



A comparative study to assess the efficacy and tolerability of per rectal misoprostol and intravenous oxytocin in prevention of primary postpartum haemorrhage in a tertiary care hospital

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ABSTRACT

Postpartum haemorrhage (PPH) is the most common cause of obstetrical haemorrhage, accounting for 16% of maternal mortality in India. The standard uterotonic agent used in active management of the third stage of labour (AMTSL) has traditionally been oxytocin or a combination of oxytocin and ergometrine maleate. Misoprostol, a new uterotonic drug has several advantages over oxytocin which makes it suitable for use in peripheral health centers. Hence, we conducted this study with an objective to compare efficacy and safety of per rectal (PR) Misoprostol with intravenous (IV) Oxytocin in prevention of primary PPH. It was a prospective, randomized controlled trial conducted at Vanivilas hospital attached to BMCRI. 200 pregnant women were enrolled in the study and were randomized to receive either IV oxytocin 10IU or PR misoprostol 800µg immediately after delivery of the anterior shoulder of the baby. Efficacy parameters were incidence of primary PPH, mean blood loss, mean haemoglobin deficit and mean haematocrit deficit. Safety profile was noted in both the groups. Incidence of primary PPH was similar in both groups ($p=0.70$). There was no significant difference between both groups in terms of mean blood loss ($p=0.13$), haemoglobin deficit ($p=0.63$) and haematocrit deficit ($p=0.57$). Shivering and fever were more common in the misoprostol than the oxytocin group ($p<0.05$), but these were mild and self-limiting. In conclusion, PR misoprostol is as efficacious as IV oxytocin, and hence can be preferred in low resource setting areas.

Keywords: Postpartum Haemorrhage, Misoprostol, Oxytocin, Efficacy, Tolerability.

INTRODUCTION

Postpartum haemorrhage (PPH) is the most common cause of obstetrical haemorrhage. It accounts for one quarter of maternal mortality worldwide and 16% in India [1]. PPH is defined as any amount of bleeding from or into the genital tract following birth of the baby upto the end of puerperium which adversely affects the general condition of the patient as evidenced by rise in pulse rate and fall in blood pressure. Primary PPH is the bleeding occurring within 24 hours after delivery of baby [2]. Uterine atony is the most common cause of primary PPH.

Active management of the third stage of labour (AMTSL) which includes early cord clamping, controlled cord traction for placental delivery and intravenous uterotonic therapy is an effective measure to prevent PPH [3]. The standard uterotonic agent has traditionally been oxytocin or a combination of oxytocin and ergometrinemaleate [4]. These uterotonic agents stimulate uterine contractions which cause compression of the maternal blood vessels at the placental site after delivery of the placenta and controls bleeding [5].

The disadvantages with oxytocin are its short half-life, due to which it has to be administered by continuous IV infusion in order to maintain steady state plasma concentration for continued action, its instability at room temperature, hence need for continuous refrigeration, both these requirements are difficult to meet at primary health care settings.

Prostaglandins, a new group of uterotonics, are increasingly being employed as adjunctive therapy to standard oxytocin and ergometrine to treat PPH resulting from uterine atony [7]. Misoprostol is a prostaglandin E₁ analogue which selectively binds to myometrial EP₂/EP₃ prostanoic receptors, thereby promoting uterine contractility [6]. It may be given by oral, sublingual, intravaginal, rectal route or via direct intrauterine placement. Its advantages over oxytocin are its low cost, thermostability, light stability, longer shelf life and lack of requirement for sterile needles and syringes for administration, making it an attractive option for use in low resource setting areas. A frequently reported side-effect of misoprostol is the occurrence of shivering and pyrexia. Side-effects are less marked when the rectal route of administration is used [6].

