RESEARCH ARTICLE

A comparative analysis of the efficacy of intrauterine misoprostol in conjunction with oxytocin versus oxytocin monotherapy for the prophylaxis of primary postpartum haemorrhage

Afnan Rizwan[1], Muhammad Hassaan Farooq[2], Uzma Nayyer[3], Asma Irfan[4], Mahwish Farooq[5], Maryam Siddique[6]

Abstract

Objective: To determine the effectiveness of intrauterine misoprostol along with oxytocin versus oxytocin monotherapy for the prevention of primary postpartum haemorrhage.

Method: The quasi-randomised controlled trial took place at the Akbar Niazi Teaching Hospital, Islamabad, Pakistan, from February to August 2021, and comprised women who underwent lower segment caesarean section and at full-term pregnancy who had risk factors for experiencing postpartum haemorrhage. The subjects were randomised into experimental group A and control group B. Group A subjects received both misoprostol and oxytocin, while those in group B received oxytocin only. Data was analysed using SPSS 26.

Results: Of the 120 subjects, 60(50%) were in group A with mean age 28.72±5.82 years and mean gestational age 38.02±1.1 weeks. The remaining 60(50%) subjects were in group B with mean age 29.47±4.72 years and mean gestational age 37.50±1.5 weeks. Group A subjects had fewer changes in haemoglobin levels post-operation than those in group B ($p<0.05$). The number of operative towels used, contractility time of the uterus, and need for other drugs to control haemorrhage were significantly different in group A compared to group B.

Conclusion: Misoprostol along with oxytocin was found to be more effective in reducing blood loss in patients with postpartum haemorrhage.

Keywords: Postpartum haemorrhage, Misoprostol, Oxytocin, Postoperative blood loss. (JPMA 75: 405; 2025)

DOI: https://doi.org/10.47391/JPMA.11080

Introduction

Postpartum haemorrhage (PPH) is one of the biggest and most prominent reasons for maternal mortality in South Asia, covering about one-quarter of maternal deaths, and such deaths are 100 times more common in under-resourced countries. It can also lead to a lot of maternal morbidities, which may include several blood transfusions, hospital stays for a longer period, and surgical approaches that lead to loss of reproductive functions.[1] PPH is categorised as minor in which bleeding is about 500mL to 1,000mL, moderate in which bleeding is between 1,000mL and 2000mL, and severe in which bleeding is >2000mL. The atonic uterus causes 70% of primary PPH, and a lot of medical and surgical interventions are needed to prevent and treat it.[2] Over the years, efforts have been made to improve protective measures for PPH which led to the addition of misoprostol to the list of preventive drugs for PPH. Operative deftness plays an important role in lowering the incidence of primary PPH during caesarean section (CS), but uterotonic agents have a greater role in preventing or reducing bleeding from the uterus in case of PPH.

Misoprostol, which is a prostaglandin E1 analogue, has shown its efficacy in the form of a stimulant in the myometrium of the pregnant uterus by promoting an increase in intracellular calcium, which helps in contraction of the myometrium.[3] Its effectiveness and efficacy have been proved by its administration sublingually as a preventive measure of primary PPH. Prostaglandin E1 has a longer half-life, and it remains stable at room temperature. The active metabolites act on the prostaglandin receptors and help in changing the physical as well as the chemical structure of the cervix, leading to its dilation.[4]

On the other hand, oxytocin is also a uterotonic drug, which is unstable at higher temperatures, and needs an appropriate storage system, but it comes with lesser adverse effects, and it needs training of obstetricians or technicians on how to conduct labour after oxytocin administration.[5]

The current study was planned to determine the effectiveness of intrauterine misoprostol along with oxytocin versus oxytocin monotherapy for the prevention of primary PPH.

[1,3]Department of Gynaecology, Dr. Akbar Niazi Teaching, Hospital, Islamabad, Pakistan; [2,6]4th Year MBBS Student, Islamabad Medical and Dental College, Islamabad, Pakistan; [4]Department of Physiology, Islamabad Medical and Dental College, Islamabad, Pakistan; [5]Department of Gynaecology, City Hospital, Gujrat, Pakistan.

