

Original Research Article

Impact of pre-operative 200 µg (P/R) per rectal misoprostol on blood loss during and after Cesarean delivery

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Abstract

Background: Intra-partum and early postpartum blood loss are increased in conjunction with Cesarean delivery. Misoprostol is a potent uterotonic agent that has been extensively studied in the prevention and treatment of PPH after vaginal delivery, however, its use in conjunction with CD has not been investigated as much.

Objective: To evaluate the effect of preoperative administration of rectal misoprostol on blood loss during and after elective Cesarean delivery.

Materials and methods: A randomized controlled trial was conducted among 200 women scheduled for elective Cesarean delivery. The study group (n=100) received 200 µg of misoprostol. The control group (n=100) received placebo. The main outcome measures were intra-operative blood loss, postpartum blood loss at 24 hours, and difference between preoperative and postoperative hematocrit values.

Results: The mean intra-operative and postpartum blood loss was lower in the study group than the control group: 374 ± 69.9 ml and 131 ± 31.8 ml versus 401 ± 79.9 and 145 ± 35.6 ml, respectively. The difference between the preoperative and postoperative hematocrit values was also significantly lower in the study group than the control group (4.3 ± 2.26 and 5.25 ± 2.61 , $p = 0.006$). Admissions to the neonatal intensive care unit and Apgar scores at 1 and 5 minutes were comparable between the two groups.

Conclusion: Preoperative administration of 200 µg rectal misoprostol significantly reduced blood loss related to elective Cesarean delivery.

Key words

Misoprostol, Intra operative and Post operative blood loss, Per rectal.

Introduction

The achievement of safe childbirth by Cesarean delivery (CD) was one of the greatest medical advances of the 20th century. Indeed, CD is now the most frequent operation performed in the USA, constituting approximately one-third of all deliveries annually [1]. Epidemiologic data report a CD incidence of 20–30% worldwide, with comparable rates in high-income and low-income countries [2]. The current rate of CD, which is approximately 4–5-fold greater than that of the 1970s, can be attributed to factors such as assumed benefit to the fetus, low maternal risk, social preference, and fear of litigation. Annually about 530000 women die in world as a consequence of pregnancy or child birth. Annually 14 million women suffer postpartum haemorrhage (PPH); 2% of deaths occur 2-4 hours after haemorrhage starts. In other words, of 14 million PPH cases each year, 2% leads to death. Intra-partum and early postpartum blood loss are also increased in conjunction with CD.

Postpartum hemorrhage is the leading cause of preventable maternal mortality in the developing world, and its prevention is assumed to be an important and rational strategy, and has been identified as a key component of safe motherhood. Oxytocin is routinely used to prevent uterine atony and excessive uterine bleeding during Cesarean delivery. However, despite its effectiveness, 10-40% of women need additional uterotonic therapy [3, 4]. Secondary uterotonic agents such as methyl ergometrine or 15-methyl prostaglandin F_{2α} are associated with adverse effects when administered within a dose range likely to be effective. By contrast, anesthesiologists consider oxytocin to be a dangerous drug with serious adverse effects such as hypotension, tachycardia, and myocardial ischemia. Because no guidelines yet standardize the practice of oxytocin infusion, minimizing blood loss during delivery—whether vaginal or

abdominal—is an important preventive health objective aimed at reducing postpartum anemia and related morbidity. It has been reported that the prevalence of postpartum anemia in low-income countries is approximately 50–80% [6]. The major cause of postpartum anemia is blood loss at delivery, especially in presence of prepartum anemia. Postpartum anemia constitutes an appreciable health problem among women of reproductive age and is associated with reduced quality of life, impaired cognition, emotional instability, and depression.

Misoprostol is a potent uterotonic agent that has been extensively studied in the prevention and treatment of PPH after vaginal delivery, however, its use in conjunction with CD has not been investigated as much. Notwithstanding the large number of studies conducted on doses and infusion rates of oxytocin, and doses and routes of administration of misoprostol, the ideal practice remains controversial. The aim of the present study was, therefore, to assess the effect of rectally administered misoprostol on blood loss during and after CD.

