Original article

Comparison of the Effect of Rectally Administered Misoprostol Versus Intramuscular Oxytocin in Addition to Oxytocin Infusion for the Prevention of Post-Partum Hemorrhage in Cesarean Section

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ABSTRACT

Background: Post-partum hemorrhage (PPH) is known in to occur in more than 10% of cesarean sections. Generally intravenous or intramuscular oxytocin is commonly used for prevention of PPH, nevertheless, in some studies rectally administered misoprostol has been shown to be superior to oxytocin in this regard. This route is also linked with fewer side effects and longer half-life. This study was designed to compare the outcome of per rectal misoprostol versus I.M oxytocin in the prevention of post-partum hemorrhage in cesarean section.

Patients and methods: A randomized controlled trial was conducted at the Department of Obstetrics and Gynaecology, Sir Ganga Ram Hospital, Lahore from 1st November 2021 to 30th April 2022. Women undergoing cesarean section were either given 10 IU of injection oxytocin intramuscularly or 800 micrograms Misoprostol per rectally in addition to IV oxytocin infusion in all patients. Difference in hemoglobin levels before and after the cesarean section were compared. Pre-designed data collection performa were used for data collection and the data were analyzed using SPSS version 25.0.

Results: A total of 88 patients were randomized in to two groups of 44 patients each. The mean age of participants in misoprostol group was 30 ± 4 years and in oxytocin group was 29 ± 5 years. The most common indications for cesarean sections were fetal distress due to multiparity, which was present in 33 (37.5%) cases, followed by prolonged labor in 22 (25%), polyhydramnios with fetal malpresentation in 20 (22.7%), and multiple gestation with malpresentation of first fetus in 13 (14.5%) cases. The mean change in hemoglobin was lower in the misoprostol group (0.7 ± 0.26 g/dL) than the oxytocin group (1.17 ± 0.45 g/dL) and the results showed statistical significance (p = 0.000).

Conclusion: Rectally administered misoprostol is superior to intramuscular oxytocin in the prevention of post-partum hemorrhage and can be used as an alternative in patients undergoing cesarean section.

Keywords:

Cesarean section, postpartum hemorrhage, misoprostol, oxytocin

INTRODUCTION

Cesarean section is considered as the most common obstetrical procedure performed in women of reproductive age group.[1] In the last few decades, the rate of cesarean section has increased considerably both in developed and developing countries.[2] This rise has resulted in a consequent rise in the procedural complications associated with it. These include secondary subfertility due to post-surgical adhesion, abnormal placentation, ruptured uterus, hemorrhage and the need for blood transfusions.[3, 4] There is an increased blood loss associated with cesarean section due to several factors such as surgical incision, manual removal of placenta and impaired uterine tissue contractility which occurs due to inadequate time for retraction of myometrial fibers.[5] Generally, post-partum hemorrhage (PPH) is defined as an estimated blood loss of more than 500 ml in normal vaginal delivery and more than 1000 ml in cesarean section.[6] However, in countries where anemia is common, even a much smaller amount of blood loss can often lead to serious clinical consequences.[7] As per global estimates, the incidence of post-partum hemorrhage after cesarean section is around 10.8%, although it may be higher in some African and Asian countries.[8, 9] The single most common cause is uterine atony which is responsible for almost 70-80% of the cases.[10] Oxytocin, a cyclic non-peptide, reduces the blood flow through the uterus by causing rhythmical contraction of uterus and constriction of spiral arteries.[11] It is commonly used drug for the

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prevention of PPH. However, it requires a specific storage temperature, and being parentally administered, requires a skilled person during its administration.[11] Misoprostol, a prostaglandin E1 analogue, originally used for gastric ulcer treatment, is employed in various gynaecological conditions such as cervical ripening, induction of labor and termination of pregnancy.[12, 13] Misoprostol has strong uterotonic properties, is cheaper than oxytocin, shows more heat stability and can be given through oral, rectal or vaginal route.[13] A randomized controlled trial conducted by Afkhan *et al*., showed that both rectal and sublingual misoprostol were superior to oxytocin in preventing PPH ($p < 0.005$) and the difference in bleeding between the two routes of misoprostol was insignificant ($p > 0.05$).[14] The use of misoprostol in the prevention of post-partum hemorrhage has been recommend by the World Health Organization (WHO), particularly in conditions where oxytocin is not readily available.[15]