Correspondence: Asma Irfan. e-mail: asma.irfan@imdcollege.edu.pk

ORCID ID: 0000-0003-1093-626X

Submission complete: 24-10-2023 **1st Revision received:** 26-01-2024

Acceptance: 18-12-2024 **Last Revision received:** 17-12-2024

Patients and Methods

The quasi-randomised controlled trial took place at the Akbar Niazi Teaching Hospital, Islamabad, Pakistan, from February to August 2021. After approval from the ethics review board of the Islamabad Medical and Dental College, Islamabad, Pakistan, the sample size was calculated using the Raosoft sample size calculator with level of significance 5%, population size 175, test value of population means of blood loss in misoprostol+oxytocin group 680ml and anticipated population mean value of blood loss in oxytocin alone group 740ml.[6] The sample was raised using non-probability consecutive sampling technique. Those included were women who underwent lower segment CS (LSCS) and at full-term pregnancy of >37 weeks who had risk factors for experiencing PPH.[7] Women who underwent vaginal deliveries, those with bleeding or clotting disorder, patients with maternal cardiac, renal and hepatic diseases or with morbidly adherent placentas, or those who underwent preterm deliveries were excluded.

After taking informed consent, the subjects were randomised using the sealed opaque envelope method into experimental group A and control group B. The participants and the recruiter were both blinded to the group allocation.

Women in group A were given 600mcg of misoprostol through the intrauterine route after the delivery of the placenta along with 10IU of oxytocin intravenously (IV). The surgeon put the misoprostol tablet in the uterine cavity at the fundus while suturing the first layer of the uterus. The women in group B were given 10IU IV oxytocin as per the WHO protocol.[8]

Data was collected using a predesigned proforma. In both groups, preoperative haemoglobin (Hb) was checked 24 hours before the surgery, and postoperative Hb was tested 48 hours after the surgery. Mean blood loss was documented by comparing the mean values of preoperative and postoperative Hb, and also the amount of blood loss was estimated using the standardised visual estimation method, which was corrected by calculating the volume of blood loss during CS delivery and 6 hours postoperatively. The whole blood loss equalled the total loss of blood during CS delivery, which was calculated by adding the volume of the suction bottle to the blood-soaked sponges, called the weighing method. All these were added to the volume of blood loss after CS which was measured by using blood collection drape, counting the number of towels used during the surgery, and noting the need for any other additional drug, like tranexamic acid, repeating oxytocin, or additional misoprostol. Side effects, including fever, nausea, vomiting, shivering, and any need for blood transfusion were also documented.

Data was analysed using SPSS 26. Data was expressed as mean+standard deviation or as frequencies and percentages as appropriate. Cross-tabulation and logistic regression were done to see the association between dependent and independent variables. P<0.05 was considered statistically significant.

Results

Of the 120 subjects, 60(50%) were in group A with mean age 28.72±5.82 years and mean gestational age 38.02±1.1 weeks. The remaining 60(50%) subjects were in group B with mean age 29.47±4.72 years and mean gestational age 37.50±1.5 weeks. The mean preoperative and postoperative Hb levels in group B were 11.75±1.1mg/dl and 10.41±1.2mg/dl, respectively, compared to 11.76±1.1mg/dl and 10.9±1.1mg/dl in group A (p=0.02) (Figure).

The number of operative towels used, contractility time of the uterus, and need for other drugs to control haemorrhage were significantly low in group A compared to group B (Table, Figure)

Table: The mean number of operative towels used and the mean contractility time with respect to drugs used.

Drugs	Contractility Time (minutes)					*p*-value	Operative towels (n)			*p*-value
	2	3	4	5	7		2	3	4	
Oxytocin	1	18	41	0	0	0.000	2	26	32	0.000
Oxytocin and Misoprostol	17	37	3	2	1		12	37	11	

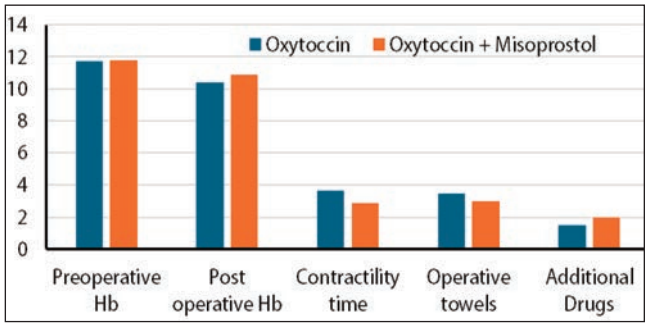

Figure: The effect of oxytocin alone and in combination with misoprostol on mean values of pre-operative haemoglobin, post-operative haemoglobin, contractility time, number of operative towels and additional drugs required.

