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Research Article

Pre-Operative or Post-Operative Misoprostol in Caesarean Delivery: Does It Differ?

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Abstract

Purpose: To compare the effectiveness of the rectally administered misoprostol pre-operative versus post-operative in minimizing intraoperative blood loss and prevention of postpartum hemorrhage in cesarean delivery.

Material and Methods: This study included 180 pregnant women at term (37 - 40 weeks) undergoing Caesarean delivery under regional anesthesia. Group I (n = 84) received 400µg rectal misoprostol preoperatively, and Group II (n = 82) received 400µg rectal misoprostol postoperatively. Hematocrit level was measured and recorded at admission as a preoperative routine investigation and repeated 24 hours following cesarean delivery. The patients were evaluated in terms of operative time, operative blood loss and any side effects of administered drugs.

Results: The demographic characteristics of participants as age, parity and gestational age were comparable between the two groups. As regard the estimated blood loss (M ± SD) during cesarean section in group I (preoperative misoprostol) was 372.33 ± 25.997 ml, in group II (postoperative misoprostol) was 722 ± 34.089 ml (p = 0.001). Hematocrit value after cesarean section was significantly lower in group II than in group I (P = < 0.001). The 2 groups were not different in terms of side-effects except for abdominal pain (P value 0.02).

Conclusion: Administration of rectal misoprostol prior caesarean appears to be safe, more effective than postoperative administration for decreasing the amount of blood loss during cesarean section.

Keywords: *Post-Partum Hemorrhage; Preoperative Misoprostol; Postoperative Misoprostol; Uterotonics*

Introduction

Postpartum hemorrhage (PPH) continues to be a leading cause of maternal morbidity and mortality worldwide. According to the World Health Organization estimates, more than 585.000 women die every year from pregnancy- related cause, of which 25% were due to severe bleeding [1].

In a survey performed at the center of prevention from diseases, hemorrhage was a direct cause of mortality in 18% of maternal deaths [2]. Postpartum hemorrhage has many causes, but uterine atony remains the most common cause of PPH representing about 80% of all causes of postpartum hemorrhage [3,4]. Active management of the third stage of labor by administration of uterotonic drugs reduces the risk of postpartum hemorrhage, postpartum anemia as well as the need for blood transfusion. The most commonly used uterotonic drugs include oxytocin, methylergonovine, carbetocin, and prostaglandins [5].

Misoprostol is a synthetic prostaglandin E1 analogue; it is wildly used for management of the third stage of labor and for intractable postpartum hemorrhage as a last resort when other medical interventions failed. It has a potent uterotonic effect, cheap, stable at room temperature, easily administered and has few adverse effects. It is well absorbed when administered by oral, vaginal, rectal, and sublingual routes. Side effects of misoprostol include shivering, pyrexia, nausea, vomiting, and diarrhea [6].

Rectal misoprostol is the best route for patient undergoing caesarean delivery due to slower absorption, fewer side effects. The mean T_{max} after rectal administration is 40 - 65 minutes [7,8], although a recent study reported a much shorter T_{max} of 20 minutes [9]. This delayed timing of absorption is thought to be beneficial when misoprostol is given prior to surgery as by the end of caesarean section, the maximum effect was obtained [8,10].

Many research studies were conducted to evaluate the role of rectal misoprostol as a preventive measure for postpartum hemorrhage. Some of these studies advocate its use for prevention of postpartum hemorrhage [11-14], while other studies concluded that misoprostol was not as effective as expected [15,16]. Other studies concluded that use of misoprostol must be stopped [17,18].

For this wide gap of controversy in the results of previous studies about the use of misoprostol for prevention of postpartum hemorrhage with cesarean section. Also the timing of misoprostol administration was not fully studied; this study was conducted to compare preoperative with postoperative rectal misoprostol for decreasing the postpartum hemorrhage.

Patients and Methods

Design and setting of study: This study is a single blinded, randomized clinical trial. This study was conducted at Obstetrics and Gynecology Department, Tanta University, Tanta, Egypt, in the period from January, 1, 2016, to August 31, 2016.

Patients: The study included 180 cases recruited according to inclusion and exclusion criteria. They were randomly allocated into 2 groups of preoperative misoprostol and postoperative misoprostol.

Inclusion criteria were pregnant at term (37 – 40) weeks, and elective planned cesarean section done under regional anesthesia. Exclusion criteria were any condition that prolong surgery or cause uterine atony such as: cesarean section under general anesthesia as it causes uterine atony necessating more uterotonics, antepartum hemorrhage, and maternal hypertension, maternal anemia, coagulation disorders, previous 2 or more cesarean section, failed trial patient, multiple gestation, fetal macrosomia, polyhydramnios, and previous rupture uterus.

