*Review / Derleme*

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# Efficacy and safety of rectal misoprostol versus intravenous oxytocin on reducing blood loss in cesarean section: A PRISMA-compliant systematic review and meta-analysis of randomized clinical trials

## *Sezaryen doğumda kan kaybını azaltmada intravenöz oksitosin ile rektal misoprostolün etkinliğinin ve güvenliğinin karşılaştırılması: PRISMA uyumlu sistematik bir inceleme ve randomize klinik çalışmaların meta-analizi*

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**Abstract**

Blood loss is an inevitable complication and a major contributor to maternal morbidity and mortality at cesarean deliveries. We detected a potential preference regarding the efficacy and safety of rectal misoprostol over oxytocin as a uterotonic agent. We searched PubMed, Scopus, Web of Science, Cochrane, and other databases for the relevant trials from inception to September 2022. We included randomized clinical trials (RCTs) that compared rectal misoprostol versus intravenous oxytocin to control bleeding in women undergoing cesarean delivery. Our primary outcomes were the intra- and postoperative blood loss, and hemoglobin drop after delivery. Secondary outcomes included the need for blood transfusion, need for additional uterotonics, difference in operative time, as well as safety outcomes such as the incidence of shivering, pyrexia, nausea, and vomiting. Our search strategy revealed 1007 unique records, of them we retrieved full texts of 19 articles to check their adherence to our eligibility criteria. Seven RCTs with 1,090 participants were included. We found a significant reduction in postoperative blood loss [MD: -27.9; 95% confidence interval (CI): (-53.85, -2.10); p=0.03], and Hb drop after delivery [MD: -11; 95% CI: (-0.19, -0.03); p=0.01]. There is no significant difference regarding intraoperative blood loss, operative time, need for blood transfusion, or need for additional uterotonics. We could not find a significant difference between the two groups regarding safety outcomes, except for a higher shivering incidence in the misoprostol group [RR: 0.33; 95% CI; (0.16, 0.70); p=0.004]. We found a significant reduction in postoperative blood loss with a potentially favorable safety profile in women who administrated rectal misoprostol compared with oxytocin administration. Our findings recommend and prefer rectal misoprostol as a cheaper and effective uterotonic agent over oxytocin, which is expensive and requires an adequate cold chain for transportation and storage.

**Keywords:** Misoprostol, oxytocin, cesarean section, blood loss, postpartum hemorrhage

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**Öz**

Kan kaybı sezaryen doğumlarda kaçınılmaz bir komplikasyondur ve maternal morbidite ve mortaliteyi artırır. Bir uterotonik ajan olarak rektal misoprostolün oksitosine kıyasla etkinlik ve güvenliğinin daha iyi olduğuna dair bir yaklaşım bulunmaktadır. Başlangıçtan Eylül 2022'ye kadar ilgili denemeler için PubMed, Scopus, Web of Science, Cochrane ve diğer veri tabanlarını aradık. Sezaryen ile doğum yapan kadınlarda kanamayı kontrol etmek için rektal misoprostol ile intravenöz oksitosini karşılaştıran randomize klinik araştırmaları (RKÇ) dahil ettik. Primer sonlanım ölçütlerimiz intra ve postoperatif kan kaybı ve doğumdan sonra hemoglobin düşüşü idi. İkincil sonlanımlar arasında kan transfüzyonu ihtiyacı, ek uterotonik ihtiyacı, ameliyat süresindeki fark ve ayrıca titreme, ateş, mide bulantısı ve kusma insidansı gibi güvenlik sonuçları yer aldı. Arama stratejimiz 1007 kayıt ortaya çıkardı, uygunluk kriterlerimize uyup uymadıklarını kontrol etmek için bunlardan 19 makalenin tam metnini aldık. Bin doksan katılımcılı 7 RKÇ dahil edildi. Postoperatif kan kaybında [MD: -27,9; %95 güven aralığı (GA): (-53,85, -2,10); p=0,03] ve doğumdan sonra Hb düşüşünde (MD: -11; %95 GA: [-0,19, -0,03; p=0,01) anlamlı bir azalma bulduk. İntraoperatif kan kaybı, operasyon süresi, kan transfüzyonu ihtiyacı veya ek uterotonik ihtiyacı açısından iki grup arasında anlamlı bir fark yoktu. Misoprostol grubunda daha yüksek titreme insidansı dışında güvenlik sonuçları açısından iki grup arasında anlamlı bir fark bulamadık [RR: 0,33; %95 GA; (0,16, 0,70); p=0,004]. Oksitosin uygulamasına kıyasla rektal misoprostol uygulanan kadınlarda potansiyel olarak olumlu bir güvenlik profili ile postoperatif kan kaybında önemli bir azalma bulduk. Bulgularımız, pahalı olan ve taşıma ve depolama için bir soğuk zincir gerektiren oksitosine göre daha ucuz ve etkili bir uterotonik ajan olarak rektal misoprostolün tercih edilmesini desteklemektedir.

**Anahtar Kelimeler:** Misoprostol, oksitosin, sezaryen, kan kaybı, postpartum kanama

## Introduction

Postpartum hemorrhage (PPH) is a serious condition and is considered the main contributor to death in nations that are both developing and developed[1]. PPH is characterized as a blood loss of more than 500 mL during 24 h after a normal vaginal birth or more than 1000 mL following a cesarean section[2]. PPH can complicate up to 5% of births in both developed and developing nations[3]. The World Health Organization (WHO) has reported 100,000 deaths yearly due to PPH.

Cesarean section (CS) is the most frequent major surgical operation done on women in the United States; around one million CS are performed each year, and 15% of births worldwide occur by CS[4]. The rising rate of CS is concerning because blood loss throughout CS is nearly double that of vaginal delivery, and the necessity of blood transfusion, with all its risks, is also greater after CS than after vaginal births[5].

Uterine Atony is the cause of up to 80% of PPH leading to postnatal anemia, and hemorrhagic shock so a rapid transfusion and surgical interventions are needed[6]. Oxytocin is considered as the first line of treatment for PPH[7]. Despite being effective and safe, oxytocin has certain drawbacks: 10-40% of the women who received it were found to require supplementary uterotonics. The use of oxytocin has been linked to tachycardia, hypotension, and antidiuresis[8].

Misoprostol is an analog of prostaglandin E1 that is used to prevent and treat PPH because of its uterotonic effect. Misoprostol is readily accessible, inexpensive, and stable at room temperature. It is easy to administer via multiple routes (oral, sublingual, vaginal, rectal, and intrauterine), has minimal adverse effects and has few contraindications for use. According to certain research, oxytocin and misoprostol both work well to prevent intra and postoperative bleeding[8,9].

Misoprostol may be given orally, or sublingual. Due to the difficulty in use oral or sublingual misoprostol in general or spinal anesthesia and based on pharmacological studies proving that the blood level of rectal misoprostol is the same of oral misoprostol[10], therefore rectal misoprostol is a suitable alternative to oxytocin. We performed a comprehensive review and meta-analysis to evaluate the effectiveness and safety of preoperative rectal misoprostol compared with oxytocin for minimizing blood loss during and after CS.

