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The Efficacy and Safety of Intrauterine Misoprostol During Cesarean Section in Prevention of Primary Post-Partum Hemorrhage - A Randomized Controlled Trial

Research Article

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Abstract

Postpartum hemorrhage remains the most common cause of maternal death globally [1]. and has persisted in low-income countries due to the prevalence of home deliveries and limited access to life-saving uterotonic drugs in these countries [2-5]. Many of the global gains in reducing maternal mortality can be attributed to developments in preventing and treating Postpartum Hemorrhage (PPH) [6,7]. PPH is often associated with the failure of the uterus to contract after delivery and is categorized as blood loss of 500 mL or more following a vaginal delivery or 1,000 mL after cesarean delivery [8,9]. PPH is categorized as primary if it occurs within 24 hours of delivery and secondary if excessive blood loss occurs at 24 hours or more after delivery. To compare the efficacy and safety of intrauterine misoprostol with intravenous oxytocin during Cesarean Section (CS) in prevention of primary post-partum hemorrhage. A total of 150 pregnant women at term (37-40 weeks) gestation who were scheduled for either elective or emergency caesarean delivery were enrolled. They were equally randomized into two groups: women who received 400mcg intrauterine misoprostol in addition to intravenous infusion of 10 IU oxytocin as Group I while women who received an intravenous infusion of 10 IU oxytocin after delivery of the neonate as Group II. The Primary outcome measures were Estimated Blood Loss (EBL) during caesarean section and need for additional uterotonic drugs intraoperatively. Secondary outcomes included the occurrence of excessive blood loss (>1000mL) within the first 6 hours postoperatively and the occurrence of any maternal or fetal side effects. The difference in the postoperative haemoglobin and postoperative hematocrit was found to be highly significant between the two groups (10.12 ± 1.55 vs 9.24 ± 1.52; $p < 0.01$) and (2.48 ± 1.38 vs 3.75 ± 1.77; $p < 0.001$) respectively. Estimated blood loss in two groups was found to be very highly significant (440.19 ± 257.75 vs 677.38 ± 343.04; $p < 0.001$). Intraoperative blood loss was significantly lower in the group I compared to group II (408.27 ± 123.34 vs 486.04 ± 135.84; $p < 0.001$). Blood loss during the first 6 hours after delivery was also lower in the group I (58.87 ± 9.86 mL vs 63.29 ± 12.39 mL; $p < 0.05$). Fewer women in the intrauterine misoprostol group needed additional uterotonics (7 vs 11; $p > 0.05$). The difference in the side effects of both the groups was found to be statistically non-significant. Apgar scores at 1 and 5 minutes were comparable in both the groups. The combined use of intrauterine misoprostol (400 mg), when added to oxytocin infusion during caesarean section is effective in decreasing the intraoperative blood loss, post-operative blood loss and prevent postpartum hemorrhage.

keywords: Intrauterine misoprostol; Intraoperative estimated blood loss; Cesarean section; Postpartum hemorrhage

Introduction

PPH remains the most common cause of maternal death globally [1]. PPH is categorized as primary if it occurs within 24 hours of delivery and secondary if excessive blood loss occurs at 24 hours or more after delivery. First, the initial Hemoglobin (Hb) level of a woman affects her survival rate from PPH [2]. Recently, a strong correlation was found between low Hb (Hb < 10) and the risk of PPH, as well as an association between severe anemia and emergency hysterectomy [3].

Postpartum Hemorrhage (PPH) from uterine atony is the leading cause of maternal mortality that can occur in both vaginal and cesarean deliveries [4]. PPH is categorized as blood loss of 500 mL or more following a vaginal delivery or 1,000 mL after cesarean delivery [5,6].

Nowadays, Cesarean Section (CS) is increasing in both developed and developing countries [7,8]. Oxytocin has been routinely used to prevent uterine atony and excessive uterine bleeding during CS. However, despite its effectiveness, 10-40% of cases need additional uterotonics to ensure good uterine contraction [9-11]. The role of misoprostol, a prostaglandin E1 analog, in the prevention and treatment of PPH has evolved due to its long shelf life and multiple routes of administration, which make it more suitable for low-resource settings with limited skilled providers [12,13]. Not only is the uterotonic treatment of PPH important in the reduction of adverse maternal outcomes but it can help avert more medical interventions, including the administration of Intravenous (IV) fluids, additional drug therapy, blood transfusion, and surgery [14]. The purpose of this article is to assess the efficacy and safety of intrauterine misoprostol for the treatment of primary PPH.