Materials and methods

This study was conducted in Modern Government Maternity Hospital under Osmania Medical College, Hyderabad which is a tertiary referral centre. It was conducted from January 2013 to June 2014. Double blinded, randomized controlled trial was conducted among 200 women scheduled for elective Cesarean delivery. Study population were recruited from MGMH who were posted for elective Cesarean delivery. The study was approved by ethics committee. Informed consent was taken from all study subjects after explaining the advantages and disadvantages.

200 women who met the inclusion criteria were randomly allocated into two groups.

Inclusion criteria

Uncomplicated singleton pregnancy, GA of 39 completed weeks, Up to fifth parity, scheduled elective repeat Cesarean delivery.

Exclusion criteria

Unsure due date and multiple pregnancy, Hypertension Diabetes mellitus, Abnormal sonography, Abnormal laboratory results, Traumatic PPH, Foetal distress, Medical and coagulation disorders, History of complications at previous pregnancy. Women undergoing scheduled elective first CD were excluded from participation because it was speculated that the indication for CD – whether maternal (e.g. hypertension) or fetal (e.g. post maturity) might interfere with results.

Assessment of blood loss

In subjects who filled the inclusion criteria, history was taken. The patient details, Gravida, parity, gestational age are noted down. Indication for the present Cesarean and associated co-morbid factors were noted. Clinical evaluation and routine laboratory investigations with particular emphasis on blood indices and coagulation profile were performed. Women with abnormal test results were excluded from the study. Detailed sonographic examination documenting placental localization, estimated fetal weight, and biophysical profile were performed in all cases shortly before operation, women with abnormal sonographic findings were excluded from the study. Eligible participants were randomized into two groups women in the study group (n=100) received a total preoperative dose of 200µg misoprostol tablet, while women assigned to the control groups (n=100) each received 1 placebo tablet. Misoprostol and placebo tablets were inserted rectally after catheter placement just before spinal anesthesia.

Cesarean delivery was performed was under spinal anesthesia, through low transverse skin incision and lower segment Cesarean, by 4 senior obstetricians who were blinded to the allocation. In addition, the operating room staff including the attending pediatrician, was blinded to the

allocation. All participants received 10 IU of oxytocin in 500 ml lactated Ringer solution, which was infused over a period of 30 minutes after cord clamping. The time interval between drug administration and delivery of fetus was noted in both study group and control group. The placenta was removed by controlled cord traction after spontaneous separation. The uterus was closed by continuous unlocked sutures in 2 layers using Ethicon vicryl 0 suture. Peritoneum and muscle layers were not closed and the rectus sheath was closed using the same suture material.

Assessment of blood loss started after uterine incision by gravimetric method. During the operation an isolated suction was used for evacuation of amniotic fluid through a small incision over the uterus, and another one used for collection of blood. A dedicated nurse was responsible for collection of blood and amniotic fluid in 2 separate suction sets, and for weighing surgical swabs and linen before and after operation. Fixed sized mops of 20×10 cm were used in the present study. The weight difference would be equal to 1 ml of blood. The collected blood in suction bottle would be added to the blood in swabs and clots. A highly accurate digital balance was used for weighing swabs.

The surgeon requested additional uterotonic agents on the basis of clinical findings during surgery. Additional oxytocin was added to the standard oxytocin infusion before secondary uterotonic agents if intra operative blood loss exceeded 500 ml. Additional oxytocin was considered as additional uterotonic intervention for the purposed of data analysis. Inj. Methyl ergometrine 0.2 mg IM and inj. 15-methyl prostaglandin F₂ α 250 µg IM were used as secondary uterotonic agents. Postpartum blood loss during the first 24 hours after surgery was assessed by weighing pads and clots. Preoperative and post operative hemoglobin estimated by Drabkins cyanhemoglobin method and hematocrit 1 hour before surgery, 24 hours after surgery by Wintrob's centrifugation method. The neonatal outcome including: APGAR score, the need for neonatal intensive

care unit (NICU) admission and neonatal death were assessed in the two groups. The drug side effects as regards postoperative fever, vomiting and shivering were compared in both groups.

