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Systematic reviews and meta-analyses comparing mortality in restrictive and liberal haemoglobin thresholds for red cell transfusion: protocol for an overview of systematic reviews

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ABSTRACT

Introduction There has been a significant increase in the number of systematic reviews and meta-analyses of randomised controlled trials investigating thresholds for red blood cell transfusion. To systematically collate, appraise and synthesise the results of these systematic reviews and meta-analyses, we will conduct an overview of systematic reviews.

Methods and analysis This is a protocol for an overview of systematic reviews. We will search five databases: MEDLINE, Embase, Web of Science Core Collection, PubMed (for prepublication, in process and non-Medline records) and Google Scholar. We will consider systematic reviews and meta-analyses of randomised controlled trials evaluating the effect of haemoglobin thresholds for red blood cell transfusion on mortality. Two authors will independently screen titles and abstracts retrieved in the literature search and select studies meeting the eligibility criteria for full-text review. We will extract data onto a predefined form designed to summarise the key characteristics of each review. We will assess the methodological quality of included reviews and the quality of evidence in included reviews.

Ethics and dissemination Formal ethics approval is not required for this overview as we will only analyse published literature. The findings of this study will be presented at relevant conferences and submitted for peer-review publication. The results are likely to be used by clinicians, policy makers and developers of clinical guidelines and will inform suggestions for future systematic reviews and randomised controlled trials.

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Strengths and limitations of this study

- Our overview will include a formal assessment of methodological quality of included reviews and of the quality of evidence in included reviews.
- There are currently no overviews of systematic reviews investigating the impact of restrictive and liberal haemoglobin thresholds for transfusion.
- Our search will be restricted to reviews published in the English language as we do not have access to professional translators.

INTRODUCTION

Rationale

Anaemia, a global public health problem,[1 2] is common in low-income, middle-income and high-income countries.[3] A systematic review and meta-analysis on preoperative anaemia reported that 39% of patients were admitted anaemic. These anaemic patients had threefold higher odds of death, fourfold higher odds of acute kidney injury and twice the odds of infection when compared with patients not anaemic on admission.[4] Anaemia is also associated with increased red blood cell transfusion, highlighting that transfusion is commonly the default option for raising haemoglobin levels.[5] However, red blood cell transfusion is associated with increased mortality, morbidity, hospital and intensive care unit length of stay, readmissions and cost, in a dose-dependent relationship.[6 7]

In an attempt to study the potential risks and benefits of anaemia and transfusion, randomised controlled trials have investigated the difference between using lower haemoglobin thresholds for transfusion with higher thresholds. In an early landmark trial in 1999, Hébert *et al*[8] sought to study these risks in intensive care unit patients. Their study randomised patients to either a restrictive haemoglobin threshold for red blood cell transfusion or a liberal threshold. Patients in the restrictive arm were transfused if the haemoglobin level dropped below 70 g/L and levels were maintained at 70 to 90 g/L. Patients in the liberal arm were transfused if the haemoglobin level dropped below 100 g/L with levels maintained at

100–120 g/L. The authors concluded that using a restrictive haemoglobin threshold for transfusion was at least as effective and possibly superior to a liberal haemoglobin threshold in terms of mortality. Since that large study, many randomised controlled trials comparing outcomes between pretransfusion haemoglobin thresholds have been published in a variety of patient populations. Subsequently, there has been a significant increase in systematic reviews and meta-analyses synthesising the results of these trials. An initial review of the literature identified 14 systematic reviews and meta-analyses reporting mortality as an outcome[5 9–21] that pooled a total of 47 unique randomised controlled trials. These 14 meta-analyses have been published in the last 5 years.

To systematically collate, appraise and synthesise the results of these systematic reviews and meta-analyses, we will conduct an overview of systematic reviews. This overview will provide readers with a single document summarising systematic reviews and meta-analyses on red cell transfusion thresholds published to date.[22]Clinicians and policy makers are likely to find this overview as an ideal starting point for information relating to red cell transfusion research.[22]

Furthermore, conducting this overview is important as systematic reviews of randomised controlled trials are considered the highest level of evidence[23] and are therefore more likely to impact practice and the development of clinical guidelines and policy making. There are currently no overviews of systematic reviews investigating the impact of restrictive and liberal haemoglobin thresholds for transfusion. This overview will include a formal assessment of the methodological quality of included reviews and of the quality of evidence in included reviews.

