

Prevention of post-partum hemorrhage by rectal Misoprostol: A randomized clinical trial

Mozhgan Firouzbakht,
Azadeh Kiapour¹,
Shabnam Omidvar²

Department of Nursing and Midwifery, ¹Basic Science, Babol Branch, Islamic Azad University, ²Nursing and Midwifery, Babol Medical Sciences University, Babol, Iran

Address for correspondence:

Dr. Shabnam Omidvar, Department of Nursing and midwifery, Babol Medical Sciences University, Babol, Iran. E-mail: shomidvar@yahoo.com

Abstract

Background: Post-partum hemorrhage (PPH) is a common cause of maternal mortality in developing countries. This trial was conducted to study the effectiveness and safety of rectal misoprostol for PPH. **Aim:** To assess the effectiveness and safety of misoprostol and comparing with oxytocin for prevention of PPH. **Materials and Methods:** Women were randomized to receive either two 200 µg rectal misoprostol tablets (study group) or 20 units oxytocin in 1000 cc normal saline intravenously (control group). The outcomes were incidence of PPH, amount of blood loss, duration of labor, incidence of side effects, pre- and post-delivery hemoglobin, and use of additional uterotonics. **Finding:** The incidence of PPH was 12% in the study group and 10% in the control group ($P > 0.05$). No significant difference was observed between the groups hematocrit ($P > 0.05$). Other variables including severe PPH and duration of the third stage of labor were similar in both groups. **Conclusion:** Rectal misoprostol was as effective as intravenous oxytocin for preventing post-partum hemorrhage with the same incidence of side effects and is recommended to be use as an uterotonic agent to manage third stage of labor routinely.

Key words: Active management, misoprostol, oxytocin, post-partum hemorrhage, third stage

INTRODUCTION

A major cause of maternal mortality is post-partum hemorrhage (PPH). The incidence of PPH has been reported from <5% to >10%. These figures remain at least 100 times higher than those in developed countries.^[1]

The World Health Organization estimates that 20 million morbidities are consequences of PPH every year, (accounting for one-third of maternal deaths).^[2] The causes of death are multi-factorial, and prevention requires a multi-disciplinary response.^[3]

The primary cause of PPH is uterine atony. The third

stage of labor is potentially the most dangerous for the mother, and active management is necessary. Active management of the third stage of labor is composed of immediate administration of an uterotonic, controlled cord traction for placental delivery, and uterine massage. This procedure is internationally recognized as an evidence-based intervention that reduces PPH caused by uterine atony up to 60%.^[2] Conventional oxytocic agents used include oxytocin, the ergot alkaloids ergonovine (ergometrine) and methylergonovine (methylergometrine), syntometrine (which consists of 5 IU oxytocin [Syntocinon] and 0.5 mg ergometrine), and prostaglandins such as carboprost.^[4-7] Moreover, oxytocins is an injectable uterotonic, that is unstable at high temperature, and requires cold storage and skills that birth attendants, who do not practice active management of the third stage of labor, might not possess.^[2,4,8] Several side effects may occur with the use of these agents including nausea, vomiting, elevated blood pressure, headache, tachycardia, and bronchospasm.^[4-5,7]

Misoprostol, a prostaglandin E₁ analogue, is used orally to prevent or as treatment of gastric/duodenal ulcers caused by using non-steroidal anti-inflammatory

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agents. Misoprostol has also been investigated for preventing PPH, using either the oral or rectal route of administration.^[4-5] Misoprostol produces less serious side effects, and gastrointestinal disturbances are less frequent. The oral route has been associated with dose-related shivering and pyrexia (temperature >38°C). Some experts believe that the rectal route may be advantageous because it may lessen the gastrointestinal side effects. Thus, misoprostol can be administered rectally to patients who are vomiting or unable to take oral medications, those who are under general anesthesia, or those with heavy vaginal bleeding.^[6,8-10]

A study from Ghana, comparing the effects of rectal misoprostol with intramuscular oxytocin for routine management of the third stage of labor, it was confirmed that administrating of 400 µg rectal misoprostol is as effective as 10 IU intramuscular oxytocin to minimize blood loss during the third stage of labor. Rectal misoprostol has a lower incidence of side effects than the equivalent oral dose. The study confirmed the utility of misoprostol as a safe and effective uterotonic for use in rural and remote areas of developing nations where other pharmacologic agents may be less available.