Data were collected and statistically analyzed by using statistical packaged for social sciences (SPSS-15).

Results

100 were randomly assigned to misoprostol group and 100 to placebo group. All women received allocated intervention, completed follow up and were analysed according to group assignments. A comparative study was undertaken to study the effect of rectal misoprostol on blood loss during and after caesarean delivery.

The mean age in misoprostol group (group A) was 23.14±3.06 while in control group (group B) was 23.90 ± 3.76. Gravida 2 was the major group followed by gravida 3 (**Table – 1**).

Table - 1: Demographic details in study.

Age (Years)	Group A (Misoprostol) (n=100)	Group B (Placebo) (n=100)
≤ 20	16	24
21-25	60	48
26-30	24	21
>30	---	7
Mean ±SD	23.14±3.06	23.90±3.76
Gravida		
Gravida 2	62	65
Gravida 3	29	27
Gravida 4	7	5
Gravida 5	2	3
Mean ±SD	2.47± 0.717	2.47± 0.72
No of previous Cesarean deliveries		
1	72	65
2	28	32
Mean	1.27 ± 0.446	1.34 ± 0.524

The difference between preoperative and postoperative Hb values p value of 0.009 which

is statistically significant. It also shows that the mean of hematocrit difference was lower in study group than in control group HCT difference between two groups was statistically significant. It also shows that mean intra-operative blood loss was lower in the study group than in the control group (374 ± 69 ml versus 401± 79 ml; p = 0.01) and is statistically significant. The mean postpartum blood loss was also lower in the study group than in the control group (131 ± 31.7 ml versus 145 ± 35.6 ml; p = 0.006) and is statistically significant (**Table – 2**).

The incidence of side effects in each group 20% cases in misoprostol group (group A) while in 14% cases in control group and the difference was not statistically significant (p value = 0.25) as per **Table - 3**.

Apgar at 1 and 5 min was comparable between both groups. These values are not statistically significant. The percentage of cases requiring additional oxytocics was significantly higher in control group than in study group (**Table – 4**).

Discussion

Misoprostol is an evidence-based alternative to other uterotonic agents which require a cold chain, skilled administration, and have untoward effects in therapeutically effective doses. Further, the drug's wide availability, low-cost, stability at room temperature and ease of use make it an ideal drug for use in such settings. Prophylactic administration of misoprostol rectally after caesarean delivery is increasing nowadays to decrease blood loss after CS delivery. Previous studies have addressed protocols to limit excessive blood loss during elective CD.

In the present study 60% of the total subjects were in the age group 21-25 years in study group and 48% in control group. Majority of them are second gravida, 62% in study group and 65% in control group. No significant differences were seen in age and gravidity in both the groups. Majority of them in the present study are of one previous Cesarean section, 72% in misoprostol

group and 65% in control group. Both study and control groups were comparable with respect to preoperative haemoglobin and hematocrit. The preoperative haemoglobin in study and control groups mean ± SD is 10.73±1.114 and 10.8 ± 1.044 respectively. The mean±SD of preoperative HCT in study and control groups was 34.26±2.8 and 34.3±3.2 respectively. All the

above variables were similar to that reported in Elsedek and Sood Atul kumar [5, 6] study. In this study we compared the safety and efficacy of preoperative rectal misoprostol and oxytocin in the prevention of PPH .Our analysis showed that there was no statistically significant difference in baseline characteristics in the two groups.

Table - 2: Comparison of various variables in study.

