TITLE: Misoprostol Administration for the Treatment of Post-Partum Uterine Atony: Clinical Effectiveness, Safety, and Guidelines

DATE: 19 August 2013

RESEARCH QUESTIONS

1. What is the clinical effectiveness of misoprostol for the treatment of post-partum uterine atony, in order to prevent hemorrhage?

2. What is the safety of misoprostol for the treatment of post-partum uterine atony, in order to prevent hemorrhage?

3. What are the evidence-based guidelines regarding the treatment of post-partum uterine atony and post-partum hemorrhage following oxytocin administration?

KEY MESSAGE

Eight relevant systematic reviews, two randomized controlled trials, and four evidence-based guidelines were identified regarding the prevention and treatment of post-partum hemorrhage following vaginal birth.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 7), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. To address research questions one and two, No filters were applied to limit the retrieval by study type. To address research question three, methodological filters were applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and August 6, 2013. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

Disclaimer: The Rapid Response Service is an information service for those involved in planning and providing health care in Canada. Rapid responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. Rapid responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

Copyright: This report contains CADTH copyright material and may contain material in which a third party owns copyright. This report may be used for the purposes of research or private study only. It may not be copied, posted on a web site, redistributed by email or stored on an electronic system without the prior written permission of CADTH or applicable copyright owner.

Links: This report may contain links to other information available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners’ own terms and conditions.
RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews (SRs), and meta-analyses are presented first. These are followed by randomized controlled trials (RCTs) and evidence-based guidelines.

Eight relevant systematic reviews, two RCTs, and four evidence-based guidelines were identified regarding the prevention and treatment of post-partum hemorrhage following vaginal birth. No health technology assessments were identified. Studies were excluded if they specified that they were pertinent specifically to low-income countries or low-resource settings. Due to the volume of literature identified, RCTs published earlier than the search date of the most recent systematic review (literature searched in January, 2013), as well as additional references of potential interest, are provided in the appendix.

OVERALL SUMMARY OF FINDINGS

Clinical Effectiveness

Five\(^1,3,5,7,8\) of the included systematic reviews and the two\(^9,10\) included RCTs reported information regarding the clinical effectiveness of misoprostol for the prevention or management of post-partum hemorrhage (PPH). One of the systematic reviews did not provide results in the abstract.\(^6\)

For the prevention of PPH, oxytocin was found to be more effective than misoprostol in two SRs\(^1,7\) and one RCT.\(^9\) Both oral and sublingual misoprostol were found to be more effective than placebo in preventing severe PPH in one SR,\(^8\) but a second SR\(^3\) found that misoprostol was not associated with a significant effect on PPH. In one SR,\(^8\) misoprostol at a dose of 600 µg was not found to be more effective than 400 µg. In the RCT that compared 400 µg misoprostol (delivered rectally) versus 20 units of oxytocin to women in the third stage of labour, both groups had similar rates of post-partum hemorrhage.\(^10\)

Further detail is available in Table 1.

Safety

Five of the included SRs\(^2-5,8\) and the two included RCTs\(^9,10\) reported information regarding the safety of misoprostol for the prevention or management of PPH. One of the systematic reviews did not provide results in the abstract.\(^6\)

The most common misoprostol-related adverse events were found to be fever\(^2-5,8\) and shivering.\(^3,5\) The incidence of fever seemed to be dose-related, with doses ≥ 600 µg found to be the dose most associated with fevers,\(^2,4,8\) and the authors of one study concluded that 400 µg was a safer dose.\(^8\) The rectal route of administration was associated with fewer instances of fever than both the sublingual and oral routes in one SR.\(^4\)

Misoprostol had similar morbidity when compared to other uterotonic\(^8\) in one SR, and all other treatments\(^2\) in another. Authors of one study suggested using the lowest possible dose of misoprostol, due to the chance of adverse events, because it neither increased nor decreased severe morbidity or mortality.\(^2\)
Further detail is available in Table 1.