In a developing country like ours where resources are scarce, misoprostol can emerge as an effective tool in prevention and treatment of PPH. Hence we conducted this study with the objectives of comparing the efficacy and tolerability of per rectal Misoprostol to intravenous Oxytocin in prevention of primary PPH

EXPERIMENTAL SECTION

It was a Prospective, Randomized, Open label, Parallel group, Comparative study conducted at Vanivilas hospital attached to BMCRI. 200 pregnant women were selected by simple random sampling and included in the study as per the selection criteria. Inclusion criteria were pregnant women at term expected to have vaginal delivery and those giving written informed consent. Exclusion criteria were women not giving written informed consent, expected to undergo caesarean section, known allergic or hypersensitivity reaction to prostaglandin administration, heart disease associated with pregnancy, uterine tumour associated with pregnancy, secondary PPH, if any one of risk factors for PPH are present (grand multipara, multiple gestation, polyhydramnios, anaemia or presence of blood coagulation disorder, history of antepartum haemorrhage, history of PPH in previous pregnancies, prolonged labour or precipitate labour). Ethics committee clearance was taken. Study subjects were then randomly assigned to 2 groups of 100 each. Group 1: received 800 µg of PR misoprostol and Group 2: received 10 IU of IV oxytocin in 500 ml of normal saline (NS)

Either of the drugs was given to the patient at the time of delivery of anterior shoulder of the baby. Demographic data, history, clinical examination (general and obstetrical), details of uterotonic given, efficacy and tolerability outcomes were recorded in the study proforma. Efficacy was assessed in terms of primary and secondary outcomes. Primary outcome was taken as the incidence of PPH in both groups. Secondary outcomes were taken as amount of blood loss, use of other oxytocics, if patient required blood transfusion, hysterectomy, shift to ICU, death due to PPH, laboratory investigations (decrease in haematocrit and haemoglobin concentration 24 hours postpartum). Tolerability was assessed by recording adverse drug reactions to the uterotonics for a duration of 24 hr post administration. Data in the two groups was analysed using percentages, mean, standard deviation, student t-test. Level of significance was taken as 5%. Power of the study was taken as 80% and confidence interval 95%.

RESULTS AND DISCUSSION

A total of 200 women were included in the study, 100 in the oxytocin group and 100 in the misoprostol group. Baseline characteristics in both the groups were similar as shown in table no 1.

Table No 1: Baseline characteristics in the two groups

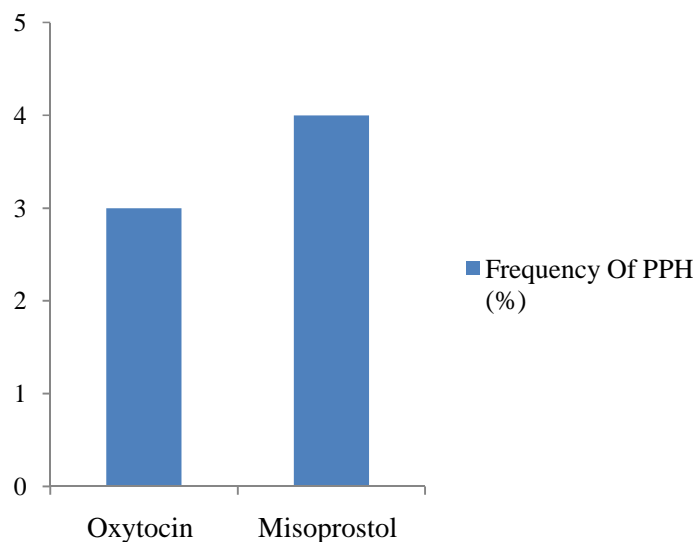
Characteristics	Oxytocin group Mean (SD)	Misoprostol group Mean (SD)	p value	CI
Age (Years)	28.52 (3.10)	28.82 (2.80)	0.4735	-1.12 to 0.52
POG (Weeks)	36.26 (0.59)	36.28 (0.47)	0.7912	-0.16 to 0.12
Parity	1.11 (0.87)	1.29 (0.90)	0.1520	-0.42 to 0.06
Haemoglobin (g/dl)	12.45 (0.93)	12.53 (0.98)	0.5544	-0.35 to 0.18
Haematocrit (%)	33.78 (1.68)	33.86 (1.49)	0.7220	-0.52 to 0.36