Patients were allocated by simple randomization and alternate allocation into 2 groups:

Group I (Preoperative Misoprostol): Received 2 tablets of misoprostol (400 ug) rectally after regional anesthesia and shortly before skin incision.

Group II (Postoperative Misoprostol): Received 2 tablets of misoprostol (400ug) rectally after the end of Caesarean section.

Randomization was done by simple method with numbered container, then allocation by alternate method.

Methods: All patients received the same regimen of management for example: intraoperative oxytocin after delivery of fetus (10 IU), same antibiotics and analgesics. The need for additional uterotonics as oxytocin or ergometrine, additional antibleeding drugs or the need for blood transfusion was recorded for all patients.

Estimation of blood loss during cesarean section was determined by: (i) measuring the amount of blood collected in suction bottles after delivery of placenta plus weight of soaked towels and (ii) comparing pre and postoperative maternal Hematocrit level with the use of computerized programs using weight, height, pre and postoperative hematocrit to calculate estimated blood loss. Post-delivery care was performed such as monitoring the blood pressure, pulse, temperature, and amount of bleeding during first 24 hours after delivery measured by weight method by the following equation: soaked towel weight-dry towel weight = difference in grams, then every gram= 1 ml blood loss [19].

The levels of Hemoglobin and Hematocrit were measured and recorded at hospitalization and 24 hours after cesarean delivery. At this interval, the patients were evaluated in terms of possible complications and side effects of administered drugs such as abdominal pain, vomiting, diarrhea, shivering and pyrexia).

Ethical Approval: Before starting the study, an approval from The Ethical Committee of Faculty of Medicine, Tanta University was obtained. All aspects of this study were completely explained for all the participant patients and a written informed consent was taken from them.

Statistical Methods: Data was analyzed by SPSS software version 18. Quantitative data were shown as a mean and standard deviation and qualitative data as frequency. Comparison of quantitative data by using paired t-student test. Comparison of qualitative data was performed by chi-square. $P \leq 0.05$ was considered statistically significant.

Results

A total of 180 patients were enrolled in this study with the following flow chart. (Figure 1).

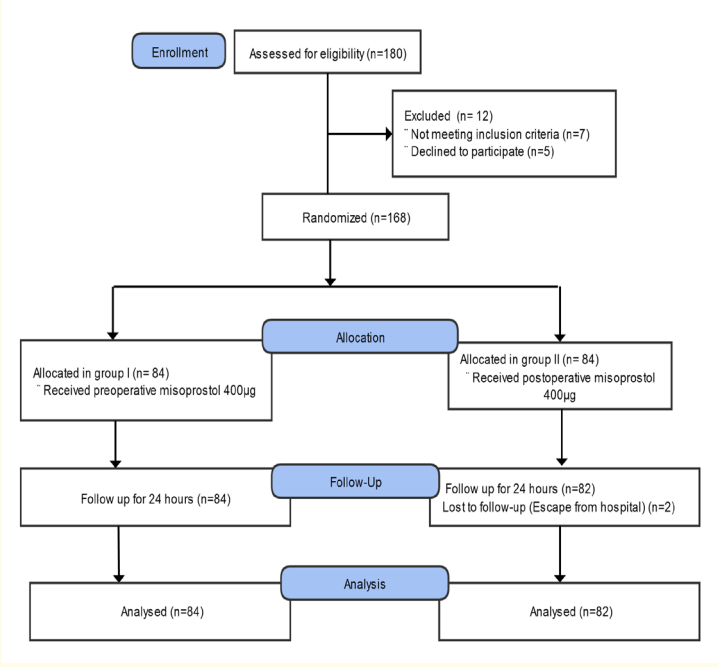

Figure 1: *Flow chart of enrolled patients.*

Demographic data of studied cases were nearly the same Mean age in group I was 25.4 ± 5.2 years, in group II was 26.7 ± 5.6 years; with no significant difference was observed between three studied groups (P = 0.28). Also, Mean gestational age in group I was 38.4 ± 1.10 weeks, in group II was 38.5 ± 1.13weeks; no significant difference was observed between 2 groups (P = 0. 82). (Table 1)