Guidelines

The included guidelines from the World Health Organization\textsuperscript{11} and from the Society of Obstetricians and Gynaecologists of Canada\textsuperscript{12} make the following recommendations regarding oxytocin and misoprostol:

- When oxytocin is not available, 600 µg\textsuperscript{11,12} to 800 µg\textsuperscript{12} misoprostol is recommended (400 µg may be just as effective with a lower incidence of side effects\textsuperscript{11}) for the prevention of PPH. This can be via oral,\textsuperscript{11,12} sublingual,\textsuperscript{12} or rectal administration.\textsuperscript{12}
- When oxytocin is not available or has failed, a prostaglandin, such as 800 µg sublingual misoprostol, is recommended for the treatment of PPH. There is a risk of fever at that dose.\textsuperscript{11}

In cases of PPH and uterine atony, the included UK\textsuperscript{13} guideline outlines several measures to be followed until the bleeding stops. These include bimanual uterine compression, intravenous syntocinon, intramuscular ergometrine, intramuscular carboprost, and 1000 µg rectal misoprostol. See the full guideline for further detail. The summary of the included American guideline does not specify which, but states that uterotonics should be used as first-line therapy for PPH caused by uterine atony and that a multidisciplinary approach may be necessary.\textsuperscript{14}

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patient Population</th>
<th>Study Objectives</th>
<th>Intervention; Comparator</th>
<th>Effectiveness Outcomes</th>
<th>Safety Outcomes</th>
<th>Author Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gizzo, 2013\textsuperscript{1}</td>
<td>Women in the third stage of labour; number of studies NR</td>
<td>Review the indications and contraindications of uterotonics for the prevention of PPH</td>
<td>Available uterotonics</td>
<td>Oxytocin indicated as first choice for PPH prevention; misoprostol not as effective as oxytocin but can be used if oxytocin not available</td>
<td>NR</td>
<td>Oxytocin should be administered prophylactically in the third stage of labour; the use of uterotonics should be individualized.</td>
</tr>
<tr>
<td>Hofmeyr, 2013\textsuperscript{2}</td>
<td>Women who received post-partum misoprostol to prevent or treat PPH 78 studies, 59,216 women</td>
<td>Review maternal deaths and morbidity in RCTs examining misoprostol use for the prevention of PPH</td>
<td>MP vs. placebo, no treatment, or another uterotonic</td>
<td>MP vs. all comparators: No significant difference in mortality outcomes</td>
<td>NR</td>
<td>MP was not found to increase or decrease mortality or severe morbidity when used to prevent or treat PPH. ≥600µg MP was associated with an increased risk of fever, authors supported the use of the lowest appropriate dose.</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Patient Population</td>
<td>Study Objectives</td>
<td>Intervention; Comparator</td>
<td>Effectiveness Outcomes</td>
<td>Safety Outcomes</td>
<td>Author Conclusions</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------</td>
<td>------------------</td>
<td>--------------------------</td>
<td>------------------------</td>
<td>----------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Olefile, 2013</td>
<td>Post-partum women (not specified); 3 studies, 2,346 women</td>
<td>Assess evidence for the effectiveness of MP for the prevention and treatment of PPH</td>
<td>MP vs. placebo</td>
<td>MP not found to be effective in preventing PPH</td>
<td>Shivering and fever were significantly more common in MP-treated patients than in those receiving placebo</td>
<td>MP was not associated with a significant effect on PPH. Suggested further study regarding dose and route of administration.</td>
</tr>
<tr>
<td>Elati, 2012</td>
<td>Post-partum women; 33 studies, 38,478 women</td>
<td>To determine the incidence and risk of MP-related fever in post-partum women</td>
<td>MP vs. control</td>
<td>NR</td>
<td>SL MP: 15% of patients with fever Oral MP: 11.4% with fever Rectal MP: 4% with fever RR MP vs. active control or placebo: 5</td>
<td>High dose, sublingual MP was associated with highest rate of fever; unclear if this was MP-only related.</td>
