Contents lists available at IOCS

Science Midwifery

Journal Homepage: www.midwifery.iocspublisher.org

The use of misoprostol as a prevention for post-partum hemorrhage after cesarean ection

Thomas Yohan Junardi[1], Yessica Mishellin Awaloei[2]
[1]RSUD dr. Loekmono Hadi Kudus
[2]Faculty of Medicine and Health Sciences, Atma Jaya University

A R T I C L E I N F O

Article history:

Received Mar 31, 2023
Revised Apr 19, 2023
Accepted Apr 30, 2023

Keywords:

Caesarean Section
Misoprostol
Postpartum Hemorrhage

ABSTRACT

This systematic literature review was organized to evaluate a potential uterotonic agent named misoprostol, as the choice to prevent and manage PPH. Compiled this systematic review using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guide to analyze the role and efficacy of misoprostol for the prevention of post-partum bleeding after cesarean section. A literature search was conducted on five databases, namely MEDLINE, The Cochrane Library, Wiley Sciencedirect, and Google Scholar based on the PRISMA guide lists. Quality and risk assessments were carried out through the Cochrane Risk of Bias Tool 2.0 checklist and any disagreements among the authors that were resolved by discussion. Literature search and selection resulted in ten studies that met the inclusion and exclusion criteria. Misoprostol has been shown to reduce post-caesarean bleeding compared to other agents. Evaluation then was carried out through decreased hemoglobin, hematocrit, visual evaluation of bleeding, as well as the need for additional blood transfusions and uterotonic agents. The high incidence of PPH in caesarean section and the magnitude of the accompanying risks indicate the importance of a form of PPH prevention to improve the safety of mother and baby. The results obtained from this study showed the safety and effectiveness of misoprostol in the treatment of PPH after caesarean section.

Corresponding Author:

Thomas Yohan Junardi,
RSUD dr. Loekmono Hadi Kudus,
Jl. Dr. Lukmono Hadi No.19, Cobowo, Ploso, Kec. Jati, Kabupaten Kudus, Jawa Tengah 59348
Email: thomasyohanj@gmail.com

INTRODUCTION

Cesarean section (CS) is an obstetric intervention which aims to save lives and prevent birth complication (Hobday et al., 2020; Li et al., 2018). Cesarean action in time to time is increasing globally and becoming one of the highest surgical interventions for women (Karim *et al.,* 2020). Although cesarean section is often carried out, it can cause severe complications in both pregnant women and the fetus (Sukmawati, 2018). One of the main complications often found in cesarean section is Post-partum hemorrhage (PPH) (Butwick *et al.,* 2017; Ragab *et al.,* 2016).

PPH is one of the main causes of maternal morbidity and mortality, particularly in developing countries (Liu e*t al.,* 2021). PPH is defined as bleeding condition up to 500 ml in normal

delivery and 1000 ml in delivery by cesarean section or caesarean delivery. The prevalence of PPH reached 14 million cases and 70,000 of those cases ended in maternal mortality. Data shows more than 20% of maternal mortality which are caused by PPH (Singangutti, 2018; M. Sweed et al., 2019). Even if PPH can be prevented and overcome, patients can cause permanent complications, such as reproductive system disabilities (World Health Organization, 2022). The lack of comprehensive governance guidelines and delays in treatment worsens the prognosis of PPH (Bláha & Bartošová, 2022). Moreover, the lack of researches and evidences related to the safety of recent interventions is one of the obstacles to this treatment (Akter et al., 2022; Sallam & Shady, 2018). Currently, the main therapy in PPH treatment is oxytocin. However, it is not an ideal drug for the prevention of PPH (Hobday et al., 2020; "The Efficacy and Safety of Intrauterine Misoprostol During Cesarean Section in Prevention of Primary Post-Partum Hemorrhage - A Randomized Controlled Trial," 2022)v. Side effects, such as increased heart rate, antidiuretic, and antiplatelet effects are not uncommon in the provision of oxytocin (Othman *et al.,* 2016). Therefore, various studies related to uterotonic agents continue to be carried out, one of the main agents that has the potential treatment PPH is misoprostol (Muhammad et al., 2019; Sallam & Shady, 2018).