Ayyad and Abu Omar (2004) determined that rectal misoprostol is as effective as intravenous oxytocin for preventing PPH with the same incidence of side effects and recommended its use as a uterotonic agent for routine management of the third stage of labor.^[11]

A recent Pakistani study, which was conducted to assess effectiveness and safety of rectal misoprostol for treating PPH, demonstrated that misoprostol is an effective treatment for PPH and that it might be an alternative to parenteral prostaglandins. Given that misoprostol is an inexpensive and stable drug, it has considerable potential to reduce maternal mortality from PPH in developing countries.^[2] The efficacy of misoprostol for preventing PPH has also been well demonstrated in trials in Iran (2009), Afghanistan (2010), and Ethiopia (2010).^[12-14] A meta-analysis provided consistent evidence to support a recommendation for use of misoprostol to prevent PPH when oxytocin is unavailable.^[15]

The aim of this study was to compare the effectiveness and safety of oxytocin and rectal misoprostol for preventing PPH.

MATERIALS AND METHODS

This study was a randomized clinical trial. The participants were 100 patients who had a singleton, gestational age of

37 weeks or more and spontaneous vaginal delivery at Imam Ali Hospital, Amol, Iran from March 15 to January 30, 2010. Exclusion criteria were patients undergoing cesarean section, patients with hemoglobin <8 gm%, pregnancy-induced hypertension, grand multiparity, coagulation abnormalities, positive history of PPH, or other medical disorders. Patients were randomly divided into 2 groups to receive either two 200 µg rectal misoprostol tablets (study group) or 20 units oxytocin in 1000 cc normal saline intravenously (control group). Baseline maternal characteristics included age and parity. Significant obstetric history was recorded. Blood pressure levels were noted before and after delivery. PPH was defined as blood loss in excess of 500 cc or 10% drop in Hb from admission to the time of mother discharge (12 hours after delivery). Blood loss was estimated in the third stage of labor by placing a plastic pan under the patients at the time of placental separation and the number, and weight of soaked pads at the time of episiotomy repair (volume in cc = weight in grams) were determined. Blood loss was quantified by the weight and number of soaked towels or by changes in Hb concentration or hematocrite value. The primary outcome was to objectively estimate the amount of blood loss. The hemoglobin concentration was recorded before delivery. A second Hb was estimated before discharge (12 hours post-partum). Differences in the Hb values before and after delivery were estimated in each group. Other variables included agents used for augmentation of labor, mode of delivery, and birth weight. Secondary outcomes were the length of labor and the length of the third stage of labor, the need for additional agents to control vaginal bleeding, and the need for a blood transfusion.

The side effects of each medicine such as nausea, vomiting, diarrhea, shivering, and headache were noted.

Data were analyzed on an intent-to-treat basis by parametric (t-test and chi-sq test) and non-parametric tests (Mann-Whitney U-test), using SPSS version 15 analytical software, (SPSS, Inc., Chicago, IL, USA). A $P < 0.05$ was considered as significant.

RESULTS

A total of 100 women were enrolled and randomized to receive either rectal misoprostol ($n = 50$) or infusion oxytocin ($n = 50$) during the study period. In present study, no significant differences were observed between the groups regarding baseline characteristics [Table 1].

No significant differences were observed between the groups for changes in Hb concentration. ($P = 0.80$).

No significant differences were observed between the groups for the length of the first, second, and third stages of labor ($P = 0.54$, $P = 0.59$, $P = 0.98$), respectively. The estimated blood loss during the third stage in the misoprostol group decreased significantly ($P = 0.003$), but no significant difference was observed for blood loss after birth, length of the third stage, or need for a blood transfusion. No other women required an operative intervention (such as manual removal of placenta, dilatation and curettage, laparotomy, or hysterectomy) or had estimated blood loss >1000 ml. No difference was observed for additional uterotonics between the two groups ($P = 0.737$) [Table 2].

The incidence of shivering was 14% in the misoprostol group compared with 4% in the oxytocin group. Our observations elicited that the incidence of other side effects such as nausea, vomiting, and headache were essentially similar [Table 3].