Discussion

One of the most frequent operations on women aged 15-45 years is LSCS.[9] One of the issues that can arise during or even after surgery and cause maternal morbidity globally is PPH.

Misoprostol has been used for many years in gynaecological and obstetrical cases. It causes the cervix

to ripen and the uterus to contract. This leads to its involvement in dealing with the cases of PPH.[10] The use of misoprostol as an adjunct to oxytocin for preventing PPH has been a topic of significant interest and investigation in recent years. Misoprostol, a synthetic prostaglandin E1 analogue, has uterotonic properties that can enhance uterine contraction and control bleeding. The current study's findings provide valuable evidence supporting the efficacy of intrauterine misoprostol in combination with oxytocin for PPH prevention in line with earlier studies.[10]

Adding 600mcg of misoprostol to 10IU IV oxytocin in PPH reduced blood loss.

One of the key advantages of using misoprostol in addition to oxytocin is its ability to act directly on the uterine muscle, facilitating stronger and more sustained contractions. This mechanism is particularly important in cases of atonic uterus, where the uterine muscle fails to contract adequately, leading to excessive bleeding. The addition of misoprostol may help overcome this uterine atony and enhance the haemostatic process.[11]

Furthermore, the current study demonstrated a reduced incidence of complications associated with PPH when misoprostol was used in conjunction with oxytocin. Complications, such as blood transfusion requirements, prolonged hospital stays, and the need for surgical interventions, were notably lower in the combination group. These findings emphasise the potential of misoprostol to not only control bleeding, but also mitigate the overall burden of PPH-related morbidity.

It is worth noting that the use of misoprostol does carry some risks, including uterine hyperstimulation and subsequent foetal distress.[12] However, the current study did not note any significant increase in adverse foetal outcomes associated with the administration of intrauterine misoprostol in addition to oxytocin. Nonetheless, careful monitoring of the mother and the foetus is crucial when implementing this combined approach to ensure optimal safety.

One study found no difference in mean blood loss between the misoprostol and oxytocin groups, but, following surgery, the first 4 hours were crucial in which less blood was lost in the misoprostol group than in the oxytocin group.[13] In another trial, a combination of intrauterine misoprostol with intravenous oxytocin substantially lowered the predicted intraoperative blood loss.[14]

Sublingual misoprostol and oxytocin together resulted in a significant decrease in the mean haematocrit drop, and the need for further uterotonics when compared to oxytocin alone.[15] Furthermore, the systematic review's findings showed that buccal misoprostol combined with oxytocin decreased the need for further uterotonics compared to oxytocin alone. Rectal misoprostol reduced intraoperative and postoperative blood loss, the average drop in haematocrit, and the need for additional uterotonics when combined with oxytocin.[16]

In one of the studies, it has been shown that PPH can be prevented by combination therapies compared to monotherapy. The oxytocin, when combined with other drugs, such as misoprostol and ergometrine, showed better and quicker control of bleeding. The same study also showed that there was no difference in the action and control of misoprostol and ergometrine when combined with oxytocin.[17]

It is important to note that while the study was conducted in a specific population, the results are still applicable to a broader patient population. Additionally, as with any intervention, proper training, and adherence to established protocols are crucial to ensure safe and effective use.

Conclusion

The addition of 600mcg of intrauterine misoprostol to IV oxytocin significantly reduced blood loss in PPH patients compared to those who received only IV oxytocin.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References