Misoprostol is a synthetic prostaglandin analogue that has been widely used in the prevention and control of post-partum bleeding (Mishra et al., 2021; Shrestha et al., 2011; Sukmawati E et al., 2018). Beside being widely distributed and easily available, misoprostol is also a cost-effective alternative agent (Ragab *et al.,* 2016). However, the use of misoprostol either single or in combination has not been implemented in the treatment of PPH. Therefore, this systematic literature review was compiled to summarize existing research related to the use of misoprostol and its potential in the treatment of post caesarean operative PPH. There is some evidence that suggests misoprostol may supplement the action of oxytocin in preventing post-partum haemorrhage (PPH) (Morfaw et al., 2019).

RESEARCH METHOD

Compiled this systematic review using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guide to analyze the role and efficacy of misoprostol for the prevention of post-partum bleeding after cesarean section (Sugiyono, 2019). The review was conducted using several databases, such as PMC, SAGE Journals, ScienceDirect, Wiley Online Library, and ResearchGate to identify literatures associated

Table 1. Literature Search Keywords

Database	Keywords	Number of Studies
MEDLINE	((misoprostol) AND (caesarean delivery)) AND (post-partum hemorrhage)	753
The Cochrane Library	((misoprostol) AND (caesarean delivery)) AND (post-partum hemorrhage)	26
Wiley	((misoprostol) AND (caesarean delivery)) AND (post-partum hemorrhage)	237
Sciencedirect	Priapism AND caesarean delivery AND post-partum hemorrhage	418
Google Scholar	misoprostol AND caesarean delivery AND post-partum hemorrhage	4.430

Literature that matched with the inclusion and exclusion criteria using five electronic databases including MEDLINE, *the Cochrane Library*, *Wiley*, *Sciencedirect*, and *Google Scholar* and the keywords used can be seen in Table 1. The studies included in this literature review use in Indonesian or English languages. Journal selection started from the title and abstract was carried out independently by the authors. The existence of differences of opinion was resolved by discussing

and exchanging ideas between authors. This study used inclusion criteria including: (1) randomized controlled trial (RCT) studies; (2) study participants are from pregnant women who will have the cesarean section; (3) interventions in the form of misoprostol administration; and (4) analyzing the effectiveness of misoprostol for the prevention of post-partum hemorrhage after cesarean section. Exclusion criteria used in the study include: (1) inaccessible studies; (2) not a research article. The author independently reviewed the content of each literature and performs data extraction from the following variables: (1) the author; (2) year of publication; (3) study characteristics included study design, sampling method, and study location; (4) the subject of study included the number of samples and the characteristics of the participants; (5) interventions and comparison groups from the study; and (6) study results included estimation of intraoperative and post-partum hemorrhages after cesarean section that could be estimated through Hemoglobin (Hb), Hematocrit (Ht), visual estimation, the need for additional uterotonic agents, and the need for blood transfusions. In order to assess the quality and risk of bias, the authors employed the Cochrane *Risk* of Bias Tool 2.0 review list in accordance with guidelines by the Cochrane Collaboration. This guide evaluates the accuracy of the literature using five domains including: randomization process; deviation from the desired intervention; measurement of the results of the study; missing data; and selection of results. The score was given according to the four domains according to the risk of bias obtained. The risk magnitude of each study was assessed and categorized into "low", "high", and "unclear". Assessment of the quality and risk of bias was carried out by the authors collaboratively through discussion.

