International Journal of Gynaecology and Obstetrics Research
www.gynaecologyjournal.in
E-ISSN: 2663-3612, P-ISSN: 2663-3604
Received Date: 25-05-2019 Accepted Date: 27-06-2019; Published: 04-07-2019
Volume 1; Issue 3; 2019; page No. 52-57

Effect of misoprostol as compared to oxytocin in reducing postpartum hemorrhage after labor induction: A prospective randomized controlled trial

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Abstract
Background: The use of Oxytocin for labor induction may cause receptor exhaustion and thus making its use in the third stage of labor ineffective in reducing postpartum blood loss as compared to other uterotonics.
Objective: To investigate whether rectally administered Misoprostol during the third stage of labor is more efficient than Oxytocin in reducing postpartum blood loss in patients with initial labor induction by Oxytocin.
Methods: In a prospective randomized controlled trial, women who were admitted for labor induction using Oxytocin were randomly assigned to receive either 1000 mcg Misoprostol per rectum (study group) or 20 units Oxytocin intravenously at a rate of 150ml/h (control group) in the third stage of labor immediately following cord clamping. The third stage of labor was managed actively in all patients. Other uterotonics were administered only if blood loss seemed more than usual. Blood loss was estimated by the obstetrician and differences in hemoglobin were measured before and after delivery.
Results: Multivariate analysis showed that the adjusted odds ratio regarding estimated blood loss was 1.96, hence patients in the Oxytocin group are more likely to have blood loss >500 compared to patients in the Misoprostol group (P=0.07). The percent drop in hemoglobin was 1.21 more in the Oxytocin group with a trend towards significance (p=0.08). The adjusted beta coefficient was 1.29 regarding percent drop in hematocrit, thus patients in the Oxytocin group tend to have higher drop in hematocrit There was no difference in postpartum diarrhea or fever but shivering was confined to the Misoprostol group (8.4%).
Conclusion: Rectal 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.

Keywords: Postpartum hemorrhage, Labor induction, Oxytocin,misoprostol, uterine atony

Introduction

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) [1]. In industrialized countries, PPH usually ranks in the top 3 causes of maternal mortality, followed by hypertension and embolism [2]. In the developing world, several countries have maternal mortality rates in excess of 240 maternal deaths per 100,000 live births [3]. 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 [2]. The most recent Practice Bulletin from the American College of Obstetricians and Gynecologists reported that aside from the risk of maternal death due to PPH, the sequelae may include hypovolemic shock, adult respiratory distress syndrome, pituitary necrosis (Sheehan syndrome), coagulopathy, and the loss of fertility [4].

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 [5]. Another definition of PPH is a decline in hemoglobin levels (between ante and postpartum) of 10% [6].

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 [7]. Primary PPH is caused by uterine atony in 80% or more of cases [8, 9]. 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 [10, 11]. The routine use of oxytocic drugs remains the most effective with the fewest adverse events [4].

Misoprostol, a synthetic prostaglandin E1 analogue, is used for induction of labor. It stimulates uterine contractions which is an important mechanism in controlling PPH [12]. 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 [13].

The fact that the incidence of labor induction in obstetrics is high at our service (which is a well-established risk factor for PPH) and along with the hypothesis of Oxytocin receptor exhaustion after labor induction with Oxytocin, we aimed to compare the effect of Oxytocin (used traditionally in the third stage of labor) with that of rectal Misoprostol in reducing the amount of blood loss in our obstetric population.

Materials and Methods

Our study was carried out at Makassed General Hospital, a tertiary-level maternity unit performing about 1000 deliveries annually. It took place during the period between November 2016 and December 2017. The study was approved by the Ethics and Research Committee.

Women whose ages range between 18 and 40 years, with single viable pregnancy, in cephalic presentation, at full term and whom labor was induced by Oxytocin were eligible for inclusion.