Various studies have shown that the combination of misoprostol and oxytocin is more effective in the prevention of postpartum hemorrhage.[16, 17] In a local study by Shah *et al.,* the mean blood loss in the rectal misoprostol group was less as compared to IV oxytocin group (776±285.7 ml vs 817±1318 ml, $p = 0.043$).[18] Misoprostol is not routinely used for the management of past-partum hemorrhage in our setup. Availability of local evidence will serve to formulate guidelines for the routine use of misoprostol. This study was thus designed to compare the mean post-operative change in hemoglobin concertation after administration of per rectal misoprostol versus intramuscular oxytocin in addition to oxytocin infusion in patients undergoing cesarean section.

PATIENTS AND METHODS

A randomized controlled trial was conducted at the Department of Obstetrics and Gynaecology, Sir Ganga Ram Hospital, Lahore from 1st November, 2021 to 30th April, 2022 after taking approval from the College of Physicians and Surgeons Pakistan (CPSP). Informed consent was taken from women undergoing cesarean section (elective or emergency) for any indication such as gestational amenorrhea >37 weeks on LMP, grand multiparity of more than 5, fetal distress, polyhydramnios (AFI >25cm) with malpresentation, multiple pregnancies (on ultrasonography) or prolonged labor before inclusion in the study. Women with known allergic reaction to any of the drugs used in this study, patients with bleeding disorders, patients requiring per-operative blood transfusion and those with history of previous cesarean section were excluded from the study. A non-probability consecutive sampling technique was used and a sample size of 88 cases (44 in each group) was calculated using 95% confidence level, 80% power of study and taking expected mean change in hemoglobin as 0.20 ± 1.31 g/dl in misoprostol versus 0.63 ± 0.30 g/dl in oxytocin group.[19, 20] After admissions, patients were given 500 mL normal saline preload and a 5 ml venous blood sample for hemoglobin was taken. Patients were distributed in two equal groups using computer generated table of random numbers. The cases in Oxytocin group (Group A) received 10 IU of injection oxytocin intramuscularly, after the delivery of baby during cesarean section and in Misoprostol group (Group B), 800 micrograms tablet of misoprostol was given per rectally after spinal anesthesia and before painting and draping. Oxytocin infusion (40 IU in 500mL isotonic crystalloid at 125 ml/hour) was started in participants of both the groups after the delivery of baby. After cesarean section, patients were shifted to the post-natal ward and observed for any episode of heavy bleeding. Hemoglobin was rechecked after 24 hours. Outcome was assessed by comparing difference in hemoglobin levels before and 24 hours after the cesarean section. All the cesarean sections were performed by the researcher under supervision of a consultant gynaecologist to minimize bias. Patients at high risk of intraoperative blood loss due to tears or extension of incision were excluded from the study and managed according to the hospital protocol. The confidentiality of the data was maintained and patients reserved the right to be excluded from the study any time during the conduction of research.

Pre-designed data collection performa were used for the collection of data. Continuous variables such as age, baseline and postoperative Hb concentration and change in Hb concentration were presented as mean + S.D. Categorical variables such as indications of cesarean section were presented as frequency and percentages. The data were then entered into Excel sheets and later transferred and analyzed using SPSS version 25.0. Age of study participants and change in hemoglobin levels before and after cesarean section were described as mean and standard deviation. Mean change in Hb was compared in both groups using Independent sample T-test. Effect modifiers such as age and indication for cesarean section were addressed in both groups through stratification. Post-stratification T-test was applied. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

