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And on behalf of the *World Journal of Gastroenterology* Editorial Team



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: **6658_review_revised_20131225.doc**). We have included our point-by-point responses and attached the revised manuscript as requested in your earlier correspondence.

Title: Propofol sedation during endoscopic treatment for early gastric cancer compared to midazolam

Author: Shinsuke Kiriyaama, Hiroshi Naitoh, Hiroyuki Kuwano

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6658

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated

2. Revision has been made according to the suggestions of the reviewer

Reviewed by 00506211

I reviewed the article "Sedation management with high safety and satisfaction level during endoscopic treatment for early gastric cancer" The author is reviewing the safe method of conscious sedation during endoscopic procedures.

- The author does not propose a clear plan of reviewing different gastric endoscopic treatments and the customized anesthesia protocol - based on length of surgery, patient ASA classification and access to qualified personnel. - No clear primary objective and end points specified in the introductory part, motivating the need of this review. - The conclusion should be more elaborated based on his references.

A) Based on the comments of the reviewers, we have reviewed 12 additional articles and 7 more comparison studies. We have therefore revised the manuscript and added the following:

Selection methods for literature to be reviewed

In order to select the most appropriate articles to review, we searched PubMed for articles using the search terms "gastric cancer," "endoscopy," "treatment," and "sedation". Research articles on hypopharyngeal cancer, submucosal tumors, screen endoscopy, metallic stenting, and gastronomy procedure were excluded in this review. In total, 19 articles were selected for evaluation on this topic.

Of these, 7 comparison studies published after 2010 showed that propofol alone, propofol combined, or general anesthesia had more useful possibilities than midazolam (Table 1).

In the 12 studies concerning endoscopic treatment of gastric cancer that are not comparative studies on sedation, propofol sedation was used in 9 articles (75%) (Table 2), and the use of midazolam alone was reported in 3 articles (50%) prior to 2009; however, this number decreased after 2010. Therefore, the literature suggests that propofol is most commonly used for sedation during endoscopic treatment for gastric cancer.

(From Page 4, line22 to Page 5, line 9)

Minor revisions:

- To explain "piecemeal" surgical significance.

A) To further clarify the term "piecemeal," the statement has been changed to:

"However, EMR is associated with a relatively high risk of local recurrence when performed

piecemeal (in multiple flagments).” (From Page 5, line20 to Page 5, line 21)

- To explain the difference between “safe sedation” vs. “safer sedation” when the author conclude that “Further evaluation is necessary for safer sedation management.”

A) Upon consideration of the reviewers comment, this sentence has been changed to reduce confusion to now read:

“Safe and curative gastric endoscopic treatments are more commonly performed under sedation. Propofol has been increasingly used as the preferred sedation drug and is both safe and useful. However, further evaluation is necessary for safe sedation management.”

(From Page 10, line9 to Page 10, line 12)

- The manuscript needs a general review of paragraphs construction – consistency, point of view, structure.

A) Based on the comment by the reviewer, we have reviewed an additional 12 articles and 7 comparison studies and have included their findings in the manuscript.

Reviewed by 02542021

Overall, general points were well reviewed in this article. There were some points of consideration.

1. The conclusion or primary objective is vague. If author’s main objective is the merit of propofol, the review should give enough reasons of the merits of propofol with introducing comparative studies. Comparisons of various methods for sedation in detail are more attractive for readers than long description of sedation procedure of propofol. In addition, the overall structure of manuscript for drawing the conclusion is weak. The abstract and conclusion need to be revised for clear objective.

A) Both the Abstract and Conclusion have been revised based on this comment. We have also reviewed an additional 12 articles and 7 comparison studies and have included an interpretation of these findings in the manuscript.

2. For reader’s easy understandings, some additive methods such as tables or figures would be helpful.

A) We have included 2 tables that summarize the information.

3. The explanation of endoscopic treatment and procedures seems to be long.

A) Based on this comment, we have reduced the length of this section.

4. The evidence for improvement of patient satisfaction or quality of life when using propofol is lack. Related reference or objective evidence should be suggested.