Exclusion criteria were prophylactic use of other uterotonics, retained placenta, delivery by Cesarean section, and attending refusal to participate. In order to compare the effect of each medication alone on the amount of blood loss, we then excluded those patients who received blood transfusion or additional uterotonics since this will affect the drop in Hb. All admitted patients who were eligible were included in the study. Then, the parturients were randomly assigned according to computer generated numbers to receive either 1000mcg of Misoprostol rectally or 20 units of Oxytocin intravenously to run at a rate of 150ml/hr. Informed consent was obtained from the patients. The medications were given just after cord clamping and before delivery of the placenta. Active management of the third stage of labor was carried out simultaneously with early cord clamping, gentle downward traction of the placenta to hasten its delivery, and uterine massage in addition to the uterotonic according to assignment of the patient. Assessment of the uterine condition was done by the obstetrician or his assistant, together with visually estimating the amount of blood loss. Once uterine atony or EBL of more than 500 ml was noticed, another uterotonics was administered according to the condition and at the discretion of the obstetrician.

Failure to achieve adequate uterine contraction and to control PPH by the routine uterine massage urged the use of either different uterotonics or surgical intervention if necessary. Blood transfusion was ordered for the cases whose visual estimation of blood loss was more than 1000ml or when the patient was hemodynamically unstable. A base Hb and hematocrit levels were withdrawn on admission and another reading 12 hours postpartum.

The primary outcome was a ≥10% drop in hemoglobin, while the secondary outcomes were the mean hemoglobin drop, the mean estimated blood loss (EBL), 2g/dl drop in hemoglobin, fever > 38°C, diarrhea, and shivering.

Statistical analysis

The Statistical Package for Social Sciences (SPSS, version22.0) was used for data analysis. Chi square was used for dichotomous while student's t-test was used for continuous variables. Patients who received extra uterotonics or received blood transfusions, though were accounted for in the description of outcome, yet they were excluded in the final analysis since this will affect the drop in Hb. To adjust for the effect of confounding variables, we carried out multivariate regression analyses, specifically, logistic regression for categorical variables, or linear regression for continuous variables. P of ≤0.05 was considered significant.

Results

The 616 women who met the inclusion criteria for the study were randomly assigned to receive 1000mcg Misoprostol rectally (study group) or 20 units of Oxytocin intravenously (control group). However, 227 cases were excluded: 110 received additional uterotonics prophylactically, 65 due to physician refusal to participate in the study, and 52 underwent C section. Thus, we were left with 389 women, 171 in the study group and 218 in the control group (Figure. 1). Those who required extra uterotonics were then excluded from the analysis aiming to compare the effect of each medication alone on Hb drop. The final number of patients analyzed was 383, 168 in the study group and 215 in the control group.

Comparison between the two groups showed no differences regarding the selected maternal characteristics Table 1). Intrapartum characteristics were similar in both groups, including induction cause, proportion of women who received epidural anesthesia, length of first and second stages of labor and birth weight (Table 1).

The mean admission hemoglobin was 0.01 higher in the Oxytocin group compared to the Misoprostol group while the mean postpartum hemoglobin was 0.15 lower in Oxytocin group yet the difference is not statistically significant. The mean hemoglobin drop was 0.01 higher in patients who received Oxytocin with a trend towards significance (P=0.05). Similarly, the difference in percent drop in hemoglobin was approximately significant between the two groups being 1.39 more in the Oxytocin group. There was a no significant difference between the two groups with regard to ≥ 10% drop in hemoglobin which occurred in 38.1% and 44.2% of the participants in the Misoprostol and Oxytocin group respectively with P=0.23 (CI 95% 0.85-1.94). The 2g/dl drop in hemoglobin was similar in both groups (11.9% vs.17.7% for the Misoprostol and Oxytocin groups respectively). There was no statistical difference with respect to mean hematocrit level at admission and postpartum, the latter being 0.45 lower in the Oxytocin group. The percent drop in hematocrit was 1.45 more in the Oxytocin group showing a trend to significance (P=0.08). Similarly, the estimated blood loss (≥500) was 1.96 times lower in the Misoprostol group (6.5% versus 12.1% in the Oxytocin group, P=0.07) (Table 2).

