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Greater Incidence of Emergence Agitation in Children after Sevoflurane Anesthesia as Compared with Halothane

A Meta-analysis of Randomized Controlled Trials

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Background: **Sevoflurane is a popular inhalational anesthetic for general anesthesia in children. The higher incidence of emergence agitation has been suspected after sevoflurane anesthesia as compared with halothane, whereas some controlled studies showed conflicting results. In this report, the authors performed a meta-analysis of randomized controlled trials to compare the incidence of emergence agitation in children after sevoflurane or halothane anesthesia.**

Methods: **A comprehensive literature search was conducted to identify clinical trials that compared the incidence of emergence agitation in children anesthetized with sevoflurane *versus* halothane. Two reviewers independently assessed each report to meet the authors inclusion criteria and extracted data. The data from each trial were combined using the Mantel-Haenszel fixed-effect model to calculate the pooled odds ratio and 95% confidence interval. Funnel plots were used to assess publication bias. Subgroup analysis was used to clarify the effects of age, surgical procedure, pain treatment, and premedication on the incidence of emergence agitation.**

Results: **The authors identified 23 studies that met their inclusion criteria. Overall, 1,252 patients received sevoflurane and 1,111 had halothane. Heterogeneity of data was statistically refuted. The pooled odds ratio for all studies was 2.21, with a 95% confidence interval of 1.77–2.77 ($P < 0.0001$). Publication bias was not apparent in a funnel plot. All subgroup analyses showed a higher incidence of agitation after sevoflurane anesthesia.**

Conclusions: **This meta-analysis revealed that emergence agitation occurred more frequently with sevoflurane than with halothane anesthesia in children.**

SEVOFLURANE is a popular inhalational anesthetic for general anesthesia in children. It is especially characterized by a lower blood/gas partition coefficient, less irritation to the airway, less cardiodepressive effect, and less toxicity to the liver or kidney as compared with other volatile anesthetics. Anesthesiologists prefer those characteristics for pediatric use. However, concern has been raised over its propensity to result in significant excitatory emergence in the immediate recovery phase of sevoflurane anesthesia. Emergence agitation is a major source of dissatisfaction for parents, nurses, and others taking care of these children. The irritable, uncooperative, incoherent child who is inconsolably crying, moaning, kicking, or thrashing is at risk for injury and requires extra nursing care and supplemental sedative and/or analgesic medications, which may delay patient discharge from hospital.

Pediatric anesthesiologists mostly agree that sevoflurane causes a higher incidence of emergence agitation,[1–3] whereas some controlled studies comparing sevoflurane and halothane showed conflicting results.[4,5] The conflicting results may arise from the differences of study design, the background of study patients, and study quality. Under the existence of many confounding factors regarding emergence agitation, it is hard to draw from a single study a definitive answer about whether sevoflurane results in a higher probability of emergence agitation in children. Various methods, including treatments against surgical pain and prescriptions of sedative premedication, have been tried to prevent emergence agitation after sevoflurane anesthesia, but their validities have not been well clarified.

Meta-analysis is a statistical tool that can be used to evaluate the literature in both qualitative and quantitative ways, accounting for variations in characteristics that can influence the overall estimate of outcomes of interest. Statistical aggregation of randomized trials through meta-analysis allows for increased power to detect potential differences in clinical outcomes. In this report, we performed a meta-analysis of randomized controlled trials to compare the incidence of emergence agitation in children after sevoflurane or halothane anesthesia.

Materials and Methods

We conducted a systematic review according to the Quality of Reporting of Meta-analyses (QUOROM) recommendations for improving the quality of meta-analyses.[6]

A comprehensive literature search was performed using MEDLINE, EMBASE, American College of Physicians Journal Club database, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Database of Abstracts of Reviews of Effects. Every effort was made to find studies reporting on emergence agitation or equivalent state after sevoflurane or halothane anesthesia in children. Although there seemed to be no widely accepted definition of emergence agitation

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after general anesthesia, we generally agreed on the definition proposed by Sikich and Lerman[7]: a disturbance in a child's awareness of and attention to his or her environment, with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behavior in the immediate postanesthesia period. The following text searches, search headings, and their combinations were used: *sevoflurane*, *halothane*, *child*, *agitation*, and *delirium*. A manual search of references listed in reports and reviews was also performed. Only articles written in English were included. The date of the most recent search was April 15, 2007.

