Peer Review File

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Reviewer 1

Comments to the authors:

Overall a great article reviewing a key aspect of perioperative medicine that often gets overlooked. Only a few minor points that I'd make:

Lines 59-62: This sentence begins describes a 20% reduction in blood transfusions, and goes on to state that there were signficantly less blood transfusions after PBM. Is this one and the same, or does the latter need further qualification?

Reply: I assume you are referring to lines 74-79? There was a 20% oevrall reduction in blood transfusions and also a significant reduction in overall 2 year survival.

Line 67-68: "This cut-off may be outdated and that 130g/L for all." This needs expansion to form a full sentence. Also, if a reference is needed, the application of 130g/L for all is directly mentioned in *Munoz et al, An International Consensus Statement on the Peri-operative Management of Anaemia and Iron Deficiency, Anaesthesia; 2016.*

Reply: Sentence has been changed, thanks for the reference!!

Line 93: A comma may be required - "Advances in technology have meant that through improved compatibility matching**,** adverse reactions…"

Reply: Comma added later in sentence

Line 96-97: Presumably it was the blood transfusions that was associated with a higher 30-day mortality etc? This sentence could be seen as slightly ambiguous otherwise.

Reply: Added a bit to clarify that it was blood transfusion receipt that caused higher mortality to make sure it is clear.

Line 111: The inclusion of the reference in the middle of a sentence is inconsistent with the rest of the body of text.

Reply: Changed to end of sentence

Line 114: Although it is alluded to toward the end of the subsection, I feel it may be worth pointing out earlier that ID and IDA are subtly different, particularly given that

some centres now opt for parenteral iron in post-operative anaemia where patients have been identified as iron deficient (without anaemia) pre-operatively.
Reply: Added sentence about ID being present with or without concurrent anaemia.

Line 170: "Initial General Practitioner referral", presumably is referral for surgery?
Reply: GP referral should spark GP to start investigating and treating anaemia before referral for surgery.

Line 181: Prehabilitation doesn't need to be hyphenated/isn't in most of the published literature I've read.
Reply: Changed

Line 200: "Meticulous attention to blood loss…" Given it's describing blood sparing surgical techniques, would it be better to refer to "meticulous attention to haemostasis"?
Reply: Changed

Line 260: When referring to restrictive transfusion regimes, is it worth explicitly stating when 80g/L is used over 70g/L?
Reply: 70 has been agreed as new lower cut off and often people need to follow local policies

Line 261: "Metanalysis" needs correction to "meta-analysis".
Reply: Changed

Line 279: I think "thee" may be a typo?
Reply: Changed

Line 279 – 281: May be minor, but the order in which you introduce PBM and then continue to mention restrictive transfusion triggers, immediately before concluding that patients should subsequently arrive with optimal haemoglobin stores makes it sound as though it's the transfusion triggers that results in optimal heamoglobin stores, rather than PBM.
Reply: Sentences split to remove the ambiguity.

Reviewer 2

Comments to the authors:
Really good concise review – goes through all aspects of PBM

The layout could be improved by the use of sub-headings – RBC transfusions/ESAs/IV iron – could all be under Treatment of Perioperative Anaemia.
Could also tie in PBM a bit more by using the three pillars as sub-headings for example; instead of 'Preoperative measures to assess and treat anaemia', it could be 'Pillar 1: Optimising Haemopoiesis'.
Reply: Ultimately personal preference and I think separating it out allows the reader to quickly find the area that they may be specifically interested in.

Abstract:
Line 35/36: "intraoperative blood loss catastrophic" – think it was meant to be catastrophic after intra-op. Also, quite a wordy sentence overall.
Reply: Sentence cut down and rearranged

Introduction:
Line 48 – have instead of has
Reply: Changed

Line 49 – don't need "this was". Also, NHSBT – acronym not explained previously
Reply: Changed

Background:
Lines 59-62: mention the reduction in blood transfusions twice – at beginning and end of the sentence.
Reply: I have expanded the paragraph as it needed to be more explicit that where a patient was transfused they received less units as a separate finding to the overall reduction in blood transfusions.

Anaemia:
Line 68 – sentence not finished? …"and that 130g/L for all"
Reply: Changed and expanded with reference

Treatment of perioperative anaemia:
Line 86 – risks quoted are mainly for blood transfusion not ESAs – which are mainly thrombotic and some evidence of increased mortality in cancer patients
Reply: Sentence states that the are related to both transfusions and ESAs.

Transfusion Triggers
NICE guidance is for restrictive triggers only transfusing when <70 apart from patients with major haemorrhage/ACS and chronic anaemia – I'm not sure anyone transfuses if

below 100g/L routinely anymore?
Reply: Paper specifically quotes use of 90 or 100 in previous liberal regimes, totally agree that people don't use them anymore.

Conclusion:
Line 279 – Thee (spelling)
Reply: Changed

Reviewer 3
Comments to the authors:
Line 68: outdated and that 130g/L for all. This sentence doesn't read well or make much sense. Please revise.
Reply: Changed

Line 96: Please check % of patients receiving transfusion – confirm it is 14% and not 16%
Reply: Rechecked article and definitely 14%

Line 99 (Line 86/87): ESA represent a difficult area perioperatively! No mention in use of ESA on effect on tumour growth. May be worth adding in about the anaesthesia consensus statements from Munoz 2017 and Mueller JAMA 2018 not recommending the use of ESA in elective surgery. Differing advice from anaesthetics and oncology? Possibly mention the review of the NICE guidance from April 2018 - *Owing to the potential negative effect on survival, tumour progression, the use of erythropoiesis-stimulating agents has gone out of favour as a standalone treatment of chemotherapy-induced anaemia (Weigl et al, 2017)* and that clinicians will adhere to these instructions to mitigate against harm etc
Reply: Thanks, have added JAMA reference and note to elective surgery.

Line 147: 'Currently there is mounting evidence that there is no increased risk of infection, cardiovascular events, or all-cause mortality'. Consider revising this statement given the ongoing confusion and the ongoing research in this area. Review article covers all patients receiving parenteral iron not specific to perioperative period.
Reply: Have added about being area of ongoing research

Line 166/7 & 173/4: Consider mentioning potential optimal timing of IV iron to receive maximal benefit for Hb rise and avoidance of perioperative hypophospataemia?
Reply: Optimal timing still area of contention with some quoting 2 weeks while others 6 weeks.

Line 201: Consider referencing use of tranexamic acid and balance against potential side effects

Reply: Reference added

Line 216: ‘cell salvage to be safe and effective in obstetric and colorectal surgery’ requires reference

Reply: Reference added

Line 279: spelling error on the

Reply: Changed