## Materials and Methods

### Review Protocol

The current work was carried out in accordance with the principles of the Cochrane Handbook for Systematic Reviews of Interventions[11]. We completely adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement when writing our manuscript[12]. The research protocol was recorded in the International Prospective Register for Systematic Reviews (PROSPERO), ID: CRD42022363622. Because of the context of the study, no ethical approval was necessary.

### Search Strategy

The following electronic databases were systematically searched: PubMed, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials from inception until September 2022. We used the following search terminologies: "misoprostol", "oxytocin", and "cesarean section". Supplemental Table 1 shows the exact literature search strategy for each database. To prevent missing any research and to ensure high-quality screening, all of the listed studies' references were checked. Furthermore, the Clinicaltrials.gov and the WHO Clinical Trials Registry were considered during our search for details of unpublished and ongoing trials.

### Eligibility Criteria

We included studies that matched the following criteria: (i) Patients: Women undergoing CS, (ii) Intervention: Rectal misoprostol, (iii) Comparison: IV oxytocin, (iv) Outcomes: Efficacy and safety endpoints, and (v) Study design: Randomized clinical trials (RCTs). On the other hand, we excluded non-human studies, conference abstracts, non-RCTs, cohorts, case-control, case series, and non-English studies.

**Table 1.** Summary of the included trials

| Study ID | Country | Trial duration | Total sample size, n | Study arms | |
|---|---|---|---|---|---|
| | | | | Intervention | Control |
| Adanikin 2013[15] | Nigeria | Between August 2011 and October 2011 | n=50 | Misoprostol 600 µg (rectal) | Oxytocin 20 IU (IV) |
| Chaudhuri 2009[16] | India | Between December 2007 and May 2009 | n=190 | Misoprostol 800 µg (rectal) | Oxytocin 40 IU (IV) |
| Chaudhuri 2014[17] | India | Between May 2011 and April 2012 | n=192 | Misoprostol 800 µg (rectal) | Oxytocin 20 IU (IV) |
| Fazel 2013[18] | Iran | During 2009 | n=100 | Misoprostol 400 µg (rectal) | Oxytocin 10 IU (IV) |
| Milhan 2019[19] | Indonesia | Between January 2018 and March 2018 | n=84 | Misoprostol 800 µg (rectal) | Oxytocin 20 IU (IV) |
| Ozori 2022[21] | Nigeria | NA | n=140 | Misoprostol 600 µg (rectal) | Oxytocin 40 IU (IV) |
| Shah 2021[20] | Pakistan | Between April 2019 and October 2019 | n=334 | Misoprostol 800 µg (rectal) | Oxytocin 5 IU (IV) |

NA: Not available, IU: International unit, IV: Intravenous

### Screening and Study Selection

We used Endnote software to gather the various entries from different databases and eliminate duplicates. The collected references were checked for relevancy. The screening was conducted in two steps: First, title and abstract screening, and then full-text screening for the final selection. Two separate authors finished the screening and resolved these disagreements.

### Quality Assessment

To evaluate the quality of each RCT and assess the risk of bias in the included trials, two authors used the second version of the Cochrane Risk of Bias assessment tool[13]. The tool examined domains such as randomization process, deviation from the planned interventions, incomplete outcome data, outcome measurement, and selection of the reported result. The reviewers graded the risk of bias in each category and assessed the overall quality of the studies as "low", "some concerns", or "high". In the case of disagreements, the group discussed until they reached a consensus. As per Egger et al.[14], determining publication bias using Egger's test for funnel plot asymmetry is unreliable when fewer than ten studies are pooled. Therefore, we could not use this test to detect publication bias in our study.

### Data Extraction and Outcomes

Two independent authors extracted data from the included studies. Extracting the summary of the included studies included country, trial duration, total sample size, and study arms (intervention group and control group). Baseline characteristics of the enrolled participants included the route of administration, the number of participants, age (years), gestational age (weeks), parity, the type of anesthesia, and type of CS. Efficacy endpoints involve intraoperative blood loss (mL), postoperative blood loss (mL), mean difference in hemoglobin (mg/dL), operative time (min), the need for blood transfusion, and the need for additional uterotonic agents. Safety endpoints involve the incidence rate of shivering, pyrexia, and vomiting. Disagreements were solved later by group discussion.

### Statistical Analysis

We used the Review Manager software (RevMan, version 5.4 for Windows) from the Cochrane Collaboration to conduct our meta-analysis. We combined continuous and dichotomous data and calculated a 95% confidence interval (CI). We employed the Mantel-Haenszel and Inverse-Variance methods for analyzing dichotomous and continuous data, respectively. We evaluated the degree of heterogeneity using the chi-square and I-square ($I^2$) tests and visually assessed forest plots. We considered significant heterogeneity present when the chi-square test yielded a p-value of less than 0.1, and the I2 test indicated more than 50. We used fixed-effects and random-effects models for analyzing homogeneous and heterogeneous results, respectively. We considered p-values of less than 0.05 for the endpoints to be statistically significant. We conducted subgroup analyses based on the various doses of rectal misoprostol (400 µg, 600 µg, and 800 µg).

## Results

### Literature Search

Following the removal of duplicates, the literature search strategy yielded a total of 1,007 citations. Nineteen articles were trustworthy enough for full-text screening after our title and abstract screening. Finally, seven studies[15-21] were included in the quantitative synthesis (Figure 1) No missing articles were found after examining the included studies' references.

### Characteristics of the Included Trials

Seven RCTs with a total number of 1,090 patients; of these, 546 were allocated to the rectal misoprostol group, and 544 were allocated to the oxytocin group. The RCTs were executed in India, Nigeria, Iran, Indonesia, and Pakistan. Rectal misoprostol dosage ranges from 400-800 µg, and oxytocin dose ranges

from 5-40 international units (IU). The summary and baseline characteristics of the included studies are shown in Tables 1 and 2, respectively.

### Quality Assessment

Five RCTs[15-17,19,21] were evaluated as having a "low" risk of bias. However, two RCTs[18,20] were evaluated as having "some concerns" and a "high" risk of bias, respectively. Fazel et al.[18] because they provide no specifics on the method of randomization and allocation concealment. Shah et al.[20] provided no information about the randomization process, and there were missing data regarding efficacy and safety endpoints such as the number of patients who needed a blood transfusion and the incidence of nausea (Figure 2).