DISCUSSION

This study confirmed the utility of rectal misoprostol for routine management of the third stage of labor. Misoprostol (400 µg) administered rectally was effective for minimizing blood loss when utilized to actively manage the third stage of labor, as measured by changes in Hb concentration before and 12 hours after delivery. This dose and route of administration are well tolerated, and usual side effects such as shivering and increasing temperature were not prevalent. Karkanis *et al.* reported that No difference in Hb was observed between the groups of women who randomly received 400 (µg) rectal misoprostol after delivery of the infant or 5 units of parenteral oxytocin or 10 units oxytocin intramuscularly with delivery of the anterior shoulder.^[16] The duration of the third stage of labor was not different between the two groups. Bugalh *et al.*'s observation also confirmed similar results.^[17] Nasr *et al.* conducted a randomized trial with 514 women to receive either 400 (µg) rectal misoprostol or one ampoule of syntometrin. The results showed that the incidence of PPH, duration of third stage of labor, and the drop in Hb were similar between the two groups.^[12] Ayyad and Abu Omar also reported rectal misoprostol to be effective to stop severe delivery-induced hemorrhage after failure of syntocinon.^[11]

These studies provide further evidence for the utility of misoprostol as an effective uterotonic that provides a simple therapeutic option for health care providers in developing nations to use against obstetric hemorrhage. PPH is regarded as one of the major causes of maternal mortality and morbidity in developing countries.

Table 1: Demographic characteristics

Characteristics	Misoprostol N=50	Oxytocin N=50	P
Maternal age (year)	24.3±4.3	24.9 ±5	0.539
Parity			
Nulipar	26 (52%)	27 (54%)	0.99
Multipar	21 (42%)	22 (44%)	
Gestational age (week)	38.7±1.8	39±2.3	0.645
Weight of baby (kg)	3.42±0.49	3.3±0.41	0.78
Pre-delivery hemoglobin (gr/dl)	12.6±1.12	12.3±1.28	0.206
Mode of delivery			
Spontaneous delivery	11 (22%)	10 (20%)	0/803
Episiotomy	33 (66%)	29 (58%)	0/67
Laceration	6 (12%)	11 (22%)	0/709
Length of labor			
1 st stage (hours)	11.19±6.02	10.8±4.7	0/54
2 nd stage (minutes)	29.6±20.02	25.9±18.3	0/59

Data are presented as mean±SD

Table 2: Primary and secondary outcomes

Characteristics	Misoprostol N=50	Oxytocin N=50	P
Vaginal bleeding≥500 cc	6 (12%)	5 (10%)	0/828
Average blood loss (ml)	436.6±21404	415.06±227.2	0/069
Average blood loss in third stage	136±111.3	162.4±115.2	0/003
Average blood loss in post-partum	143.3±122.7	105.08±86	0/017
Change in Hb (gr/dl)	1.15±1.28	1.41±1.3	0.0468
Post partum Hb	11.8±1.03	11.53±1.34	0.28
Length 3 rd stage (minute)	5.08±3.07	5.49±2.45	0.198
Additional utrotonic agent	3 (6%)	4 (8%)	0.523

Data are presented as mean±SD

Table 3: Medication side effects

Characteristics	Misoprostol 50 (%)	Oxytocin 50 (%)	P
Nausea	5 (10)	3 (6)	0/42
Vomiting	2 (4)	0 (0)	0/52
Shivering	10 (20)	5 (10)	0/035
Headache	3 (6)	2 (4)	0/29

Consequently, active management of the third stage of labor should be practiced by routinely use of intravenous oxytocin. Misoprostol was chosen as a substitute for oxytocin to prevent PPH because it has similar advantages to oxytocin but with minimal side effects.^[11] Misoprostol is an inexpensive medicine, which is easily available. It is easy to use and does not require special storage conditions (i.e., can be stored easily at room temperature; is thermo-stable and light stable; does not require specific conditions for transfer) and has a shelf life of several years. These advantages make it a useful medicine for reducing the incidence of PPH in developing countries. The rectal route was chosen because of ease of administration, and because it avoids gastrointestinal side effects such as nausea, vomiting, and diarrhea; therefore, it can be given to women who have nausea and vomiting.^[11]

CONCLUSION

Rectal misoprostol seems to be safe and effective for preventing PPH and is recommended for use to manage the third stage of labor.

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