	Groups		Test of significance	(P)
	Group I Preoperative Misoprostol (NO = 84) (M±SD)	Group II Postoperative Misoprostol (NO = 82) (M ± SD)		
Age (years)	25.46 ± 5.20	26.73 ± 5.63	1.28	0.280
Parity	1.3 ± 0.4	1.5 ± 0.7	1.330	0.854
Gestational age (weeks) at delivery	38.46 ± 1.10	38.35 ± 1.13	0.18	0.820
BMI	23.3 ± 2.70	22.98 ± 3.40	1.21	0.540
Preoperative Hematocrit level	35.90 ± 4.5	35.77 ± 2.4	2.34	0.345
Indications of CS Malpresentaion Previous Cs Oligohydramnios Maternal request	 33 (39.26%) 43 (51.19%) 3 (3.57%) 5 (59.52%)	 28 (34.15%) 41(50.00%) 6 (7.32 %) 10 (12.20%)	3.459	0.233

Table 1: *Demographic data of studied groups.*

As regard operative data, Operative time was nearly equal in the 2 groups with no significant difference (P = 0.154). The estimated blood loss (M ± SD) during cesarean section in group I was 372.33 ± 25.997 ml, in group II was 722 ± 34.089 ml(P = 0.001). There was statistically significant decrease in the estimated blood loss with the group I over group II (P = 0.001). (Figure 2). There was an additional use of oxytocin in group II for 25 cases (30.49%), and additional hemostatic drugs for 30 cases (36.58%). The need for additional oxytocin and hemostatic drugs was 0% in group I. The need for blood transfusion was for five cases (6.09%) in group II and no cases (0.00%) required blood transfusion in group I. (Table 2)

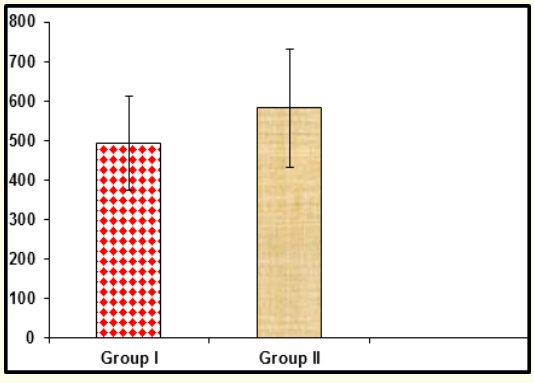

Figure 2: *Comparison between the studied groups regarding estimated blood loss during cesarean section.*

	Groups		Test of significance	(P)
	Group I Preoperative Misoprostol (NO = 84)	Group II Postoperative Misoprostol (NO = 82)		
Operative time (minutes) Min-Max (M±SD)	40 - 60 49.25 ± 4.614	39 - 65 50.123 ± 6.956	1.8854	(0.154)
Operative blood loss (ml) Min-Max (M±SD)	363-388 372.33 ± 25.997	660-845 722 ± 34.089	321.398	(0.001)*
Need for additional measures Additional Oxytocin	0 (0.0%)	25 (30.49%)	11.27	(0.024)*
Hemostatic drug	0 (0.0%)	30 (36.58%)		
Blood transfusion	0 (0.0%)	5 (6.09%)		
Postoperative blood loss (24 hours)	190.55 ± 30.45	237.65 ± 23.78	10.452	0.001
Postoperative hematocrit (24 hours post-caesarean section) Min-Max (M±SD)	33.55 ± 0.7	29.29 ± 0.7	0.22	< 0.001

Table 2: *Operative data in studied groups.*

The postoperative blood loss in the first 24 hours was reduced in group I than in group II with mean blood loss of (190.55 ± 30.45 ml and 237.65 ± 23.78 ml) respectively.

There was no significant difference between the level of hematocrit before & after cesarean section in both groups (P = 0.22). Postoperative hematocrit value after 24 hours of delivery was significantly higher in group I than in group II (P = < 0.001).

The most common side-effect was abdominal pain which was reported by 3 cases in group I and 8 cases in group II with significant difference between both groups (p value = 0.002), Hyperthermia was reported by 4 cases in group I and 7 cases in group II, Chills was reported by 2 cases in group I and 4 cases in group II, lastly vomiting was reported by one case in group I and 2 cases in group II. No cases of a headache or diarrhea were reported. (Table 3)

Parameter	Group I Preoperative Misoprostol (NO = 84)		Group II Postoperative Misoprostol (NO = 82)		Test of significance X^2	P
	N	%	N	%		
Abdominal pain	3	3.57	8	9.76	4.57	*0.002
Hyperthermia	4	4.76	7	8.54	3.663	0.160
Chills	2	2.38	4	4.88	0.523	0.769
Vomiting	1	1.19	2	2.44	7.500	0.023

Table 3: *The frequency of side effects in the studied groups.*

Discussion

PPH is one of the most common obstetric complications leading to maternal death worldwide. Its incidence is increasing and it affects 1-5% of all deliveries. Uterine atony is the most common cause of PPH and is responsible for about 80% of PPHs [20,21].