A total of 88 patients were included. Mean age of all the participants was 29.6 + 4.7 years (range 19-39 years). Mean age of patients in misoprostol group was 30 ± 4 years and in oxytocin group was 29 ± 5 years. Pre-operative hemoglobin levels ranged from 7.2g/dL to 13.7g/dL with a mean value of 10.5 ±1.2 g/dL. In the misoprostol group, mean pre-operative hemoglobin was

Table 1: Baseline characteristics of participants in both groups

Characteristics	Group			
	Misoprostol (n = 44)		Oxytocin (n = 44)	
	Mean	S.D	Mean	S.D
Age (years)	30	+ 4	29	+ 5
Pre-op Hb (g/dL)	10.2	+ 1.3	10.8	+ 1.1
Indications	**Frequency (n)**	**Percentage**	**Frequency (n)**	**Percentage**
Multiparity	19	57.6%	14	42.4%
Prolonged Labour	9	40.9%	13	59.1%
Poly-hydramnios with malpresentation	12	60.0%	8	40.0%
Multiple Gestation with malpresentation of first fetus	4	30.8%	9	69.2%

Table 2: Comparison of change in Hb in both groups

Characteristics	Misoprostol	Oxytocin	p - value
Frequency	44	44	0.000*
Mean	0.75	1.17	
Std. Deviation	0.26	0.45	

T-test was applied to compare mean values.
* p - value ≤ 0.05 was considered significant

Table 3: Stratification for age and indication of caesarean section for change in Hb in both groups

Characteristics	Misoprostol group			Oxytocin group			p - value
	n	Mean Hb	S.D	n	Mean Hb	S.D	
30 years and above	24	0.78	0.27	20	1.12	0.43	0.003*
Less than 30 years	20	0.71	0.24	24	1.12	0.48	0.001*
Multiparity with fetal distress	19	0.72	0.21	14	1.1	0.42	0.002*
Poly-hydramnios with malpresentation	12	0.84	0.3	8	1.18	0.44	0.059
Multiple Gestation with malpresentaion	4	0.7	0.37	14	1.1	0.42	0.046*
Prolonged Labour	9	0.71	0.23	13	1.09	0.6	0.092

T-test was applied to compare mean values.
* p - value < 0.05 was considered significant

10.2 ± 1.3 g/dL and in oxytocin group, it was 10.8 ± 1.1 g/dL. The most common indications for cesarean sections were fetal distress due to multiparity, which was present in 33 (37.5%) cases, followed by prolonged labor in 22 (25%), polyhydramnios with fetal malpresentation in 20 (22.7%) and multiple gestation with malpresentation of first fetus in 13 (14.5%) cases. The baseline characteristics of study participants in both groups are given in Table 1.

Comparison of mean change in hemoglobin levels in both the study groups was done through Independent sample T-test. In the misoprostol group, the mean change in hemoglobin was noted to be 0.7 ± 0.26 g/dL and in the oxytocin group, the mean change in hemoglobin was 1.17 ± 0.45 g/dL. The mean change in hemoglobin was lower in the misoprostol group than the oxytocin group and the results showed statistical significance (p = 0.000). Table 2 shows the comparison of mean change in hemoglobin levels in both the study groups. The results were stratified for age and the indication for cesarean section to assess the effect of these variables on the study outcome. Patients were grouped into less than 30 years of age and 30 years or more. The difference in mean change in hemoglobin in oxytocin and misoprostol group was statistically significant across the both age groups (age > 30 years, p = 0.003; age < 30 years, p = 0.001). Similarly, significant difference in the study groups was observed when the indication for cesarean section was multiparity with fetal distress (p = 0.002) and multiple gestation with malpresentation of first fetus (p = 0.046). The association of age and indications for cesarean section with the study outcome are given in Table 3.