Haemoglobin (g%/dl)	Group A (Misoprostol) (Mean ±SD)	Group B (Placebo) (Mean ±SD)	P Value
Before Delivery	10.73±1.114	10.80±1.004	0.647
1 day after delivery	9.6±1.18	9.36±1.15	0.147
Hb difference	1.14±0.735	1.44±0.88	0.009
Hematocrit			
Pre-operative Hematocrit	34.26±2.809	34.30±3.2	0.92
Post-operative Hematocrit	30.48±3.428	29.26±3.58	0.01
Haematocrit Difference	4.305±2.26	5.253±2.61	0.006
Blood Loss			
Intra-operative Blood Loss	374±69	401±79.9	0.01
Post-operative Blood Loss	131.8±31.7	145±35.6	0.006

The primary outcome measures in the study were intra-operative blood loss, postpartum blood loss at 24 hours, and difference between preoperative and postoperative hematocrit values. In our study the mean interval between drug placement and delivery of fetus was 6.128 with standard deviation of 0.84 minutes in the study group and 5.91 with standard deviation of 1.04 minutes in control group (p = 0.001).In randomised controlled trial conducted by Elsedek, et al. [5] the mean time until delivery in min was 6.33±3.65 minutes in the study group and 5.85±4.15 minutes in control group (p = 0.12) as per **Table - 5**. In our study with 200 µg preoperative rectal misoprostol the mean intra-operative blood loss was 374 ml with a standard deviation of 69 ml in study group while in control group the mean intra-operative blood loss was 401 ml with a standard deviation of 79.9 ml which is lower in study group than in control group with a p value of 0.01 which is statistically significant and similar to that reported in two studies. Blood loss at caesarean is difficult to

assess accurately. In a study, visual assessment of blood loss was 33% less than the drape estimate correlating well with photospectrometry. In the present study to obviate the above limitation, perioperative change in Hb between preoperative and the second postoperative day was also done to assess the blood loss indirectly. The mean postpartum blood loss was 131 ml with a standard deviation of 31.8 ml with a p value of 0.06. The postpartum blood loss was also lower in the study group than in the control group which is statistically insignificant. The proportion of blood loss between 500 and 1000 ml was less in misoprostol group. In Mervat elsedek, et al. [5] study with 400 µg of preoperative rectal misoprostol, the mean intra-operative blood loss was significantly lower in the study group than in the control group (429 ± 234 ml versus 620 ± 375 ml; p = 0.001).The mean postpartum blood loss was also lower in the study group than in the control group (185 ± 95 ml versus 324 ± 167 ml; p = 0.001). In a prospective study conducted by

Sood Atul kumar, et al. [6] with 400 µg of sublingual misoprostol, the mean intra-operative blood loss was significantly less in misoprostol group as compared to placebo which is (595 ± 108 versus 651±118 ml, p = 0.025). Proportion of blood loss between 500 and 1000 ml was lesser with misoprostol.

Table - 3: Side effects in present study.

Side Effects	Group A (Misoprostol)	Group B (Placebo)
Nil	80	86
Nausea and Vomiting	4	3
Shivering	9	6
Diarrhoea	3	2
Pyrexia	4	3
P value	0.25	

In a clinical trial done by Ahmed, et al. [7] comparing pre and postoperative rectally administered 600 g of misoprostol the mean blood loss during and after CS delivery was significantly lower in the pre-operatively rectally administered misoprostol group (620± 291) when compared to post-operative rectally administered misoprostol group (898 ± 321) and this difference was statistically significant with p value < 0.05. In our study the difference between pre-operative and post-operative haemoglobin values was lower in study group than the control group. The mean hemoglobin difference in study group was 1.14 with a standard deviation of 0.73 g/dl while in control group was 1.44 with a standard deviation of 0.88 g/dl. The p value for haemoglobin difference is 0.009 based on unpaired t test which is statistically. The post operative haemoglobin level (24 hours) was significantly lower in control group (9.36 ± 1.15) than the study group (9.6 ± 1.18) with p value of 0.147 which is statistically not significant.

Table - 4: Comparison of outcome variables in the study cohort.