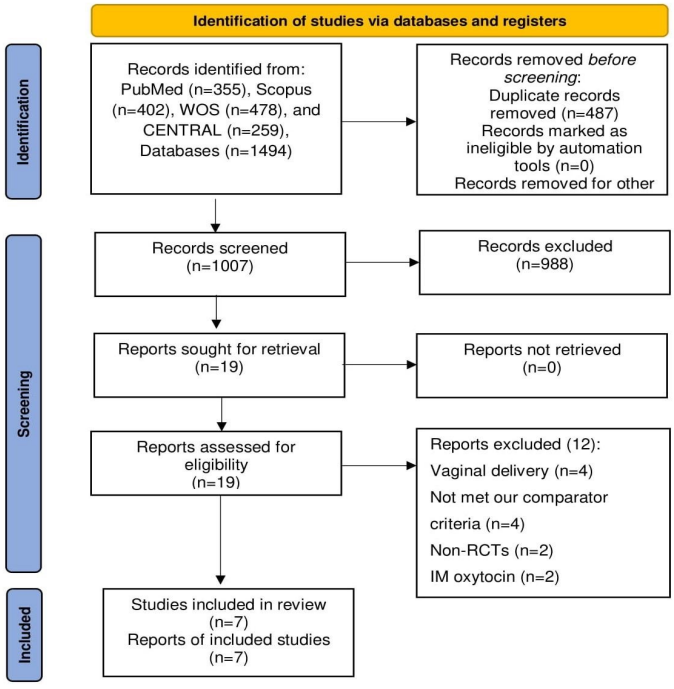


**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

## Meta-analysis of Efficacy Endpoints

### A. Intraoperative Blood Loss (mL)

Intraoperative blood loss (mL) has been investigated in four RCTs[15-17,20], including 622 women. No significant difference between rectal misoprostol at all three administrated doses and the oxytocin group in reducing blood loss intraoperatively [n=4 RCTs, MD=-21.05; 95% CI: (-80.29, 38.19); p=0.49]. Subgroup analysis according to the rectal misoprostol dose did not reveal any significant findings (Figure 3).

### B. Postoperative Blood Loss (mL)

Postoperative blood loss was reported in four RCTs with a total of 766 patients. Three trials used 800 µg[16,17,20] and one investigated 600 µg[15]. We found a statistically significant reduction in terms of postoperative blood loss in the overall rectal misoprostol group [n=4 RCTs, MD: -27.98; 95% CI: (-53.85, -2.10); p=0.03] and specifically in women who were administrated 800 µg compared to the oxytocin group [n=3 RCTs, MD: -44.05; 95% CI: (-67.34, -20.75); p<0.001] (Figure 4).

**Table 2.** Baseline characteristics of the included trials

| Study ID | Group | Route | Participants, n | Age (years) | Gestational age (weeks) | Parity | Type of anesthesia | Type of CS |
|---|---|---|---|---|---|---|---|---|
| Adanikin 2013[15] | Misoprostol | Rectal | n=25 | 30.6±6.33 | 39.03±1.62 | 1.88±1.42 | General or spinal | Emergency |
| | Oxytocin | IV | n=25 | 30.84±5.69 | 39.07±1.26 | 1.76±1.09 | | |
| Chaudhuri 2009[16] | Misoprostol | Rectal | n=96 | 23.95±3.39 | 39.46±1.69 | NA | Spinal | Elective or emergency |
| | Oxytocin | IV | n=94 | 24.32±4.98 | 39.18±1.36 | NA | | |
| Chaudhuri 2014[17] | Misoprostol | Rectal | n=96 | 23.5±4.5 | 39±1.08 | NA | Spinal | Emergency |
| | Oxytocin | IV | n=96 | 23.2±3.7 | 38.8±1.2 | NA | | |
| Fazel 2013[18] | Misoprostol | Rectal | n=50 | 26.6±5.4 | 38.65±0.58 | 1.85±0.92 | Spinal | Elective |
| | Oxytocin | IV | n=50 | 27.1±5.3 | 38.66±0.85 | 1.91±0.86 | | |
| Milhan 2019[19] | Misoprostol | Rectal | n=42 | NA | NA | NA | Spinal | Elective |
| | Oxytocin | IV | n=42 | NA | NA | NA | | |
| Ozori 2022[21] | Misoprostol | Rectal | n=70 | 32.4±6.2 | 38.2±1.1 | 2±0.6 | Spinal | Elective or emergency |
| | Oxytocin | IV | n=70 | 32.4±5.2 | 38.3±1.4 | 2±0.4 | | |
| Shah 2021[20] | Misoprostol | Rectal | n=167 | 30.6±6.5 | NA | NA | Spinal | Elective |
| | Oxytocin | IV | n=167 | 30.6±6.5 | NA | NA | | |

NA: Not available, IV: Intravenous, CS: Cesarean section

### C. Mean Difference in Hemoglobin (mg/dL)

Three RCTs (n=482) reported the mean difference in hemoglobin (mg/dL)[16-18]. Two trials used 800 µg, while Fazel et al.[18] used 400 µg. Administration of 800 µg misoprostol rectally was associated with a significant reduction in hemoglobin drop postoperatively [n= 2 RCTs, MD: -11; 95% CI: (-0.19, -0.03); p=0.01]; however, no significant difference was detected between 400 µg and oxytocin groups (Figure 5).

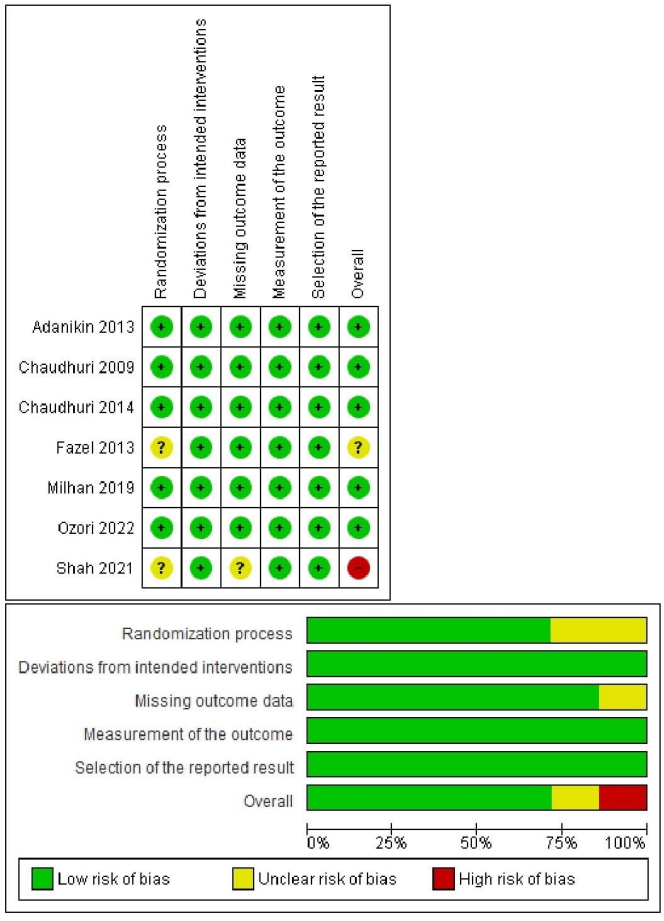


**Figure 2.** Risk of bias (ROB) summary and graph

### D. Operative Time (min)

Operative time was mentioned in three RCTs with a total of 290 patients[15,18,20]. Our results found no significant difference between rectal misoprostol and Oxytocin in reducing the operative time [n= 3 RCTs, MD: -1.36; 95% CI: (-3.32, 0.59); p=0.17] (Figure 6).

### E. The Need for Blood Transfusion (%)

Four studies (n=622) reported women who needed a blood transfusion. We could not detect a statistically significant difference between rectal misoprostol and oxytocin in reducing the number of patients who needed blood transfusion [n=4 RCTs, RR: 0.37; 95% CI: (0.10, 1.39); p=0.14] (Supplemental Figure 1).

