EDITORIAL

How to mitigate confounding factors in observational studies

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Emergency agitation (EA) is one of the most challenging postoperative complications that involve mental excitement and reported incidence in 11–25% following pediatric general anesthesia [1–3]. EA can lead to adverse events such as accidental removal of intravenous catheters, wound damage, and burden for nurses and the parent. Although EA and emergency delirium are sometimes used interchangeably in previous reports, EA is an emotional disturbance or mental excitement, including emergency delirium and cognitive dysfunction. In contrast, emergency delirium is unstable mental change with cognitive dysfunction [2, 4].

Recently, Miyake et al. studied their hypothesis that continuous propofol infusion during sevoflurane anesthesia reduces the incidence of EA compared to sevoflurane anesthesia without propofol [5]. They retrospectively compared a group that was treated with sevoflurane alone with another group that was treated with sevoflurane and propofol (6 mg/kg/h or less) within a cohort of 244 children aged 0 to 16 while adjusting for known risk factors. The authors found the odds ratio of EA was significantly low in the combination group compared to the sevoflurane group (adjusted odds ratio: 0.48, 95% confidence interval: 0.25–0.91, $p = 0.024$). In the study, the authors treated known risk factors including age, sex, premedication, and surgical procedures as

confounding factors and adjusted for them in the analysis that compares the two groups. In addition, the authors also adjusted for attending anesthesiologists as a confounding factor in a sensitivity analysis since management against EA depends on the attending anesthesiologist. Moreover, they considered intraoperative doses of fentanyl and droperidol as mediators in the analysis since these agents were affected by anesthetic methods.

Multivariable logistic regression analysis can adjust for factors that affect both the exposure and the outcome, often known as confounding factors and compute the odds ratio of the outcome in association with the exposure, when the outcome is binary [6]. The authors revealed the odds of the outcome (EA) associated with the exposure (anesthetic method; the combination group compared with the sevoflurane group) decreased by 52% through a multivariable logistic regression analysis adjusting for confounding known risk factors. The authors could not obtain and adjust for patient behavior during induction, which was deemed as another known risk factor. Moreover, the authors developed a mixed-effect multivariable logistic regression model, including fixed effects and random effects, as a sensitivity analysis that adjusts for attending anesthesiologists as a confounding factor in addition to the known risk factors. A fixed effect refers to a factor that continuously influences the target population under analysis, while a random effect refers to a factor that randomly influences the target population under analysis [7]. In the mixed model, the authors included attending anesthesiologists as a random effect and the aforementioned known risk factors as fixed effects. The model revealed the odds of the outcome decreased by 53% comparing combination group with the sevoflurane group. This result, in which the odds ratio is almost the same as that of the main analysis without attending anesthesiologists as a confounding factor, not only suggests the robustness of the findings of this study but also implies that attending anesthesiologists is not a confounding factor.

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A mediator is a factor that provides a mechanism that affects or explains how the outcome is caused by the exposure, while a confounding factor is a factor that affects both the exposure and the outcome that could potentially distort the relationship between the two. Mediation analysis can demonstrate a causal relationship between the exposure, the mediator, and the outcome with an effect size, such as odds ratio, derived from the regression coefficient by incorporating the mediator into the regression equation [8, 9]. The effect of exposure to outcome without considering a mediator is referred as the total effect. When the mediator is considered, the effect of exposure to outcome mediated and not mediated through the mediator are referred as the indirect effect and the direct effect, respectively (Fig. 1). Suppose the direct effect is smaller than the total effect when calculating effect size on mediation analysis. In this case, we can deem the mediator as being on the causal pathway and suggest the mechanism of the causal relationship from it. In this study by Miyake et al., the direct effect and the total effect were the same, both being odds ratio of 0.48, and consequently the indirect effect was odds ratio of 0.99. The odds ratio of indirect effect equals to the odds ratio of the total effect divided by the direct effect. These results indicate the amount of intraoperative fentanyl and droperidol does not affect the outcome as a mediator (Fig. 1). This result demonstrates the mechanism of reducing the incidence of EA by continuous propofol infusion during sevoflurane anesthesia is not dependent on the amount of intraoperative fentanyl and droperidol.

