized comparative study, we found low dose 200 µg sublingual misoprostol and 10 IU intramuscular oxytocin after vaginal delivery similarly effective in active management of third stage of labor with comparable mean blood loss. Though overall

blood loss with oxytocin was less, suggesting better efficacy; the difference was not statistically significant. This finding is in agreement with previous studies carried out in Nigeria by Afolabi et al. [18] and Oboro and Tabowei [19] using higher dose of misoprostol. The proportion of subjects in the misoprostol group who experienced PPH was similar to that of oxytocin. The need for additional oxytocics for the treatment of PPH between the two groups was also comparable. This finding agrees with works of Afolabi et al. [18] Oboro and Tabowei, [19] and Chaudhuri et al. [20] The use of BRASSS-V drapes also ensured a more precise determination of postpartum blood loss and this may have reduced cases that would have been erroneously regarded as cases of PPH [21]. Misoprostol was approximately significantly effective in lowering the decrease in hemoglobin level in women whom labor was induced by Oxytocin as compared to those who received intravenous Oxytocin postpartum. This decrease in hemoglobin levels is clinically important, since it decreases the total iron requirements needed for a patient to restore secondary to her blood loss postpartum [22]. This will add another benefit to the physician and the patient by better compliance to the prescribed iron therapy. The secondary outcomes of EBL and mean drop in hemoglobin levels were also higher in Oxytocin group with a trend towards significance, thus, supporting furthermore the hypothesis of Oxytocin receptor desensitization [23]. We relied on 10% Hb decrease as the primary outcome because it is not subject to any personal bias though is affected by many factors other than the blood lost during delivery (e.g. hemoconcentration found in conditions with contracted plasma volume. Visual estimation of blood loss enables the obstetrician to interfere earlier to manage any excessive blood loss and is used anyway in every day's practice. Although the actual blood loss is an objective measure and is less subject to human error but it is time consuming and impractical to be used for diagnosis and was not welcomed by most obstetricians [18,22,23]. The side effect profile was similar in the misoprostol group compared with oxytocin group. This is consistent with previous studies. The noted incidence of side effects with misoprostol group were however lower than that of previous studies where higher doses of misoprostol were used [18,19,22,23,24]. Availability of parenteral oxytocics for management of third stage of labor remains largely a hospital-based practice confined mostly to urban centers. In developing countries, most deliveries take place outside the hospital therefore making the use of parenteral oxytocics unlikely and even in the hospital-based deliveries, the challenge of maintaining cold chain for oxytocin is enormous.

CONCLUSION

Misoprostol administered in the third stage of labor after labor induction by Oxytocin showed a trend towards significantly reducing postpartum blood loss and incidence of postpartum hemorrhage. 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.

Conflict of Interest: None.

REFERENCES:

1. Andolina K, Daly S, Roberts N, et al. Objective measurement of blood loss at delivery: is it more than a guess? *American Journal of Obstetrics & Gynecology*. 1999;180:p. S69.
2. Ueland K. Maternal cardiovascular dynamics. VII. Intrapartum blood volume changes. *American Journal of*

Obstetrics and Gynecology. 1976; 126(6) :671–677.

3. Stafford I, Dildy GA, Clark SL, Belfort MA. Visually estimated and calculated blood loss in vaginal and cesarean delivery. *American Journal of Obstetrics and Gynecology*. 2008;199(5):p. 519.
4. Mousa HA, Alfirevic Z. Treatment for primary postpartum haemorrhage. *Cochrane Database of Systematic Reviews*. 2007;(1)CD003249
5. Lu MC, Fridman M, Korst LM, et al. Variations in the incidence of postpartum hemorrhage across hospitals in California. *Maternal and Child Health Journal*. 2005;9(3):297–306.
6. Callaghan WM, Kuklina EV, Berg CJ. Trends in postpartum hemorrhage: United States, 1994–2006. *American Journal of Obstetrics and Gynecology*. 2010;202(4):p. 353.
7. Creanga AA, Syverson C, Seed K, Callaghan WM. Pregnancy-related mortality in the United States, 2011–2013. Obstet Gynecol. 2017; 130:366-73.
8. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014; 2:e323-33.
9. WHO, UNICEF, UN Population Fund and the World Bank. Trendsin maternal mortality: 1990 to 2010. WHO, UNICEF, UNFPA and The World Bank estimates. Geneva: World Health Organization, 2012.
10. Leduc D, Senikas V, Lalonde AB, et al. Active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. J Obstet Gynaecol Can. 2009; 31:980-93.
11. Atukunda EC, Mugyenyi GR, Obua C, et al. Measuring postpartum haemorrhage in low resource settings: the diagnostic validity of weighed blood loss versus quantitative changes in hemoglobin. PloS One 2016; 11:e0152408.
12. Mousa HA, Blum J, Abou El Senoun G, Shakur H, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database Syst Rev. 2014; 2:CD003249.
13. Bateman BT, Berman MF, Riley LE, Leffert LR. The epidemiology of postpartum hemorrhage in a large nationwide sample of deliveries. Anesth Analg. 2010; 110:1368-1373.
14. Wetta LA, Szychowski GM, Seals S, et al. Risk factors for uterine atony/postpartum hemorrhage requiring treatment after vaginal delivery. Am J Obstet Gynecol. 2013; 209:51- e1.
15. Begley CM, Gyte GM, Devane D, Mcguire W, Weeks A. Active versus management for women in the third stage of labour. Cochrane Database Syst Rev. 2015; 3:CD007412.
16. Jangsten E, Mattsson L, Lyckestam I, Hellstorm A, Berg A. A comparison of active management and expectant management of the third stage of labour: a Swedish randomized controlled trial. BJOG. 2011; 118:362-369.
17. Alfirevic Z, Aflaifel N, Weeks A. Oral misoprostol for induction of labour. Cochrane Database Syst Rev. 2014; 6:CD00133.
18. Afolabi EO, Kuti O, Orji EO, Ogunniyi SO. Oral misoprostol versus intramuscular oxytocin in the active management of the third stage of labour. Singapore Med J 2010; 51:207-11.
19. Oboro VO, Tabowei TO. A randomized controlled trial of misoprostol versus oxytocin in the active management of the third stage of labour. J. Obstet Gynaecol 2003; 23:13-6.
20. Chaudhuri P, Biswas J, Mandal A. Sublingual misoprostol versus intramusanlar oxytocin for prevention of post-partum haemorrhage in low-risk

women. Int J Gynaecol Obstet 2012; 116:138-42.
21. Patel A, Goudar SS, Geller SE. Drape estimation versus visual assessment. Int J Gynaecol Obstet 2006; 93:320-4.
22. Enakpene CA, Morhason-Bello IO, Enakpene CO, Arowojolu AO, Omigbodun AO. Oral misoprostol for the prevention of primary post-partum hemorrhage during third stage of labour. J Obstet Gynaecol Res 2007;33:810-7.
23. Badejoko OO, Ijarotimi OI, Awowole IO, Loto OM, Badejoko BO, Olaiya D, et al. Adjunctive rectal misoprostol versus oxytocin infusion for prevention of post-partum haemorrhage in women at risk: A randomized controlled trial. J Obtet Gynaecol Res 2012; 38:1294-301.
24. Robinson C, Schumann R, Zhang P, Young RC. Oxytocin induced desensitization of the oxytocin receptor. Am J Obstet Gynecol. 2003; 188:497-502.