

**Date: 31<sup>st</sup> March 2021**

**Editor in Chief**

**World Journal of Gastrointestinal Surgery**

**Re: Manuscript NO: 63149**

**Title: Perioperative steroid administration reduces overall complications in patients undergoing liver resection: A meta-analysis**

Many thanks for peer review of our manuscript. We agree to the transfer of our manuscript to the World Journal of Gastrointestinal Surgery. Please find the response to reviewer comments and also necessary edits in manuscript with track changes.

**Reviewer #1:** Manuscript Title: ‘Perioperative steroid administration reduces overall complications in patients undergoing liver resection: A meta-analysis’ This meta-analysis compares eight RCTs including 590 patients, and the findings states that perioperative steroid administration is associated with significant reduction in postoperative complications, with improvement in biochemical and inflammatory markers, also. The manuscript adequately describes the background, present status and significance of the subject, and methods (data analysis, and clinical trials) in adequate detail. The authors interpret the findings adequately and appropriately, highlighting the key points concisely, and clearly, pointing their relevance to the literature stated, and the discussion is accurate and does it discuss the paper’s relevance to clinical practice. The figures, diagrams and tables are of good quality and appropriately illustrative, and most of all, the manuscript meets the requirements of biostatistics (PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis).

**Response #1:** Many thanks for appreciating our work and no edits are as such made.

**Reviewer #2:** The paper by Hao-Han Hai entitled ‘Perioperative steroid administration reduces overall complications in patients undergoing liver resection: A meta-analysis’ is a meta-analysis that investigated the association between the administration of perioperative steroids and the occurrence of postoperative complications in patients undergoing hepatectomy. This study appropriately selected eight randomized controlled trials (RCTs) involving 590 patients using the PRISMA diagram, and the selection criteria were described. The results showed that the overall complications were significantly reduced by perioperative steroid administration, and outcomes such as improvement in serum bilirubin, CRP, and IL-6 levels were also noted. Generally, hepatectomy is a highly

invasive procedure, and the effectiveness of perioperative steroid administration to postoperative course of hepatectomy is of essential concern to surgeons. Although this meta-analysis is a clinically important study, some issues need to be addressed.

Comment 1: There are many types and methods of steroid administration, and the dosage and timing of administration for each agent have been provided in this study. However, there is a difference in the potencies of hydrocortisone, methylprednisolone, and dexamethasone. Methylprednisolone and dexamethasone are reported to contain approximately 5 and 20 times potent respectively compares with hydrocortisone. We need to consider carefully to address these studies as similar RCTs, and please discuss this point.

Response 1: Thank you for the comment. Indeed, different steroids with varied potency will have an impact on outcomes. We are mindful of this and have generated some discussion too. In the method section under the heading ‘Use of Steroids’ we have stated - We elected not to exclude the study by Hayashi et al. merely due to difference in choice of steroid as the dose and duration were appropriately modified for equipotency for efficacy. To ensure that this aspect deserves the emphasis, we have added the following in the discussion section:

[“This is especially so as the studies included have different methods of steroids administration, using steroids of different potency and dosage.”](#)

Comment 2: As per the selection criteria for RCTs, the papers not written in English or Mandarin were excluded. However, it should be noted that the adoption of RCT only written by Mandarin would not be biased against only English RCTs.

Response 2: Thank you for the comment. We agree that any language (not only Mandarin) publications would amount to bias if search is restricted to English language. Since, our study team has a member who is familiar with Mandarin, it was agreed that we would include both English as well as Mandarin language publications. Thus, exclusion of other languages was agreed based on study team abilities. We have stated this in the section on study selection criterion – “The co-author (APY) is a native Mandarin language speaker and translated the Mandarin report into English.” The inclusion of the paper in Mandarin (Zi et al.) contributed 79 patients, corresponding to 13.4% of the overall cohort.

Comment 3: PONV has been listed in the first part in the Discussion, but PONV is associated with anesthesiology and the mechanism of the steroid is considered to be different. Please explain in the Discussion if this information is required.

Response 3: Thank you for your comment. PONV is multifactorial and has diverse pathophysiology. General anesthesia indeed contributes to PONV. There are reports that steroids reduce incidences of PONV by varied actions, and helps in early discharge as well as in day case surgery planning. In a systematic review including 17 clinical trials, Karanicolas PJ et al. reported that prophylactic dexamethasone decreases the incidence of PONV after laparoscopic cholecystectomy relative to placebo (RR 0.55, 95% CI, 0.44-0.67) (Citation 21 in our study). We have

taken your comment as advised. Authors observed both dose dependent as well as independent effect. The included RCTs also included PONV as a parameter and thus, we have reported in our meta-analysis. The Discussion is edited as follows:

[Recently, the anti-inflammatory and immune-modulating benefits of steroids are exploited to reduce postoperative nausea and vomiting \(PONV\) and pain. PONV is associated with general anesthesia implicated in causing aspiration pneumonia, wound complications, psychological distress, and prolonged hospital length of stay; and thus, perioperative steroid use remains attractive to improve clinical outcomes.](#)

**Comment 4** Please provide the detailed information of complications including their extent by using the Clavien-Dindo classification if possible.

**Response 4:** Thank you for the comment. We agree that a unified system (like Clavien-Dindo) of classifying morbidity is very good for reporting clinical data. Out of 8 included studies, only one study reported (Donadon et al., 2016) complications by Clavien-Dindo classification. Thus, our meta-analysis is unable to report outcomes using the Clavien-Dindo system. We have put this in the limitation section with a suggestion that future studies should report morbidity using a standardized classification system:

[“Only one study reported morbidity outcomes using an established classification system, thus limiting the clinical utility of morbidity data<sup>\[13\]</sup>.”](#)

**Comment 5:** The article does not provide the information of any steroid-induced adverse events. It will be of interest to the readers. Although most steroid-induced infections are likely to be related to surgery, the extent of adverse events due to steroid-induced hyperglycemia and other factors should be provided if possible.

**Response 5:** Thank you for the comment. The studies included did not separately specify complications attributable to steroid administration. Thus, we are unable to report on this.

**Comment 6:** Please describe the statistical methods for each complication in the Methods section.

**Response 6:** Thank you for the comment. For greater clarity and detail, the Methods section has been edited to include:

[“Odds ratios \(OR\) and 95% confidence intervals \(CI\) were calculated using the Cochrane Mantel Haenszel method test based on the random effects model or dichotomous data, while continuous data were calculated using weighted mean differences and 95% CI.”](#)

**Comment 7** In Table 3, there are some reports without information of the control protocol, and please provide the information if available.

Response 7: Thank you for the comment. All the available information on control protocol were provided. Out of the eight studies, four studies did not include information on the control protocol (Hayashi et al., 2011, Muratore et al., 2003, Pulitano et al., 2007, Yamashita et al., 2001)

**Reviewer #3:** Interesting piece of investigation.

Comment #3: Thank you for kind comments.

**Scientific Editor:**

Comment #1: The “Author Contributions” section is missing. Please provide the author contributions.

Response #1: Thank you for the comment. We have added the authors’ contributions section as requested.

Comment #2: The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response #2: Thank you for the comment. We have provided the figures via a powerpoint document (63149-Figures.pptx) and tables on a word document (63149-Tables.docx) as requested.

Comment #3: PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout

Response #3: Thank you for the comment. We have revised our references accordingly and added the Pubmed numbers and DOI citations numbers, where available.

Comment #4: The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.

Response #4: Thank you for the comment. We have added the article highlights section at the end of the main text as requested.

Thank you.

**Yours Sincerely,**

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