

Peer Review File

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Reviewer A

General Comments

1. While the manuscript discussed patient blood management (PBM) in relationship to the COVID pandemic, there are too many areas that just discussed patient blood management applications in general and were extraneous to the central topic.

2. Recommend to just focus on PBM and COVID-19.

3. Suggest to use on the following sections for this manuscript:

- Adapting donor selection criteria (lines 183-202)
- COVID-19 pandemic related challenges to hospital PBM service (lines 276-307)
- PBM in hematologic malignancies (lines 318-383)
- RBC transfusion strategy (lines 422-431)
- PBM in obstetrics (lines 446-468)
- PBM in elective gynecologic surgery (495-531)
- Conclusions (lines 540-562)
- Table 1 (lines 940-947)

We thank you for your comments. Our vision for this paper was to create an up-to-date comprehensive PBM review. Therefore, we included a brief introduction to PBM, the summary of the most landmark pre-pandemic PBM papers, the overview of papers relevant to PBM published during the COVID-19 pandemic (2020 til 2022) and finally provide a commentary on how the PBM practice had to adapt locally and globally. We believe that launching directly into 2020-2022 PBM literature without a context would have been confusing to the readers. Moreover, by keeping it a comprehensive review, the paper is likely to maintain its relevance post-pandemic. Since the field of PBM is so vast, we decided to focus this review on reducing unnecessary RBC transfusions and limit discussion to the patients undergoing major elective surgery, patients with

malignant hematological conditions and elective gynecological surgery and obstetrics.
We agree with the proposed subheadings and have revised accordingly.

Specific Comments

1. Adapting donor selection criteria (lines 183-202) and Table 1 (lines 940-947)- please discuss how the decision was made to lower the hemoglobin of donors and reduce the days of deferral for travel to a malaria endemic area, and if this was a blood center (Canadian Blood Services) or regulatory authority (Health Canada) decision.

The Canadian Blood Services proposed these changes and they were approved by Health Canada.

2. Table 1 (line 945)

The date the article was cited– states YYYY MM DD, please complete.

This has been corrected, thank you.

Reviewer B

This manuscript reported that PBM intervention could improve patient outcomes and sustain blood supply during the COVID-19 pandemic. The authors also shared the experience in blood supply in Canada during pandemic, and reviewed and described the PBM intervention, focusing on elective major non-gynecological surgeries, hematological cancers and obstetrics and elective gynecological surgeries.

Comments:

1. Since the manuscript should be a narrative review, it was suggested that the authors should give a subtitle for section(s), rather than using the introduction-method-discussion section form.

Thank you for this helpful suggestion. We re-organized the paper into sections for ease of reading.

2. The title was concerned with PBM during the COVID-19 pandemic. However, few reference articles concerning the impact of COVID-19 on transfusion were cited and discussed in the manuscript. The authors should take the literature review especially for articles that were published in recent two years, disclosing what's changed with PBM intervention during the pandemic and what kind of challenges that we could face during the pandemic; and discuss more about PBM intervention during the pandemic especially in the sections of elective surgeries and obstetrics.

Thank you for this suggestion. Our initial review failed to identify any original articles and instead only revealed a few reviews, including one narrative review on this topic. We then performed a formal literature search with a librarian's assistance and were able to identify additional articles. These were included in the revised paper. We already had a section on challenges/changes experienced in PBM in elective surgery, but have added these details to the other sections.

3. Strategies to sustain adequate blood inventory and supply in blood centers or the blood bank in hospitals in other countries during the pandemic should be reviewed and discussed.

We focused on our own experience, since of course we were most familiar with what was happening locally. However, this is a valid criticism and we have added more details about the experience of other countries. These details were identified by the updated literature review.

3. To avoid confusion for readers, the authors should unify the units of Hb in the main text and tables (use g/dL or g/L only).

Thank you for pointing this out. We agree! We have changed all hemoglobin values to g/dL.

Reviewer C

This narrative review is about the impact of the COVID-19 pandemic on the Canadian blood supply and how the principles of patient blood management (PBM) could be applied during a pandemic or other disruptions to healthcare delivery or blood supply. This specific review focus on major elective surgery, women's health (obstetrics and gynecological surgery) and hematological malignancies. You also described local blood system and patient management challenges and how your PBM practice has adapted during the pandemic. The conclusion of this narrative review is that prioritization of PBM during the pandemic or blood shortage may lead to improved patient outcomes and help sustain the blood supply.

Several considerations could be suggest in the substance of the text:

The background of your narrative review is well written and perfectly synthesizes the objective of your work.

Thank you.

Methods section is unfortunately not accurate enough. An extensive literature research involves an analyze not only on PubMed but also on CochraneTM databases, Embase, www.clinicaltrials.gov... It will be also appropriate if you confirm your analyze with this extensive research.

Thank you for your comments. We re-ran the search and updated the methods section to be more clear as to how articles were searched and selected.

The first chapter on the impact of COVID-19 on the Blood System in Canada is very interesting.

It is not clear why you identify different section as non-gynecological and gynecological surgery according to the PBM program for theses elective surgeries. In practice, the management of these patients is the same for the preoperative period.

