Prophylactic Midazolam and Clonidine for Emergence from Agitation in Children After Emergence From Sevoflurane Anesthesia: A Meta-analysis

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ABSTRACT

Background: Emergence agitation (EA) after emergence from sevoflurane anesthesia is a common phenomenon in children. The efficacy of prophylactic midazolam or clonidine in preventing EA is controversial.

Objective: We performed a meta-analysis of clinical trials of the 2 drugs to evaluate their ability to prevent EA in pediatric patients after emergence from sevoflurane anesthesia.

Methods: A comprehensive literature search was conducted to identify clinical trials that observed the effect of midazolam and clonidine on preventing EA in children after their emergence from sevoflurane anesthesia. All data were examined using the Mantel-Haenszel model to calculate the pooled odds ratio (OR) and 95% CI. I^2 was used to assess heterogeneity. Subgroup analysis was used to assess the effects of preoperative analgesics, routes of administration, and dose, and funnel plots were used to check publication bias.

Results: After a comprehensive literature search, we found 12 papers that met the criteria for inclusion in this analysis, with a total of 447 children in the midazolam group and 767 children in the clonidine group. We found that both midazolam and clonidine decreased the incidence of EA (OR = 0.45 [95% CI, 0.29–0.70], $P = 0.0004$, $I^2 = 46\%$; and OR = 0.24 [95% CI, 0.13–0.43], $P < 0.00001$, $I^2 = 48\%$, respectively). Subgroup analysis indicated that preoperative analgesia may decrease the effect of midazolam against EA, whereas for clonidine, neither the route of administration (intravenous or caudal) nor the dose affected the results. Funnel plots did not detect publication bias in the midazolam group, but a bias was detected in the clonidine group.

Conclusions: This meta-analysis suggests that prophylactic administration of midazolam or clonidine could significantly decrease the incidence of sevoflurane-induced EA in pediatric patients. (*Clin Ther*. 2013;35:1622–1631)

Key words: anesthesia, children, clonidine, emergence agitation, midazolam, sevoflurane.

INTRODUCTION

Sevoflurane is a popular agent for the induction and maintenance of pediatric anesthesia. It offers several advantages, including a relative lack of airway irritation, a more rapid onset and recovery, and greater hemodynamic stability than other potent inhaled agents.[1] However, it is also well-known that sevoflurane is associated with a high incidence of emergence agitation (EA) in children,[2,3] although the exact mechanisms remain unknown. EA, characterized by excited and disoriented behavior on awakening from general anesthesia, presents a high risk of self-injury, especially in children. At present, there is no clear strategy for preventing EA, and many drugs, including propofol, dexmedetomidine, ketamine, fentanyl, and others, have been used to decrease the incidence of EA.[4] Premedication with midazolam or clonidine for decreasing the incidence of EA induced by sevoflurane remains controversial, with some studies indicating no effect and others demonstrating their usefulness.[5–9]

Because a meta-analysis is a useful statistical method with which to evaluate therapeutic effects of drugs based on the results of multiple studies by both qualitative and quantitative methods, as well as to identify factors that can influence the overall estimates of outcomes of interest, we performed a meta-analysis

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to evaluate the effectiveness of midazolam and clonidine premedication in decreasing the incidence of EA in children after their emergence from sevoflurane anesthesia.

MATERIAL AND METHODS

This systematic review and meta-analysis was conducted according to the Quality of Reporting of Meta-analyses (QUOROM) recommendations for improving the quality of meta-analyses.[10]

We conducted a comprehensive literature search for trials of midazolam and clonidine in the prevention of EA from databases, including PubMed, EMBASE, MEDLINE, and the Cochrane Database of Systematic Reviews, and included the following search terms: *midazolam*, *clonidine*, *sevoflurane*, *agitation*, *delirium*, *behavior*, and *children* or *infant* and combinations of these, without restriction of the year of publication. Only articles published in English were included. If full texts could not be found, the authors were contacted to obtain original information as necessary.

All articles were independently accessed by 2 anesthetists according to the following inclusion criteria: randomized, controlled trial; double-blinded, sevoflurane anesthesia; absence of neurologic disease; standardized anesthesia protocols; results reporting the incidence of EA or an equivalent state after emergence from general anesthesia; standardized definition of EA between control and experimental groups in each study; and children <12 years of age. Disagreements were resolved by consensus. Articles with insufficient data, review articles, editorials and letters, case reports, and non-English papers were excluded.

All statistical analyses were performed using Review Manager 5 software (RevMan 5, The Cochrane Collaboration, Oxford, United Kingdom). The odds ratio (OR) of the incidence of EA was computed using the Mantel-Haenszel method (fixed or random models) to represent the odds of EA occurring in the premedication group compared with the control group. A 95% CI for an OR of <1 indicated efficacy in preventing EA and P values <0.05 were considered statistically significant. The impact of differences of study design, including premedication with analgesics or concomitant premedication, use of regional block, administration route (intravenous or caudal), and dose, which resulted in heterogeneity among the included studies, was assessed by the I^2 index. According to the Cochrane Review guidelines, $I^2 > 50\%$ with $P < 0.1$ is considered the threshold for heterogeneity, indicating that the OR was calculated with a random-effects method. If heterogeneity was excluded, we used the fixed-effects method to calculate the pooled OR.

Further, because we were aware that analgesics or other concomitant premedications, regional block, administration route (intravenous or caudal), and dose could be significant confounding factors on the incidence of EA, we analyzed the data according to subgroups. In addition, when heterogeneity was found, additional analysis was carried out by removing studies one by one according to the presence of regional block or analgesic premedication and route of administration and dose. The results are expressed as OR, 95% CI, and P value for statistical significance and I^2 and P value for heterogeneity.

The potential for publication bias was evaluated by funnel plots. An asymmetric funnel plot indicated the presence of publication bias, whereas a symmetric plot suggested that there was no publication bias.

RESULTS

Using electronic databases, 367 articles were searched by the preplanned search terms with 355 excluded by the inclusion criteria, so that 12 relevant articles were finally identified for the meta-analysis. The details of the selection criteria are summarized in **Figure 1**. There were 5 midazolam trials[7,11–14] (**Table I**) and 7 clonidine[5,8,9,15–18] (**Table II**) trials in the meta-analysis, with 447 children in the midazolam group and 767 children in the clonidine group.

In the studies of the efficacy of midazolam pretreatment for prevention of EA in children after emergence from sevoflurane anesthesia, there were 247 children in the treatment groups and 200 in the control group. Midazolam was given orally (0.2–0.5 mg/kg) 10 to 45 minutes before induction of anesthesia and was shown to have a significant effect for decreasing the incidence of EA induced by sevoflurane anesthesia in children (OR = 0.45 [95% CI, 0.29–0.70]; $P = 0.0004$) (**Figure 2**). Testing for heterogeneity gave $I^2 = 46\%$, $P = 0.12$ (**Figure 2**). In subgroup analysis, when we removed studies with preoperative analgesia, the heterogeneity was significantly decreased ($I^2 = 0\%$, $P = 0.56$) (**Table III**), and the prophylactic effect of midazolam against EA was more pronounced (OR =