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LITERATURE REVIEW

Prophylactic Misoprostol-Oxytocin Combination in Preventing Postpartum Hemorrhage : A Meta-Analysis

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Abstract

Background: *Postpartum hemorrhage (PPH) remains the leading cause of maternal mortality worldwide. Active management of the third stage of labor, including prophylactic uterotonics, is essential in reducing PPH incidence. Oxytocin is the first-line agent; however, misoprostol has been considered as an adjunct due to its stability, accessibility, and effectiveness. This meta-analysis evaluates the efficacy of the misoprostol-oxytocin combination compared to oxytocin alone in preventing PPH.*

Methods: *A systematic literature search was conducted following PRISMA guidelines using PubMed, ScienceDirect, and Cochrane Library up to November 28, 2024. Randomized controlled trials (RCTs) comparing the misoprostol-oxytocin combination versus oxytocin alone for PPH prevention were included. Statistical analysis was performed using Review Manager 5.4, with mean difference (MD) and relative risk (RR) as effect measures. Heterogeneity was assessed using the I^2 statistic.*

Results: *A total of seven RCTs met the inclusion criteria. The misoprostol-oxytocin combination significantly reduced the risk of PPH compared to oxytocin alone (RR 0.71; 95% CI 0.55–0.91; p=0.007; I^2=54%). Blood loss was significantly lower in the combination group (MD -33.77 mL; 95% CI -62.27 to -5.26; p=0.02; I^2=80%). Hemoglobin drop was also reduced (MD -0.75 g/dL; 95% CI -1.48 to -0.01; p=0.02; I^2=84%). However, the combination therapy was associated with a higher incidence of pyrexia.*

Conclusion:*The combination of misoprostol and oxytocin is more effective than oxytocin alone in reducing postpartum blood loss and hemoglobin drop. Despite increased pyrexia rates, its benefits in preventing PPH may outweigh the risks, particularly in high-risk populations. Further large-scale studies are needed to refine dosing strategies and assess long-term outcomes.*

Keywords: *Postpartum Hemorrhage (PPH); Misoprostol; Oxytocin*

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INTRODUCTION

For many years, the medical and research communities throughout the world have focused on excessive bleeding after delivery, which is the primary cause of maternal fatalities globally [1, 2, 3]. Administering injectable uterotonics is an essential part of treating PPH brought on by an atonic uterus. In hospital-based settings, oxytocin and/or ergometrine are the most often utilised drugs. One method of preventing postpartum haemorrhage is active management of the third stage of labour, which is a set of procedures [4, 5]. This method often entails early clamping of the umbilical cord, controlled cord traction, and a prophylactic injection of 5 or 10 international units of oxytocin following the delivery of the anterior shoulder in vaginal births or immediately following delivery in caesarean deliveries [6, 7, 8]. Research suggests that the risk of postpartum haemorrhage can be effectively decreased by routinely managing the third stage of labour [9, 10, 11]. Because of its excellent effectiveness and low frequency of side effects, oxytocin is the first-choice agent [12, 13, 14].

Beyond the use of traditional uterotonics, several medical and surgical procedures have also been researched as adjuvant and alternative therapeutic options for postpartum haemorrhage. Misoprostol, a prostaglandin E1 analogue, has been used off-label for this indication due to its potent uterotonic effects, convenience of oral administration, stability at room temperature, accessibility, and affordability [15, 16, 17]. It has been demonstrated that oral misoprostol at a dosage of 600 mcg is both safe and effective in preventing PPH [18, 19]. Misoprostol has only been advised for the prevention of PPH in situations when injectable conventional uterotonics are not accessible since it is less efficacious than injectable oxytocin [20]. There are no established misoprostol regimens for routine usage as an adjuvant or stand-alone therapy for postpartum haemorrhage [21].

Prostaglandins are frequently used in obstetric medicine to prevent and, in particular, cure postpartum haemorrhage. They also have uterotonic effects [22, 23, 24]. The most often used off-label prostaglandin for preventing postpartum haemorrhage is misoprostol, a prostaglandin E1 analogue, due to its many benefits, which include low cost, convenience of administration through numerous routes, and thermal stability (easy storage) [25]. The greatest prophylactic for postpartum haemorrhage is oxytocin, according to a major multicenter, double-blind, randomised experiment that compared misoprostol with oxytocin for the treatment of the third stage of labour [26]. However, shortly after, Caliskan et al. proposed that misoprostol and oxytocin may work in concert to enhance prevention [27]. As part of active treatment of the third stage of labour, we hypothesised that regular oxytocin with misoprostol would reduce the rate of postpartum haemorrhage more than oxytocin alone.