Materials and Methods

This prospective randomized controlled trial was conducted in the Department of Obstetrics and Gynecology in collaboration with the Department of Pathology, JNMCH, AMU, and Aligarh during 2019-2021 after institutional ethical clearance. A total of 150 pregnant women at term (37-40 weeks) gestation who were scheduled for either elective or emergency cesarean delivery were enrolled. Informed written consent was obtained for all women after discussing the nature and aim of the study as well as the potential maternal or fetal adverse effects. The exclusion criteria were anemia (Hemoglobin < 8 g), cardiac disease, renal disease, liver disease, twin pregnancy, pregnancy with obstetric hemorrhages such as placenta previa, placental abruption, and vasa previa, pregnancy with coagulopathy or thrombocytopenia or blood dyscrasias, and Pregnancy-Induced Hypertension (PIH) with Hemolysis, Elevated Liver Enzyme, And Low Platelets (HELLP) syndrome, with a history of prostaglandin allergy and duration of surgery more than 120 minutes. The sample size in each group was 75 women. All women were assigned randomly to one of two study groups. The first group received 400 micrograms of misoprostol intrauterine inserted at the cornual part bilaterally, divide in each side after placental delivery combined with 20 units of oxytocin infusion. The second group received 20 units of oxytocin infusion only after delivery. The dose of oxytocin was 20 units plus 1,000 ml of 0.9% normal saline solution started with 250 ml in 10 minutes (0.5 units/min) and then 120 ml/hr (0.04 units/min) for 12 hours. The main outcome measurements were the volume of intraoperative blood loss and the different measurements in hemoglobin/hematocrit levels preoperative and 24 hours after the operation. Intraoperative blood loss was measured by blood in the suction apparatus after operation plus the different weights of abdominal swabs and gauzes before and after the operation. We calculated 1 gram of the different weights equal to 1 ml of blood loss. Postoperative drop in hemoglobin/hematocrit was calculated by the difference between preoperative (when the women were admitted) and 24 hours postoperative (from incision time) from the central lab. Secondary outcome measurements were the requirement of additional uterotonic agents, misoprostol related side effects which included shivering, pyrexia, nausea, vomiting and headache, Pyrexia and hyperpyrexia were defined as a temperature higher than 38oC and 40oC respectively. The intrauterine misoprostol route was defined by the insertion of misoprostol into the uterine cornu at both sides after placental delivery. Intravenous infusion of oxytocin 20 units in 1,000 ml saline solution was started at 0.5 unit/min for 10 min, followed by 0.04 unit/min for 6 hours after delivery (2.4 units/hr). Additional uterotonic agents were used by the obstetricians based on clinical findings during surgery and recorded by anesthesiologists.

Statistical Analysis

Categorical variables were reported as count and percentage and analyzed by chi-square test or Fisher's exact test based on expected value. Continuous variables were reported as mean with SD and analyzed by Student's t-test and rank-sum test depending on data distribution. The power of the test < 0.05 was considered as the level of significance.

Results

A total of 150 pregnant women were enrolled in this study after fulfilling the inclusion and exclusion criteria. They were randomly allocated into two groups (Table 1). 75 pregnant women received misoprostol intrauterine combined with oxytocin infusion as Group I and 75 pregnant women received only oxytocin infusion as Group II. There were no statistical differences between the two groups concerning maternal age, gravidity, body mass index, blood pressure, gestational age, and duration of cesarean section.

Table 1: Patient and pregnancy characteristics in the studied Groups.

Basic characteristics (Mean ± SD)		Group I (n = 75)	Group II (n =75)	p value
Maternal age		25.99 ± 3.63	25.68 ± 4.09	p > 0.05
Booked status		53 (70)	43 (57.3)	p > 0.05
Gravidity		1.63 ± 0.48	1.61 ± 0.49	p > 0.05
Body mass index		32.14 ± 1.79	31.88 ± 1.32	p > 0.05
Gestational age		38.6 ± 0.8	38.1 ± 0.8	p > 0.05
Blood pressure	SBP	133.05 ± 118.42	122.88 ± 11.44	p > 0.05
	DBP	76.96 ± 8.33	79.95 ± 13.00	
Previous 1 CD		18 (24)	26 (34)	p > 0.05
Previous 2 CD		08(10.6)	08 (10.6)	
Indications for caesarean section	Previous 1 CD with ST	11 (14.6)	13 (13.7)	p > 0.05
	Previous 2 CD	10 (13.33)	8 (10.6)	
	Cord prolapse	2 (2.66)	2 (2.66)	
	CPD	4 (5.33)	9 (12)	
	FD	40 (53.33)	36 (48)	
	Malpresentation	8 (10.6)	7 (9.3)	
Duration of CD (min)	72.53 ± 23.57	72.53 ± 23.57	72.00 ± 24.84	p > 0.05