The two authors independently accessed each article to meet the following inclusion criteria. Disagreements were resolved by consensus. To enter our analysis, the studies had to be a prospective randomized trial, compare halothane and sevoflurane, report the results of ambulatory procedures on children aged younger than 12 yr, and report the incidence of emergence agitation or equivalent state after general anesthesia. We were careful to avoid including data from duplicate publications. We did not include articles from any studies with insufficient data; however, we tried to contact the corresponding author to collect unpublished data for our analysis. We also excluded studies regarding neurologically impaired patients.

Unmasked quality assessment on the selected published studies was performed by two investigators on composite aspects of study quality (six aspects in total, with scores 0 or 1: randomization, standardized anesthesia protocol, blindness of outcome measurement, comparability, withdrawals, definition of emergence agitation). Differences in opinion were settled by consensus. Data abstraction was also performed independently by two authors using standardized data collection forms. Data extracted from eligible studies included the following items: patient age, type of surgical procedure, premedication, and use of regional anesthesia in supplement to general anesthesia. Dichotomous data on the incidence of emergence agitation after sevoflurane or halothane anesthesia was also extracted from eligible studies.

Statistical Analysis

All statistical analysis was performed using RevMan 4.2.10 (The Cochrane Collaboration, Oxford, United Kingdom).

An analysis of the incidence of emergence agitation was performed using the odds ratio (OR). The OR represents the odds of emergence agitation occurring in the sevoflurane group compared with the halothane group. An OR of more than 1 means that sevoflurane is expected to cause more frequent emergence agitation than halothane does. It is considered statistically significant at the $P < 0.05$ level if the 95% confidence interval (CI) does not include value 1.0. Because eligible studies showed clinical and methodologic diversity, the heterogeneity of collected data was assessed using a homogeneity test based on the χ^2 test and I^2. The I^2 statistic was used to assess the impact of heterogeneity on the results. This statistic indicates the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error.[8] Because of the low power of this test, especially when trials have a small sample size or are few in number, we determined a minimum cutoff P value of 0.10 and I^2 value of 50% as a threshold of homogeneity to avoid false-negative results; $P < 0.10$ and $I^2 > 50\%$ indicated heterogeneity and prevented us from relying on the combination of the study results. If significant heterogeneity was denied statistically, the Mantel-Haenszel fixed-effect method was used to calculate the pooled OR. The studies that contained a zero in one cell for the number of events resulted in problems with the computation of the ratio measurement, so a value of 0.5 was added to both groups of that particular study.

Sensitivity analysis was performed by recalculating the pooled OR using data with a study quality rating greater than 4. Because we were aware that age, preoperative anxiety, surgery type, and postoperative pain could be significant confounding factors on the incidence of emergence agitation, we classified the following subgroups and analyzed them separately:

1. Study patients aged younger than 7 yr
2. Study protocols including routine premedication with benzodiazepines
3. Study patients anesthetized for myringotomy tube insertion
4. Study patients anesthetized for minor inguinal or urologic surgery, all with regional blocks appropriate for surgical analgesia

Publication bias with unpublished studies that show no significant difference can limit the validity of meta-analyses. To assess the potential for publication bias, a funnel plot was constructed of OR against associated SEs.[9] An asymmetrical funnel plot can reflect the publication bias, in which the OR estimates suggesting strong associations in an expected direction are preferentially published. The Begg test[10] was used to assess asymmetry of the funnel plot.