Numbers needed to treat (NNT) to prevent one case of PPH was estimated to be 8.7 (CI 95%, 4.4 to 537.0]. Four participants needed blood transfusion and all were in the Oxytocin group. One patient in the Oxytocin group underwent bilateral uterine artery ligation to control her bleeding. Shivering was confined to the

Misoprostol group and occurred in 11 women (8.4%) of that group and all were self-limiting and not distressing to the patients. Fever (> 38°C PO) was present in 21 women in the Misoprostol group (13.5%) and only 1 woman in the Oxytocin group (0.64%). Diarrhea occurred in 7 (5.3%) women in the Misoprostol group and none of the Oxytocin group. It was self-limiting and required no treatment.

After controlling for all the variables listed at the end of Table 3, the results of the multivariate analysis showed that the adjusted odds ratio regarding estimated blood loss was 1.96, hence patients in the Oxytocin group are more likely to have blood loss >500 compared to patients in the Misoprostol group (P=0.07). Moreover, the adjusted beta coefficient was 0.14, so patients in the Oxytocin group are more likely to have difference in hemoglobin though the difference is not statistically significant (P=0.10). The percent drop in hemoglobin was 1.21 more in the Oxytocin group with a trend towards significance (p=0.08). The adjusted beta coefficient was 1.29 regarding percent drop in hematocrit, thus patients in the Oxytocin group tend to have higher drop in hematocrit (Table 3).

Discussion

Evidence linking labor induction with postpartum blood loss was found in a West Indian clinical trial that noted a statistically significant increase in blood loss in women who experienced all forms of labor induction when compared to spontaneous labor onset (14). Moreover, a Cochrane review comparing Oxytocin alone for cervical ripening and induction of labor versus expectant management found there was an overall relative risk of 1.24 (95% CI, 0.856 –1.81) for the development of PPH (15). The prophylactic administration of a uterotonic agent to reduce blood loss as part of active management of third stage, either immediately after delivery of the baby or after delivery of the placenta is a generally accepted practice, and prospective trials showed that such use decreases blood loss and reduces the need for therapeutic oxytocics (16, 17). 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. 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.

Arrowsmith *et al* working on myometrial stripes in vitro, compared spontaneous with Oxytocin-induced labor and demonstrated significant reduction in the Oxytocin binding sites in the induced labor group (13). Continuous exposure of human myometrial cells to Oxytocin leads to a significant loss in their capacity to respond to Oxytocin, and that is believed to be due to Oxytocin receptor desensitization. Robinson *et al* observed Oxytocin receptor desensitization starting at 3 hours of exposure of human myometrial cells to Oxytocin in vitro (21).

Our study showed that 1000mcg of postpartum rectally administered 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 was shown by the lower 10% or more drop in hemoglobin levels in the study group, where odds ratio was 1.29 (CI 95%, 0.85-1.94), demonstrating its protective effects. 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. 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. 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. There was no significant difference between the two groups regarding the distribution of risk factors for PPH (duration of labor induction, macrosomia, instrumentation, and history of PPH (Table 1). The side effects of the study medication were mild, well tolerated by the patient and did not require significant management.

The limitations of our study were the inability to be double blinded and to increase the sample size due to financial reasons. To our knowledge, no previous study has tested the hypothesis of Oxytocin receptor desensitization in vivo on patients undergoing labor induction by Oxytocin. Our study showed that Misoprostol in a high dose 1000mcg given rectally together with the active management of the third stage in labor following induction by Oxytocin is effective in reducing blood loss postpartum; however more numbers are needed to prove its efficacy in decreasing incidence of uterine atony.