Incidence of PPH was taken as the primary outcome. The incidence of PPH in the two groups is shown in table no 2. Out of 100 women in the oxytocin group 3 of them had PPH- 2 had severe PPH and one had mild. These cases received additional oxytocin until the bleeding stopped. 2 pints of blood was transfused to 1 patient. In the misoprostol group 3 out of 100 women had PPH. Additional 200µg of PR misoprostol was given in these cases. There was 1 case of severe PPH in this group which required 2 pints of blood transfusion. There was no significant difference in the incidence of PPH in two groups ($p>0.05$)

Table No 2: Incidence of primary outcome in the two groups

Groups	No of PPH cases	%	p value	Confidence interval (CI)
Oxytocin	3/100	3	0.7004	-0.04 to 0.06
Misoprostol	4/100	4		

Figure No 1 : Frequency of PPH in the two groups



There was no statistically significant differences in the two groups in terms of secondary outcomes(table no 3) .

Figure No 2: Mean blood loss in the two groups

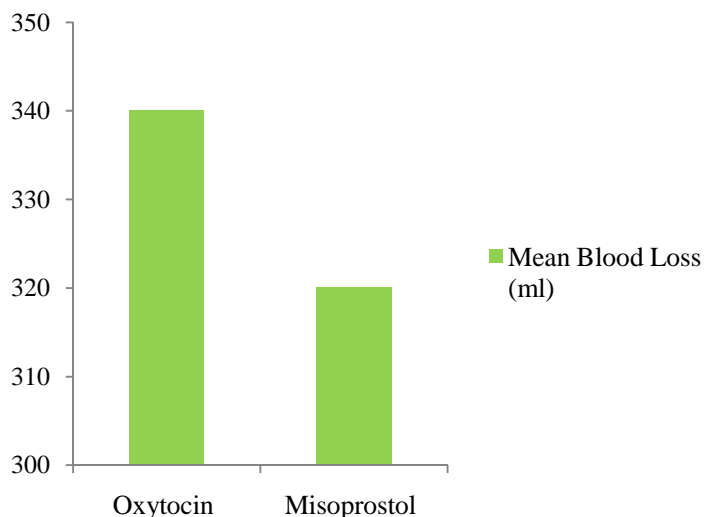


Figure No 3: Mean Hb deficit in the two groups

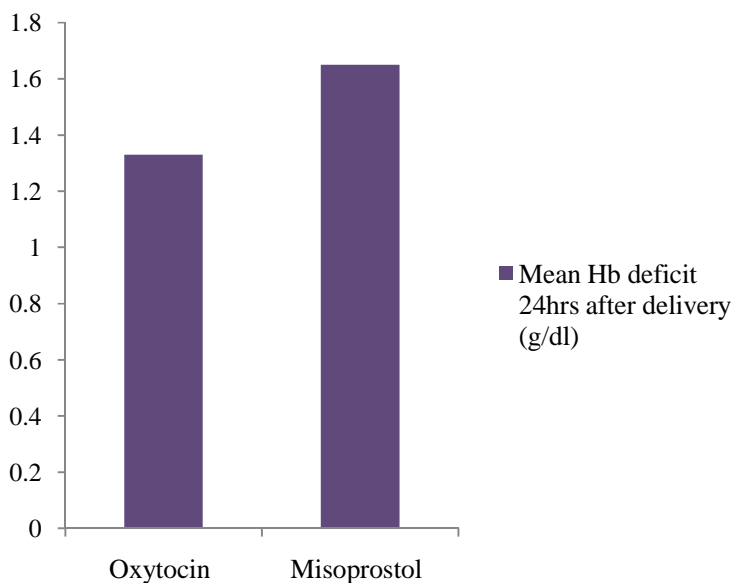


Figure No 4: Mean haematocrit deficit in the two groups

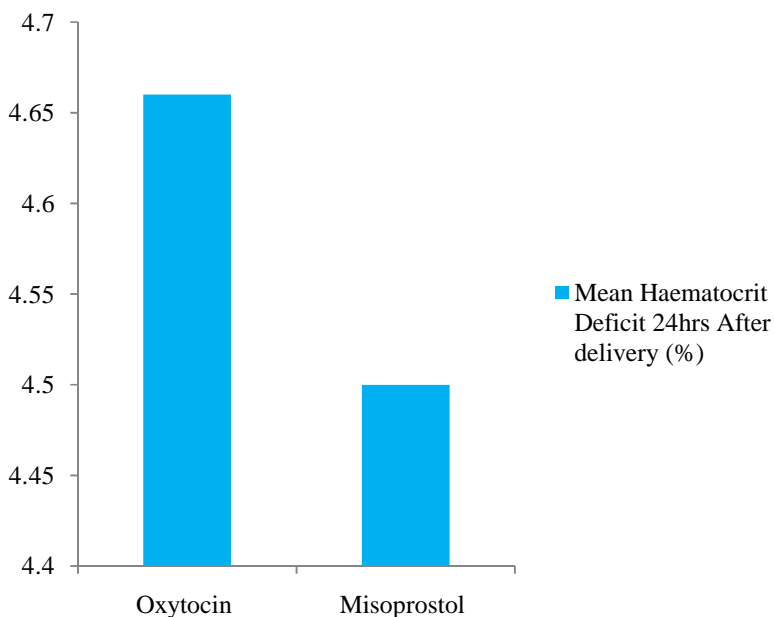


Table No 3: Secondary outcomes in the two groups

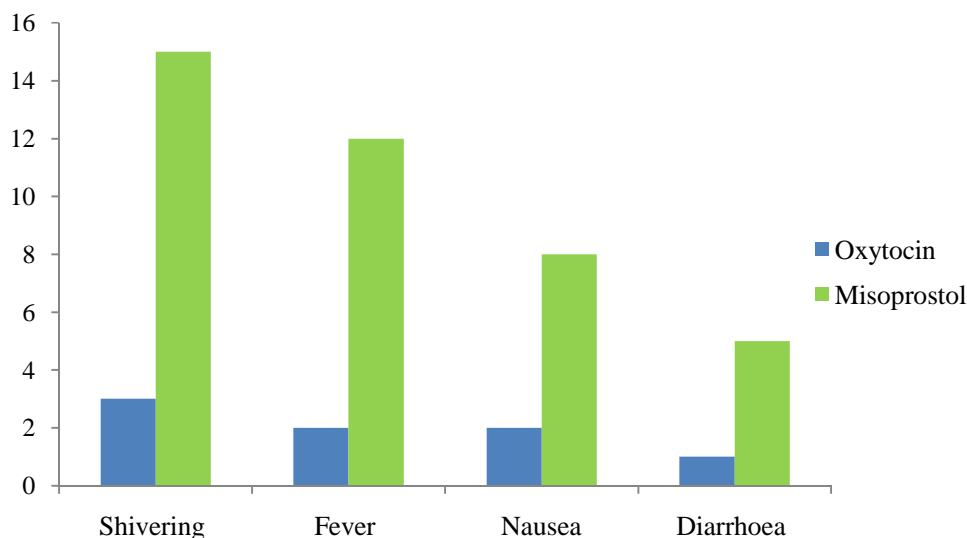
Characteristics	Oxytocin group Mean (SD)	Misoprostol group Mean (SD)	p value	CI
Blood loss (ml)	340.72 (89.58)	321.72 (87.78)	0.1314	-5.7 to 4.37
Haemoglobin deficit g/dl (in PPH cases)	1.33 (1.0)	1.65 (0.71)	0.6384	-1.96 to 1.32
Haematocritdeficit %(in PPH cases)	4.66 (2.08)	4.5 (1.9)	0.57	-0.4 to 0.72

Adverse effects noted in the two groups are given in table no 3. Adverse effects were observed for 24hours after administration of uterotonic drug. Adverse effects were more common in the misoprostol group with shivering being the most common ($p < 0.05$). All the side effects were mild and self-limiting.