### F. The Need for Additional Uterotonic Agents

The need for an additional uterotonic agent was investigated in three RCTs enrolling 522 women. Our results found no significant difference between different doses of rectal misoprostol and oxytocin in reducing the need for additional uterotonics [n=3 RCTs, RR: 1.06; 95% CI: (0.66, 1.70); p=0.81] (Supplemental Figure 2).

### Meta-analysis of Safety Endpoints

Four RCTs compared postoperative safety outcomes in 532 patients[15-18,20]. Postoperative shivering and pyrexia were reported in all four studies. A statistically significant increase was detected in the number of shivering women in the rectal misoprostol group compared with the oxytocin group [n=4 RCTs, RR: 0.33; 95% CI; (0.16, 0.70); p=0.004]. No significant difference was found between the two groups regarding postoperative pyrexia, nausea, and vomiting (Supplemental Figures 3-5).

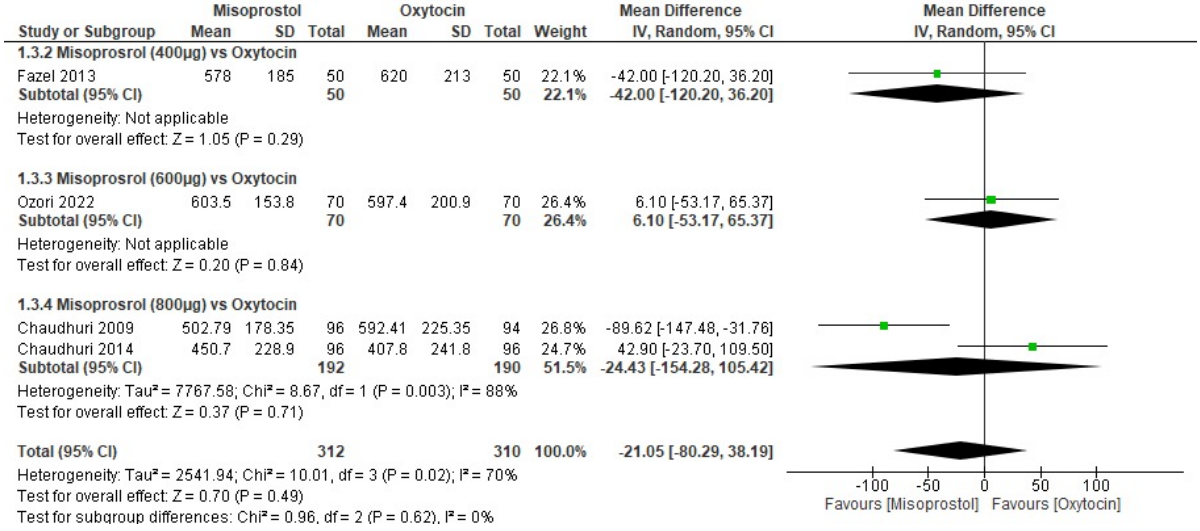


**Figure 3.** Meta-analysis of intraoperative blood loss (mL)

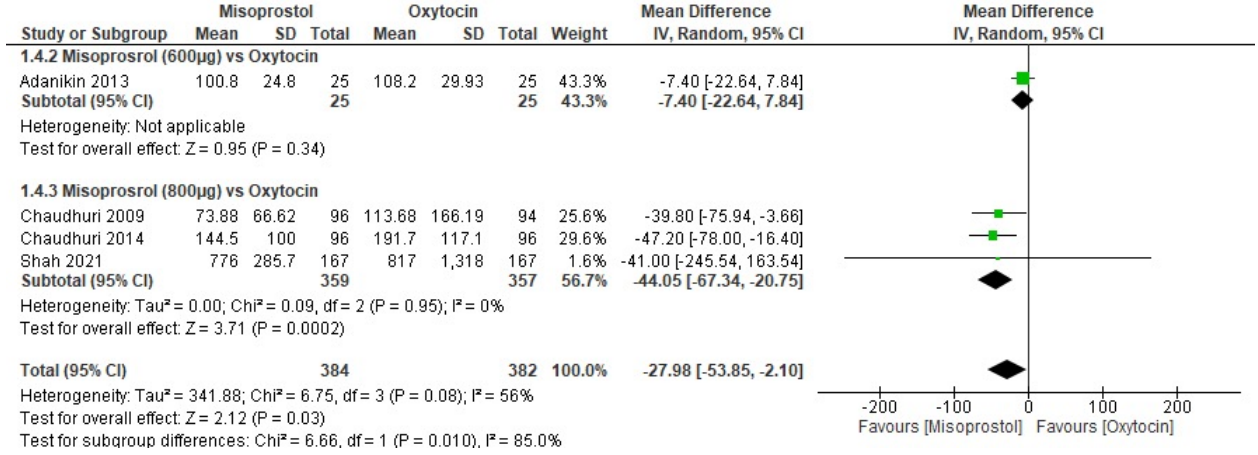


**Figure 4.** Meta-analysis of postoperative blood loss (mL)

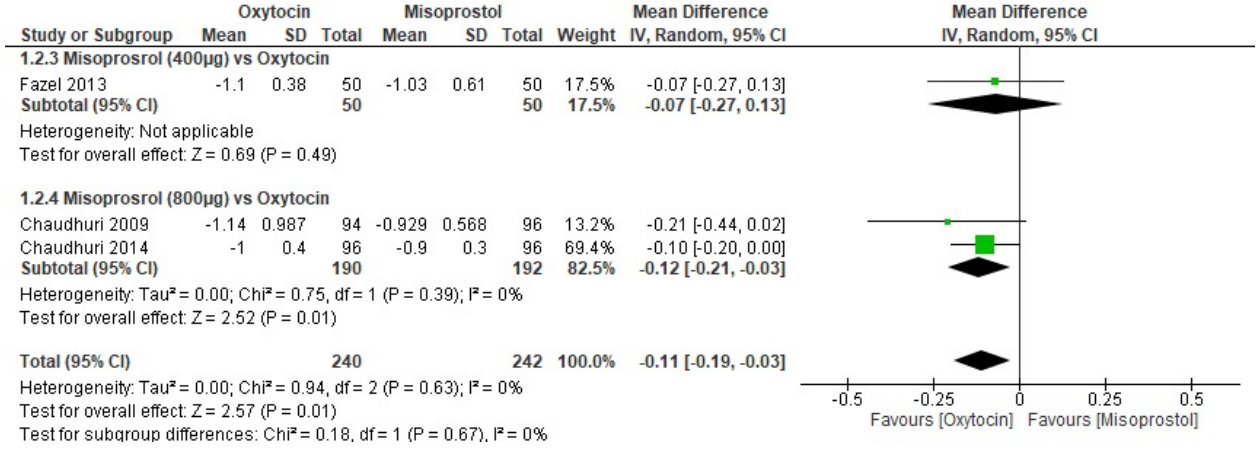


**Figure 5.** Meta-analysis of the mean difference in hemoglobin (mg/dL)

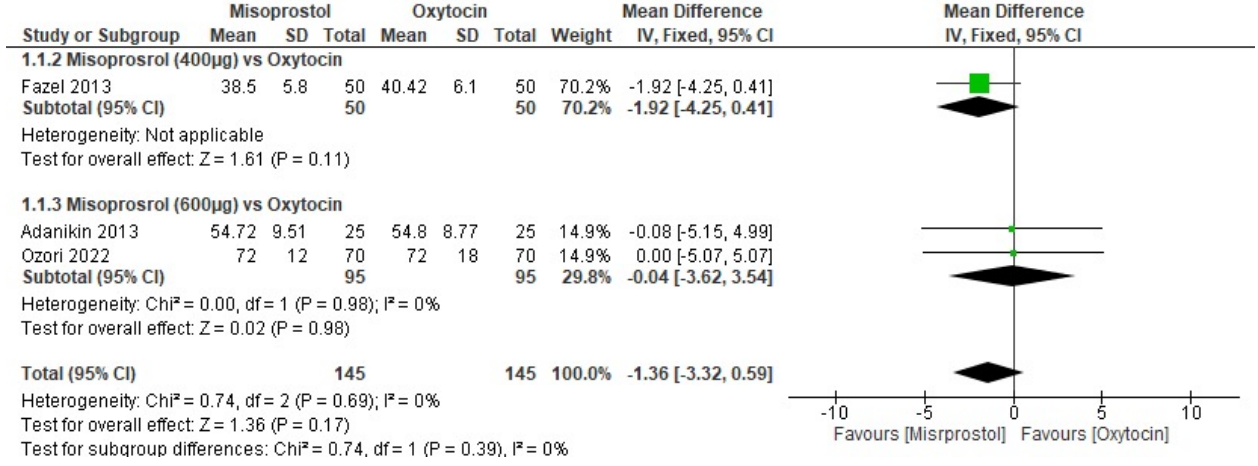


**Figure 6.** Meta-analysis of operative time (min)

## Discussion

### Finding Summary

We can summarize our findings in three main points: (I) rectal misoprostol can significantly reduce postoperative blood loss and hemoglobin drop in women undergoing CS compared with oxytocin, (II) no significant difference between the two study groups regarding intraoperative blood loss, need for blood transfusion, need for additional uterotonics, or operative time, and (III) there are some safety concerns on misoprostol in terms of postoperative shivering.

### Our Results in the Context of Literature

There are three previous systematic reviews in the literature discussing the efficacy of misoprostol, including the rectal route, compared with oxytocin in reducing blood loss among women who underwent CS[8,9,22]. However, each review included only one RCT; two of them included the same study[16], and one study included Elsedeek's study[23]. We have excluded Elsedeek's study because the study participants had already taken 10 IU intravenous oxytocin, which is incompatible with our criteria. This study is the first to specify on the rectal route of misoprostol and compare it with the routinely administrated oxytocin. Thus, we cannot discuss our results against the results of the previous studies due to the comparison heterogeneit; otherwise, we will stress on the advantage of misoprostol over oxytocin and the feasibility of the rectal route.

### Intraoperative Blood Loss

Conde-Agudelo et al.[8] revealed that oral and sublingual misoprostol did not have significant superiority over oxytocin in reducing intraoperative blood loss. Addition, the other two reviews found that the efficacy of sublingual and oral misoprostol had no significant difference compared with oxytocin, which is consistent with our results. However, Maged et al.[22] found that the intrauterine misoprostol group had lower blood loss in comparison with the oxytocin group.

### Postoperative Blood Loss

A review reported that there was no significant difference between oxytocin and neither oral nor sublingual misoprostol in terms of postoperative blood loss, which is inconsistent with our findings that showed a significant difference[22]. This disagreement might be referred to the number of included studies, as we included four studies, while the previous review included two studies in each route.

### Mean Difference in Hemoglobin

Maged et al.[22] found that sublingual misoprostol did not significantly differ from oxytocin in reducing hemoglobin loss during CS, whereas oxytocin significantly decreased the hemoglobin loss compared with oral misoprostol. Otherwise, intrauterine misoprostol was associated with a significant reduction in hemoglobin drop postoperatively in comparison to oxytocin, which agrees with our findings concerning rectal misoprostol.