Variable	Study Group (n=100)	Control Group (n=100)	P Value
Time until delivery	6.12 ± 0.8	5.91 ± 1.04	0.0001
Apgar at 1 and 5 min	9.2 ± 0.6	9.0 ± 0.8	0.23
NICU admission	6	7	0.77
Intra-operative Blood Loss	374 ± 69.9	401.5 ± 79.9	0.01
Postpartum blood loss per 24 h (ml)	131 ± 31.8	145 ± 35.6	0.06
Use of additional oxytocics	8	18	0.03
Hb difference	1.14 ± 0.73	1.44 ± 0.88	0.009
Haematocrit difference	4.30 ± 2.26	5.25 ± 2.61	0.006
Adverse Effects	20	14	0.25

In Sood Atul kumar, et al. [6] study, the mean postoperative haemoglobin was significantly higher in misoprostol group (9.79 ± 0.99 vs 9.51± 0.56, p =0.023). Perioperative Hb fall was significantly less in misoprostol group (0.87±0.29 vs 1.01±0.26g, p = 0.0018). In Ahmed, et al. [7] study postoperative hemoglobin level (24 hours) was significantly lower in the post –operative rectally administered misoprostol group, (9.8±1.24) than the pre-

operatively rectally administered misoprostol group (10.5 ± 1.31) with p value 0.034. However the change in Hb level between the pre-operative level and postoperative level was obviously higher in post-operative rectally administered misoprostol group (1.2 ± 0.67) (p = 0.032). In our study the difference between the preoperative and postoperative hematocrit values was also lower in the study group than the control group (4.305 ± 2.26 versus 5.253±2.61: p < 0.001 for

both comparisons) which is similar to Elsedeeck, et al. [5] study the difference between the preoperative and postoperative hematocrit values was also significantly lower in the study group than the control group (4.62±2.45 versus 8.15±3.84; p = 0.02).

Table - 5: Comparison of results of present study with close study in misoprostol group.

Variable	Elsedeeck study [5]	Present study
Age	31.27±3.65	23.35± 2.34
Parity	1.8±1.3	2.47 ±0.71
No of previous CD	1.5 ±0.9	1.27 ±0.44
Preoperative hemoglobin g/dl	11.3±0.7	10.73±1.14
Preoperative hematocrit, %	34.3 ±3.2	34.26 ±2.80
Time until delivery, min	6.33 ± 3.65	6.12 ±0.84
Intra-operative blood loss	429 ±234	374 ±69
Postpartum blood loss	185 ±2.45	131±31
Hematocrit difference	4.62±2.45	4.30±2.26
Use of additional oxytocics	7%	8%
APGAR at 5 min	9.2±0.6	9.0 ±0.8
NICU admission	3%	6%
Side effects	5.5%	14%

In our study, the percentage of cases requiring additional oxytocics was significantly higher in the control group than in the study group (18% versus 8%; p = 0.03) which is similar to that in Elsedeeck study in which the percentage of cases requiring additional oxytocics was 7 % in study group and 18% in control group with p value = 0 .001 which is statistically significant. Jennifer, et al. [8], reported the same findings however in their study they used buccal route, not the rectal route for drug administration.

In Sood Atul Kumar, et al. [6] study the need for additional uterotonic agents was significantly less in misoprostol group. Misoprostol appears in circulation within 20-30 min but stays longer. Thus it may be useful to combine both drugs using i.v. oxytocin to achieve initial effect followed by misoprostol for more sustained effect. This may be helpful in high risk patients who are at increased risk of bleeding, but have contraindications for use of secondary uterotonic agents.

In Ahmed, et al. [7] study the additional need for other uterotonic drugs to control blood loss

during CS delivery was markedly noticed in women who received post-operative misoprostol compared to women who received pre-operative misoprostol, p = 0.05. In our study the common side effects are shivering, nausea, vomiting and pyrexia whose incidence is comparable between two groups. In Elsedeeck study [5] only 24 of the 400 participants developed transient postpartum fever, with no significant difference between the two groups. In Sood Atul Kumar, et al. [6] study there was increased incidence of shivering. However, there was no difference in pyrexia, nausea or vomiting, which is similar to that reported in literature. The need for blood transfusion (7%) and other infusions was higher in control group compared to study group (3%). Dose of misoprostol in various studies has ranged from 200 to 800 µg as the side effects are dose related, a dose of 200 µg was chosen in the present study to minimize maternal adverse effects with optimal therapeutic benefit. Oral, buccal, rectal, and sublingual routes have been used in different studies.