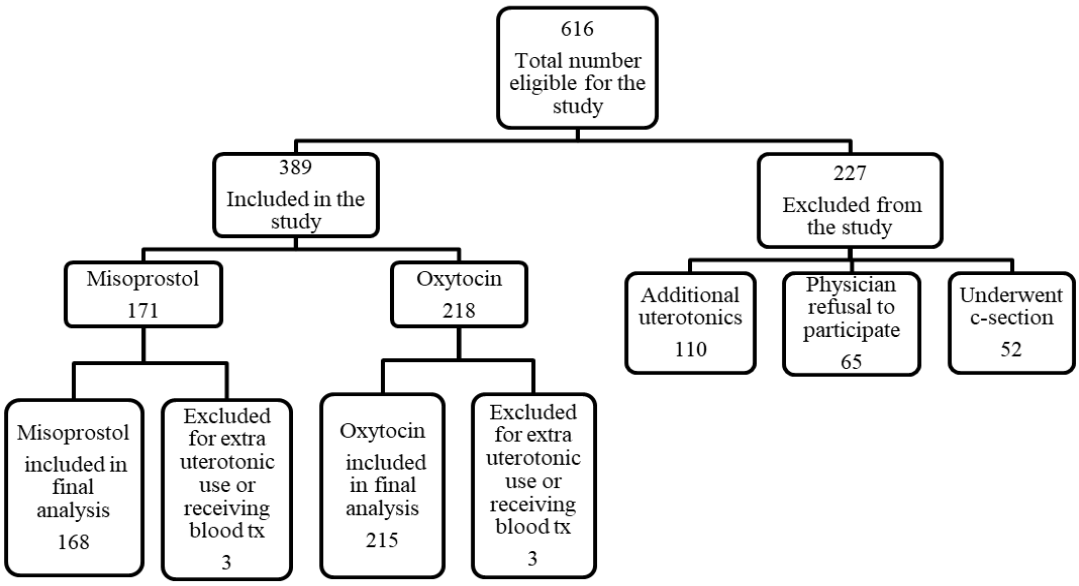

Fig 1: Distribution of participants

Table 1: Baseline, clinical, and intrapartum characteristics of patients

	Group		
	Misoprostol N=168	**Oxytocin N=215**	**P-value**
Age, mean(±SD)	28.28 ± 5.83	28.22 ± 6.03	0.92
Gestational age, mean(±SD)	38.67 ± 1.24	38.49 ± 1.79	0.26
Gender, male	90 (53.6)	99 (46.0)	0.14
Followed by private attending	168 (100.0)	213 (99.1)	0.21
Class, mean (±SD)	3.98 ± 0.19	3.95 ± 0.32	0.38
1	0 (0.0)	1 (0.5)	0.73
2	1 (0.6)	2 (0.9)	
3	2 (1.2)	4 (1.9)	
4	165 (98.2)	207 (96.3)	
5	0 (0.0)	1 (0.5)	
Gravida, mean(±SD)	2.80 ± 1.75	2.60 ± 1.58	0.22
PARA, mean(±SD)	1.35 ± 1.25	1.24 ± 1.23	0.42
Aborta, mean(±SD)	0.46 ± 0.80	0.35 ± 0.67	0.17
History of postpartum hemorrhage	2 (1.2)	3 (1.4)	1.00
Induction cause			0.41
Elective	132 (78.6)	156 (72.6)	
Postdatism	6 (3.6)	12 (5.6)	
PROM	30 (17.9)	44 (20.5)	
HDP	0 (0.0)	2 (0.9)	
Macrosomia	0 (0.0)	1 (0.5)	
Intrapartum characteristics			
First stage of delivery(min), mean(±SD)	386.19 ± 211.70	392.42 ± 230.92	0.78
Second stage of labor(min), mean(±SD)	27.06 ± 26.34	24.77 ± 23.65	0.37
Birth weight (g), mean(±SD)	3207.71 ± 475.19	3311.86 ± 2157.03	0.54
Instruments used as vacuum	35 (20.8)	32 (14.9)	0.13
Epidural anesthesia	76 (45.2)	91 (42.3)	0.57
ATONY	31 (18.5)	51 (23.7)	0.21
PPH	10 (6.0)	27 (12.6)	0.03
Episiotomy	147 (87.5)	200 (93.0)	0.07
Treatment	41 (24.4)	61 (28.4)	0.38
Transfusion	0 (0.0)	3 (1.4)	0.26