DISCUSSION

The present study was conducted to compare the effects of misoprostol and oxytocin for the prevention of post-partum hemorrhage in patients undergoing cesarean section. A comparison of both the drugs was made in terms of mean change in hemoglobin levels before and after the cesarean section. In the misoprostol group, the change in hemoglobin was significantly lower than that of the oxytocin group with a statistically significant p-value of 0.000. Hemoglobin change is an indirect measure of the amount of bleeding in the peri-operative period.[21] Therefore, these results point towards the effectiveness of rectal misoprostol in reducing the amount of bleeding during cesarean section.

Rectal misoprostol is known to have a steady serum rise with lower peak serum concentration and longer half-life. This may account for the low side effect profile as compared to oral/sublingual route.[22] The longer half-life of rectal misoprostol has an additional beneficial effect of prolonging uterine contraction and preventing a delayed hemorrhage. A previous study conducted on 192 women, who did not have any risk factors for post-partum

hemorrhage, showed that there was a significant reduction of blood loss in the misoprostol group compared with the oxytocin group (144.5 ± 100.1 ml vs 191.7 ± 117.1 ml, p < 0.0001). The two groups were similar in terms of the secondary outcome parameters.[23] In a local study conducted by Khan *et al.,* patients undergoing myomectomy were either given misoprostol or a placebo. There was a significant difference in the blood loss in both groups. The mean blood loss was 328.4 ml in misoprostol group as compared to 484.4 ml in placebo with a statistically significant p-value of 0.002. It was concluded that even a single dose of rectal misoprostol can significantly reduce blood loss during abdominal myomectomy.[24] As the mechanism of blood control is through uterine contraction, therefore, the same can be said about other conditions involving uterine atony such as cesarean section. However, in an Egyptian study, misoprostol was found to be inferior to carbetocin in terms of blood loss (410.4 + 5.0 ml in misoprostol vs 292.2 + 32.8 ml in carbetocin, p < 0.001) and need for uterine massage (20.0% in misoprostol vs 5.2% in carbetocin, p = 0.007). Adverse events were also more common in misoprostol group (p = 0.745).[25]

In the present study, rectal misoprostol was given in combination with IV infusion of oxytocin which was given as a standard protocol in both group. Study by Jones *et al.,* on the use of misoprostol in combination with intravenous oxytocin, showed that misoprostol combination reduces the incidence of PPH by 48%.[16]. A systematic review conducted by Li *et al.,* showed results similar to the present study in which the mean blood loss was less in the misoprostol combination group as compared to control group (p < 0.01).[26] Although in the systematic review, in contrast to the present study, the misoprostol group was not compared with the I.M oxytocin group, nevertheless, the results favor the use of misoprostol in prevention of post-partum hemorrhage.

A study conducted in Nepal randomized 200 women to receive either 400mcg of rectal misoprostol before the cesarean section or intravenous oxytocin infusion. There was a significant reduction in blood loss in patients treated with misoprostol with a statistically significant p-value of <0.01.[27] In an Irani study conducted on 400 subjects randomized to receive either misoprostol or oxytocin, it was observed that the rate of bleeding >500 cc was significantly higher in oxytocin group than misoprostol group (33% vs. 19%) (p = 0.005).[28] Also, need of excessive oxytocin for management of post-partum hemorrhage was significantly lower in misoprostol group than oxytocin group (18% vs. 30%) (p = 0.003). Decrease in hematocrit was significantly higher in oxytocin group than misoprostol group (1.6 ± 2.2 vs 1.3 ± 1.6).[28]