Specificity in the gynecological management is described to reduce blood loss with menstrual suppression strategies. But this point could be associated in the sub section of the chapter 2: reducing blood loss.

We believe that patients undergoing elective gynecological surgery are different (for ex. all patients are female and have very high prevalence of isolated iron deficiency anemia due to heavy menstrual bleeding). This patient population is also frequently under-diagnosed and under-treated. For these reasons, we decided to keep this section separate, to call attention to these patients.

In the discussion section, you recommend some strategies that are not in accordance with clinical guidelines but often based on your experiences or based on specific articles. These propositions cannot be left as such in your manuscript because they are not based on sufficient level of evidence. For example, you suggest administrating ESA in addition to iron supplementation to reduce RBC transfusion rate in adult preoperative patients with anemia whatever the type of surgery. However, in the Evidence-based Recommendations for Preoperative Anemia Management as per International Consensus Conference on Patient Blood Management, “short-acting erythropoietin in addition to iron supplementation must be considered only in adult preoperative patients with hemoglobin below 13g/dL and undergoing elective major orthopedic surgery”.

Thank you for this valuable comment. ESA have been shown to reduce transfusions in many different major elective surgeries, not just orthopedic surgery. ESA have also been shown to be safe in many surgical patient populations. Some of these studies, systematic reviews were not considered in the ICC-PBM guidelines because they were published after the review of evidence for these guidelines has been completed (evidence collected mostly in 2017 – five year ago!; consensus conference early 2018 and publication in 2019); others were not captured because of how PICO questions were phrased and how evidence was gathered. Please also note that this recommendation was also conditional (GRADE defines this as a conditional recommendation implies that we believe most people would want the recommended course of action but that many would not) and based on weak evidence. The advice to

use ESA in anemic patients prior to any major surgery is also on ESA label in many countries, including ours. Our advice is based on evidence and experience (ONTraC program – 25 hospitals), though is contrary to the ICC-PBM guidelines. We have explicitly stated that, and we stand by our advice. This advice is also particularly poignant during the COVID-19 pandemic blood shortages, where ESA administration prior to major surgery may have reduced utilization of scarce RBC.

At several occasions in this narrative review, you write, “we recommend....” (l 395, l 416, l 430). This formulation is inappropriate because this is not guidelines manuscript. Please, modify these formulations

This is a fair point and replaced recommend with “advise”.

« We observed lower hemoglobin and higher rates of perioperative RBC transfusion in female patients (unpublished data) » (l 299 -300). It is not appropriate to maintain this information because of unpublished data that are not be approved by reviewers (we do not have information on the number of patients, the hemoglobin level, the transfusion rate ...).

We understand your concerns. However, these observations have not been previously published and yet served as a justification for our approach. We added more detail and clearly stated that these were unpublished (and hence not peer reviewed) observations. If this is unsatisfactory, we could remove this section.

« In our hospital, we use a transferrin saturation (TSAT) $\leq 20\%$ and/or ferritin $< 100\text{ug/L}$ to diagnose iron deficiency in preoperative patients (l 211-212). This definition is very large. You use iron deficiency definition in case of TSAT $\leq 20\%$ whatever ferritin level? (i.e even if ferritin level is higher than 300 ug/L?)

In short, the answer is yes, we use the definition of TSAT $\leq 20\%$, since high ferritin in these patients (even 300) is a reflection of inflammation, not iron overload. However, we decided to remove this section and instead referred the readers to our published

PBM protocols (ONTraC).

Several considerations could be suggest in the form of the manuscript:

The populations of interest are not always describe in the same way : “We conducted a brief review of literature with specific focus on elective surgery, women’s health and hematological malignancies » (1 45 46)

And after “This review will address the use of these agents in elective major surgery, pregnancy and postpartum and in patients with hematological cancers » (1 91 92). Please be more specific about the population analysed and use the same works in your narrative review .

Thank you for pointing this out, we made changes to use consistent language throughout.

It will be more appropriate to organize paragraphs as follow:

Chapter 2 : PBM In Elective Major Non-Gynecological Surgery

Chapter 3 : PBM in Elective Gynecological Surgery

Chapter 4 : PBM in Obstetrics

Chapter 5 : PBM in Hematological Malignancies

As previously explain, you can merge chapter 2 and 3 in only one chapter.

It will be more appropriate to insert “COVID-19 pandemic related challenges to hospital PBM service » in the chapter 1 : Impact of COVID-19 on the Blood System in Canada

Thank you, we will re-organize the paper into relevant sections. However, combining our hospital’s PBM experience with that of our blood supplier is not appropriate. Our blood supplier is national/country-wide, whereas PBM is a regional/local service.

It will be more efficient and comprehensive if a table summarizes the 4 PBM interventions sections

This is a good point. We struggled with creating an appropriate table or summary visual

abstract. For 4 different patient populations, the approach is still the same three pillars (diagnosis and management of anemia/reducing blood loss/restrictive transfusion strategy) and so we could not come up with anything which was not repetitive.

Please limit the number of abbreviation.

Thank you, we reviewed the paper and made changes to limit abbreviations wherever possible.