Rectal route was chosen because it avoids oral intake associated with slower absorption, lower

peak levels, sustained effect and reduced adverse effects when compared with oral and sublingual routes. In this study with regard to neonatal outcome, the mean apgar score at 5 minutes was 9.2 ± 0.6 in the study group and 9 ± 0.8 in the control group and these values were not significantly different between the 2 groups. NICU admissions are 6 % in study group and 7% in control group and the main reason for NICU admission was respiratory distress. This agrees with the results obtained by Elsedek who reported that the preoperative administration of misoprostol rectally did not cause any fetal adverse effects in the study group. A systematic review of measured postpartum blood loss with and without prophylactic uterotonics for prevention of postpartum haemorrhage reported contradictory results to most of the literature and superiority of oxytocin. By contrast, most of the relevant individual studies reported higher effectiveness for misoprostol than for oxytocin.

Chaudhuri and colleagues [8] used the rectal route for administration of misoprostol. They compared 800 µg of misoprostol with 20 IU of oxytocin; timing was at peritoneal incision and the outcome in terms of intra-operative and postoperative blood loss favoured misoprostol. Rectal administration of a drug at the time of peritoneal incision has been argued to be inconvenient and perhaps interfere with infection control procedures.

Acharya, et al. [4] compared the effects of 400 µg of oral misoprostol with those of 10 IU of oxytocin; intra-operative blood loss was lower with misoprostol but with increased postoperative shivering. Studies of sublingual misoprostol reported similar results [9]. Omitting a standard practice with known efficacy (like oxytocin infusion) for a new practice with a non-standardized dose and route of administration (like misoprostol) might not be in the best interest of patients. Two studies have combined misoprostol and oxytocin [10, 11]. The first study evaluated the effect of adding 200 µg of sublingual misoprostol after delivery of the fetus to 20 IU of oxytocin given routinely to all cases

and reported that the addition of misoprostol was effective in reducing blood loss. The second study enrolled a small sample ($n = 56$) of parturient women undergoing emergency CD who received 5 IU of intravenous oxytocin after cord clamping and were randomized to further receive either misoprostol orally or oxytocin infusion intravenously [12]. No difference in blood loss was detected between the 2 groups, although there was no control group included to assess whether either intervention had any added value.

In cochrane review on prostaglandins for prevention of postpartum hemorrhage, it was concluded that neither intramuscular prostaglandin nor misoprostol was preferable to conventional injectable uterotonics as part of the active management of the third stage of labour especially for low risk women [13]. However, in this meta-analysis which included 37 misoprostol trials, only three pertained to caesarean delivery misoprostol has been recommended in a dose of 600 mcg to 400 mcg by oral or sublingual route for prevention of PPH in the absence of active management of third stage of labor or non-availability of injectable conventional uterotonics [14, 15]. Cesarean delivery is carried out in a setting where conventional oxytocics are available and active management of third stage of labour is invariably practiced. misoprostol may have a role as an adjunct to oxytocin in prevention of postpartum hemorrhage in high risk women, where other uterotonic agents are either contraindicated or not available. In the present study, 200 mcg misoprostol by rectal route appears to be promising. Two recent trials have confirmed efficacy of rectal misoprostol in reducing blood loss at caesarean delivery [16]. Larger studies are needed to validate the efficacy of misoprostol and to find the optimal dose and the route of administration at caesarean delivery. Within the context of the present study, early (preoperative) administration of 200 µg of rectal misoprostol was effective at reducing intra-operative and postpartum blood loss after elective CD managed by intravenous oxytocin.

Conclusion

The mean intra-operative and postpartum blood loss was significantly lower in the misoprostol group than the placebo group. The difference between the preoperative and postoperative hematocrit values was also significantly lower in study group than control group. Admissions to the NICU and Apgar scores at 5 minutes were comparable between two groups. Need for additional oxytocics were lower in misoprostol group compared to control group. Frequency of side effects was not statistically different between two groups. Preoperative treatment with 200µg rectal misoprostol significantly reduced blood loss related to elective Cesarean delivery.

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