Other Factors Affect the Occurrence of Perioperative Respiratory Adverse Events

To the Editor:

With great interest, we read the article by Ramgolam *et al.*, which reports inhalational *versus* IV induction of anesthesia in children with a high risk of perioperative respiratory adverse events.[1] In addition to the limitations described in the discussion, we noticed other questions that may have influenced their findings.

First, it may be not in the interest of patients because preoxygenation was not routinely used, but preoxygenation should and could be used. It is well known that preoxygenation can delay the onset of apnea-induced arterial oxyhemoglobin desaturation.[2–4] Because the "cannot intubate, cannot ventilate" situation is unpredictable, the need for preoxygenation is desirable in all patients.[5,6] Preoxygenation should be performed, especially in high-risk patients.[7] Although all children in this study were high-risk patients, only children with at least two clinically relevant risk factors for perioperative respiratory adverse events could be recruited.[1] Also, the children were given up to 66% N_2O in oxygen for 20 s to 30 s before sevoflurane; the time was nearly adequate for deep breathing preoxygenation.[1] Maximal preoxygenation (ETo_2 = 90%) can be accomplished in children faster than in adults; with tidal volume breathing, an ETo_2 of 90% can be reached within 100 s in almost all children, which could be shortened to 30 s with deep breathing.[8,9]

Second, the data shortage of patient response to laryngeal mask airway (LMA) insertion reduced the reliability of the results. As we know, if LMA was inserted at different anesthesia depths between two groups, the result might be quite different. Though LMA was performed for all children who did not react to a bimanual jaw thrust maneuver, it did not mean the intubation responses were the same. Only with complete data can we judge the anesthesia depths of two groups.

Third, it would be more beneficial to clarify the results if the infants age 1 yr or younger were separated from the 0.0 to 3.0 yr age group because the incidence of perioperative respiratory adverse events in infants was doubled from the 15% in a general pediatric population.[10] As per protocol, difference already existed in the 0.0 to 3.0 yr age group, given that it was 17% and 26% in IV group and inhalation group, respectively. The incidence of perioperative respiratory adverse events would be higher in the inhalation group if the difference mainly came from the infants. We believe that addressing the above issues could further increase the value of this study.

Competing Interests

The authors declare no competing interests.

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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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