Finally, the authors assessed whether an unknown confounding factor had potentially affected the analysis results; in other words, they assessed whether they had sufficiently adjusted for confounding factors in their analysis. The author chose to use E-value to conduct this assessment. E-value informs how strongly an unknown confounding factor could affect the exposure and the outcome and in turn negate the causal relationship between the two. E-value provides the influence of an unknown confounding factor on the exposure and the outcome as some numeric estimate [10]. This study used risk ratio instead of odds ratio, to represent E-value and revealed that if the risk ratio of an unknown confounding factor on the association between anesthetic method and EA is over 2.25, then the observed odds ratio of the exposure on the outcome would change from 0.48 to 1 should the unknown factor become adjusted for. This result indicates the observed causal relationship, that is, continuous propofol infusion during sevoflurane anesthesia decreases EA, is negated if the risk ratio is over the E-value threshold. The authors evaluated that an unknown factor with a risk ratio of 2.25 is unlikely to exist, implying their causal results are unlikely to be negated. However, they also suggested the possibility that the causal relationship under study could not be fully explained even with the adjusted confounding factors in the presence of unknown confounding factors,

Fig. 1 The relation between the exposure, the outcome, and the mediator on causal pathway
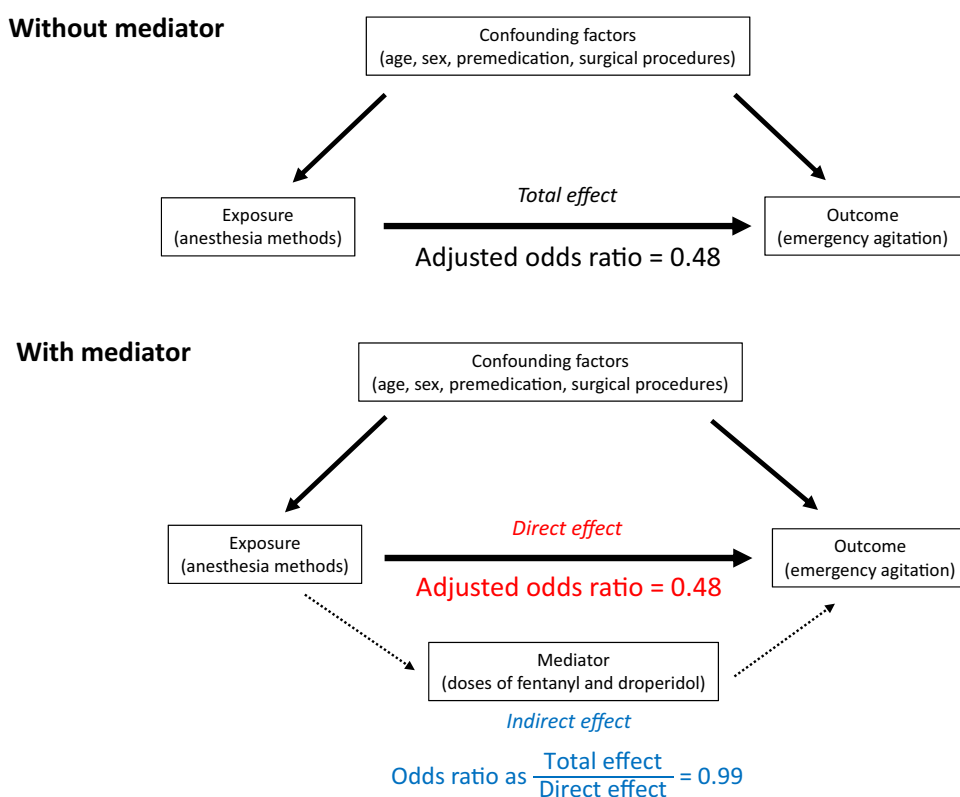
regardless of their strength and impact. Thus, it is still difficult to derive further interpretation of the results.

This study by Miyake et al. was a retrospective cohort conducted in the limitation of data resources that dealt with a variety of confounding factors. It revealed continuous propofol infusion during sevoflurane anesthesia decreases the incidence of EA. Although the robustness of this study is verified by a sensitivity analysis and E-value, the most useful, robust, and validated method to explore the intervention effect of interest is a randomized control trial (RCT). Randomized control trials can avoid selection bias and confounding effectively. However, recently, Hayes et al. evaluated the robustness of existing one hundred seventy-two RCTs in pediatric anesthesiology using fragility index (FI). The FI was used to estimate the number of outcome events, which need to change (i.e., an event to a non-event), for a result to turn from statistically significant to non-significant [11]. The recent study by Hayes et al. showed an FI of 3 [interquartile range, 1–7], which means the analysis result could become "negative" if the outcomes of as few as three patients were changed to "no response" from their original "response" against the intervention effect. This warns the robustness of RCTs in pediatric anesthesiology. As such, the study by Miyake et al. warrants future RCTs designed with well-planned adequate power and a subsequent systematic review with meta-analysis of such RCTs.

Declarations

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