PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Guidelines on the intraoperative transfusion of red blood cells: a protocol for systematic review
AUTHORS	Baker, Laura; Park, Lily; Gilbert, Richard; Martel, Andre; Ahn, Hilalion; Davis, Alexandra; McIsaac, Daniel; Saidenberg, Elianna; Tinmouth, Alan; Fergusson, Dean; Martel, Guillaume

VERSION 1 - REVIEW

REVIEWER	Andrew Shih Vancouver Coastal Health Authority/University of British Columbia, Canada
REVIEW RETURNED	17-Feb-2019

GENERAL COMMENTS	Baker et al present a protocol for a systematic review for guidelines on the intraoperative transfusion of red blood cells. As the authors have noted, there is a marked gap in the literature base in this area that needs to be addressed in clinical care. This likely due to the large number of variables associated with intraoperative transfusion as well as the difficulty of performing studies to optimize transfusion in the unstable/bleeding patient. The search (notably its breadth), protocol, and assessments proposed are methodologically rigorous and suggest the multidisciplinary team is well equipped to tackle this important research question. Major Recommendations p.9, line 195: The authors may want to consider what variables are important a priori that guidelines should take into consideration in determining appropriateness for transfusion; and explicitly make those variables part of the data abstraction process. The authors provide some variables as examples that would work well. Highlighting gaps in even considering the appropriate variables in current guidelines I believe would add more value to this review, since as the authors imply, little literature is likely to be found in this area. Minor Recommendations p.4, line 70: The authors may consider highlighting that transfusion reactions in the intra-operative setting are likely underreported given the inability to report symptoms and the ease to which transfusion reactions can be simply attributed to intra-operative complications. In addition, perioperative transfusion itself is a predictor of poor outcomes in patients, suggesting while

	transfusion is a life-saving intervention, its benefits must be balanced against risks. p.6, line 129: "As eluded..." should be "As alluded..." p.8, line 188: Presumably resolution will be done independently? Please clarify.

REVIEWER	Lise J Estcourt NHS Blood and Transplant, Oxford UK
REVIEW RETURNED	19-Feb-2019

GENERAL COMMENTS	This is a protocol for a systematic review of guidelines looking for specific recommendations for intraoperative transfusion guidance. The authors highlight the fact that the AABB recommendations do not state specific guidelines for intraoperative transfusion. However, the guidelines do state specifically a “hemoglobin transfusion threshold of 8 g/dL for patients undergoing orthopedic or cardiac surgery”. This includes intraoperatively but will include the immediate perioperative period as well. Most trials that included a restrictive threshold included the perioperative period as well. A good example is the Mazer trial that included over 5000 participants undergoing high risk cardiac surgery. It randomised patients to receive a restrictive threshold during the intra and immediate post-operative period. If the review authors exclude this type of evidence and these sorts of statements, then there is likely to be minimal evidence as most guidelines will include both the intra and immediate post-operative period within their recommendations. If the authors want to identify those studies that included intraoperative restrictive thresholds rather than just restricting the threshold post-operatively then it might be more useful to look at the studies rather than the guidelines. Is there a benefit of having such a restrictive definition when the evidence available is for a broader period of time? I have some general points that I felt will help the clarity of the review. I think one issue that hasn’t clearly been addressed is the definition of an operation. The American College of Surgeons has a very broad definition of surgery. “Surgery is performed for the purpose of structurally altering the human body by incision or destruction of tissues and is part of the practice of medicine. Surgery also is the diagnostic or therapeutic treatment of conditions or disease processes by any instruments causing localized alteration or transportation of live human tissue, which include lasers, ultrasound, ionizing radiation, scalpels, probes, and needles. The tissue can be cut, burned, vaporized, frozen, sutured, probed, or manipulated by closed reduction for major dislocations and fractures, or otherwise altered by any mechanical, thermal, light-based, electromagnetic, or chemical means. Injection of diagnostic or therapeutic substances into body cavities, internal organs, joints, sensory organs, and the central nervous system is also considered to be surgery (this does not include

	administration by nursing personnel of some injections, such as subcutaneous, intramuscular, and intravenous when ordered by a physician). All of these surgical procedures are invasive, including those that are performed with lasers, and the risks of any surgical intervention are not eliminated by using a light knife or laser in place of a metal knife or scalpel. Patient safety and quality of care are paramount, and the College therefore believes that patients should be assured that individuals who perform these types of surgery are licensed physicians (defined as doctors of medicine or osteopathy) who meet appropriate professional standards" It would be very useful for the authors to define what they mean by surgery/operation as it is quite difficult to define and as many procedures that were only performed by surgeons in an operating theatre in the past, and are major operations e.g. elective repair of an aortic aneurysm, can now be performed as endovascular procedures. The definition by the American College of Surgeons would include any type of invasive procedure. How will intra-operative be defined, will it include all time in the same location (e.g. theatres and recovery room) that the procedure is being performed. Will it be from first administration of any form of anaesthetic until completion of the procedure, or will it be from first incision? Please clarify. Is there going to be any time limit on the guidelines identified. Surgical practice has changed significantly over time and old guidelines may not be appropriate for current practice.? How will older guidelines be handled? Minor points The correct nomenclature for US dollars is USD rather than $US. Red cell prices vary significantly from country to country, it may be more useful to put an approximate range of cost if possible.