RESULTS AND DISCUSSIONS

A literature search produced 5.864 studies from five databases. The first stage was started with the selection of literature through titles and abstracts resulting in 71 relevant studies. After excluding 11 studies due to obstruction of access and eight duplicate studies, 52 studies were obtained that were included in the screening process of the entire study text. A total of 42 studies did not meet the inclusion and exclusion criteria for the following reasons: 11 studies since they had different target participants, 19 studies because of differences in expected research results, and 12 studies because the study design was not an RCT. The flow of the literature search has been summarized in Figure 1.

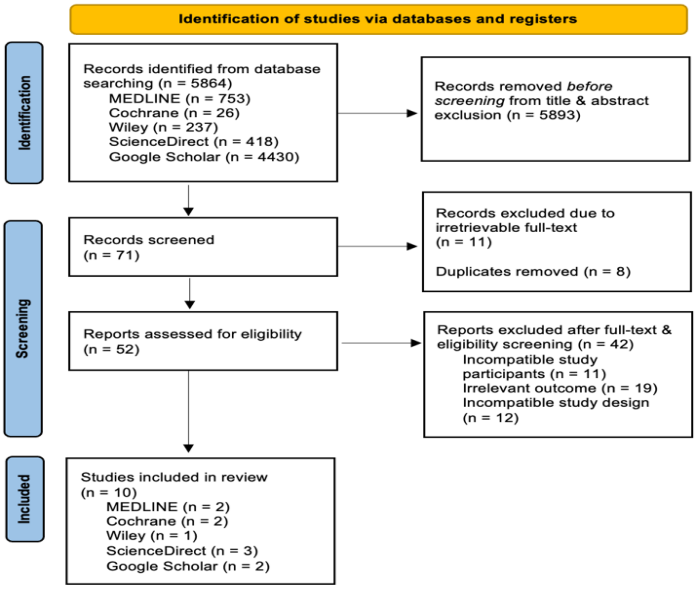

Figure 1. PRISMA 2020 Literature Search Results

The bias risk assessment of each study was carried out comprehensively using the Cochrane Risk of Bias Tool 2.0 review list in accordance with guidelines by the Cochrane Collaboration. The entire study describes the process of random and concealment allocations from the division of RCT groups. Most studies have sufficient information and meet the criteria for a list of views so that they are classified as "low risk". 2.651 research subjects were included in this systematic literature review. All participants consisted of pregnant women who underwent cesarean section with sufficient gestational age. There were five studies that excluded patients with bleeding risk factors, such as eclampsia, multiparity, and placenta previa. One study kept to include patients with low risk factors and the other four studies involved only participants with PPH risk factors.

All studies in this literature review analyzed the role of misoprostol in the treatment of postoperative PPH. There were four studies comparing misoprostol administration as an intervention group with oxytocin as a control group. Four other studies compared misoprostol with tablets and placebo injections. One study analyzed the optimum dose of intravenous administration of misoprostol and one study compared the effectiveness of misoprostol administration before and after cesarean section.

Post-partum hemorrhage (PPH) is a leading cause of maternal mortality. Its first-line of prevention often entails uterotonic drugs like oxytocin and misoprostol which constitute a core point of management. The results of the study were analyzed based on visual estimation of bleeding, hemoglobin (Hb), hematocrit (Ht) levels, the need for additional uterotonic agents, blood transfusions, and side effects evaluated in three studies. Moreover, there were six studies that analyzed misoprostol administration only and four other studies combined it with oxytocin. Concerning from the administrative route, three types of administration routes, namely sublingual, rectal, and intravenous (IV) had been analyzed. One study showed the advantages of sublingual misoprostol over rectal. The results showed that the hematocrit of the sublingual misoprostol group was higher postoperative cesarean compared to the rectal group. Several other studies have also revealed the advantages of sublingual misoprostol over rectal and intravenous misoprostol (Othman *et al.,* 2016; Sweed *et al.,* 2018). Despite the differences in administrative routes, misoprostol administration is still superior than oxytocin only.

