Author's response to reviews

Title: Appropriate dose of dexmedetomidine for prevention of emergence agitation after desflurane anesthesia for tonsillectomy or adenoidectomy in children: up and down sequential allocation

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Author's response to reviews: see over
Reviewer 2

Major concerns

1. The patients were enrolled until obtaining six crossover pairs according to the Dixon’s sequential allocation method. We did not need to perform power analysis for calculate sample size.

   (1) Advances in and Limitations of Up-and-down Methodology, Anesthesiology 2007; 107:144–52


   (3) Targeting smooth emergence: the effect site concentration of remifentanil for preventing cough during emergence during propofol–remifentanilaesthesia for thyroid surgery

2. I understand your opinion. For various reasons such as policy of government and clinical experiences in our center, anesthetic regimen of our center can be seen as unfamiliar for some reviewers.

   In Korea, bolus injection of propofol in children is prohibited by Korean FDA. Because the range of age in present study is 2-12 years old, we use thiopental for anesthetic induction instead of propofol in present study.

   As you said, atropine is not contraindication. In some text book (Smith’s Anesthesia for Infants and Children, 8th Edition, p796) atropine may be given for anticholinergic effect in children undergoing tonsillectomy during anesthetic induction.

   Though we gave thiopental for anesthetic induction because children are nervous when their parents leave them, sedation is often uncertain in some children through anesthetic induction period. Thus we use sevoflurane as induction agent.

3. Thank you for your comment. The agitation was defined as like previous studies (same 5 point scale, score ≥ 4 define agitation), which show that dexmedetomidine can prevent emergence agitation in children.(1-2)

   (1) Pediatric Anesthesia 2006 16:748-753

   (2) Pediatric Anesthesia 2005 15:1098-1104

   Dexmedetomidine has analgesic effect. We thought dexmedetomidine may be a part of minimal analgesic regimen. In previous reports to investigate the analgesic effect of
dexmedetomidine on post-operative pain, dexmedetomidine has shown analgesic effect as potent as morphine or reduce post-operative opioid requirement. In one of these previous study postoperative severe pain incidence after tonsillectomy was 53% in placebo group receiving acetaminophen, which is higher than that (almost 25%, 5/21 patients) of present study. As your advice I add these concerns in discussion section.

(3) Pediatric anesthesia 23 (2013) 446-452
(4) Anesth Analg 2010;111:490-5
(5) Pediatric Anesthesia 2005 15:762-766

4. I totally agree with you. We set age range based on the definition of 'child'. Though the choice of age group is 2-12 years, actual age range of patients included in our study is 3-7 years. We think influence of age in present study might be not significant considering the age range of previous study (3-10 years) showing high incidence of EA in preschool children by Aono et al. There are several studies about EA to include preschool and school children together though they are randomized controlled trials. However the range of age should have been more narrow. I add your opinion in the limitation section.

1) Pediatric Anesthesia 2006 16:748-753
3) Anesth Analg 2010;111:1004-10

5. I understand your concern. In children response to the premedication is too diverse to predict. As you guess, we thought no premedication can reduce influence of this unpredictable effect of premedication. Children in our center stay with their parents in day-operation center and they receive thiopental when their parents leave them. Accepting your opinion, I described possibility the change of dexmedetomine dosage to prevent EA if children receive a premedication.

6. Thank you for your comment. Unfortunately we did not record the consumption of desflurane. Instead, we add mean endtidal desflurane concentration during anesthesia period (Table 2)

7. I understand your opinion. We also knew there are some scales to determine agitation in children. The aim of our study was evaluate the dose of dexmedetomidine to prevent agitation in children. Dexmedetomidine has proven it's preventive effect on agitation in several studies performed in children. These studies used same agitation scale with our study though they were published after Sikich N, et al validated PAED. The dose of dexmedetomidine (0.5 mcg/kg) administered in first child of our study was based on the results of these studies. We thought using same scale to determine agitation may be proper to design our study and to compare our result with those of previous studies. However, as
your advice, the definition of EA in present study could have been more reliable if we use additional EA scale together. I add limitation of using single EA scale in present study.

1) Pediatric Anesthesia 2006 16:748-753
2) Pediatric Anesthesia 2005 15:1098-1104

Thank you for all your comment. We agree with your concerns and describe them in discussion and limitation section. I modified the conclusion of present study as your comment. I marked revised part of manuscript in red color.

Minor concerns:

- Reference 7: I replaced reference 7 with other study to report effect of dexmedetomidine to prevent EA.
- Table 1: I corrected score 4 ‘consolable crying’ as your comment.
- Discussion (first paragraph, line 5): I rewrote the sentence you mentioned clear.
- Discussion (second paragraph): First sentence was revised.
- Discussion (fourth paragraph): Fourth paragraph of discussion was rewritten to focus on the concerns related with EA scale used in present study.
Reviewer 3

Thank you very much for all your comments and advices. I did my best to fulfill your requests. However you may be unsatisfied with revised manuscript and cover letter. Please let me know if you still have any concern unsolved.

The patients were enrolled until obtaining six crossover pairs according to the Dixon’s sequential allocation method. We did not need to perform power analysis for calculate sample size. This study is not randomized comparison clinical research.

(1) Advances in and Limitations of Up-and-down Methodology, Anesthesiology 2007; 107:144–52


(3) Targeting smooth emergence: the effect site concentration of remifentanil for preventing cough during emergence during propofol–remifentanil anaesthesia for thyroid surgery

We offered information about the study (purpose of study, what procedures and medications children will receive, possible benefits and complications of study, the right of subject, etc), and possible complications caused by dexmedetomidine administration including hemodynamic (bradycardia, hypotension), prolonged sedation, delayed recovery from anesthesia and allergic reaction. Information about risk of this study was explained with written informed consent, which was approved by our institutional review board.

As your comment, I reorganized the results section in manuscript to document over what has been done.

From arrival at the operating room to discharge from post-anesthetic care unit, the children were monitored with electrocardiography, pulse oximetry, capnography, and noninvasive arterial blood pressure at 2.5 min interval. As you mentioned, what we concerned is to evaluate the event of complication of dexmedetomidine (bradycardia or hypotension). In the results section, we added whether bradycardia or hypotension occurred during perioperative period.
We rewrote the introduction in the manuscript. The reason of switching volatile agent in present study was described. I hope introduction would explain the aim of this study more clearly.

As your comment, I revised the limitation section in discussion.