Methods

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standards were followed in the conduct and reporting of this meta-analysis. A thorough search of the literature was carried out up until November 28th, 2024, using PubMed, ScienceDirect, and the Cochrane Library. The specified keywords for the literature search were "(("postpartum

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haemorrhage"[All Fields] OR "postpartum hemorrhage"[MeSH Terms] OR ("postpartum"[All Fields] AND "hemorrhage"[All Fields]) OR "postpartum hemorrhage"[All Fields]) AND ("oxytocin"[MeSH Terms] OR "oxytocin"[All Fields] OR "oxytocin s"[All Fields] OR "oxytocine"[All Fields] OR "oxytocins"[All Fields]) AND ("misoprostol"[MeSH Terms] OR "misoprostol"[All Fields] OR "misoprostol s"[All Fields]) AND ("combinable"[All Fields] OR "combinated"[All Fields] OR "combination"[All Fields] OR "combinational"[All Fields] OR "combinations"[All Fields] OR "combinative"[All Fields] OR "combine"[All Fields] OR "combined"[All Fields] OR "combines"[All Fields] OR "combining"[All Fields] OR ("combinable"[All Fields] OR "combinated"[All Fields] OR "combination"[All Fields] OR "combinational"[All Fields] OR "combinations"[All Fields] OR "combinative"[All Fields] OR "combine"[All Fields] OR "combined"[All Fields] OR "combines"[All Fields] OR "combining"[All Fields]))) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])". This procedure would include articles with pertinent titles and abstracts so they could be thoroughly assessed and put through further qualitative and quantitative examination.

Inclusion and exclusion criteria

The following inclusion criteria were used to filter the studies: 1) research on the impact of misoprostol and oxytocin together on postpartum haemorrhage with measurable results, and 3) the study's main findings include dose, onset, duration, and preservative usage. The following exclusion criteria were then established: 1) full-text publications that could not be retrieved; and 2) research designs, interventions, or outcomes that were deemed unsuitable. **Figure 1** illustrates the specifics of the research search approach.

Data extraction and risk of bias assessment

Subsequently, we extracted data from our selected articles. Quality assessment was done collaboratively by all reviewers until consensus were reached. Risk of bias assessment was carried out using RoB-2 tools provided by Cochrane.

Statistical Analysis

Review Manager version 5.4 (Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration) was used to conduct the meta-analysis. The standard metric for assessing the impact of the intervention on the main outcome was the Mean Difference (MD) and its 95% confidence interval (CI). Random-effects models were used to pool effect estimates since clinical heterogeneity was expected. If the p-value is less than 0.005, the analytical result is deemed significant. The Higgins I-squared (I2) statistical model was used to examine heterogeneity. The results of the heterogeneity test were categorised as low (25%–50%), moderate (50–75%), high (<75%), and insignificant (0–25%).

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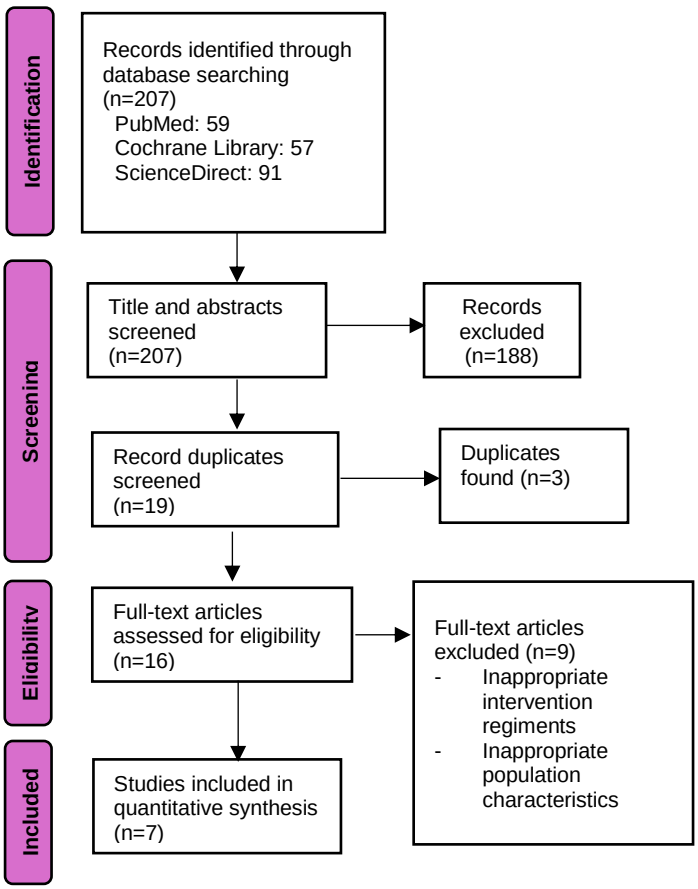


Figure 1. Diagram flow of literature search strategy for this meta-analysis

RESULT AND DISCUSSION

Included studies

207 studies from all databases were found in the first search. After the titles and abstracts were screened, 188 of them were eliminated. Furthermore, three of them were eliminated because they were duplicates. Nine other studies were then eliminated because their demographic characteristics and intervention strategies were irrelevant to this analysis. Seven research were ultimately incorporated for quantitative synthesis. In terms of risk of bias assessment, out of all included studies, all of them showed a low risk of bias. This means that all the included studies were of lower risk of bias and relatively good qualities.