One study examined the most optimal time to give misoprostol. Misoprostol administration before delivery was compared to administration when placental cord clamping was performed. Based on the timing of administration, the results of observations showed lower estimates of intra- and postoperative cesarean hemorrhages in study subjects who received misoprostol before surgery. The need for additional uterotonic agents was also found to be lower in the group. In addition, measurements of Hb levels were also carried out and the results revealed higher Hb levels in subjects who received misoprostol before cesarean section.

Misoprostol had been proven to be able to prevent not only PPH but also bleeding situation that occurs during surgery. Of the ten studies included, four revealed intraoperative bleeding was lower than the control group, and the difference was significant. The majority of studies gave misoprostol of 400 µg (n=8). Two studies provided 200 µg and 800 µg misoprostol, and there was one study evaluating the administration of 600 µg misoprostol.

All studies included in this systematic review showed the effectiveness of misoprostol in the prevention of PPH. There was only one study that showed the difference in bleeding between the intervention and control groups that was not significant. This is most likely because the study used a dose of 200 µg of misoprostol which has not been effective enough in reducing PPH bleeding.

Analysis of all studies evaluating the administration of 400 µg misoprostol showed the effectiveness of such doses in treating PPH bleeding. Besides, this has been proven by other studies as well (Rasri, 2018). The results revealed that the dose differences of 400 µg, 600 µg, and 800 µg did not show significant differences in results. However, a dose of 400 µg has been recommended as an effective minimal dose while still considering the small potential side effects that might arise. Other studies have revealed that the use of misoprostol at a dose of 800 µg could be considered when oxosine is not available (Prata & Weidert, 2016).

Although misoprostol side effects such as chills or fever were known to be higher than oxytocin only, they have been shown to no harm or other complications occured (Bilgin & Kömürcü, 2019; Krugh & Maani, 2021). The majority of these side effects could improve without requiring additional pharmacotherapy management (Lontaan et al., 2023). The safe, effective, and easy-to-obtain use of misoprostol could make misoprostol an appropriate precaution for postoperative PPH, especially in areas with limited facilities and still difficult to reach (Durham *et al.*, 2018). Management guidelines can be designed to assist medical personnel in using misoprostol for post-cesarean postoperative PPH on a wide scale (Hobday *et al.*, 2020).

CONCLUSION

The high incidence of PPH in cesarean section and the magnitude of the risks that accompany it indicate the importance of a form of PPH prevention to improve the safety of mothers and babies. In terms of the safety and effectiveness of misoprostol, this drug can be used as a prevention of PPH after cesarean section. Summarizing the results of existing studies, misoprostol is recommended to be provided before delivery with an effective minimum dose of 400 µg. Further research should be carried out on the effectiveness of misoprostol for pregnant women and the health of the fetus.

References

Akter, S., Hossain Khan, M. S., Khatun, K., Nahar, S., & Akter, S. (2022). Efficacy and Safety of Misoprostol for Prevention of Post-Partum Haemorrhage: A Comparative Study. *Journal of National Institute of Neurosciences Bangladesh*, *7*(2). https://doi.org/10.3329/jninb.v7i2.58111

Bilgin, Z., & Kömürcü, N. (2019). Comparison of the effects and side effects of misoprostol and oxytocin in the postpartum period: A systematic review. *Taiwanese Journal of Obstetrics and Gynecology*, *58*(6), 748–756. https://doi.org/10.1016/j.tjog.2019.09.004

Bláha, J., & Bartošová, T. (2022). Epidemiology and definition of PPH worldwide. *Best Practice and Research: Clinical Anaesthesiology*, *36*(3–4), 325–339. https://doi.org/10.1016/j.bpa.2022.11.001

Butwick, A. J., Ramachandran, B., Hegde, P., Riley, E. T., El-Sayed, Y. Y., & Nelson, L. M. (2017). Risk Factors for Severe Postpartum Hemorrhage after Cesarean Delivery: Case-Control Studies. *Anesthesia and Analgesia*, *125*(2), 523–532. https://doi.org/10.1213/ANE.0000000000001962