Results

Using electronic databases, we initially identified 271 articles for review. Of those, 228 studies were excluded because they were unrelated studies, review articles, editorials, letters, or non-English literature. The other 43 articles were thoroughly checked to meet our inclusion criteria. Six studies were excluded because they did not match the inclusion criteria. Incidence of emergence

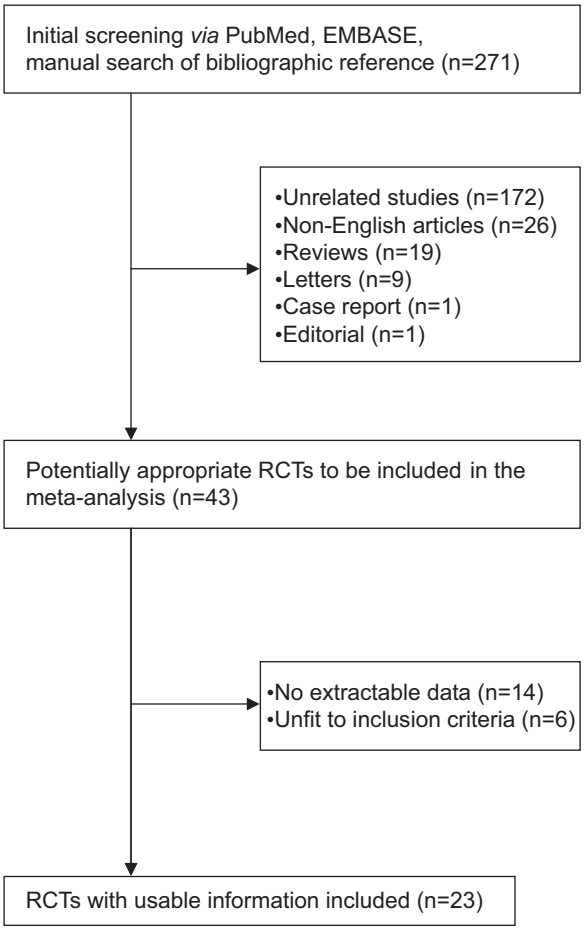

Fig. 1. Meta-analysis flowchart. RCT = randomized controlled trial.

agitation was not available in 14 studies, and failed to obtain data from respective investigators. Therefore, 23 studies[1–5,11–28] were identified by the defined search strategy and fulfilled the inclusion criteria, containing the necessary data for the planned comparison. The process of identifying eligible studies is illustrated in figure 1, and the details of selected trials are summarized in table 1. As shown in table 1, the included trials compared sevoflurane and halothane anesthesia in minor surgical or diagnostic procedure in children; hence, we considered it appropriate that the results of the respective studies were combined for analysis.

In 23 trials, a total of 1,252 patients anesthetized with sevoflurane and 1,111 patients anesthetized with halothane were evaluated for the incidence of emergence agitation. The pooled OR of the incidence of emergence agitation with sevoflurane was 2.21 (95% CI, 1.77–2.77; $P < 0.0001$). The major results of the meta-analysis comparing sevoflurane and halothane are summarized in figure 2. The test for heterogeneity gave $\chi^2 = 29.69$, $I^2 = 25.9\%$, and 22 degrees of freedom ($P = 0.13$). These results warranted the use of the Mantel-Haenszel method to calculate the pooled OR.

Sensitivity analysis was used by recalculating the pooled OR using high-quality studies. The pooled OR of 1.82 (95% CI, 1.37–2.41; $P < 0.0001$) was obtained when subgroup analysis was performed for the 14 studies that had a study quality rating greater than 5. Furthermore, we conducted subgroup analyses to explore the effects of known confounding factors on the incidence of emergence agitation (table 2). When the pooled analysis was restricted to the studies of patients aged younger than 7 yr, the pooled OR was 1.88 (95% CI, 1.39–2.54; $P = 0.0001$). In 12 studies, the study protocol included sedative premedication for all patients. In the subgroup of routine premedication, the pooled OR was 1.77 (95% CI, 1.26–2.47; $P = 0.0009$). We found 6 studies of myringotomy procedure. In myringotomy studies, the pooled OR was 1.79 (95% CI, 1.26–2.53; $P = 0.001$). Five trials studied emergence agitation in children who had inguinal or minor urologic surgery and appropriate regional block with local anesthetics. When we calculated the pooled OR of pain-treated inguinal surgery, sevoflurane anesthesia also showed a higher incidence of emergence agitation (OR = 3.20; 95% CI, 1.65–6.22; $P = 0.0006$).