1. Alalfy M, Lasheen Y, Elshenoufy H, Elzahaby IM, Kaleem HW, El Sawah H, et al. The efficacy of intrauterine misoprostol during cesarean section in prevention of primary PPH, a randomized controlled trial. J Matern Fetal Neonatal Med 2020;33:1459-65. doi: 10.1080/14767058.2018.1519796
2. Bell SF, Watkins A, John M, Macgillivray E, Kitchen TL, James D, et al. Incidence of postpartum haemorrhage defined by quantitative blood loss measurement: a national cohort. BMC Pregnancy Childbirth 2020;20:271. doi: 10.1186/s12884-020-02971-3
3. Wray S, Arrowsmith S, Sharp A. Pharmacological Interventions in Labor and Delivery. Annu Rev Pharmacol Toxicol 2023;63:471-89. doi: 10.1146/annurev-pharmtox-051921-122822
4. Sadeghi Afkham M, Hashemnejad M, Esmaelzadeh Saeieh S, Ataei M, Valizadeh R. Prophylactic effect of rectal and sublingual misoprostol on postpartum hemorrhage in mothers with preeclampsia following cesarean section surgery; a double-blind randomized controlled trial. Ann Med Surg (Lond) 2022;80:104175. doi: 10.1016/j.amsu.2022.104175
5. Salati JA, Leathersich SJ, Williams MJ, Cuthbert A, Tolosa JE. Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. Cochrane Database Syst Rev 2019;4:CD001808. doi: 10.1002/14651858.CD001808.pub3
6. Raosoft, Inc. Sample size calculator. [Online] 2004 [Cited 2022 September 10]. Available from URL: http://www.raosoft.com/samplesize.html

7. Ende HB, Lozada MJ, Chestnut DH, Osmundson SS, Walden RL, Shotwell MS, et al. Risk Factors for Atonic Postpartum Hemorrhage: A Systematic Review and Meta-analysis. Obstet Gynecol 2021;137:305-23. doi: 10.1097/AOG.0000000000004228
8. World Health Organization (WHO). WHO recommendation on routes of oxytocin administration for the prevention of postpartum haemorrhage after vaginal birth. [Online] 2020 [Cited 2025 January 13]. Available from URL: https://www.who.int/publications/i/item/9789240013926
9. Srivastava S, Chaurasia H, Kumar Singh KHJ, Chaudhary P. Exploring the spatial patterns of cesarean section delivery in India: Evidence from National Family Health Survey-4. Clin Epidemiol Glob Health 2020;8:414-22. doi: 10.1016/j.cegh.2019.09.012
10. MacDonald ME. Misoprostol: The Social Life of a Life-saving Drug in Global Maternal Health. Sci Technol Hum Values 2021;46:376-401. doi: 10.1177/0162243920916781
11. Morfaw F, Fundoh M, Pisoh C, Ayaba B, Mbuagbaw L, Anderson LN, et al. Misoprostol as an adjunct to oxytocin can reduce postpartum-haemorrhage: a propensity score-matched retrospective chart review in Bamenda-Cameroon, 2015-2016. BMC Pregnancy Childbirth 2019;19:257. doi: 10.1186/s12884-019-2407-3
12. Liu LY, Nathan L, Sheen JJ, Goffman D. Review of Current Insights and Therapeutic Approaches for the Treatment of Refractory Postpartum Hemorrhage. Int J Womens Health 2023;15:905-26. doi: 10.2147/IJWH.S366675
13. Gent J, Oliver E, Quigley H, Sharp A. Effectiveness of dinoprostone gel, misoprostol vaginal insert and dinoprostone vaginal insert for induction of labour in twin pregnancies. Eur J Obstet Gynecol Reprod Biol 2023;286:23-7. doi: 10.1016/j.ejogrb.2023.04.024
14. Maged AM, Wali AA, Metwally AA, Salah N. The efficacy of misoprostol in reducing intraoperative blood loss in women undergoing elective cesarean section. A systematic review and meta-analysis. J Obstet Gynaecol Res 2022;48:2038-70. doi: 10.1111/jog.15318.
15. Sringamwong W, Saokaew S, Mongkhon P. Optimal dose of misoprostol combined with oxytocin for preventing postpartum hemorrhage in cesarean section: A randomised controlled trial. Ann Med Surg (Lond) 2022;78:103931. doi: 10.1016/j.amsu.2022.103931
16. Amin Ibrahim RA. Combined Use of Misoprostol Plus Oxytocin versus Oxytocin Alone to Reduce Blood Loss during Cesarean Section. The Egyptian Journal of Hospital Medicine 2022;88:3299-303. DOI: 10.21608/ejhm.2022.248113
17. Jones AJ, Federspiel JJ, Eke AC. Preventing postpartum hemorrhage with combined therapy rather than oxytocin alone. Am J Obstet Gynecol MFM 2023;5:100731. doi: 10.1016/j.ajogmf.2022.100731

Author Contribution:
AR, MHF, UN: Data collection, writing, conducting analysis, literature review, editing and final approval.
AI, MF: Writing, conducting analysis, literature review, editing and final approval.
MS: Data collection, analysis, writing, literature review, editing and final approval.