Objectives

The objective of this overview is to compare and contrast evidence from systematic reviews and meta-analyses of the effects of restrictive and liberal haemoglobin threshold strategies on mortality. Specifically, we aim to answer the following research question: does mortality differ between systematic reviews and meta-analyses of randomised controlled trials comparing restrictive to liberal haemoglobin thresholds for red blood cell transfusion? To achieve this objective, our study will explore the similarities and differences in the full texts of systematic reviews and meta-analyses and the individual studies they include. We will descriptively report the results of our findings.

METHODS AND ANALYSIS

Overviews of systematic reviews are a relatively new and evolving area of research, and therefore, a variety of methodological approaches exist. We developed this protocol based on recommendations published in a series of articles discussing the development and evaluation of overview methods.[24 25] This protocol was reported in alignment with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 checklist.[26]

Eligibility criteria

Types of reviews

We will include systematic reviews and meta-analyses, published between 2008 and 2018, pooling mortality outcomes from randomised controlled trials. The reason for restricting our search dates is because we aim to assess the most recent literature, and earlier meta-analyses are likely to be updated. This restriction does not mean we exclude randomised controlled trials published prior to 2008, as updated systematic reviews and meta-analyses are likely to pool trials without date restrictions. We will exclude systematic reviews without meta-analyses, and systematic reviews and meta-analyses of observational studies. The latter will be excluded as reviews of randomised controlled trials will provide a complete summary of the effect of red cell transfusion thresholds on mortality. Our search will be restricted to systematic reviews published in the English language as we do not have access to professional translators. Additionally, we will exclude abstracts as well as meta-analyses updated by more recent publications.

Participants

We will include all meta-analyses pooling patients randomised to red cell transfusion strategies. We will exclude meta-analyses of trials exclusively in neonatal and preterm infant populations.

Interventions/comparisons

Meta-analyses pooling individual trials randomising patients to different haemoglobin thresholds for red blood cell transfusion will be included. The comparison of interest is restrictive haemoglobin thresholds compared with liberal haemoglobin thresholds for red blood cell transfusion. Though not always the case, restrictive transfusion thresholds are often defined as haemoglobin levels between 70 and 80 g/L, and liberal transfusion thresholds are most commonly defined as haemoglobin levels between 90 and 100 g/L.[5]

Outcomes

The outcome of interest is mortality. We will include meta-analyses pooling mortality events. We will report on any mortality time points reported within the included reviews and highlight reviews pooling mixed mortality time points when reporting results. Our overview will not include morbidity outcomes. Although these outcomes are important and often reported as secondary outcomes, they are not without limitations. For example, the definition, grade and severity of morbidity events pooled by systematic reviews and meta-analyses vary considerably and, as a result, are more subjective in interpretation.[5 17 27]

Information sources

Our overview will search for systematic reviews from the following databases: Medline, Embase, Web of Science

Box 1 Ovid Medline search strategy

1. *Blood transfusion/
2. *Erythrocyte Transfusion/
3. 1 or 2
4. (threshold* or targeted or trigger* or restrict* or liberal* or aggressive or conservativ*).mp.
5. 3 and 4
6. transfus*.mp.
7. ((red cell* or red blood cell* or RBC* or PRBC* or h?emoglobin or h?emocrit or HB or HCT) adj3 (threshold* or targeted or trigger* or restrict* or liberal* or aggressiv* or conservativ*)).mp.
8. 6 and 7
9. 5 or 8
10. exp Mortality/
11. Treatment outcome/
12. mo.fs.
13. (mortality or outcome*).mp.
14. 10 or 11 or 12 or 13
15. 9 and 14
16. (((“systematic review” or “systematic reviews” or metaanaly* or meta-analy* or systematic literature review* or meta synthesis or metasynthesis or overview* or (cochrane adj2 review*) or (umbrella adj2 review*) or unpublished or citation* or references or scales or papers or datasets or rapid review or evidence synthesis or (integrative adj2 review*)).mp. or consensus development conference.pt.) and ((literature or articles or publications or publication or bibliography or published or database* or trials or internet or textbooks or (clinical and studies)).ab,ti. or treatment outcome*.mp.)) not (letter or newspaper article).pt.
17. 15 and 16
18. limit 15 to (meta analysis or systematic reviews)
19. 17 or 18

Core Collection, PubMed (for prepublication, in process and non-Medline records) and Google Scholar. Results will be restricted to English language literature published between 2008 and 2018.

Search strategy

A draft search strategy using Ovid MEDLINE, one of the planned electronic databases to be searched, is presented in box 1. A medical librarian (RM) will create and run a search string to identify relevant articles. The search strategy will undergo internal peer review.