VERSION 1 – AUTHOR RESPONSE

Responses to Reviewer 1 (Dr. Andrew Shih):

1) Thank you for this suggestion. We agree, highlighting variables of interest a prior will strengthen the presentation of our results and ability to draw conclusions. We have modified the statement pertaining to variables of interest to make it more explicit:

"We will identify whether or not the following variables are accounted for in identified decision rules or recommendations: patient comorbidities-specifically a history of coronary artery disease, hemodynamics (hypotension, tachycardia, or presence of vasopressor support), estimated blood loss, evidence of cardiac ischemia, and evidence of end organ ischemia in addition to cardiac."

2) We have added the following content to our introduction, as suggested:

"Another aspect unique to the unconscious patient under general anesthesia, subject to dynamic changes in hemodynamics for a number of reasons, is our limited ability to identify transfusion

reactions. Although literature in this area is lacking, it would be reasonable to hypothesize that transfusion reactions in the intra-operative setting are underreported. This, in combination with the evidence that patients who receive intraoperative transfusions suffer increased short and long term morbidity, advocates for careful consideration of transfusion administration (1) (2) (3)."

3) Correction has been made

4) Correct, this clarification has been made:

"Any disagreement regarding relevancy will be resolved by a senior author, independent from the reviewers."

Responses to Reviewer 2 (Dr. Lise J Escourt)

1) Thank you for this comment. This is a topic we have devoted considerable thought to.

The AABB guideline was carefully considered when establishing our inclusion and exclusion criteria (4). In reviewing this guideline, we identified that 4 of the 20 cited trials pertaining to the surgical patient encompassed the intraoperative period (5) (6) (7). Therefore, the vast majority of trials pertaining to the surgical patient did not randomize patients or apply transfusion rules until the post-operative period. Upon review of their "evidence summary" accompanying their recommendation, they do not make the distinction as to whether the trials pertained to intraoperative or post-operative period. We are in agreement that the the recommendations provided by the AABB encompass the intraoperative patient, however, based on the wording of the recommendation and organization of the accompanying evidence summary, the intraoperative period was not considered as a unique, independent entity. As the objective of this systematic review is to identify guidance of utility to the provider managing a surgical patient under general anesthesia, a period unique to their pre- or post-operative course, we decided to only include guidance explicitly stating their application to the intraoperative setting.

We are in agreement with Dr. Escourt that a review of trials is of interest. We do however feel that the independent exercise of identifying, evaluating the quality of and summarizing current available guidance is a valuable independent exercise. To address the concern of the anticipated lack or limited guidance satisfying our eligibility criteria-we can confirm that a minimum of 5 guidelines have been identified (currently undertaking full text review). We therefore feel this review is of value. It is also an important step in the process of future guideline development, which is of ultimate interest. Additionally, depending on the findings of this review, in the event high quality, recent guidance fails to exist, we plan on conducting a systematic review of trials randomizing patients to different transfuse rules or indicators.

2) The intraoperative setting has been further clarified to:

"in patients undergoing general anesthesia in an operating room"

3) No time limit has been identified as the objective is to capture all guidance reporting on the management of the intraoperative patient, which as the reviewer has suggested, is anticipated to be limited. However, we are in agreement that guidelines reflective of more recent evidence warrant separate consideration. We have therefore added the following subgroup analysis:

"guidelines published following publication of the TRICC trial in May 1997 will be considered separately in our descriptive analysis (8). The rationale for this being that the prevailing theme of current practice is a result of this trial."

4) Correction made.

5) Additional references added to reflect range of prices-Systematic review of cost of RBC transfusion cited.

"At an estimated price tag of 102-761 USD per unit, RBC transfusions are costly (9) (10) (11) (12)."

VERSION 2 – REVIEW

REVIEWER	Andrew Shih University of British Columbia
REVIEW RETURNED	17-Mar-2019

GENERAL COMMENTS	The authors have addressed my concerns and suggestions in the revisions. I look forward to seeing the results on the study.

REVIEWER	Lise Estcourt NHS Blood and Transplant UK
REVIEW RETURNED	08-Mar-2019

GENERAL COMMENTS	As the authors have a narrow description of perioperative (undergoing general anaesthetic in the operating room) it should be reflected in the abstract and title. Currently have to read full text to be aware of the narrow criterion

VERSION 2 – AUTHOR RESPONSE

Responses to Reviewer 2 (Dr. Lise J Escourt):

1) We have made modifications to the abstract to make it more explicit that we are interested in guidelines pertaining to the anaesthetized patient undergoing surgery by stating:

“The objective of this systematic review is to explore the availability, quality and content of clinical practice guidelines (CPG) reporting on the indication for allogenic RBC transfusion during surgery.” (Line 37-39)

However, we are hesitant to change the wording of the title as we are of the opinion the statement “intraoperative” correctly identifies the setting. A quick pubmed search of “intraoperative” in the title heading field in articles published in BMJ Open, over the last 5 years, identified 8 hits. Review of the associated abstracts verifies that use of this word was similar to our intended definition of intraoperative referring to the patient undergoing a procedure in the operating room, under general anesthesia. A pubmed search of “intraoperative,” not restricted by journal produced 24918 hits. Review of the first 20 articles verified that the use of “intraoperative” was utilized to describe the operative setting.

If following reviewing our rationale for not wanting to alter the title, Dr. Escourt feels strongly the title will mislead readers, we will be happy to oblige to her recommendation.