A funnel plot was used to detect possible publication bias in the meta-analysis (fig. 3). In this study, the existence of major publication bias was not supported statistically by the Begg test (Kendall correlation coefficient = 0.0988; Z value = 0.6603; $P = 0.5091$).

Discussion

Our meta-analysis revealed that sevoflurane anesthesia more often resulted in emergence agitation than did halothane in pediatric patients. The results of our analysis are consistent with the current consensus among pediatric anesthesiologists. Several previous studies reported that sevoflurane anesthesia caused children to have a higher incidence of emergence agitation as compared with halothane, but some prospective studies performed to evaluate this point found no significant difference between the two anesthetics. Indeed, 20 of 23 trials that met our inclusion criteria yielded an OR of greater than 1 for emergence agitation due to sevoflurane, whereas only 8 studies showed a statistically significant difference (fig. 2). The reasons for conflicting results include differences in study design and quality. Some trials could have insufficient power to adequately explore the differences between two anesthetics. The use of meta-analytic techniques allowed the inclusion of 2,363 patients, of which 1,252 had sevoflurane anesthesia and 1,111 had halothane anesthesia. This sample size would otherwise be impossible to accumulate in a reasonable time in a randomized control trial, and the large sample size made it possible to detect the significant differences of incidence between the two anesthetics.

Table 1. Characteristics of Included Studies

Study	Year	Patient Age	Type of Surgery	Premedication (Route)	Analgesics (Route)	Regional Block	Study Quality	Remarks
Lerman *et al.*[1]	1996	1–12 yr	Elective ambulatory surgery	None	ND	ND	6	
Aono *et al.*[2]	1997	3–10 yr	Circumcision, inguinal hernia repair	0.2 mg/kg diazepam (oral)	None	Caudal block, wound block	6	Preschool and school children data were used
Beskow and Westrin[3]	1999	8 mo–11 yr	Minor surgery (hernia, circumcision, *etc.*)	0.4 mg/kg midazolam, 0.02 mg/kg atropine (rectal, oral)	None	ND	4	Data less than 11 yr old were used for analysis. Recovery score > 5 was considered as agitation
Davis *et al.*[4]	1999	1–5 yr	BMT	0.2 mg/kg midazolam (nasal)	None *vs.* 1 mg/kg ketorolac (intravenous)†	None	5	
Hallén *et al.*[5]	2001	3–8 yr	BMT	0.3 mg/kg midazolam (rectal)	25 mg/kg paracetamol (rectal)	None	5	
Cravero *et al.*[11]	2000	6 mo–10 yr	BMT	None	25 mg/kg acetaminophen (rectal)	None	5	
Johannesson *et al.*[12]	1995	1.1–7.5 yr	ENT surgery (BMT, adenoidectomy)	0.35 mg/kg midazolam, 0.035 mg/kg atropine (rectal)	10 mg/kg paracetamol (rectal)	None	2	
Murray *et al.*[13]	2002	< 7 yr	BMT	None	None *vs.* 0.1 mg/kg oxycodone* (oral)†	None	3	
Weldon *et al.*[14]	2004	1–6 yr	Inguinal hernia repair	0.5 mg/kg midazolam (oral)	10 mg/kg ibuprofen* (oral)	Caudal block	6	Data from 5 min after PACU arrival were used
Kain *et al.*[15]	2005	3–10 yr	Elective outpatient surgery	None	ND	None	5	
Cravero *et al.*[16]	2000	6 mo–10 yr	MRI	None	None	None	6	High threshold definition data were used.
Galinkin *et al.*[17]	2000	9 mo–6 yr	BMT	0.2 mg/kg midazolam, 10 mg/kg acetaminophen (oral)	None *vs.* 2 μg/kg fentanyl (nasal)†	None	6	
Lapin *et al.*[18]	1999	6 mo–6 yr	BMT	None *vs.*† 0.5 mg/kg midazolam (oral)	15–30 mg/kg acetaminophen (rectal)	None	5	
Moore *et al.*[19]	2003	3–12 yr	Day surgery	None	ND	ND	4	
Sury *et al.*[20]	1996	6 mo–6 yr	General, urologic, plastic, orthopedic surgery	Atropine if indicated	None	ND	2	
Viitanen *et al.*[21]	2000	1–3 yr	Adenoidectomy	None	12.5 mg/kg diclofenac (rectal)	None	5	
Welborn *et al.*[22]	1996	1–7 yr	Adenoidectomy with BMT	0.5 mg/kg midazolam (oral)	None	None	5	
Villani *et al.*[23]	1998	3–12 yr	Urologic, abdominal, orthopedic surgery	0.05 mg/kg flunitrazepam (oral)	None	None	3	
Chiu *et al.*[24]	1999	1–10 yr	Urologic surgery	2 mg/kg trimeprazine (oral)	20–30 mg/kg paracetamol (rectal)	Ilioinguinal, caudal block	4	
Rieger *et al.*[25]	1996	2–10 yr	Adenoidectomy, BMT	0.5 mg/kg midazolam, 0.02 mg/kg atropine (rectal)	None	None	5	The patients had mild URI
Bebawy *et al.*[26]	2005	2–6 yr	Inguinal hernia repair	0.5mg/kg midazolam (oral)	2 mg/kg diclofenac* (rectal), 1 μg/kg fentanyl (intravenous)	Wound block	5	
Hsieh *et al.*[27]	1999	3 mo–1 yr	Urologic surgery	None	None	Ilioinguinal block	3	
Naito *et al.*[28]	1991	1–7 yr	Laser therapy for port wine stain	None	None	None	3	

