Primary postpartum hemorrhage (PPH) is defined as blood loss of ≥ 500 mL within 24 hours after giving birth. PPH is associated with considerable morbidity, and is a leading cause of maternal mortality in Canada and worldwide. Approximately 4.8% of pregnant women in Canada experience PPH, and PPH results in approximately 1.5 maternal deaths per 100,000 live births.

Fluid resuscitation is an important component of managing patients with PPH. Crystalloids and colloids are intravenous fluids used to expand the volume within the circulatory system in situations of blood loss. Examples of crystalloids include normal saline (sodium chloride 0.9%), 5% dextrose in water, and Ringer’s lactate. Colloids differ from crystalloids in that they contain insoluble molecules which act to preserve osmotic pressure within the blood, whereas crystalloids reduce osmotic pressure due to hemodilution. Examples of colloids include albumin, dextran, gelatin, and hydroxyethyl starch.

Hydroxyethyl starch is a form of plant starch that has been partially hydrolyzed to extend the duration of action of the molecule. Although hydroxyethyl starch has been used for a number of years in patients requiring fluid resuscitation, hydroxyethyl starch appears to increase the risk of a number of adverse events including mortality, acute kidney injury, refractory pruritus, and hemorrhage relative to crystalloids and other colloids. However, these studies included patients undergoing cardiac surgery and patients admitted to intensive care. It is unclear whether these adverse events are increased in patients with PPH.

The purpose of this Rapid Response report is to identify studies and clinical practice guidelines evaluating the clinical effectiveness, safety, and recommendations regarding the use of hydroxyethyl starch in patients with PPH.
RESEARCH QUESTIONS

1. What is the clinical effectiveness of hydroxyethyl starch compared with other plasma volume expanders for patients with postpartum hemorrhage?

2. What are the harms associated with the use of hydroxyethyl starch for patients with postpartum hemorrhage?

3. What are the guidelines associated with the use of hydroxyethyl starch for patients with postpartum hemorrhage?

KEY FINDINGS

One clinical practice guideline was identified that recommends the use of isotonic crystalloids over colloids (including hydroxyethyl starch, albumin, modified gelatin, or dextran) for intravenous fluid replacement of women with PPH. This recommendation is based on evidence extrapolated from studies that included critically ill patients, including patients with trauma, burns, sepsis, and surgery. None of the studies included patients with PPH.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 8), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2004 and August 18, 2014.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the identified publications for relevancy to identify publications for full-text review. Full-test publications were reviewed for inclusion in this report based on the criteria listed in table 1.

<table>
<thead>
<tr>
<th>Table 1: Selection Criteria</th>
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<tbody>
<tr>
<td><strong>Population</strong></td>
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<tr>
<td>Q1, Q2, and Q3: Patients with postpartum hemorrhage</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
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<tr>
<td>Q1, Q2, and Q3: Hydroxyethyl starch (colloid)</td>
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<td><strong>Comparator</strong></td>
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<tr>
<td>Q1, Q2, and Q3: Other plasma volume expanders (colloids and crystalloids and albumin)</td>
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<tr>
<td><strong>Outcomes</strong></td>
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<tr>
<td>Q1: Clinical effectiveness</td>
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<tr>
<td>Q2: Safety</td>
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<tr>
<td>Q3: Guidelines</td>
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<tr>
<td><strong>Study Designs</strong></td>
</tr>
<tr>
<td>Q1 and Q2: Health technology assessments, systematic review, meta-analyses, randomized controlled trials, non-randomized studies</td>
</tr>
<tr>
<td>Q3: Clinical practice guidelines</td>
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</tbody>
</table>
Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, if they were duplicate publications, or were published prior to January 1, 2004.

Critical Appraisal of Individual Studies

The included clinical practice guideline was appraised using the Appraisal of Guidelines, Research and Evaluation (AGREE II) tool. A numeric score was not calculated for the included clinical practice guideline. Instead, a review of the strengths and limitations of the included guideline is provided.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search identified 31 citations, with an additional 17 citations identified from the grey literature. After review of the abstracts for each citation, 18 reports were identified for full-text review. After full text review, one clinical practice guideline was included in this report. A PRISMA flowchart in Appendix 1 provides details of the study selection process.

Summary of Study Characteristics

Clinical effectiveness of hydroxyethyl starch compared with other plasma volume expanders for patients with PPH

No evidence was found for this question.

Harms associated with the use of hydroxyethyl starch for patients with PPH

No evidence was found for this question.

Guidelines associated with the use of hydroxyethyl starch for patients with PPH

One clinical practice guideline on managing women with PPH is included in this report. The guideline was created by the World Health Organization (WHO) in 2009. Table 2 lists the characteristics and evidence collection, selection and synthesis methods of the WHO guideline.

Table 2. Characteristics of the Included Guideline

<table>
<thead>
<tr>
<th>Author, Year, Origin</th>
<th>Objective of Guideline</th>
<th>Evidence Collection, Selection and Synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO, 2009</td>
<td>The objective of the guideline was to develop evidence-based guidelines on the effectiveness, safety and quality of various interventions for PPH.</td>
<td>• WHO staff from the Departments of Reproductive Health and Research, Making Pregnancy Safer, and Essential Medicines and Pharmaceutical Policies created questions on PPH interventions and outcomes</td>
</tr>
</tbody>
</table>
Author, Year, Origin

Objective of Guideline

The guideline was also developed to support the United Nations Millennium Development Goal of reducing maternal mortality by 75% by 2015 by reducing deaths due to PPH.