Study records

Selection process

Two authors will independently evaluate all titles and abstracts retrieved in the literature search and select studies meeting the eligibility criteria for full-text review. Where insufficient data are available in the abstract to determine eligibility, the full-text will be retrieved. Any differences will be resolved through discussion to reach a consensus or by using a third author to adjudicate.

Data collection process

Two authors will independently extract data from all eligible systematic reviews and meta-analyses using a predefined form designed to summarise the key characteristics of each review. Any differences in results will be resolved by discussion and reaching a consensus or by using a third author to adjudicate. If any important data elements are missing or unclear and cannot be obtained from the relevant trials, we will contact the authors for information.

Data items

Data items to be collected will include first author details, year of publication, databases searched, database search dates, population description, clinical setting (clinical specialty), inclusion criteria, exclusion criteria, total number of patients randomised, total number of trials pooled, subgroups measured (for mortality outcomes), subgroups reported (for mortality outcomes), study funding sources, conflicts of interests and whether review authors coauthor any trials included.

We will extract the following information specific to the intervention: description of the planned intervention haemoglobin thresholds pooled, differences in actual haemoglobin thresholds pooled between trials, post-transfusion haemoglobin targets or units of red cells and description of the timing of intervention pooled between trials.

For mortality outcomes, we will collect mortality time points pooled and reported, the total number of patients randomised in pooled mortality analysis, the total number of trials pooled in mortality analysis, the total number of deaths in restrictive and liberal arms, the total number of patients randomised to liberal and restrictive arms, and heterogeneity (as measured by the review authors). In terms of transfusion results, we will collect the proportion of patients receiving red blood cells, including those in restrictive and liberal arms, and the mean and SD number of units transfused in restrictive and liberal arms.

Assessment of methodological quality of included reviews

To assess the methodological quality of systematic reviews and meta-analyses included in our overview, two authors will use the 16 domains described in the AMSTAR 2 tool.[28] Any differences between author assessments will be resolved by discussion or adjudication by a third author. We will not exclude any reviews from the overview based on the results of this assessment.

Assessment of the quality of evidence in included reviews

Two overview authors will assess the quality of evidence pooled within the systematic reviews and meta-analyses using an algorithm developed to assign GRADE (Grading of Recommendations Assessment, Development and Evaluation) levels of evidence for overview of systematic review study types.[29] This approach has been previously applied[30] and has been selected to improve the transparency and consistency in our quality assessments.[24] This approach considers the number of participants pooled, risk of bias, heterogeneity and the methodological quality of systematic reviews. Disagreements over the assessment

of the quality of evidence will be resolved by discussion or adjudication by a third author.

This overview will not reassess the quality of evidence of individual randomised controlled trials included within the systematic reviews; however, we will collect data on what methods systematic reviews employed to assess the quality of individual trials and report any similarities and/or differences in assessments.

Data synthesis

Data from individual studies are likely to be pooled multiple times across the reviews included in our overview. As a result, we will not conduct a meta-analysis of results; rather, we will present a narrative synthesis of the findings from the included meta-analyses reviewed.

All meta-analyses results will be presented as rate ratios with 95% CIs. Any meta-analyses presenting ORs will be converted to rate ratios. Our analysis will present the results comparing restrictive thresholds to liberal thresholds, where any meta-analyses comparing liberal to restrictive will be presented as inverse ratios and 95% CIs.

We will include a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram to summarise study selection, and a table reporting the key characteristics extracted from included reviews. We will present the methodological quality of included reviews, assessed using the AMSTAR 2 tool, graphically with results across all 16 domains included. The extracted mortality risk ratios and 95% CIs, along with an assessment of the quality of evidence using GRADE, will be presented graphically using a forest plot. We will report the findings of our study according to the Preferred Reporting Items for Overviews of Systematic Reviews Checklist.[31] Although this checklist has been published as a pilot tool, we have chosen to apply it as it contains reporting items specific to our study design.

Patient involvement

It will not be appropriate or possible to involve patients or the public in this work as it involves a summary of research already conducted.

DISCUSSION

This study will be an overview of systematic reviews. It will summarise evidence about the effect of haemoglobin thresholds for red blood cell transfusion on mortality from multiple meta-analyses. As this study will systematically collate, appraise and synthesise results, it is likely to benefit clinicians, policy makers and developers of clinical guidelines. We expect the results of this overview to highlight gaps in the current evidence, which will inform suggestions for future randomised controlled trials and systematic reviews.

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Contributors KMT designed, developed and refined the study protocol with contributions from all coauthors (KM, FMS, SLF, JI, AH, RM and MFL). KMT and RM developed the search strategy and designed the literature search. KMT and SLF will perform the data extraction. All authors read and approved the manuscript.

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