</tr>
<tr>
<td>Tuncalp, 2012</td>
<td>Women in the third stage of labour; 72 studies, 52,678</td>
<td>To review the effect of prostaglandins on the prevention of PPH in the third stage of labour</td>
<td>PG vs. other uterotonic, control, placebo, no treatment</td>
<td>Oral and SL MP effective in preventing severe PPH vs. placebo Oral MP vs. injectable uterotonics: MP associated with higher risk of severe PPH but fewer blood transfusions</td>
<td>MP associated with more shivering, more instances of fever vs. placebo, other uterotonics</td>
<td>MP may be effective in preventing PPH (vs. placebo, no control); side effects were dose-related. Conventional injectable uterotonics may be preferable for low-risk women.</td>
</tr>
<tr>
<td>Chelmow, 2011</td>
<td>Post-partum women</td>
<td>Determine the effect of drug and non-drug interventions for the prevention of PPH</td>
<td>Drug (including MP, ergot compounds, oxytocin) and non-drug</td>
<td>NR</td>
<td>NR</td>
<td>Conclusions not reported in the abstract.</td>
</tr>
<tr>
<td>Sloan, 2010</td>
<td>Post-partum women in hospitals, and in rural areas; 29 studies</td>
<td>To determine the effect of uterotonics on post-partum blood loss</td>
<td>Uterotonic drugs</td>
<td>Oxytocin and MP had lower PPH and severe PPH rates vs. no drug Oxytocin had</td>
<td>NR</td>
<td>Oxytocin was considered more effective than MP.</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Patient Population</td>
<td>Study Objectives</td>
<td>Intervention; Comparator</td>
<td>Effectiveness Outcomes</td>
<td>Safety Outcomes</td>
<td>Author Conclusions</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------</td>
<td>------------------</td>
<td>--------------------------</td>
<td>-----------------------</td>
<td>----------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Hofmeyr, 2009&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Post-partum women; 46 studies, &gt;40,000 women</td>
<td>Review the effects and dose-related effects of MP for the prevention and treatment of PPH</td>
<td>MP vs. placebo or another uterotonic</td>
<td>MP 600 µg was not found to be more effective than 400 µg</td>
<td>MP vs. other uterotonics: similar severe morbidity</td>
<td>Authors found 400 µg MP to be safer than ≥600µg; recommend further study.</td>
</tr>
<tr>
<td>Al-Sawaf, 2013&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Post-partum women following vaginal delivery</td>
<td>Determine the effectiveness and safety of MP vs. oxytocin for the prevention of PPH</td>
<td>200 µg SL MP (n = 28) vs. 5 IU im. Oxytocin (n = 37) vs. control (n = 39)</td>
<td>Oxytocin was more effective at preventing blood loss and the need for further treatment vs. MP</td>
<td>Oxytocin was associated with tachycardia-associated blood pressure decreases</td>
<td>SL MP was less effective than oxytocin but is more stable at room temperature and may have a place in treatment.</td>
</tr>
<tr>
<td>Firouzbakht, 2013&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Post-partum women in the third stage of labour</td>
<td>Determine the effectiveness and safety of MP (PR) vs. oxytocin for the prevention of PPH</td>
<td>400 µg PR MP (n = NR) vs. 20 units oxytocin (n = NR)</td>
<td>PPH incidence: MP = 12% oxytocin = 10%</td>
<td>Side effects similar in both groups</td>
<td>Rectal MP and intravenous oxytocin have similar effectiveness and side-effect rates.</td>
</tr>
</tbody>
</table>

i.m = intramuscular; IU = international units; MP = misoprostol; n = number of patients; NR = not reported; PG = prostaglandin; PPH = post-partum hemorrhage; PR = per rectal; RCT = randomized controlled trial; RR: risk ratio; SL = sublingual; SR = systematic review; vs. = versus

<sup>a</sup>not relevant to this report, therefore results not reported
REFERENCES SUMMARIZED

Health Technology Assessments
No literature identified.

Systematic Reviews and Meta-analyses


Randomized Controlled Trials - 2013


Guidelines and Recommendations


PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca
APPENDIX – FURTHER INFORMATION:

Clinical Practice Guidelines


Review Articles


Randomized Controlled Trials – 2008 to 2012