In the present study a single combination of misoprostol was tested. However, in literature various combinations with other drugs have been mentioned. In a Brazilian study, the overall efficacy of misoprostol in prevention of hemorrhage was 84.7%. It was used as a monotherapy, second line drug or as a third-line drug along with two other drugs. When used alone, treatment failure was observed in only one case out of thirteen cases treated with misprostol.[29] Thus the efficacy of misoprostol is high whether used alone or in combination with other drugs. There is also an ambiguity regarding the optimal dose of misoprostol as different doses of misoprostol have been mentioned in previous studies. In a study by Nagasree and Smitha, there was no significant difference between 800 µg rectal misoprostol and 5 IU intravenous oxytocin groups in terms of postoperative bleeding, hemoglobin values and the need for additional uterotonics and the authors concluded that misoprostol can be used as an alternative to oxytocin.[30] Firouzbakht and colleagues, compared 200 µg of rectal misoprostol and 20 IU intravenous oxytocin groups in terms of the changes in the values of hematocrit, but no difference was determined (p = 0.28).[31] Thus misoprostol seems to be effective across various doses ranging from 200 µg to 800 µg, although determination of the optimal dose requires further studies.

A web-based survey on 130 gynaecology and obstetrics societies around the world showed that a majority of the countries lacked comprehensive guidelines regarding the use of misoprostol in the management of post-partum hemorrhage.[15] The local recommendations often did not comply with the international guidelines. Therefore, it was recommended that evidence backed, up-to-date guidelines should be established for use of misoprostol, particularly in the countries with higher maternal mortality rates.[15] Certain gynaecological associations such as Society of Obstetrician and Gynaecologists of Canada (SOGC) have already established guidelines for the use of misoprostol in high risk individuals although, as per these guidelines, oral or sublingual routes are preferred to rectal administration.[32] Therefore, the authors recommend that local gynaecological associations should formulate guidelines to determine the optimal usage of misoprostol. There is substantial literature evidence supporting the use of rectally administrated misoprostol as an effective alternative to oxytocin in prevention of post-partum hemorrhage in at risk patients who are undergoing cesarean section for different indications. In tropical developing countries, the tendency of oxytocin losing its potency is high as proper refrigeration capability is low, thus affecting the efficacy of oxytocin in prevention of post-partum hemorrhage.[33] Misoprostol on the other

hand, is stable in tropical climate while still maintaining its potency. The spectrum of side effects includes nausea, shivering, fever and gastrointestinal symptoms which are self-limiting and do not require any medical intervention as such and mostly settle within first 24 hours.[34, 35] It makes misoprostol an effective drug for the prevention of post-partum hemorrhage and reduced blood loss during and after cesarean section, when administered prior to the procedure.

Finally, the authors acknowledge that the study is not without limitations. This is a single-center study involving a tertiary care hospital. The situation in other centers of the country, particularly in those without tertiary care facilities, may be altogether different. Therefore, the results may not be generalized over whole of the population of the country. The measure for assessment of effect of the study drugs included the mean change in hemoglobin concentration as an indirect measure of intraoperative blood loss. The authors acknowledge that hemoglobin concentration can depend on various factors such as perioperative fluid administration and the hematocrit levels. Direct estimation of intraoperative blood loss would have been a more accurate measure of the efficacy of both drugs. The authors, therefore, recommend further large scale multi-centric studies with more reliable methods for estimation of the efficacy of rectally administered misoprostol in order to provide evidence for its use in patients undergoing cesarean section.

CONCLUSION

Use of misoprostol for the prevention of post-partum hemorrhage in female patients undergoing cesarean section is superior to oxytocin. It can be given safely, with ease and in all the poor-resource setups where oxytocin storage cannot be adequately managed. Rectal use of misoprostol before starting the cesarean section and after spinal anesthesia helps in the achievement of effective serum concentration of the drug at the time of delivery of the fetus. Moreover, rectal administration bypasses the gastrointestinal side effects associated with the oral intake of the drug. So, on basis of evidence obtained from this study, the routine use of misoprostol in patients undergoing cesarean section, is recommended. This will help in reducing the burden of maternal morbidity and mortality due to grave consequences of post-partum hemorrhage.

Author Contributions

Afzal R: Analysis and interpretation of data, Acquisition of data, conception and design, analysis and interpretation, Analysis and interpretation of data, proofreading, Conception and design, analysis and interpretation of data.

Akmal N: Conception and design, analysis and interpretation of data, drafting the article, critical revision for important intellectual content, final approval.

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