OPEN PEER REVIEW

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Peer Review

Anesthesiology and Pain Medicine
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Peer Review Report for "Effect of Remifentanil on Postoperative Vomiting After Strabismus Surgery in Preschool Children: A Prospective Randomized Controlled Trial"

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Review Timeline:

Submit Date:	26 Dec 2021
Revised Date:	19 Feb 2022
Accepted Date:	19 Feb 2022

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE : EIC

22 Jan 2022

Major Revision

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

##Reviewer 1:

[Q1] The authors aim to evaluate the dose dependent effect of remifentanil on POV. The bolus doses are different but maintenance are equal. Regarding the short elimination half-life of remifentanil, its effect on POV may eliminate at the end of surgery. Please clarify this.

[R] Thank you for your comment. In fact, Group H and Group L had administered remifentanil infusion, but, Group C did not receive any dose of remifentanil. We are very sorry about mistakenly description in method section and revised the method section. The bolus doses are different between Group H and Group L, but maintenance are equal. Total amount of Remifentanil was 114.4 μg (IQR 101.8-137.4) and 124.9 μg (104.3 – 198.0) in Group L and Group H, respectively. We aimed to evaluate whether the different dose of remifentanil influences the incidence of POV in children undergoing strabismus surgery (high risk surgery of POV).

[Q2] It is well known that fentanyl which is used in all patient groups can cause POV. This must be considered in the discussion.

[R] Thank you for your comment. We described in second paragraph of the discussion.

[Q3] Adding figures can effectively describe the research finding.

[R] Thank you for your comment. We think that Table 3 is a primary outcome of this study. We agreed with your opinion about figures, but we are wondering whether it would be better to show the table as a figure. If you recommend adding a figure, we will insert a new figure. Thank you.

##Reviewer 2

[Q] Dear Editor in Chief

There is lack of Novelty, due to several similar published papers.

Recommend to summarize the article, and change its' style to Brief Report.

For anesthesia management in strabismus patients it is better to avoid volatile agents due to increase risk of Malignant Hyperthermia.

Suggest to author for considering below references:

Oriby ME, Elrashidy A. Comparative Effects of Total Intravenous Anesthesia with Propofol and Remifentanil Versus Inhalational Sevoflurane with Dexmedetomidine on Emergence Delirium in Children Undergoing Strabismus Surgery. Anesth Pain Med. 2021;11(1):e109048.

Sedigh Maroufi S, Moradimajd P, Moosavi SAA, Imani F, Samaee H, et al. Dose Ginger Have Preventative Effects on PONV-Related Eye Surgery? A Clinical Trial. Anesth Pain Med. 2019;9(5):e92072.

Sirimontakan T, Artprom N, Anantasit N. Efficacy and Safety of Pediatric Procedural Sedation Outside the Operating Room. Anesth Pain Med. 2020;10(4):e106493.

Shafa A, Aledavud H, Shetabi H, Shahhosseini S. Effects of the Two Doses of Dexmedetomidine on Sedation, Agitation, and Bleeding During Pediatric Adenotonsillectomy. Anesth Pain Med. 2021;11(5):e118424.

Sincerely yours

[R] Thank you for your comment. We agreed with your opinion, and described “the use of TIVA may result in a low incidence of POV and decrease risk of malignant hyperthermia. However, we did not use TIVA because there is no commercially available flexible open TCI pump in our hospital”. In limitation section.

And, we added two new references that you recommended.

##Reviewer 3:

[Q1] The keywords should be revised according to the title. "Anesthesia ","pediatric "and "nausea "should be deleted and "strabismus surgery "and "children " should be added.

[R] Thank you for your comment. We revised the keywords as your recommendation.

[Q2] Type of study should be added in title.

[R] Thank you for your comment. We added the type of study (a prospective randomized controlled trial) in title.; “Effect of remifentanil on postoperative vomiting after strabismus surgery in preschool children: a prospective randomized controlled trial”

[Q3] What's your novelty? Explain more.

[R] Remifentanil has a context-sensitive half-life of 3 to 4 minutes. There are several studies about comparing remifentanil and other opioids (fentanyl, alfentanil etc), but we aimed to evaluate whether the different dose of remifentanil influences the incidence of POV in children undergoing strabismus surgery (high risk of POV). These effect is unknown.

[Q4] In the abstract, method and results part is too weak and need to be revised.

[R] Thank you for your comment. We revised method and results part in the abstract.

[Q5] You mentioned that remifentanil is short acting opioid, your bolus doses are different and infusion dose is similar. Did you compare 3 groups with bolus difference? Major problem.

[R] Total amount of Remifentanil was 114.4 μg (IQR 101.8-137.4) and 124.9 μg (104.3 – 198.0) in Group L and Group H. Group C did not have any dose of remifentanil. We compared three groups with total dose of remifentanil.

[Q6] In abstract, background and objective part is too long.

[R] Thank you for your comment. We revised background and objective part in abstract.

[Q7] What's your formula for sample size?

[R]

[Q8] Why did you increase bolus doses and didn't increase infusion dose? Major problem.

[R] We did not increase infusion dose because of avoiding remifentanil induced tolerance and hyperalgesia problems. Intra-operative remifentanil infusion rates of above 0.25mcg/kg/min are associated with higher tolerance. And infusion rates greater than 0.2mcg/kg/min are characterised by lower pain thresholds (Anaesthesia.2016;71:1347-1362).

[Q9] In the stem of the manuscript, when did 3 groups receive bolus doses of remifentanil?

