ANSWERING REVIEWERS

November 12, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14009-review.doc).

Title: A comparison of efficacy and safety of sedation between dexmedetomidine-remifentanil and propofol-remifentanil during endoscopic submucosal dissection

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

Reviewer 1

In other ways good designed and clinically important study I find a serious problem that can bias all the conclusions. Authors must clarify the statement: Additional propofol requirements were 16.9 ± 10.3 mg in 8 patients of DR group and 13.3 ± 5.8 mg in 3 patients of PR group (P = 0.081) (Table 6). Is it true that also patients in DR group received propofol or is this a mistake?

Answer)

Thank you for your critics. I am sorry to make you confused about our sedation protocols. Additional propofol with a small dose of 10 mg was administered in both groups as rescue sedative only when MOAA/S scale did not reach to 4-5 or the patients themselves wanted to be sedated deeper. Therefore the frequencies and doses of additional propofol use were also considered as variables to compare the sedation efficacies. P values of frequency and dose were described in text as following; Eight and 3 patients in the DR and PR groups, respectively, required propofol as a rescue sedative (P = 0.083) at 16.9 ± 10.3 mg and 13.3 ± 5.8 mg (P=0.596), respectively (Table 6).

Reviewer 2

Thank you for your critics and answer them point by point as follows.

① Patients were asked about their satisfaction with the procedure (very good, good, bearable, and unbearable) before discharge. How much time after procedure?

Answer)

Patients were asked about their satisfaction with procedure just before discharged from PACU, when they completely restored consciousness.

② Were there any differences between the results regarding adverse respiratory events?

Answer)

As these findings were noted in the result section, there were no apnea and oxygen desaturation events during our study periods in both groups. However, unfortunately, we could not evaluate the degree of hypoventilation because we did not measure $PaCO_2$. This was added in discussion section.

③ What is the preferred antidote for dexmedetomidine in case of severe adverse events?
Answer)
There seem to be no available antidote for dexmedetomidine that can reverse the excessive sedation or respiratory depression so far. However, we prepared ephedrine (against hypotension), atropine (against bradycardia), nicardipine (against hypertension), or esmolol (against tachycardia and hypertension) for adverse hemodynamic events.

④ The authors should spend time to discuss the potential cost-effectiveness of dexmedetomidine-remifentanil over propofol-remifentanil sedation. Further prospective multicentre randomized studies are needed to establish the clear-cut clinical advantage of dexmedetomidine-remifentanil over propofol-remifentanil sedation.
Answer)
As you pointed out, comparing cost-effectiveness between dexmedetomidine-remifentanil and propofol-remifentanil sedation can be worthful. However, it is not only difficult but also complicated because the insurance policy differs from country to country. So, we did not consider the cost-effectiveness as an object of our study. We partially described it in discussion section.

Reviewer 3
① Number of patients too few.
Answer)
We agree with your comment. Although we adopted the sample size from the previous study (reference 18. Eberl S, Preckel B, Bergman JJ, Hollmann MW. Safety and effectiveness using dexmedetomidine versus propofol TCI sedation during oesophagus interventions: a randomized trial. *BMC Gastroenterol* 2013; **13**: 176), a further study with large subjects may need to concrete our results. This shortcoming was described in discussion.

② Propofol given in both groups for additional effect.
Answer)
Thank you for your critics. I am sorry to make you confused about our sedation protocols. Additional propofol with a small dose of 10 mg was administered in both groups as rescue sedative only when MOAA/S scale did not reach to 4-5 or the patients themselves wanted to be sedated deeper. Therefore the frequencies and doses of additional propofol use were also considered as variables to compare the sedation efficacies. P values of frequency and dose were described in text as following; Eight and 3 patients in the DR and PR groups, respectively, required propofol as a rescue sedative (P = 0.083) at 16.9 ± 10.3 mg and 13.3 ± 5.8 mg (P=0.596), respectively (Table 6).

③ Anti-motility drug (Butylscopolamine) was used to suppress motility and so comparison of two group in forms of motility becomes inappropriate.
Answer)
I apologize to make you confused with inadequate explanation. The grade of gastric motility was assessed at the time after the scope had reached to stomach and before butylscopolamine was administered. This description was added in the method section.
Regarding butylscopolamine, it was administered in both groups only as rescue anti-motility agent according to the requirement of endoscopists during the procedure, especially epinephrine injection or submucosal dissection. Therefore we think the frequencies and doses of butypscolamine use as variables to compare the procedural efficacies.

④ The authors concluded to say DR group is better than PR group due to reduced mobility in former. However this study shows no effect of this in forms of efficacy or complications. PR group was better in form do ease of endoscopy which is a clinical parameter.
Answer)
Thank you for your important critics. We changed our conclusion as following meaning; PR sedation protocol could be substituted for DR sedation protocol.

⑤ MOAA/S assessment in table 1 should have a reference. References are not appropriately mentioned. Particularly abbreviations used for journal name are mostly incorrect.
Answer)
We added the reference of Observer's Assessment of Alertness/Sedation Scale as your suggestion.

Reviewer 4
① Both dexmedetomidine and propofol have come to use recently. So you should compare dexmedetomidine with ordinal sedative, such as midazolam.
Answer)
We appreciate your suggestion. However, midazolam is not recommended in our institute any more because of inconsistent sedation and delayed recovery. We hope to compare the efficacy among propofol, dexmedetomidine and midazolam in future.

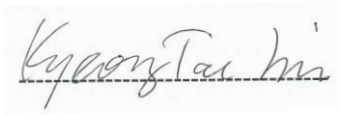
② Dexmedetomidine reduces the gastric motility, but butylscopolamine can also reduce the gastric motility. Actually, you use butylscopolamine during ESD procedure. How do you explain the participation of dexmedetomidine and propofol solely?
Answer)
I apologize to make you confused with inadequate explanation. The grade of gastric motility was assessed at the time after the scope had reached to stomach and before butylscopolamine was administered. Therefore, we think the participation of dexmedetomidine and propofol was evaluated with the grade of gastric motility. Regarding butylscopolamine, it was administered in both groups only as rescue to facilitate the ESD procedure by the request of endoscopist. Therefore we considered the frequencies and doses of butypscolamine use as variables for the procedural efficacies.

③ The basis of conclusion, that dexmedetomidine is effective and safe during ESD, is very weak.
Answer)
We agree with you and thank you for your important critics. We changed our conclusion as following meaning; PR sedation protocol could be substituted for DR sedation protocol.

④ If you can, you should point out the economic efficiency of dexmedetomidine.
Answer)
As you pointed out, comparing cost-effectiveness between dexmedetomidine-remifentanil and propofol-remifentanil sedation can be worthful. However, it is not only difficult but also complicated because the insurance policy differs from country to country. So, we did not consider the cost-effectiveness as an object of our study. We partially described it in discussion section.

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

Sincerely yours,



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