BMT = bilateral myringotomy and tubes; ENT = ear, nose, throat; MRI = magnetic resonance imaging; ND = not determined in the study protocol; PACU = postanesthesia care unit; URI = upper respiratory infection.

* Given as premedication. † Compared two groups.

The sensitivity analyses showed the strength of the evidence of higher incidence of emergence agitation after sevoflurane anesthesia (table 2). Because we were aware that the different types of surgical procedure could be a significant confounding factor on the incidence of emergence agitation, we analyzed myringotomy procedures separately as a subgroup. Myringotomy is a minimally invasive surgery and has the least signifi-

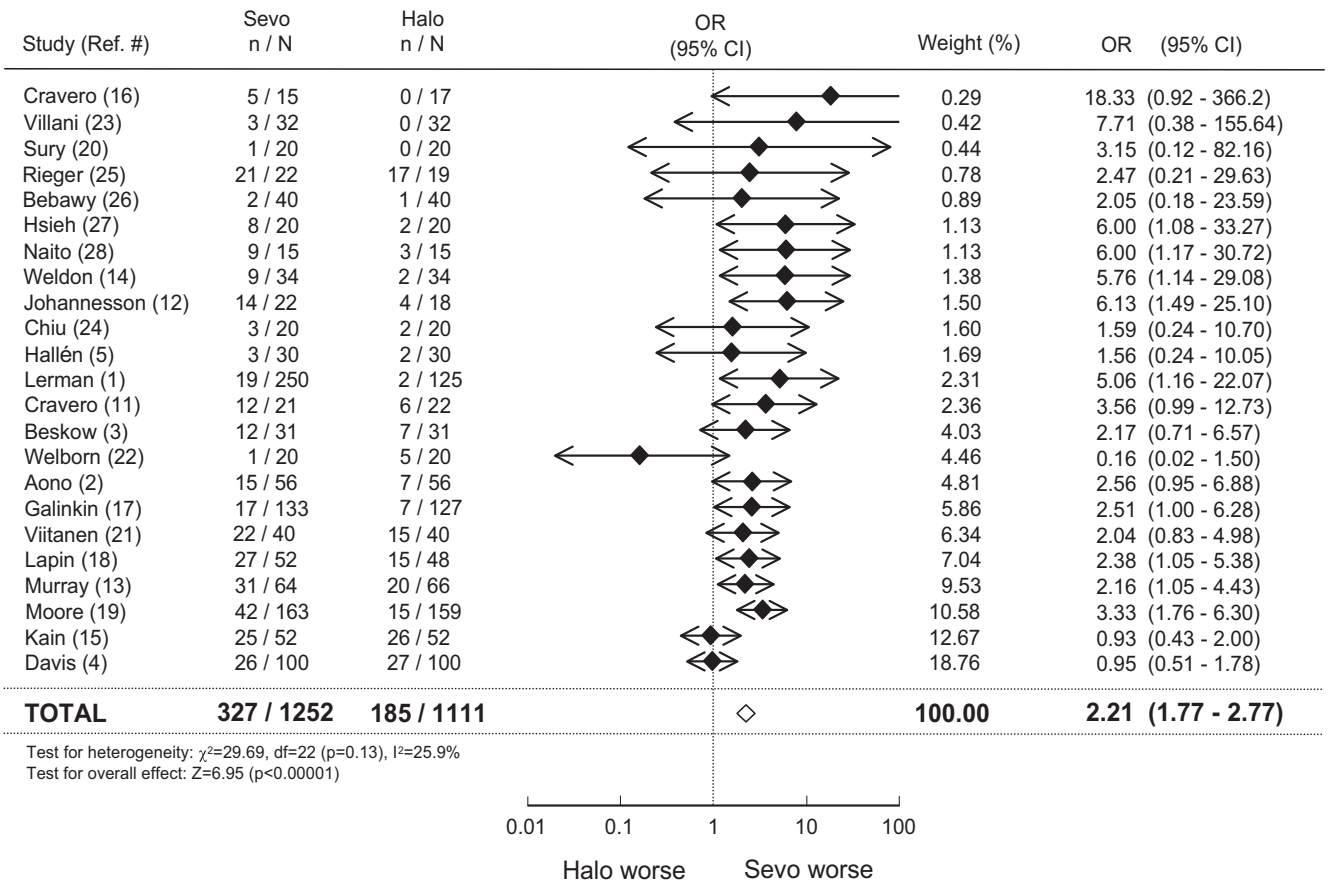

Fig. 2. Meta-analysis of emergence agitation due to sevoflurane (Sevo) *versus* halothane (Halo). The *center* of each *black diamond* is the odds ratio (OR) for individual trials, and the corresponding *horizontal line* is the 95% confidence interval (CI). The *open diamond* is the pooled result. Ref = reference.

cant difference in terms of anesthesia and surgical methods among institutions. As shown in table 2, the pooled results of 6 myringotomy studies showed a significantly higher incidence of emergence agitation in sevoflurane anesthesia. Aono *et al.*[2] reported that preschool children have a significant risk of emergence agitation. We found 11 studies that included children aged younger than 6 yr, and we analyzed them separately as a subgroup. The pooled OR indicates that sevoflurane anesthesia results in a higher incidence of emergence agitation than does halothane in the preschool age group.