Durham, J., Phengsavanh, A., Sychareun, V., Hose, I., Vongxay, V., Xaysomphou, D., & Rickart, K. (2018). Misoprostol for the prevention of postpartum hemorrhage during home births in rural Lao PDR: Establishing a pilot program for community distribution. *International Journal of Women's Health*, *10*, 215–227. https://doi.org/10.2147/IJWH.S150695

Hobday, K., Zwi, A. B., Homer, C., Kirkham, R., Hulme, J., Wate, P. Z., & Prata, N. (2020). Misoprostol for the prevention of post-partum haemorrhage in Mozambique: An analysis of the interface between human rights, maternal health and development. *BMC International Health and Human Rights*, *20*(1). https://doi.org/10.1186/s12914-020-00229-9

Karim, F., Ali, N. B., Khan, A. N. S., Hassan, A., Hasan, M. M., Hoque, D. M. E., Billah, S. M., Arifeen, S. El, & Chowdhury, M. A. K. (2020). Prevalence and factors associated with caesarean section in four hard-to-reach areas of Bangladesh: Findings from a cross-sectional survey. *PLoS ONE*, *15*(6). https://doi.org/10.1371/journal.pone.0234249

Krugh, M., & Maani, C. V. (2021). Misoprostol - StatPearls - NCBI Bookshelf. *StatPearls*.

Li, X., Zhang, W., Lin, J., Liu, H., Yang, Z., Teng, Y., Duan, S., Li, Y., Xie, Y., Lin, X., Xie, L., Peng, Q., Huang, J., Chen, J., Duan, W., Luo, J., & Zhang, J. (2018). Preterm birth, low birthweight, and small for gestational age among women with preeclampsia: Does maternal age matter? *Pregnancy Hypertension*, *13*, 260–266. https://doi.org/10.1016/j.preghy.2018.07.004

Liu, C. ning, Yu, F. bing, Xu, Y. zhe, Li, J. sheng, Guan, Z. hong, Sun, M. na, Liu, C. an, He, F., & Chen, D. jin. (2021). Prevalence and risk factors of severe postpartum hemorrhage: a retrospective cohort study. *BMC Pregnancy and Childbirth*, *21*(1). https://doi.org/10.1186/s12884-021-03818-1

Lontaan, A., Sukmawati, E., Widya Larasati, E., Sundary Lintang, S., Wayan Armini, N., Chairiyah, R., & Bayu Argaheni, N. (2023). *PIJAT DAN SPA BAYI* (Neila Sulung & Ilda Melisa (Eds.); 2023rd ed., Vol. 1). GET Press Indonesia. www.globaleksekutifteknologi.co.id

Mishra, N., Nekkanti, L. P., Barma, P., Mishra, I., & Mishra, I. (2021). Adjunctive misoprostol for prevention of post-partum haemorrhage: a pragmatic strategy of selective sequential administration. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, *10*(2). https://doi.org/10.18203/2320-1770.ijrcog20210325

Morfaw, F., Fundoh, M., Pisoh, C., Ayaba, B., Mbuagbaw, L., Anderson, L. N., & Thabane, L. (2019). Misoprostol as an adjunct to oxytocin can reduce postpartum-haemorrhage: A propensity score-matched retrospective chart review in Bamenda-Cameroon, 2015-2016. *BMC Pregnancy and Childbirth*, *19*(1). https://doi.org/10.1186/s12884-019-2407-3

Muhammad, R., Isah, A., Agida, T., & Akaba, G. (2019). A prospective study to compare the effectiveness of adjunctive rectal misoprostol or oxytocin titration in the prevention of primary post-partum haemorrhage in at risk patients. *African Health Sciences*, *19*(1). https://doi.org/10.4314/ahs.v19i1.25