### Secondary Efficacy Outcomes

Our results on rectal misoprostol were consistent with the study of Conde-Agudelo et al.[8] regarding both the need for blood transfusion and for additional uterotonic agents, they could not find a significant difference between both oral and sublingual misoprostol compared with oxytocin. However, intrauterine misoprostol significantly reduced the need for additional uterotonics compared with oxytocin.

### Safety Considerations

In this review, we found that patients who took rectal misoprostol had a higher rate of shivering and pyrexia compared with the oxytocin group. These findings agree with the results of the previous review. Conde-Agudelo et al.[8] reported that sublingual and oral misoprostol groups significantly suffered from shivering in comparison with the oxytocin group. Furthermore, there was a significant difference between the sublingual and oxytocin in terms of pyrexia, but the oral and intrauterine routes of misoprostol did not significantly differ from oxytocin.

### Misoprostol is not Inferior to Oxytocin

Despite the slight elevation in the rate of women who experienced shivering and pyrexia after rectal misoprostol administration, the significant reduction in the amount of blood loss postoperatively can demonstrate a non-inferior, even superior, aspect of using misoprostol as a reliable, non-parenteral, and low-cost uterotonic agent in busy postoperative wards of hospitals with limited resources.

The efficacy of the drug is not the only advantage that should be taken into consideration while searching for the drug of choice. The cost, preparation, and storage requirements, time and effort needed for administration, and the availability of the administration routes are critical to be kept in mind. Misoprostol has an upper hand over oxytocin as it has a lower cost (around half of the cost), which is appropriate for low-income countries [24]. Furthermore, the variability of the administration routes allows physicians to deal with different situations avoiding the risk of the parenteral route. However, it is important to mention that we cannot alleviate the need for oxytocin with its rapid action, which could be the choice in difficult situations[25]. Accordingly, we can start with rectal misoprostol, and if there is a need for additional uterotonics, we can use oxytocin. This strategy will save oxytocin in health facilities with limited resources for critically ill patients.

In a comparison of misoprostol with another oxytocic agent such as carbetocin, a recent systematic review and meta-analysis of four RCTs compared carbetocin with misoprostol in women who underwent CS[26]. They found the following: (i) the superiority of carbetocin in preventing and reducing PPH in comparison with misoprostol, (ii) the superiority of carbetocin in reducing the rate of blood transfusion, the need for additional uterotonic agents, and the need for additional surgical intervention in comparison with misoprostol, and (iii) the superiority of carbetocin in terms of safety endpoints (like fever, shivering, and heat sensation) comparison with misoprostol. However, the main limitation of this review was included both rectal and sublingual misoprosto; they could not assess the efficacy and safety outcomes according to the route of administration. Furthermore, similar findings were observed in a published meta-analysis but among women who underwent vaginal delivery[27].

### Strength Points and Limitations

This review has many strong points, including that it is the first systematic review assessing the efficacy of rectal misoprostol specifically with a reasonable number of included studies. Moreover, there was no heterogeneity in all the outcomes. However, it has some limitations: First, the variability in the methods used in the included studies to calculate the estimated blood loss; second, the different cut-off times when the blood loss was estimated; third, some studies included patients who already had some additional identifiable risk factors; fourth, the efficacy of the two drugs in reducing the blood loss during CS may be affected by the method of removing the placenta, multiple pregnancy, anatomical variabilities, and surgical skills.