In the current study, preoperative rectal administration of misoprostol versus postoperative rectal administration was compared in reducing intraoperative blood loss and prevention of postpartum hemorrhage during cesarean delivery. Age, parity and gestational age were not statistically different between the enrolled patients.

The intraoperative blood loss was significantly decreased in preoperative misoprostol group with mean blood loss of 372.33 ± 25.997 ml compared to 722 ± 34.089 ml in the postoperative misoprostol group. Abd-Ellah., *et al*. conducted a prospective study at Qena University, Egypt, on 300 patients with 150 patients allocated in preoperative and postoperative misoprostol. They found that the blood loss during caesarean section was much lower in the preoperative misoprostol group (620 ± 291 ml) than in postoperative misoprostol group (898 ± 328 ml) with significant difference (p value < 0.05) [22].

Ahmed Ragab., *et al*. conducted a study at Mansoura University, Egypt on 348 patients and found that preoperative administration of misoprostol minimized blood loss (570 ± 240 ml) than postoperative misoprostol administration (844 ± 270 ml) [8].

The current study, demonstrated that there was a significant decrease in post-delivery hematocrit levels in postoperative misoprostol group than in preoperative misoprostol group. Reduction of blood loss at cesarean section is beneficial to the patient in term of decreasing postoperative morbidity and decreased the risk associated with blood transfusion. Ahmed Ragab., *et al*. found that postoperative hemoglobin levels was significantly lower in the postoperative misoprostol than preoperative misoprostol group [8].

In the current study, there was a need for additional oxytocin and hemostatic drugs (30.49%), (36.58%) respectively in postoperative misoprostol group II where no patients required these additional drugs in preoperative misoprostol group I. The need for blood transfusion was for five cases (6.09%) in group II and no cases (0.00%) required blood transfusion in group I. Abd-Ellah., *et al*. reported a need for additional uterotonics by 53.3 % in preoperative misoprostol group versus 30 % for postoperative misoprostol group [22].

Haque., *et al*. conducted a study to compare the efficacy of rectal misoprostol versus oxytocin IM on 200 women with 100 women in each group. The results were 6% in misoprostol group required additional oxytocin while 2% in oxytocin required additional oxytocin. They concluded that per rectally administered misoprostol may be effective in the prevention of PPH as an alternative to conventional intramuscular oxytocin [23].

Conde-Agudelo., *et al*. conducted a systematic review and metaanalysis of randomized controlled trials to evaluate the efficacy and safety of prophylactic misoprostol use at cesarean delivery for reducing intraoperative and postoperative hemorrhage. They included 17 studies with3174 women enrolled in these studies. They concluded that misoprostol combined with oxytocin appears to be more effective than oxytocin alone in reducing intraoperative and postoperative hemorrhage during cesarean section [24].

Mervat El Sedeeq conducted a study at Alexandria University, Egypt to evaluate the efficacy of preoperative administration of misoprostol versus placebo. She found that marked reduction of intraoperative and postoperative blood loss (429 ± 234, 185 ± 95 ml respectively was noticed in patient who received misoprostol preoperatively while patient received placebo the intraoperative and postoperative blood loss were (620 ± 375, 324 ± 167 ml) respectively. She concluded that preoperative misoprostol 400 µg reduces blood loss related to caesarean delivery [25].

In the current study the incidence of side effects of the rectal misoprostol were abdominal pain, hyperthermia, chills, vomiting. Only abdominal pain was significantly lower in preoperative misoprostol group than postoperative misoprostol group (P vale 0.02).Other complications were not significant in both groups. Similar results were obtained by Chaudhuri., *et al*. who performed a study in 2010 to compare the efficacy of rectally administered misoprostol with intravenous oxytocin infusion in preventing uterine atony and blood loss during cesarean delivery. They found that intraoperative and postoperative blood loss was significantly lower in misoprostol group than oxytocin group. The incidence of complications like shivering and postpartum hemorrhage was significantly lower in misoprostol group than oxytocin group, with no significant difference observed between two groups in terms of side-effects [26].

Many studies concluded that administration of misoprostol plus oxytocin significantly reduced the amount of blood loss during and after cesarean section compared to oxytocin and misoprostol when given alone, and use of them was not associated with any serious side effects [27,28].

Study Limitations

Non-blinding of this study and the relatively small sample size.

Conclusion

Administration of rectal misoprostol in CS prior to incision is safe, more effective, than postoperative administration for decreasing the amount of blood loss during cesarean section and as a prophylactic uterotonic to decrease the incidence of postpartum hemorrhage after cesarean sections.

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Conflicts of Interests

All authors declare that they have no conflicts of interests.

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Volume 3 Issue 6 January 2017