Table No 3: Adverse drug reactions in the two groups

Side effects	Oxytocin (%)	Misoprostol (%)	p value	CI
Shivering	3	15	0.003	0.04 to 0.1993
Fever	2	12	0.0056	0.02 to 0.17
Nausea	2	8	0.0516	-4e-04 to 0.12
Diarrhoea	1	5	0.0973	-0.007 to 0.08

Figure No 5: Frequency of adverse reactions in the two groups (%)



Most maternal deaths due to PPH occur in low-income countries in settings. (both hospital and community) where there are no birth attendants or where birth attendants lack the necessary skills or equipment to prevent and manage PPH and shock. The Millennium Development Goal of reducing the maternal mortality ratio by 75% by 2015 will remain beyond our reach unless we prioritize the prevention and treatment of PPH in low-resource areas[7].

Khan et al[8] showed that misoprostol acid was detected in the serum in both oral and rectally administered routes as early as 7.5 min but rectally the mean serum concentration and the peak plasma concentration were lower. However, the duration of action of rectal misoprostol was longer. As the minimal therapeutic plasma concentration of misoprostol acid remains unknown, then PPH prophylaxis may be achieved at serum levels attainable by the rectal route and the higher levels attained orally may not necessarily lead to clinical superiority. These findings prompted us to use rectal misoprostol instead of oral misoprostol.

The mean age of women in our study was 28.52years in the oxytocin group and 28.82years in the misoprostol group($p>0.05$). In a study conducted by Nisa M U et al[9], mean age was 26.38years in the oxytocin group and 25.04years in the misoprostol group. Mean age was observed to be 25.8years in oxytocin group and 25.7years in the misoprostol group in a study done by Parson S M et al[4].

We found the mean gestational age in our study to be 36.26weeks in the oxytocin group and 36.28 weeks in the misoprostol group($p>0.05$). This is comparable to the study conducted by Parson S M et al [4], where in the mean gestational age was 36.9weeks in the oxytocin group and 37.1weeks in the misoprostol group. The mean parity in our study was 1.11 in the oxytocin group and 1.29 in the misoprostol group. There was no significant difference in the parity between the two groups. Nisa M U et al [9], in their study reported a mean parity of 2.3 in the oxytocin group and 2.5 in the misoprostol group.

The mean baseline Hb in our study was found to be 12.45g/dl in the oxytocin group and 12.53g/dl in the misoprostol group($p>0.05$). This was comparable to a study conducted by Shreshtha A et al[10], wherein the baseline Hb was 11.5g/dl in the oxytocin group and 11.7g/dl in the misoprostol group.

In our study the mean baseline haematocrit value in the oxytocin group was 33.78% and in the misoprostol group was 33.86% ($p > 0.05$). This was comparable to the values observed in study conducted by Dr. Ibrahim Ayyad *et al* [11].

In our study primary outcome was taken as incidence of PPH in both groups which was 3% in the oxytocin group and 4% in the misoprostol group ($p > 0.05$). Similar results were obtained by Nisa M U *et al* [9] where incidence of PPH ranged between 3-4%. Another study by Shreshtha A *et al* [10] in Nepal reported the incidence of PPH in misoprostol group (1000 μ g) as 4% which is comparable to our study, but the incidence of PPH in oxytocin group (10IU, IM) was reported as 6% which is high as compared to our study. This is probably due to variation in the route of administration of oxytocin. The incidence of PPH in the misoprostol group in our study was lower compared to study conducted by Dr. Ibrahim Ayyad *et al* [11] (4% vs 7%), probably because women with low and high risk for developing PPH were included in their study.

