

Xiu-Xia Song,
Editor-in-Chief
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Dear Editors/Reviewers

Re: Resubmission of Manuscript reference No. 32877

Thank you for the opportunity to revise our manuscript. We appreciate the careful review and constructive suggestions. It is our belief that the manuscript is substantially improved after making the suggested edits.

Please find attached a revised version of our manuscript **“Perioperative Blood Management Strategies for patients undergoing Total Knee Replacement: where do we stand now?”**, which we would like to resubmit for publication as a Review in world Journal of Orthopedics.

Your comments and those of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments.

Following this letter are the editor and reviewer comments with our responses in italics, including how and where the text was modified. Changes made in the manuscript are marked/highlighted (yellow) using track changes. The revision has been developed in consultation with all co-authors, and each author has given approval to the final form of this revision.

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in World Journal of Orthopedics

We shall look forward to hearing from you at your earliest convenience.

Yours sincerely,

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REVIEWER #1 (1200726)

This review has useful information for the readers. It would be better to add more references of TXA.

We agree with the reviewer and have added more references regarding the use of TXA. The following sentences have been added in the manuscript (lines 364-366 & 369-372 & 375-380): i) "Regarding the route of administration and plasma concentration, maximum plasma concentration of TXA is reached within 5–15 min after IV injection, 30 min after intramuscular (IM) injection and 2 h after oral tablets." ii) "On the contrary, a recent meta-analysis showed no statistically significant difference in total blood loss, drain output, transfusion requirements and thromboembolic complications between topical TXA and IV-TXA in TKA." iii) "Nevertheless, two RCTs concluded that intra-articular regimen of TXA is as effective as three doses IV regimen in preventing blood loss without any difference in thromboembolic complications. In addition to all these studies some authors have noticed that the combination of IV and intra-articular TXA is more effective than either regimen used alone."

REVIEWER #2 (2444795)

Please mention the 3 stage (pre-operative, intra-operative and post-operative) in the abstract. More detail required in the discussion as to how the three stages can complement each other.

Thank you for these observations. We added the following sentence regarding the stages in abstract (lines 75-77): “For practical and clinical reasons we will try to classify these strategies in three main stages/pillars: pre-operative optimization, intra-operative and post-operative protocols.”

In the discussion the following sentences have been added about the strategies/stages combination (lines 574-602): “Scrutinizing the recent literature, we conclude that there is no “consensus success story” about a common efficient/safe blood management strategy in TKA. And if we hazard a guess, we’d say that this consensus cannot be achieved. The current trend is the patient-specific strategy (PSS). This idea is based on the notion that each patient has a different impact on the risk of requiring a transfusion. For example the PSS in a healthy man with Hb>13 g/dl who undergoes TKA could be a “do nothing” (except Hb reaches transfusion trigger). Conversely, a Jehovah's Witness patient and/or a patient with significant cardiopulmonary compromise should be monitored carefully and more blood management strategies should be considered in order to avoid ABTs. In other words, the above methods that have been analyzed, the advantages and the disadvantages of each method, are just the different parameters that every surgeon should take on board in order to achieve the best result in a specific patient.

The take home message after our in-depth search is that the first important step in blood management is the thorough pre-operative evaluation of each patient. Consideration should be given to the existing physiologic/pathologic variables of the patient and the concomitant actions that should be taken in order to allow prompt optimization of the patient's physiologic status. The second principal arm of effective blood management is the restriction of ABTs' to patients meeting well-established transfusion criteria. Nowadays, this trigger has been decreased to 8 g/dl. The old common belief that all patients with Hb below 10 g/dl should be transfused, has been surpassed. However, when clearly the blood is indicated (clinical signs and symptoms of anemia), administration should not be delayed. Additionally, the use of TXA perioperatively (with different routes of administration) is a widely accepted, effective and safe method in reducing perioperative blood transfusion. These three steps are the “baseline” in our daily practice regarding the perioperative care of the surgical patient.”

REVIEWER #3 (3065412)

This is a well-written informative article. Regarding points for improvement, I would suggest:

1. Avoid generalisations, and provide relevant facts where implicated e.g. 'Complications associated with ABT are well-known.'

Thank you for your comment. Sentence has been edited (lines 66-68): "Complications associated with ABT including chills, rigor, fever, dyspnea, light-headedness should be early recognized in order to lead to a better prognosis."

2. Avoid the use of informal language e.g. 'In the first place, every orthopaedic surgeon should be able to plow through and understand any of these methods individually.'

Thank you for your comment. Sentence has been edited (lines 606-607): Primarily, every orthopaedic surgeon should be able to plow through and understand each method separately.

3. Please provide better evidence regarding your average estimated blood loss for TKA - 'It's reported that patients undergoing TKA may result in blood loss range from 1000ml to 2000ml which necessitates subsequent allogeneic blood transfusion (ABT) in 10%-38% of them.' 'It's more than clear that TKA is a surgery with a blood loss reaching up to 2000ml.' This seems much higher than the reviewer's current practice.

Mean blood loss have been revised and more references have been added (lines 116-118 & 556-557): " It's reported that patients undergoing TKA may result in blood loss between 1000ml and 1500ml which necessitates subsequent allogeneic blood transfusion (ABT) in 10%-38% of them." & "It's more than clear that TKA is a surgery with a blood loss reaching up to 1500ml."

4. The following sentence is not worded very clearly: 'Actually, it's been calculated that 9.8% of all transfusions being made are associated with total joint arthroplasty surgery (including fractures)' Please revise.

Sentence have been deleted as it doesn't offer a clear information to the review.

5. It is unclear why the following sentence is of relevance to the current article: 'The estimates of pre-operative anaemia prevalence in the literature ranges widely, from 5% to 75.8% in patients with end stage colon cancer.' Please clarify.

Thank you for your comment. The sentence have been deleted as it's not really relevant to the current article.

6. The authors should note the potential risks associated with EPO usage.

We agree with the reviewer and have added the following sentence regarding the EPO risks. (lines 187-191): "Adverse events have been reported in 5% of patients that have been treated with EPO. These complications include deep venous thrombosis (DVT), pulmonary embolism (PE), fever, hypokalemia, urinary tract infection, nausea, hypoxia, and vomiting."

7. Please clarify the following phrase: 'the factor-rich buffy coat'

We replaced this sentence with the following paragraph in order to make PRP preparation more clear (lines 453-457): "Platelet-rich plasma (PRP) is defined as plasma with a platelet level above peripheral blood concentration. There are two methods to obtain it: i) ready PRP kits (higher cost) and ii) a wide variation of reported protocols for standardization and preparation of PRP (most of them use two-step centrifugation protocol)."

8. Please provide more evidence to justify the following phrase: 'Drainage is being used by the majority of orthopaedic surgeons in order to decrease haematoma and succeed in patients' early post-operative rehabilitation.' This is not routine in the reviewer's practice or experience.

Thank you for your comment. An extended search in the current literature have been done. The sentence has been edited and more references regarding the use of drainage and its results have been added (lines 537-540): "Although it is commonly believed that a suction drain, placed intra-articularly reduces the formation of a haemarthrosis and enhances rehabilitation, many studies have yielded controversial results regarding its use."