### Future Directions and Recommendations

Further RCTs are needed, especially with multicenter and large sample size to compare difference doses and different routes of administration. Also, it is highly recommended to compare the efficacy of the combined regimen of misoprostol and oxytocin during and after CS to obtain the higher efficacy of these uterotonic agents. Finally, carbetocin should be investigated as a new and effective uterotonic agent during the enrollment of future RCTs.

## Conclusion

We found a significant reduction in postoperative blood loss with a potentially favorable safety profile in women who administrated rectal misoprostol compared with oxytocin administration. Our findings recommend and prefer rectal misoprostol as a cheaper and effective uterotonic agent over oxytocin, which is expensive and requires an adequate cold chain for transportation and storage.

### Ethics

**Peer-review:** Internally and externally peer-reviewed.

### Authorship Contributions

Concept: E.A., A.S., Design: E.A., Data Collection or Processing: E.A., A.S., K.A., M.E., N.A.M., H.M.F., Analysis or Interpretation: E.A., A.S., K.A., M.E., N.A.M., H.M.F., Literature Search: E.A., Writing: E.A., A.S., K.A., M.E., N.A.M., H.M.F.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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## References

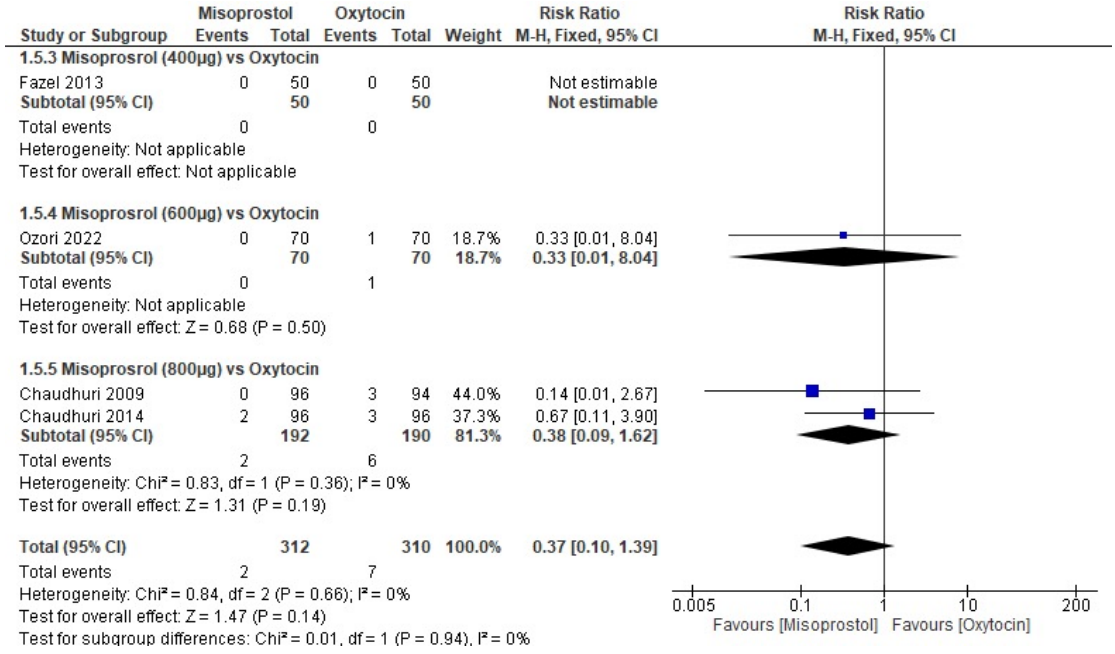
1. Adane D, Belay G, Arega A, Wassihun B, Gedefaw G, Gebayehu K. Practice and factors associated with active management of third stage of labor among obstetric care providers in Amhara region referral hospitals, North Ethiopia, 2018: A cross sectional study. PLoS One 2019;14:e0222843.
2. Sentilhes L, Vayssière C, Deneux-Tharaux C, Aya AG, Bayoumeu F, Bonnet MP, et al. Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF): in collaboration with the French Society of Anesthesiology and Intensive Care (SFAR). Eur J Obstet Gynecol Reprod Biol 2016;198:12-21.
3. Edhi MM, Aslam HM, Naqvi Z, Hashmi H. "Post partum hemorrhage: causes and management". BMC Res Notes 2013;6:236.
4. Betrán AP, Merialdi M, Lauer JA, Bing-Shun W, Thomas J, Van Look P, Wagner M. Rates of caesarean section: analysis of global, regional and national estimates. Paediatr Perinat Epidemiol 2007;21:98-113.
5. Magann EF, Evans S, Hutchinson M, Collins R, Lanneau G, Morrison JC. Postpartum hemorrhage after cesarean delivery: an analysis of risk factors. South Med J 2005;98:681-5.
6. Acharya G, Al-Sammarai MT, Patel N, Al-Habib A, Kiserud T. A randomized, controlled trial comparing effect of oral misoprostol and intravenous syntocinon on intra-operative blood loss during cesarean section. Acta Obstet Gynecol Scand 2001;80:245-50.
7. Albazee E, Sayad R, Elrashedy AA, Samy Z, Faraag E, Baradwan S, Samy A. Efficacy of oxytocics on reducing intraoperative blood loss during abdominal myomectomy: A systematic review and meta-analysis of randomized placebo-controlled trials. J Gynecol Obstet Hum Reprod 2022;51:102358.
8. Conde-Agudelo A, Nieto A, Rosas-Bermudez A, Romero R. Misoprostol to reduce intraoperative and postoperative hemorrhage during cesarean delivery: a systematic review and metaanalysis. Am J Obstet Gynecol 2013;209:40.e1-40.e17.
9. Hua J, Chen G, Xing F, Scott M, Li Q. Effect of misoprostol versus oxytocin during caesarean section: a systematic review and meta-analysis. BJOG 2013;120:531-40.
10. Khan RU, El-Refaey H. Pharmacokinetics and adverse-effect profile of rectally administered misoprostol in the third stage of labor. Obstet Gynecol 2003;101:968-74.
11. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev 2019;10:ED000142.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
13. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
14. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
15. Adanikin AI, Orji E, Adanikin PO, Olaniyan O. Comparative study of rectal misoprostol to oxytocin infusion in preventing postpartum haemorrhage after caesarean section. Nepal j obstet gynaecol 2013;8:34-7.
16. Chaudhuri P, Banerjee GB, Mandal A. Rectally administered misoprostol versus intravenous oxytocin infusion during cesarean delivery to reduce intraoperative and postoperative blood loss. Int J Gynaecol Obstet 2010;109:25-9.
17. Chaudhuri P, Mandi S, Mazumdar A. Rectally administrated misoprostol as an alternative to intravenous oxytocin infusion for preventing post-partum hemorrhage after cesarean delivery. J Obstet Gynaecol Res 2014;40:2023-30.
18. Fazel MR, Mansoure-Samimi, Esmaeil-Fakharian. A comparison of rectal misoprostol and intravenous oxytocin on hemorrhage and

homeostatic changes during cesarean section. Middle East J Anaesthesiol 2013;22:41-6.