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Quantitative Synthesis

Rate of postpartum hemorrhage

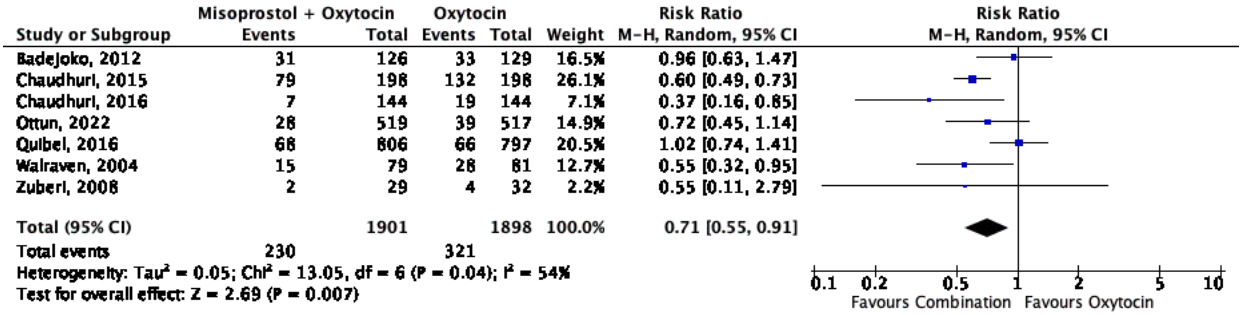


Figure 1. Forrest plot of the rate of postpartum hemorrhage in misoprostol with oxytocin and oxytocin alone.

Figure 1 presented the relative risk (RR) of the rate of postpartum hemorrhage between the combination group and oxytocin group. We found that the RR of the rate of postpartum hemorrhage between both group was 0,71 (95%CI 0,55 - 0,91; p=0,007) with moderate heterogeneity showed by an I^2 of 54%.

Blood loss

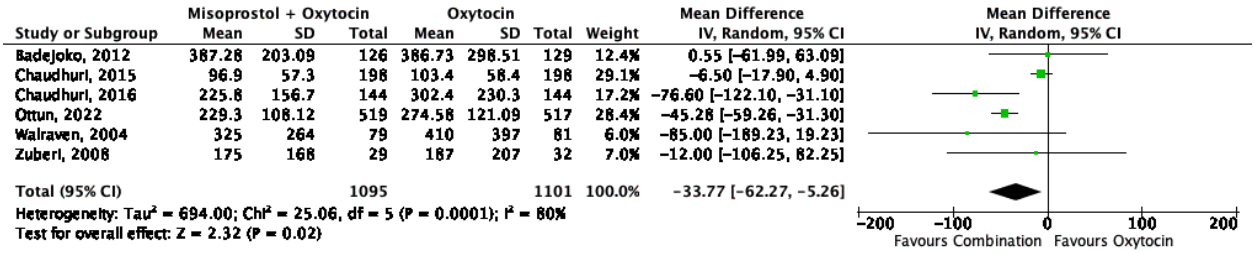


Figure 2. Forrest plot of the blood loss amount in misoprostol with oxytocin and oxytocin alone.

Figure 2 presented the mean difference (MD) of the blood loss amount between the combination group and oxytocin group. We found that the MD of the r blood loss amount between both group was -33,77 (95%CI -62,27 - -5.26; p=0,02) with high heterogeneity showed by an I^2 of 80%.

Drop in hemoglobin

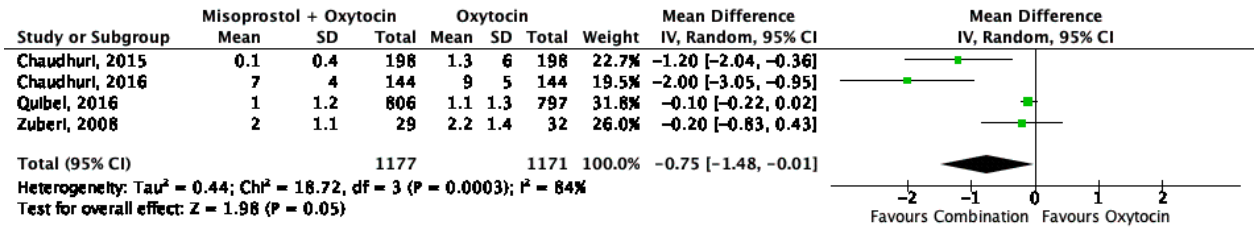


Figure 3. Forrest plot of the drop in hemoglobin in misoprostol with oxytocin and oxytocin alone.