Table 2: Outcomes in both intervention groups

		Misoprostol N=168	Oxytocin N=215	β (95% CI)	P-value
Hemoglobin (g/dl)	Admission	11.97 ± 1.24	11.98 ± 1.19	0.01 (-0.23 ; 0.26)	0.92
	Postpartum	10.96 ± 1.24	10.81 ± 1.29	-0.15 (-0.40 ; 0.11)	0.26
	Drop	0.09 ± 0.06	0.10 ± 0.07	0.01 (0.00 ; 0.03)	0.05
	Difference	1.04 ± 0.81	1.21 ± 0.95	0.17 (-0.01 ; 0.35)	0.07
	Percent drop	8.55 ± 6.32	9.95 ± 7.47	1.39 (-0.02 ; 2.81)	0.05
				OR (95% CI)	
	Difference				
	<2	148 (88.1)	177 (82.3)	Reference	
	≥2	20 (11.9)	38 (17.7)	1.59 (0.89 – 2.85)	0.12
	Percent drop				
	<10%	104 (61.9)	120 (55.8)	Reference	
	≥10%	64 (38.1)	95 (44.2)	1.29 (0.85 – 1.94)	0.23
				β (95% CI)	
Hematocrit	Admission	35.64 ± 3.47	36.77 ± 18.32	1.13 (-1.69 ; 3.95)	0.43
	Postpartum	32.85 ± 3.54	32.40 ± 3.61	-0.45 (-1.17 ; 0.27)	0.22
	Difference	2.94 ± 2.55	4.53 ± 18.49	1.59 (-1.24 ; 4.42)	0.27
	Drop	0.08 ± 0.07	0.09 ± 0.09	0.01 (-0.002 ; 0.03)	0.08
	Percent drop	8.07 ± 6.70	9.52 ± 8.80	1.45 (-0.16 ; 3.06)	0.08
				OR (95% CI)	
	Percent drop				
	<10%	110 (65.5)	128 (59.5)	Reference	
	≥10%	58 (34.5)	87 (40.5)	1.29 (0.85 – 1.96)	0.23
				OR (95% CI)	
Estimated blood loss	<500	157 (93.5)	189 (87.9)	Reference	
	≥500	11 (6.5)	26 (12.1)	1.96 (0.94 – 4.10)	0.07

Table 3: Multivariate analysis for the effect of the intervention on the outcomes

	AOR (95% CI)	P-value
Estimated blood loss (reference:<500)		
Intervention`	1.96 (0.94 - 4.10)	0.07
	aβ (95% CI)	P-value
Difference Hemoglobin		
Intervention	0.14 (-0.03 ; 0.31)	0.10
PARA	-2.25 (-2.93 ; -1.56)	<0.0001
Drop Hemoglobin		
Intervention	0.01 (-0.001 ; 0.03)	0.08
PARA	-0.17 (-0.23 ; -0.12)	<0.0001
Drop Hemoglobin percent		
Intervention	1.21 (0.13 ; 2.56)	0.08
PARA	-17.42 (-22.83 ; -12.02)	<0.0001
Difference Hematocrit		
Intervention	1.59 (-1.24 ; 4.42)	0.27
Drop Hematocrit		
Intervention	0.01 (-0.003 ; 0.03)	0.11
PARA	-0.15 (-0.22 ; -0.09)	<0.0001
Drop Hematocrit percent		
Intervention	1.29 (-0.27 ; 2.86)	0.11
PARA	-15.40 (-21.68 ; -9.12)	<0.0001

Variables included in the model were: age; gestation age; gravida; PARA (reference: by unit increase of 10); Aborta; epidural anesthesia (reference: no); birth weight.

AOR: Adjusted odds ratio
Aβ: Adjusted Beta Coefficient

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