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Improving External Validity May Jeopardize Internal Validity

To the Editor:

I read with interest the recently published article by Ramgolam *et al.*[1] that sought to find the safer way to induce anesthesia in children at risk of developing perioperative respiratory complications. I would like to congratulate the authors for their tenacity to complete the study despite the obstacles in the recruitment of the staff and patients. However, I have few concerns regarding the current study by Ramgolam *et al.*

To preserve internal validity of controlled trials and eliminate confounders, all participants in each group should receive the same treatment, and all the groups should be treated equally apart from the intervention.[2] Unfortunately, this was violated multiple times in the current study by Ramgolam *et al.* The cause of this violation is not clear. It might be an attempt to make the setting more natural to improve the external validity, or it might be because of the recruitment of new staff to complete the study. For example, a drop of oxygen saturation less than 95% was one of the outcomes; however, the fraction of inspired oxygen was variable in the inhalational group, nitrous oxide was used in half of the patients in the inhalational group, and preoxygenation was not routine in the intravenous group. Another example was that anesthesiologists were free to administer propofol in the inhalational group. Forty-nine percent of patients in the inhalational group received propofol in a dosage that is roughly equal to one third of the dose of propofol in the intravenous group. The rationale for administering propofol was not mentioned. Propofol might be administered because of the fear of, or the actual, light anesthesia in the inhalational group. This light anesthesia in the inhalational group and not the inhalational induction may be the cause of the perioperative respiratory adverse events. Patient who received propofol in the inhalational group (with possible light anesthesia) had more perioperative respiratory adverse events (49%) compared with those who did not receive propofol (39%). Although the *post hoc* analysis demonstrated that this difference was not statistically significant, this statistical insignificance may be unreliable because the subgroup analysis was underpowered. The current study by Ramgolam *et al.* was powered to determine the difference in the incidence of perioperative respiratory adverse events between children receiving an inhalational induction and an intravenous induction. For comparison of subgroups of the same size and with the same power as the overall effect, the sample sizes should be inflated fourfold.[3] It would be more appropriate if a specific minimum alveolar concentration value was targeted that was equipotent to the dose of propofol given in the intravenous group. Also, targeting a bispectral index value might be used to ensure equal depth of anesthesia in all participants.

Ramgolam *et al.* suggested that the combination of sevoflurane and nitrous oxide induces an inflammatory response in the airway, leading to the higher rate of perioperative respiratory adverse events observed in the inhalational group. First, the respiratory adverse events observed during induction develop within seconds or minutes during induction, while the mechanism proposed needs hours to develop as occurred in the study by Kumakura *et al.*[4] Second, the proposed mechanism tried to explain the development of perioperative respiratory adverse events in patients who received sevoflurane and nitrous oxide (about half of the patient in the inhalational group). However, the proposed mechanism failed to explain the development of adverse events in the remaining half who received sevoflurane and air. Surprisingly, patients who revived sevoflurane and air are supposed to have an antiinflammatory response according to the study by Kumakura *et al.*

Competing Interests

The author declares no competing interests.

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Is a Single Dose of Propofol Good Enough to Prevent Respiratory Complications beyond the Induction Phase?

To the Editor:

Ramgolam *et al*. reported that IV propofol, compared to sevoflurane induction, had protective effect against perioperative respiratory adverse events in high-risk children.[1] The investigators also calculated the relative risk for perioperative respiratory adverse events adjusted for age, sex, American Society of Anesthesiologists Physical Status, and weight. However, we feel that other identified risk factors for perioperative respiratory adverse events, which include history of prematurity,[2] obstructive sleep apnea,[3] attempts at laryngeal mask airway insertion,[4] and awake *versus* deep removal of laryngeal mask airway,[4] were not mentioned.

Regarding the nonopioid analgesia, the children had received either regional or local analgesia. However, it is not clear whether the term "regional analgesia" means caudal analgesia or peripheral nerve blocks. The reason for highlighting this issue is that caudal analgesia has been reported to reduce the incidence of laryngospasm, although the mechanism is not clearly elucidated.[5] Likewise, the authors have emphasized that the choice of opioid will have no impact on perioperative respiratory adverse events. However, it is evident that IV fentanyl is associated with coughing, the reported incidence of which is 46 to 60% in children.[6] Compared to other opioids, morphine releases significant amounts of histamine, enough to trigger bronchospasm. Therefore, it might not be wise to use morphine in a child with hyperreactive airways when better options are available. It would be interesting to see the results if the analgesia is also considered as one of the independent variables in their analysis.

The maintenance of anesthesia was done with sevoflurane in both groups. The investigators stated that the induction dose of propofol also protected against postoperative unwanted respiratory complications, even when sevoflurane was used in the maintenance phase. Does the protective effect of a single dose of propofol last beyond the induction period? If so, we would be interested to know whether there is an interaction effect between these two agents. From a previous large observational study, it is clear that propofol is superior in preventing perioperative respiratory adverse events to sevoflurane when used for maintenance.[4] Future randomized clinical trials are needed to investigate the beneficial effect of propofol when used for both induction and maintenance of anesthesia in children with high risk for perioperative respiratory adverse events.

The investigators are to be applauded for conducting this pragmatic randomized clinical trial, which has a genuine external validity and is applicable in clinical practice.

Competing Interests

The authors declare no competing interests.

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