Abbreviations: CD: Cesarean Delivery; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; CPD: Cephalopelvic Disproportion FD: Fetal Distress; SD: Standard Deviation Values are given as number (percentage) or mean ± SD.

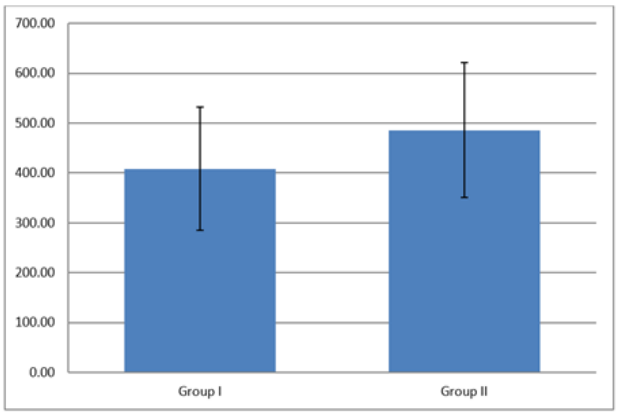

Figure 1: Intra-operative blood loss (Mean ± SD).

Discussion

It is well known as a cesarean section is an obstetric procedure that increasing worldwide in both developed and developing countries (Table 2 & Table 3). Oxytocin is used routinely to prevent uterine atony during surgery. But in some areas, further uterotonic drugs were added on to prevent bleeding [2,6]. Excessive blood loss during and after delivery represents the main cause of maternal morbidity and mortality, especially in countries with limited medical resources. It accounts for almost 25% of maternal deaths worldwide [15]. Several studies agreed that the administration of misoprostol significantly reduces blood loss during cesarean delivery, and hence PPH, but there are some conflicts regarding the side effects of misoprostol and the effect on the neonatal outcome that can differ according to the route of administration (Figure 2). Moreover, no mode of administration was shown to be superior to the other [16]. Systematic review and meta-analysis [17], there have been many types of research that try to study misoprostol in any routes to reduce postpartum hemorrhage.

Table 2: Hematologic parameters and estimated blood loss in the groups.

Variables	Groups		p value
	Group I (n = 75)	Group II (n = 75)	
Preop Hb	10.92 ± 1.50	10.83 ± 1.64	p > 0.05
Postop Hb	10.12 ± 1.55	9.24 ± 1.52	p < 0.01
Difference in Hb	0.79 ± 0.43	1.60 ± 0.62	p < 0.001
Preop Hematocrit	33.78 ± 4.19	33.59 ± 4.11	p > 0.05
Postop Hematocrit	31.31 ± 4.49	29.84 ± 4.01	p < 0.05
Difference in Hematocrit	2.48 ± 1.38	3.75 ± 1.77	p < 0.001
Distribution of estimated blood loss (EBL)	440.19 ± 257.75	677.38 ± 343.04	p < 0.001
Weight difference of soaked towels (gm)	166.27 ± 42.96	177.37 ± 39.84	p > 0.05
Blood loss in suction (ml)	242.00 ± 96.93	308.67 ± 114.01	p < 0.001
Number of soaked towel	3.77 ± 0.73	4.05 ± 0.75	p < 0.05

Abbreviations: Hb: Haemoglobin; EBL: Estimated Blood Loss

Values are given as number (percentage) or mean ± SD

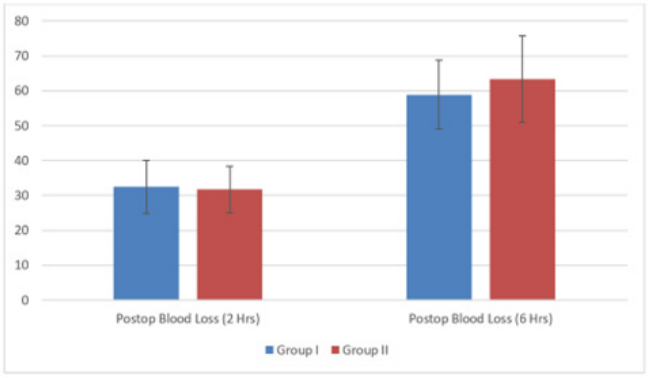

Figure 2: Post-operative blood loss (Mean ± SD) after 2hrs and 6 hrs.