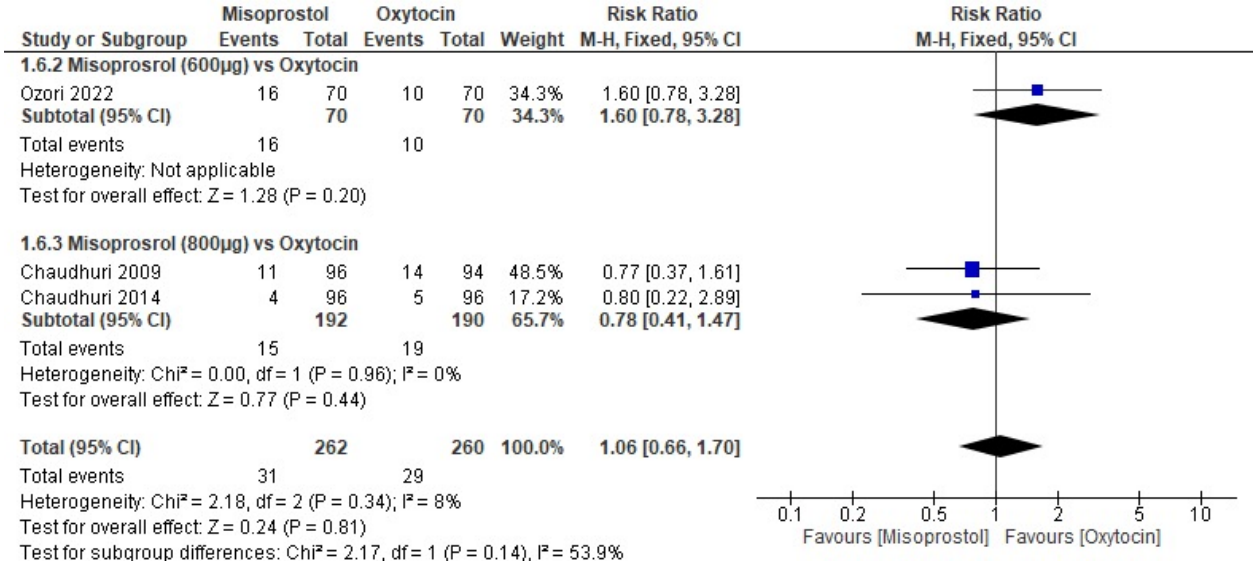
19. Milhan M, Soejoenoes A, Prawitasari S. Efikasi Misoprostol Rektal Intraoperasi Seksio Cesarea Versus Oksitosin dalam Mengurangi Jumlah Perdarahan untuk Mencegah Perdarahan Post Partum. Jurnal Kesehatan Reproduksi 2019;6:37.
20. Shah M, Urooj H, Shazma Shah, Rahim R. Efficacy of rectal misoprostol vs intravenous oxytocin in preventing postpartum hemorrhage following elective caesarean section. JPMI 2021.
21. Ozori ES, Isa I A, Nuvie O, Oweisi P W, Zakaa Z, Ochuko A M, et al. Intraoperative Blood Loss Reduction During Caesarean Delivery- Rectal Misoprostol Versus Oxytocin Infusion- A Randomized Controlled Trial. JBEMi 2022;9.
22. 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.
23. Elsedeek MS. Impact of preoperative rectal misoprostol on blood loss during and after elective cesarean delivery. Int J Gynaecol Obstet 2012;118:149-52.
24. Lawrie TA, Rogozińska E, Sobiesuo P, Vogel JP, Ternent L, Oladapo OT. A systematic review of the cost-effectiveness of uterotonic agents for the prevention of postpartum hemorrhage. Int J Gynaecol Obstet 2019;146:56-64.
25. Gibbens D, Boyd NR, Crocker S, Baumber S, Chard T. The circulating levels of oxytocin following intravenous and intramuscular administration of Syntometrine. J Obstet Gynaecol Br Commonw 1972;79:644-6.
26. Albazee E, Sadan M, Alenezi AM, Almutairi AN, Alenezi MM, Almonayea LE. Efficacy and Safety of Carbetocin Versus Misoprostol in Cesarean Section: A Systematic Review and Meta-Analysis. Cureus 2022;14:e32901.
27. Albazee E, Alrashidi H, Laqwer R, Elmokid SR, Alghamdi WA, Almahmood H, et al. Intravenous Carbetocin Versus Rectal Misoprostol for the Active Management of the Third Stage of Labor: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Cureus 2022;14:e30229.

**Supplemental Table 1.** The exact literature search strategy used in every database

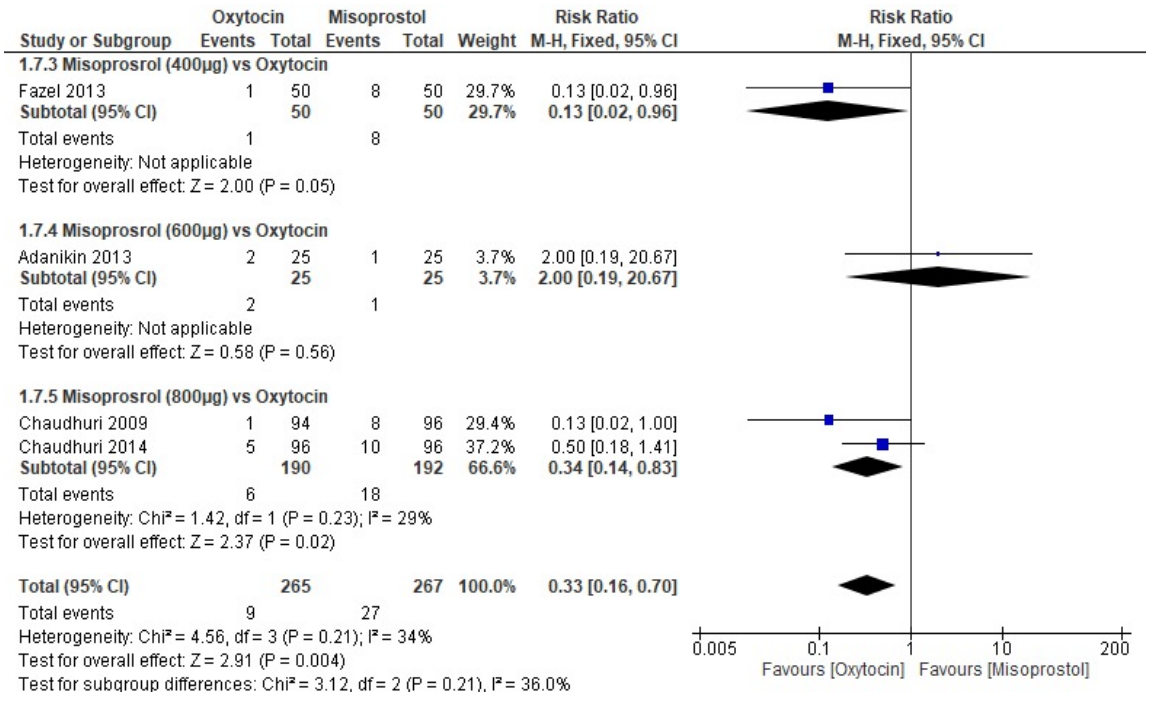
| |
|---|
| PubMed<br>All Fields: (“cesarean section” OR CS OR “C-section” OR “abdominal delivery”) AND (misoprostol OR “novo misoprostol” OR “apo misoprostol” OR cytotec OR “SC30249” OR “SC29333” OR glefos OR misodel OR mysodelle OR misotac) AND (oxytocin OR pitocin OR syntocin OR ocytocin) |
| Scopus<br>Article title, Abstract, Keywords: (“cesarean section” OR CS OR “C-section” OR “abdominal delivery”) AND (misoprostol OR “novo misoprostol” OR “apo misoprostol” OR cytotec OR “SC30249” OR “SC29333” OR glefos OR misodel OR mysodelle OR misotac) AND (oxytocin OR pitocin OR syntocin OR ocytocin) |
| Web of Science<br>All Fields: (“cesarean section” OR CS OR “C-section” OR “abdominal delivery”) AND (misoprostol OR “novo misoprostol” OR “apo misoprostol” OR cytotec OR “SC30249” OR “SC29333” OR glefos OR misodel OR mysodelle OR misotac) AND (oxytocin OR pitocin OR syntocin OR ocytocin) |
| Cochrane Central Register of Controlled Trials (CENTRAL)<br>Title Abstract Keyword: (“cesarean section” OR CS OR “C-section” OR “abdominal delivery”) AND (misoprostol OR “novo misoprostol” OR “apo misoprostol” OR cytotec OR “SC30249” OR “SC29333” OR glefos OR misodel OR mysodelle OR misotac) AND (oxytocin OR pitocin OR syntocin OR ocytocin) |



