Critical Appraisal of Evidence

Misoprostol compared to oxytocin for postpartum hemorrhage

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NNT Color recommendation	Black (Harms > benefits)
Summary Heading	Misoprostol alone or in combination with oxytocin, is not more effective than oxytocin alone for postpartum hemorrhage, but increases harms
Benefits in NNT	No one was helped (no significant reduction in blood loss or mortality/morbidity)
Benefits in Percentages	No one was helped
Harms in NNT (NNH)	1 in 43 (additional transfusion), 1 in 34 (vomiting), and 1 in 3 (shivering) with misoprostol alone 1 in 3 (fever) and 1 in 34 (vomiting) when adding misoprostol to oxytocin
Harms in Percentages	2.3% increase in blood transfusion, 2.9% increase in vomiting, and 26.8% increase in shivering with misoprostol 32.1% increase in fever and 2.9% increase in vomiting when adding misoprostol to oxytocin
Efficacy Endpoints	Additional blood loss of at least 500 mL, death
Harm Endpoints	Transfusion or maternal mortality Adverse effects including fever, hypothermia, nausea, vomiting, hypertension, headache, shivering, tachycardia, arrhythmia, diarrhea, abdominal pain
Who was in the studies	6 RCTs including women giving birth vaginally (n = 3674), and 1 RCT where women gave birth either vaginally or by caesarean (n = 64) in low resource settings

Narrative

Postpartum hemorrhage (PPH) may occur in 15% of women giving birth and is the leading cause of peripartum maternal death, with most cases occurring in low-income countries[1,2]. PPH is commonly defined as greater than 500 mL of blood loss after birth. Uterine atony is the most common cause of PPH, and oxytocin is recommended as first-line medical therapy by the American College of Obstetricians and Gynecologists (ACOG) and the World Health Organization (WHO)[3,4]. However, there are many effective (i.e., better than placebo) 'uterotonic' agents for the treatment of PPH, including misoprostol which may be used alone or in combination with oxytocin[1,5].

Submitted 03/19/2021, Accepted 03/30/2021, Published 06/04/2021
J. Évid-Based Healthc., Salvador, 2021;3:e3733
http://dx.doi.org/10.17267/2675-021Xevidence.2021.e3733
ISSN: 2675-021X
Assigned editor: Luis Claudio Correia

How to cite this article: Long B, Gottlieb M. Misoprostol compared to oxytocin for postpartum hemorrhage. J Évid-Based Healthc. 2021;3:e3733. http://dx.doi.org/10.17267/2675-021Xevidence.2021.e3733

The Cochrane Review summarized here aimed to compare the efficacy of different agents for PPH and included randomized controlled trials (RCTs) or cluster-randomized trials evaluating the benefits and harms of uterotonic agents in women with PPH after vaginal or cesarean birth[6]. Trials were eligible to compare systemically administered uterotonic agents of any dosage, route, or regimen.

The Cochrane review's primary outcomes included blood loss of >500 mL after enrollment and a composite outcome of maternal death or severe morbidity (hysterectomy, organ dysfunction, transfer to higher level of care, coagulopathy, or shock). We report only maternal mortality from this composite outcome, a patient-centered outcome reported consistently in the original trials.

The systematic review identified 7 RCTs (n = 3738) that met inclusion criteria. One trial included women giving birth vaginally or by cesarean section, while the others included only vaginal births. Agents evaluated included oxytocin (6 trial arms), misoprostol plus oxytocin (4 trials arms), misoprostol (3 trial arms), and fixed-dose oxytocin/ergometrine plus oxytocin infusion (1 trial arm). Data using this prior regimen were limited, of low certainty, and showed unclear effects. Therefore, we have not summarized this comparison.

Two trials (n = 1787) found no difference in maternal mortality for misoprostol compared to oxytocin. These trials did suggest, however, misoprostol may increase blood transfusions (relative risk [RR]: 1.5; 95% confidence interval [CI]: 1.02-2.1; absolute risk increase: 2.3%; number needed to harm [NNH]: 43). Misoprostol also increased vomiting (RR: 2.5; 95% CI: 1.4-4.5; absolute risk increase: 2.9%; NNH: 34) and shivering (RR: 2.7; 95% CI: 2.3-3.2; absolute risk increase: 26.8%; NNH: 3).

Four trials (n = 1873) of misoprostol plus oxytocin versus oxytocin alone found no primary outcome benefit with the addition of misoprostol for maternal mortality but did find an increase in adverse effects. These included fever (RR: 3.0; 95% CI: 2.6-3.6; absolute risk increase: 32.1%; NNH: 3) and vomiting (RR: 1.9; 95% CI: 1.2-3.0; absolute risk increase: 2.9%; NNH: 34).

Caveats

The quality of evidence for these analyses ranged from very low to high, with most data rated low or moderate certainty. No studies including injectable prostaglandins, ergometrine, or oxytocin/ergometrine as first-line agents were available. Most subjects were women with a singleton term vaginal birth in a low-resource setting. Women with significant comorbidities were excluded from trials, limiting generalizability. There were also differences in dosing and route across interventions. Finally, blood loss can be challenging to quantify based on visual assessment, a measurement method used in some studies, which may have influenced this outcome's accuracy.

Based on the existing evidence, misoprostol alone or in combination with oxytocin did not improve outcomes and is associated with more adverse effects, a finding supporting current recommendations from ACOG and the WHO[3,4]. Therefore, we have assigned a color recommendation of Black (harms > benefits) for misoprostol. Further study in other settings on the benefits and harms of uterotonic agents is needed.

Acknowledgements

Dr. Shahriar Zehtabchi reviewed a draft before submission. It has also been accepted and published on the NNT.com website.

Author contributions

Gottlieb M and Long B conceived the idea for this manuscript and contributed substantially to the review's writing and editing. The authors obtained approval from Dr. Zehtabchi for this submission, who also reviewed a draft of this manuscript before submission.

Competing interests

This manuscript did not utilize any grants, and it has not been presented in abstract form. This review does not reflect the views or opinions of the U.S. government, Department of Defense, U.S. Army, U.S. Air Force, Brooke Army Medical Center, or SAUSHEC EM Residency Program.

References

1. Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database Syst Rev. 2018;12:CD011689. https://doi.org/10.1002/14651858.cd011689.pub2

2. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323-333. https://doi.org/10.1016/s2214-109x(14)70227-x

3. World Health Organization. WHO recommendations: Uterotonics for the prevention of postpartum haemorrhage [Internet]. Geneva: World Health Organization; 2018. Available from: https://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1

4. Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 183: Postpartum Hemorrhage. Obstet Gynecol. 2017;130(4):e168-e186. https://doi.org/10.1097/aog.0000000000002351

5. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2012;(8):CD000494. https://doi.org/10.1002/14651858.cd000494.pub4

6. Smith WRP, Papadopoulou A, Thomas E, Tobias A, Price MJ, Meher S, et al. Uterotonic agents for first-line treatment of postpartum haemorrhage: a network meta-analysis. Cochrane Database Syst Rev. 2020;11:CD012754. https://doi.org/10.1002/14651858.cd012754.pub2