In this study, we chose the intrauterine route of misoprostol because it is the most convenient way to put misoprostol during cesarean section than other routes such as oral, sublingual, buccal, or rectal. In addition, misoprostol is an autacoid substance so its effect is stronger if it is closer to the target organ to contract the uterine muscle. It binds to myometrial cells to cause strong myometrial contractions that start at the fundus near a cornu and propagate down to the body of the uterus leading to the expulsion of tissue and reducing postpartum hemorrhage. So, we thought that insertion at uteri cornu was simple and easy to fix the tablets. It might help in their absorption to myometrial cells [18]. Proved the safety and efficacy of misoprostol administered rectally before elective cesarean delivery to decrease blood loss intraoperatively and postoperatively [19]. Reported rectal route had a significantly reduced intraoperative and postoperative blood loss but no statistically different in oral or sublingual routes when compared to oxytocin intravenous use.

The most common indication for LSCS was fetal distress followed by cord prolapse in both groups. The pre-operative hemoglobin was comparable between the two groups while the post-operative hemoglobin in Group I and Group II was found to be highly significant (p value < 0.01) which were comparable with [16,20,21] showed that the mean drop in hemoglobin was not significantly different between the two groups which is contrary to our study [22].

The estimated blood loss in the two groups was found to be very highly significant which is similar to the study [23]. The weight difference of soaked towels in both groups was comparable. Our findings are similar to but lower weight difference of soaked towels in the study [21].

The intraoperative blood loss was found to be very highly significant in the two groups. Our findings were similar to [20] where mean intraoperative blood loss in oxytocin IV and oxytocin IV + misoprostol IU group was very highly significant. Observed that misoprostol with oxytocin has been reported to be more effective than oxytocin alone in reducing intraoperative bleeding during cesarean section. The plausible reason behind the reduction in bleeding might be because of the initial rapid effect of oxytocin followed by the sustained effect of misoprostol on uterine contractility. Reported that bleeding was lower in the misoprostol group than the oxytocin group, and misoprostol was more effective in reducing blood loss and should be used in low-income areas labor which is similar to our study results. The postoperative blood loss after 6hrs was found to be statistically significant in the two groups. In the present more women from Group II need additional uterotonics which were similar to the study [20].

Most of the studies found the adverse effects were shivering and fever. In the present study maximum number of women in both groups did

not have side effects. Studies that compared the effects of misoprostol and oxytocin have shown that high-dose misoprostol (1000 gms) was effective in reducing PPH but had more side effects. It was considered that the route and dose of administration of uterotonics affected the frequency of their side effects. The difference in APGAR scores at 1 and 5 minutes was found to be statistically nonsignificant.

Table 3: Need of additional uterotonic drugs, distribution of adverse effects and neonatal outcome in the studied groups.

Variables		Group I (n = 75)		Group II (n = 75)		p value
		No	%	No	%	
Need other interventions		10	13	17	23	p>0.05
Need for additional uterotonics		7	100	11	100	p>0.05
Incidence of side effects		6	8	4	5	p>0.05
Distribution of side effects	Fever	3	50	2	60	p>0.05
	Shivering	3	50	1	20	
	Headache	0	0	1	20	
APGAR score	1 min	5.52 ± 1.54	5.52 ± 1.70			p>0.05

Conclusion

The combined use of intrauterine misoprostol (400 mcg), when added to oxytocin infusion during cesarean section is effective in decreasing the intraoperative blood loss, postoperative blood loss and thus preventing postpartum hemorrhage. Also, it reduced the need the extra ecbolics, additional intervention, and with less reduction in postoperative hemoglobin level and hematocrit level when compared to oxytocin alone. In addition, intrauterine misoprostol can be safely and conveniently administered with the only significant adverse effects being fever and transient shivering.

Ethical Approval

All procedures performed in studies involving human participants were following the ethical standards of the institution.

Informed Consent

Informed consent was obtained from all the individual participants included in the study.

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