A) To address this comment, we have included a review of an additional 12 articles and 7 comparison studies.

5. Because the benefit of propofol during ERCP had been reported previously in some reports, the conclusion needs to be revised.

A) We have removed this statement based on this suggestion.

Reviewed by 02519158

Review of article: “Sedation management with high safety and satisfaction level during endoscopic treatment of early gastric cancer” Overall it is interesting topic, worthy of publication in World Journal of Gastroenterology. Sedation and pain management in endoscopic treatment make considerable problems in practice of surgeons and anesthesiologists in gastroenterology. However, I would like to make some comments on the following points:

1) The title of article does not seem to correspond to the subject of paper. The sedation management of gastric cancer may be performed by many anesthetics (fentanyl, dexmedetomidine hydrochloride) while in article only management by propofol and midazolam is presented. It will be better if authors compare propofol management with use of any other anesthetics or make the title more precise e.g. “Sedation (...) with use of propofol comparing to midazolam”.

A) We have revised the title to better reflect the content of the article.

2) The chapters “Endoscopic treatment (...)” and “The difference (...)” could be shorten and combine with each other whereas information on pharmacological sedation should be described more thoroughly, because this is main subject of this article. It is also necessary to clearly present the risk/benefit ratio of preferred management methods if it is a method “with high safety and satisfaction level” as was claimed by the authors.

A) Based on this comment, we have modified the content and structure of these sections.

3) The chapter “Indication of sedation” could be combined with chapter “need for sedation” or generally removed. I am not sure it adds anything to the paper.

A) We have revised and combined these sections, as suggested.

4) I suggest to supplement this article in published recently in literature relevant to the topic, such as:

a) Adamina M. et al. Contemporary perioperative care strategies. British Journal of Surgery 2013; 100: 38–54

b) Triantafillidis JK et al. Sedation in gastrointestinal endoscopy: current issues. World J Gastroenterol 2013; 19: 463–481

c) Tavaré AN et al. Cancer recurrence after surgery: direct and indirect effects of anesthetic agents. Int J Cancer 2012; 130: 1237–1250

d) Rong Q-H et al. Feasibility and safety of endoscopic submucosal dissection of esophageal or gastric carcinomas under general anesthesia. Med Princ Pract 2013; 22: 280–284

e) Sasaki T et al. Recommended sedation and intraprocedural monitoring for gastric endoscopic submucosal dissection. Digestive Endoscopy 2013; 25 (Suppl. 1): 79–85

f) Chun SY et al. Safety and efficacy of deep sedation with propofol alone or combined with midazolam administrated by nonanesthesiologist for gastric endoscopic submucosal dissection. Gut and Liver, 2012; 6: 464–470

- g) Wang D et al. The use of propofol as a sedative agent in gastrointestinal endoscopy: a meta-analysis. PLOS One 2013; 8: e53311
- h) Zuo X-L et al. Propofol vs midazolam plus fentanyl for upper gastrointestinal endomicroscopy: a randomized trial. World J Gastroenterol 2012; 18: 1814-1821
- i) Takimoto K et al. Sedation with dexmedetomidine hydrochloride during endoscopic submucosal dissection of gastric cancer. Digestive Endoscopy 2011; 23: 176–181
- j) Zhou L?W et al. Effect of tramadol on perioperative immune function in patients undergoing gastric cancer surgeries. Anesthesia: Essays and Researches 2013; 7: 54-57

A) We have reviewed an additional 12 articles and 7 comparison studies and have included this information in the manuscript along with the references.

5) The article contains a few typographical and grammar mistakes. For examples, on the 3 line 4 at the top should be “management” and not “managemant”. According to me, it will be better to write in the title “management of high safety” instead of “management with high safety”. It would be a good idea to have the paper corrected by a native speaking specialist. I recommend this article for publication in World Journal of Gastroenterology after adequate corrections according to comments above.

A) We have obtained the services of Editage to help improve the language and grammar of our manuscript.

3. References and typesetting were corrected