[R] Group H and Group L received remifentanil after endotracheal intubation. Group C did not have any dose of remifentanil.

[Q10] When did you stop remifentanil infusion?

[R] We stopped remifentanil infusion after elimination of the eyelid speculum. As more clarifying the meanings, we revised “after skin closure” to “after stopping remifentanil

infusion” in method section.

[Q11] What was your program for remifentanil- induced hyperalgesia?

[R] Because we designed to avoid remifentanil-induced hyperalgesia, there was no program for that.

[Q12] Why you didn't change in infusion and change bolus doses?

[R] Intra-operative remifentanil infusion rates of above 0.25mcg/kg/min are associated with higher tolerance. And infusion rates greater than 0.2mcg/kg/min are characterised by lower pain thresholds (Anaesthesia. 2016;71:1347-1362). We did not increase infusion dose because of avoiding tolerance and hyperalgesia problems.

[Q13] Why did you use an opioid for postoperative analgesia and you didn't use of other alternatives for POV?

[R] Emergence agitation as well as POV are common in pediatric strabismus surgery. Therefore, the patients had an intravenous administration of fentanyl for reducing of emergence agitation. Intravenous fentanyl (1 μg/kg) administration before end of surgery reduced agitation from 63.3% to 36.7% after sevoflurane anesthesia in children (Pak J Med Sci. 2014 Sep;30(5):1059-63). And, we did not use other alternatives for POV.

[Q14] The group C didn't receive an opioid for intubation? Explain it.

[R] Thank you for your comment. General anesthesia was induced with intravenous administration of atropine (0.01 mg/kg), lidocaine (1 mg/kg), propofol (2 mg/kg) and rocuronium (0.6mg/kg). Administration of sevoflurane (2-4 vol%) was started immediately after loss of responsiveness to the patients. All three groups did not receive an opioid for intubation. After endotracheal intubation, patients in the Group H and L received an intravenous remifentanil infusion. We revised methods section as your recommendation for more clear meanings.

[Q15] The dose of ketorolac,1mg/kg, as an rescue analgesia is high.

[R] Thank you for your comment. These method is our hospital’s policy. We will try to revise the policy based on your opinion.

[Q16] You used ketorolac and fentanyl for emegence agitation? Explain it.

[R] After stopping remifentanil infusion, fentanyl (1 μg/kg) was intravenously administered to the patients. Intravenous ketorolac (1 mg/kg) was administered to patients who had severe emergence agitation (PAED scale ≥ 10) or severe postoperative pain (FPS score ≥ 5). If emergence agitation in a patient did not subside even after ketorolac had been administered to the patient, 0.5 μg/kg of fentanyl was intravenously administered to the patient.

[Q17] If the patients have no response to fentanyl, what was your next plan?

[R] Almost emergence agitation symptoms are subsided after administration of IV fentanyl (1mcg/kg)-ketorolac (1mg/kg)-fentanyl (0.5mcg/kg) in our hospital.

[Q18] You injected bolus doses of remifentanil after endotracheal intubation?

[R] Yes, we injected bolus doses of remifentanil after endotracheal intubation. We revised the method section to make the meaning more clearly.

[Q19] After OCR, you administered ONLY atropin?

[R] When the oculocardiac reflex (OCR; defined as a 15% decrease in HR as compared to baseline HR) occurred, we requested to stop the surgery and injected intravenous atropine (0.01 mg/kg) if the OCR lasted for more than 5 seconds. We revised the method section to make the meaning more clearly.

[Q20] Duration of operation time has significant difference in groups and this is a significant bias in the study.

[R] Thank you for your comment. Although one operation was not completed, there was a request from the surgeon to open another operating room for rapid surgical time. In this case, there was a delay from the start of anesthesia to the start of the operation. But, duration of remifentanil infusion was not significantly different between three groups.

[Q21] In the stem of the manuscript, results is too weak and need to be revised.

[R] Thank you for your comment. We revised the result section.

[Q22] what's your p- value for PAED and FBS.

[R] Thank you for your comment. We added p value for PAED and FPS in abstract and result section.

[Q23] Whats your scale for POV?

[R] There was no scale for POV in this study. The number of patients who experienced POV (incidence of POV) was primary outcome.

[Q24] Discussion part is too weak and need to be revised completely.

[R] Thank you for your comment. We revised discussion part as your recommendation.

[Q25] You checked PAED and FPS after endotracheal intubation? Explain it.

[R] PAED and FPS were evaluated after endotracheal extubation; 0 (immediately), 20, 40, and 60 min after extubation at the PACU.

Thank you very much for your comment and advice.

With your advice, we will continue to conduct related research.

We think your careful review and comments have improved our manuscript.

Thank you again.

Sincerely

OPEN PEER REVIEW

Revision (1)

REFEREE : EIC

8 Feb 2022

Minor Revision

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

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You can read the authors' responses to the reviewers' comments in the next page.

Dear reviewers

Thank you for your comment. As your recommendation, we summarized all article, and changed research article to brief report.

Thanks again.

Sincerely

Ki Hwa Lee

OPEN PEER REVIEW

Revision (2)

Farnad Imani : EIC

19 Feb 2022

Dear Authors,

We are pleased to inform you that your manuscript has been accepted for publication. The reviewers found your work to be valuable, scientifically sound, and a meaningful contribution to the field. We appreciate the effort and dedication you invested in this study, and we thank you for choosing our journal to share your research. Congratulations on this achievement, and we look forward to your future submissions.