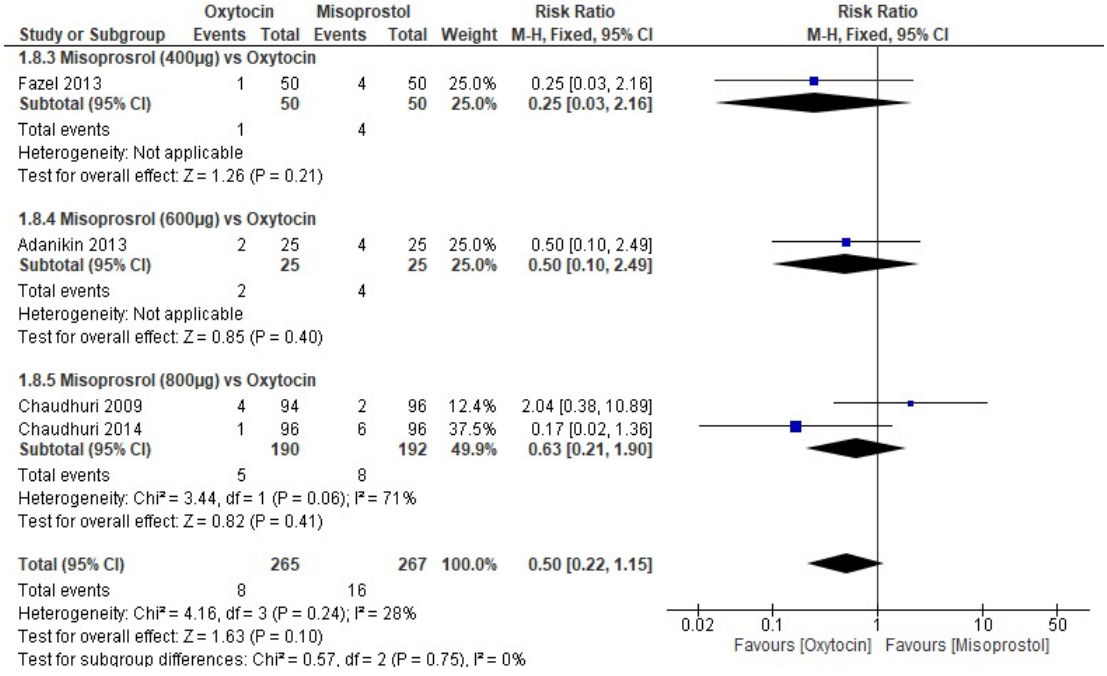

**Supplemental Figure 1.** Meta-analysis of the rate of patients who needed a blood transfusion



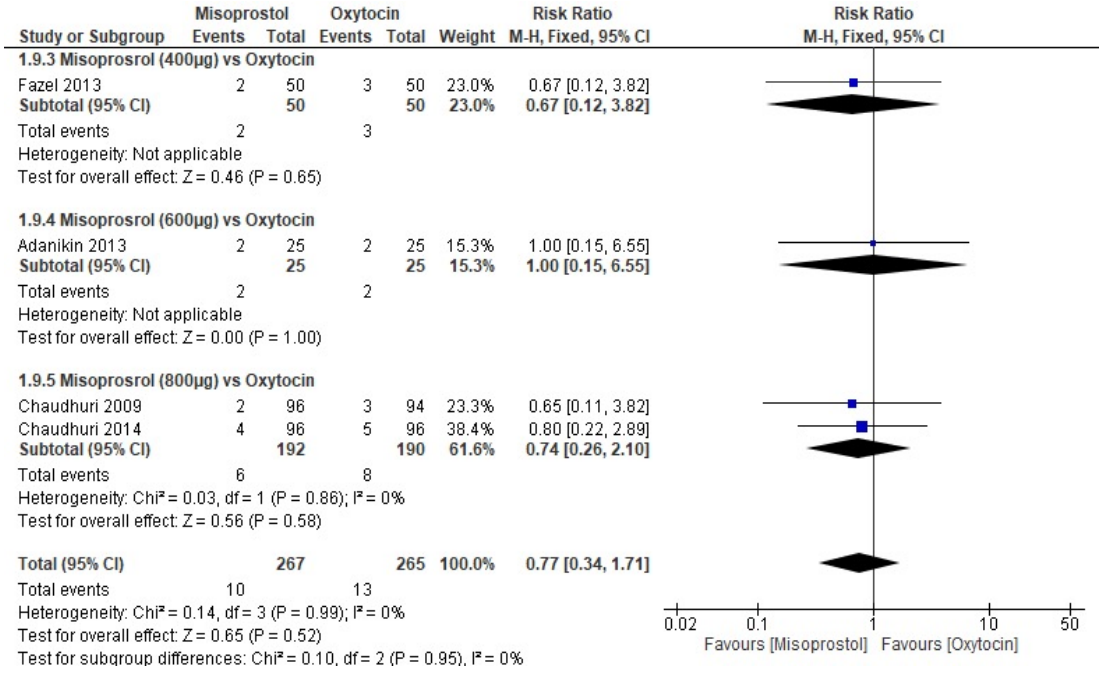

**Supplemental Figure 2.** Meta-analysis of the rate of patients who needed an additional uterotonic agents




**Supplemental Figure 3.** Meta-analysis of the rate of shivering




**Supplemental Figure 4.** Meta-analysis of the rate of pyrexia




**Supplemental Figure 5.** Meta-analysis of the rate of vomiting