Othman, E. R., Fayez, M. F., El Aal, D. E. M. A., El-Dine Mohamed, H. S., Abbas, A. M., & Ali, M. K. (2016). Sublingual misoprostol versus intravenous oxytocin in reducing bleeding during and after cesarean delivery: A randomized clinical trial. *Taiwanese Journal of Obstetrics and Gynecology*, *55*(6), 791–795. https://doi.org/10.1016/j.tjog.2016.02.019

Prata, N., & Weidert, K. (2016). Efficacy of misoprostol for the treatment of postpartum hemorrhage: Current knowledge and implications for health care planning. *International Journal of Women's Health*, *8*, 341–349. https://doi.org/10.2147/IJWH.S89315

Ragab, A., Barakat, R., & Alsammani, M. A. (2016). A randomized clinical trial of preoperative versus postoperative misoprostol in elective cesarean delivery. *International Journal of Gynecology and Obstetrics*, *132*(1), 82–84. https://doi.org/10.1016/j.ijgo.2015.06.057

Rasri, W. (2018). Intrauterine Misoprostol plus Intravenous Oxytocin for Reduction of Blood Loss in Cesarean Delivery. *Thai Journal of Obstetrics and Gynaecology*, *26*(4), 237–245.

Sallam, H. F., & Shady, N. W. (2018). Adjunctive sublingual misoprostol for secondary prevention of post-partum hemorrhage during cesarean delivery: double blind placebo randomized controlled trial. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, *7*(2). https://doi.org/10.18203/2320-1770.ijrcog20180161

Shrestha, A., Dongol, A., Chawla, C. D., & Adhikari, R. (2011). Rectal misoprostol versus intramuscular oxytocin for prevention of post partum hemorrhage. *Kathmandu University Medical Journal*, *9*(33). https://doi.org/10.3126/kumj.v9i1.6254

Singangutti, R. (2018). Intramuscular methergine versus per-rectal misoprostol for prevention of atonic post-partum haemorrhage. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, *7*(4). https://doi.org/10.18203/2320-1770.ijrcog20181341

Sugiyono. (2019). *Metode Penelitian Kuantitatif, Kualitatif, dan R&D* (1st ed.). Penerbit Alfabeta.

Sukmawati, E. (2018). wahyunita yulia sari, indah sulistyoningrum. Farmakologi Kebidanan. *Trans Info Media (TIM)*.

Sukmawati E, wahyunita yulia sari, & indah sulistyoningrum. (2018). *Farmakologi Kebidanan*. Trans Info Media (TIM). https://scholar.google.com/scholar?oi=bibs&cluster=11760770443894442881&btnI=1&hl=id

Sweed, M., El-Said, M., Abou-Gamrah, A., & Ali, M. (2019). Comparison between 200, 400 and 600 microgram rectal misoprostol before cesarian section: A randomized clinical trial. *Journal of Obstetrics and Gynaecology Research*, *45*(3). https://doi.org/10.1111/jog.13883

Sweed, M. S., El-Saied, M. M., Abou-Gamrah, A. E., El-Sabaa, H. A., Abdel-Hamid, M. M., Hemeda, H., Mansour, A. M., Shawky, M. E., El-Sayed, M. A., & Mohamed, R. M. (2018). Rectal vs. sublingual misoprostol before cesarean section: double-blind, three-arm, randomized clinical trial. *Archives of Gynecology and Obstetrics*, *298*(6), 1115–1122. https://doi.org/10.1007/s00404-018-4894-2

The Efficacy and Safety of Intrauterine Misoprostol During Cesarean Section in Prevention of Primary Post-

Partum Hemorrhage - A Randomized Controlled Trial. (2022). *International Journal on Obstetrics and Gynecology*, *2*(1). https://doi.org/10.51626/ijog.2022.02.00010

World Health Organization. (2022). WHO postpartum haemorrhage (PPH) summit. *Project Brief* , 1.