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Figure 3 presented the mean difference (MD) of the drop in hemoglobin between the combination group and oxytocin group. We found that the MD of the r blood loss amount between both group was -0,75 (95%CI -1,48 - -0,01; p=0,02) with high heterogeneity showed by an I^2 of 84%.

Discussion

The prevention of PPH brought on by uterine atony and/or clotting factor insufficiency is where harmacologic treatment is most helpful. These treatments can be administered as a combination of methylergonovine, ergometrine, prostaglandin analogues, oxytocin, carbetocin, or tranexamic acid or as individual drugs. Agents may behave in a synergistic (more than additive), infra-additive (less than additive), or additive manner when combined. When compared to no uterotonics, pharmacologic treatment with oxytocin for PPH prophylaxis is linked to a lower incidence of PPH [28]. Therefore, oxytocin is the first-line treatment for preventing PPH after all births, according to the World Health Organisation (WHO) and ACOG. If haemorrhage occurs or persists after oxytocin use, second-line uterotonic agents like methylergonovine, ergometrine, misoprostol, prostaglandin analogues, or TXA are added [29, 30, 31].

The drug–drug interaction between misoprostol and oxytocin is regarded as infra-additive in nature, despite the fact that there are no fixed-dose drug combinations of oxytocin and misoprostol [32]. This is because the combination of misoprostol and oxytocin is likely to produce little to no additive uterotonic activity and is linked to more negative side effects than oxytocin alone. Misoprostol and oxytocin together reduced the incidence of PPH ≥1000 mL by 48% in the 2018 Cochrane network meta-analysis compared to placebo/no therapy (RR, 0.52; 95% CI, 0.39–0.69). For the prevention of PPH ≥1000 mL, there were no changes in effectiveness when compared to oxytocin alone (RR, 0.88; 95% CI, 0.70–1.11) [33]. Lower dosages of misoprostol–oxytocin were shown to considerably minimise blood loss during and after lower-segment caesarean delivery in a double-blind randomised controlled trial conducted in India. This was in contrast to greater doses of oxytocin or misoprostol alone [34, 35, 36].

Our meta-analysis revealed a significant decrease in the risk of postpartum hemorrhage, blood loss volume, and drop in hemoglobin. All of these result suggest a significant beneficial effect of combining misoprostol with oxytocin in preventing postpartum hemorrhage in comparison to the standard therapy that has been widely implemented in the active management of third stage of labour using oxytocin alone.

Pyrexia, which is characterised as an unexplained, asymptomatic increase in body temperature, is a frequent adverse effect of misoprostol [37]. Despite the fact that pyrexia is self-limiting and typically of a low degree, mothers typically exhibit discomfort and anxiety when experiencing severe forms of hyperthermia [38, 39]. The date of the mother and child's first postpartum contact will be delayed by this event. Compared to previous studies using different dosages of misoprostol, this investigation found a significant proportion of pyrexia in all groups (52–62%) [37, 40, 41]. Nevertheless, pyrexia was shown in 66.7% of 800 µg intrauterine misoprostol in a 2022 randomised research trial [42]. The high rate of pyrexia associated with high misoprostol dose

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is comparable to a 2019 systematic study [40, 43, 44]. Prior research on different misoprostol dosages similarly reported nausea and vomiting in 0.8–23% of cases [40]. Perioperative antiemetic medications may be the cause of the low proportion [40].

Zuberi et al. observed that 600 µg misoprostol administered as an auxiliary therapy for PPH was "promising" in lowering PPH in Pakistan, a low-income nation [45]. However, because of a significantly lower than predicted PPH rate, they were unable to detect statistical significance. As a result, they suggested that women with PPH continue to receive it. Our results corroborate their assertion and demonstrate the necessity of a study assessing the use of a 600 µg dosage of misoprostol to prevent PPH.

CONCLUSION

In conclusion, for routine third-stage management of women with known high-risk factors for PPH, misoprostol added to the standard regimen of 10 IU of intramuscular oxytocin appears to be more effective than oxytocin alone in lowering the incidence of moderate PPH (500–999 mL), drop in hemoglobin, and postpartum blood loss. Larger cohort studies are needed in this field in the future.

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