Evidence Collection, Selection and Synthesis

- The questions were then emailed to an international panel of 144 experts, including obstetricians, midwives, neonatologists, researchers, and program experts to identify important outcomes related to PPH.
- Results of questions were then sent back to all respondents (60 individuals) for review.
- WHO then searched, reviewed and graded the evidence to answer the agreed upon questions.
- The search was conducted in November 2007 using Cochrane Library, Pubmed, Embase, and Lilacs.
- The evidence was graded using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology.
- Strength of recommendations for interventions were based on “(i) desirable and undesirable effects; (ii) quality of available evidence; (iii) values and preferences related to interventions in different settings; and (iv) cost of options available to health care workers in different settings.” – page 3

PPH: postpartum hemorrhage; WHO: World Health Organization

Summary of Critical Appraisal

Guidelines associated with the use of hydroxyethyl starch for patients with PPH

The guideline clearly describes the objective, health question, and patient population covered by the objective. The WHO sought to obtain opinions relating to the focus of the guideline from an International panel of 144 experts in PPH, including obstetricians, midwives, neonatologists, program experts, consumers, and researchers. They received responses from 60 individuals, including 46 physicians, 7 midwives, and 7 non-clinicians (researchers, consumers, and policymakers). Respondents were from all six WHO regions. The Centro Rosario de Estudios Perinatales, a WHO collaborating centre in Maternal and Perinatal Health, then conducted the literature search in November 2007 using Cochrane Library, Pubmed, Embase, and Lilacs. It is unclear how evidence was assessed for inclusion in the guideline, however. The included evidence was graded using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology. The methods for formulating the recommendations were clearly described, and health benefits, side effects, and risks were considered when formulating the recommendations. In addition, there was an explicit link between recommendations and the supporting evidence. The recommendations were unambiguous, and key recommendations were easily identifiable. The guidelines also provide plans for implementation and local adaption.
of the recommendations. In terms of limitations, it is unclear whether the guidelines were externally reviewed prior to their release, and there was no procedure for updating the guidelines provided.

Summary of Findings

Guidelines associated with the use of hydroxyethyl starch for patients with PPH

While the 2009 WHO guideline on management of PPH states that “intravenous fluid replacement with isotonic crystalloids should be used in preference to colloids for resuscitation of women with PPH”. The quality of evidence for this recommendation was rated as low, and the strength of the recommendation was rated as strong, that is, the guideline group was confident that the “desirable effects of adherence outweigh the undesirable effects”. The evidence used to develop this recommendation did not include patients with PPH, however, and was extrapolated from a systematic review that included 63 randomized controlled trials in critically ill patients with sepsis, burns, trauma, and surgery. Among the 63 included trials, 16 trials including 637 patients found no difference in risk of mortality in patients who received hydroxyethyl starch relative to those who received crystalloids (relative risk [RR]: 1.05; 95% confidence interval [CI]: 0.63 to 1.75). The WHO guidelines also mention that colloids have been associated with a greater risk for adverse events relative to crystalloids (but does not report an effect size for this relationship) and tend to be more expensive than crystalloids. Each of these reasons lead to the development of the recommendation.

Of note, a 2012 update of the WHO guidelines for PPH provides the same recommendation of isotonic crystalloid over colloid for fluid resuscitation in patients with PPH, however, it does not mention hydroxyethyl starch specifically in the review of the evidence. Also of note is that the 2013 update of the 2007 Perel systematic review that was used when formulating the 2009 WHO guidelines demonstrated an increased risk of mortality with hydroxyethyl starch compared with crystalloid (RR: 1.10; 95% CI: 1.02 to 1.19).

Limitations

There were no studies identified that compared hydroxyethyl starch to other plasma volume expanders in patients with PPH. In addition, the clinical practice guideline recommendation was extrapolated based on evidence from non-PPH study populations. As a result, it is unclear whether women with PPH who require resuscitation would experience similar clinical outcomes and side effects relative to other critically ill patients who were included in the studies, such as those with burns or sepsis.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Given the limitations associated with the currently available literature, it is unclear whether use of hydroxyethyl starch relative to other plasma volume expanders would result in improvement in outcomes or an increased risk of adverse events in patients with PPH. Based on evidence from the 2009 WHO guideline, hydroxyethyl starch does not reduce mortality relative to crystalloid agents. More recent evidence in non-PPH populations, including a 2013 CADTH review, suggests that hydroxyethyl starch may increase mortality and the risk of adverse events including acute kidney injury relative to crystalloids.
REFERENCES


APPENDIX 1: Selection of Included Studies

31 citations identified from electronic literature search and screened

30 citations excluded

1 potentially relevant article retrieved for scrutiny (full text, if available)

17 potentially relevant reports retrieved from other sources (grey literature, hand search)

18 potentially relevant reports

17 reports excluded:
- irrelevant population (9)
- irrelevant intervention (7)
- other (review article) (1)

1 report included in review