Mean blood loss in our study was 321ml in misoprostol group compared to 340ml in the oxytocin group ($p > 0.05$). Nisa M U *et al* [9], in their study, where 1800 μ g of misoprostol was used, reported mean blood loss in the misoprostol group as 304ml which is less as compared to our study. The mean blood loss in a study conducted in Nepal by Shreshtha A *et al* [10] showed mean blood loss of 156ml in the misoprostol group. Even in this study a higher dose of misoprostol (1000 μ g) was used. Mean blood loss was greater in misoprostol group in a study done by Siddique S M *et al* [12] as compared to our study (381.60ml vs 321.72ml) which could be because of the lesser dose of misoprostol (400 μ g) used in their study. However, the mean blood loss in the oxytocin group in this study is comparable to ours (334ml vs 340ml).

We found that the mean Hb deficit (antepartum -24hours postpartum) in our study was 1.33g/dl and 1.65g/dl in oxytocin and misoprostol group respectively ($p > 0.05$). Similarly in a study done by Dr. Ibrahim Ayyad *et al* [11] Hb deficit was 1.3g/dl in the oxytocin group and 1.4g/dl in the misoprostol group, these results are comparable to the values observed in our study. The mean decrease in Hb concentration was found to be 1.19 g/dl for the misoprostol group and 1.16 g/dl for the oxytocin group in a study conducted in Ghana by Parsons S M *et al* [4], the results are comparable to our study. Mean Hb deficit in a study conducted by Nisa M U *et al* [9] was 0.404g/dl in the misoprostol group, which is less compared to our study. This might be due to higher dose of misoprostol (1800 μ g) used in their study.

The mean haematocrit deficit was 4.66% and 4.5% in oxytocin group and misoprostol group respectively in our study ($p > 0.05$). These results are comparable to results obtained by Dr. Ibrahim Ayyad *et al* [11] in their study where in the mean haematocrit deficit was 4.5% in oxytocin group and 4.6% in the misoprostol group.

Side effects were more common in the misoprostol group in our study. The most common being shivering (15%) followed by fever (12%), nausea (8%) and diarrhoea (5%). Both fever and shivering with misoprostol are due to the prostaglandin E effect on central thermoregulatory centres. All these side effects were mild and self-limiting. Shivering was the most common side effect observed in misoprostol group in a study conducted by Parson S M *et al* [4]. Similarly shivering was the most common side effect observed by Nisa M U *et al* [9], but the frequency of shivering was more (25%), probably due to the higher dose of misoprostol used. Shivering was observed with lower frequency in study conducted by Dr. Ibrahim Ayyad *et al* [11] compared to ours (10% vs 15%), probably due to the lower dose of misoprostol used. Fever was most commonly reported side effect in misoprostol group by Siddique S M *et al* [12] in their study and fever with shivering was the most common side effect in the misoprostol group in a study conducted by Shreshtha A *et al* [10] as compared to shivering which was the most common side effect observed in our study.

The study had some limitations. It was an open label study. The study included only those women with low risk for developing PPH. Further studies can be conducted on high risk cases under controlled conditions.

On efficacy terms PR Misoprostol is comparable to IV Oxytocin in our study. Though side effects like shivering, fever occurred more frequently in the misoprostol group, they were mild and self-limiting. Additionally Misoprostol has several advantages over Oxytocin, it is cheap, can be stored at room temperature, easily administered by per rectal route and has shelf life of several years - due to these qualities it can be considered as an effective alternative to IV oxytocin in resource poor settings. Previous studies done in Nigeria [13], Nepal [14] and India [15] also support the use of misoprostol for prevention of PPH in low resource settings.

In conclusion, our study showed that PR misoprostol is similar in efficacy to IV oxytocin in prevention of PPH in low risk women. Though side effects like shivering and fever (were all mild and self-limiting) were more frequent in the misoprostol group, the two drugs did not show any significant difference in terms of mean blood loss, mean haemoglobin deficit and mean haematocrit deficit.

As PR misoprostol has several advantages over IV oxytocin like ease of administration, low cost, has shelf-life of several years and does not need refrigeration for storage, it can be considered as good alternative to IV oxytocin in prevention of PPH especially in the peripheral or rural settings where resources are limited.

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