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LETTER TO THE EDITOR

Considerations for interpreting clinical research findings on perioperative respiratory adverse events in children

Kumi Kataoka[1] · Makoto Sumie[1,2,3,4] · Alan Yang[2] · Kazuyoshi Aoyama[1,2]

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To the editor:

Perioperative respiratory adverse events (PRAE) are the most common cause of critical events in children undergoing anesthesia and surgery [1]. While ongoing research continues to improve our understanding of the impact of risk factors of PRAE and the effects of specific interventions on PRAE in children, there is no consensus on prophylactic pharmacologic interventions on PRAE in children yet. Qi-Wen Deng et al. recently conducted a systematic review with a meta-analysis of 29 randomized controlled trials (RCTs), including 4452 children, to evaluate perioperative pharmacologic interventions to prevent PRAE in children. In their systematic review, lidocaine (Odds ratio [OR] 0.27; 95% CI 0.17, 0.42; moderate certainty of evidence), dexmedetomidine (OR 0.31; 95% CI 0.12, 0.76; moderate certainty of evidence), B2 adrenoreceptor agonist (OR 0.45; 95% CI 0.24, 0.83; low certainty of evidence) reduced overall PRAE compared with placebo, and propofol induction reduced overall PRAE compared with sevoflurane induction (OR 0.35; 95% CI 0.16, 0.74; low certainty of evidence) [2]. Generally, there are a few considerations when interpreting the results of PRAE studies: lack of a gold standard definition for PRAE, the use of meta-analysis for a composite outcome, and the impact of broad inclusion criteria.

The absence of a universally accepted gold standard for defining PRAE poses a challenge for conducting a systematic review with meta-analyses. Many RCTs include laryngospasm, bronchospasm, oxygen desaturation, airway obstruction, coughing, and stridor in the definition of PRAE [3–6]. However, some RCTs included other events such as excessive secretions, nausea and vomiting, or biting/teeth clenching [7, 8]. Qi-Wen Deng et al. defined PRAE as a composite outcome, incorporating major events (laryngospasm and bronchospasm) along with at least two minor events (oxygen desaturation, airway obstruction, coughing, or stridor), or including at least three of the six major or minor events [2]. Recognizing the heterogeneity in PRAE definitions across their included studies, they defined PRAE by comprising any common adverse events so that they were able to assess the effect of interventions comprehensively. Nevertheless, this variability in definition can lead to a different finding from the true incidence in the population, potentially affecting the validity of the results, as the pooled overall PRAE incidence was derived from aggregated study-level data from each RCT included in the meta-analysis [9].

The broad inclusion criteria employed in this meta-analysis may have an impact on the selection of RCTs and consequently on the outcomes [10]. Qi-Wen Deng et al. acknowledged heterogeneity in the type of surgery, administration routes of pharmacologic agents, and phase of PRAE measurement across the included RCTs, and conducted subgroup analyses to assess the reliability of the primary outcome results [2]. The heterogeneity in the timing of pharmacologic agent administration and the phase of PRAE measurement may significantly impact the results, as the interplay between these factors cannot be overlooked. For instance, Karam et al. investigated "postoperative" respiratory adverse

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✉ Makoto Sumie
makoto.sumie@sickkids.ca

1 Department of Anesthesia and Pain Medicine, The Hospital for Sick Children, 555 University Ave, #2211, Toronto, ON M5G 1X8, Canada

2 Program in Child Health Evaluative Sciences, SickKids Research Institute, Toronto, ON, Canada

3 Department of Anesthesiology, St. Mary's Hospital, Fukuoka, Japan

4 Department of Anesthesiology and Critical Care Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

event using propofol for both induction and maintenance [8], whereas Ramgolam et al. focused on "perioperative" respiratory adverse event using propofol solely for induction [11]. This difference in conditions between the two RCTs may affect the outcome, which subgroup analyses alone may not fully account for.

Qi-Wen Deng et al. recognized as a limitation that the correlation between each component of their defined PRAE affected the results of the meta-analysis [2]. If there is a positive correlation within the composite outcome, the treatment effect may be overestimated, whereas a negative correlation could result in an underestimation. Furthermore, inaccurate specification of the correlation could lead to inconsistent estimates of effects [12]. For instance, consider two PRAEs with different components: one comprising laryngospasm with oxygen desaturation, and the other comprising laryngospasm with coughing. Clinically, laryngospasm can induce oxygen desaturation; however, it does not always lead to coughing. Therefore, while the effect of lidocaine on oxygen desaturation inherently includes its effect on laryngospasm, its effect on coughing would be evaluated separately from laryngospasm. Consequently, the effect of lidocaine on the PRAE defined as laryngospasm with oxygen desaturation could be overestimated compared to the PRAE defined as laryngospasm with coughing.

Establishing a standardized definition of PRAE is crucial for ensuring consistency and comparability across studies, thereby enhancing the validity of future studies on PRAE. Moreover, future meta-analyses should correctly account for the correlation between components of composite outcomes to prevent biased effect estimates. Future RCTs with consistent administration timing and routes of pharmacologic agents, along with clear distinctions between high-risk populations and types of surgery, will provide more robust evidence.

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Declarations

Conflict of interest There is no conflict of interest.

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