The etiology of emergence agitation derives from multiple factors, including pain, preoperative anxiety, type of surgical procedures, personal character of the patient, too rapid awakening, and type of anesthetics. No sole factor can explain the etiology of emergence agitation. Although pain is definitely a major reason for emergence agitation, screaming as a result of pain should be distinguished from emergence agitation. However, especially in younger children, it is sometimes not possible to distinguish between them. It is widely believed that reducing or eliminating pain decreases the incidence of emergence agitation after sevoflurane anesthesia. Several studies demonstrated that regional block,[14,29] opioids,[17,30] and nonsteroidal antiinflammatory drugs[4] decrease the incidence of emergence agitation. However, emergence agitation often occurs even after adequate pain treatment or after procedures that are not associated with pain. Indeed, our subgroup analyses clearly indicated that sevoflurane anesthesia still causes a higher

Table 2. Effects of Subgroup Analysis on Meta-analysis Comparing Sevoflurane and Halothane

Subgroup	References	Pooled OR (95% CI)	*P* Value	Heterogeneity *P* Value
High-quality studies (score > 4)	1,2,4,5,11,14–18,21,22,25,26	1.82 (1.37–2.41)	< 0.0001	0.09
Premedication with benzodiazepines	2–5,12,14,17,18,22,23,25,26	1.77 (1.26–2.47)	0.0009	0.15
Myringotomy	4,5,11,13,17,18	1.79 (1.26–2.53)	0.001	0.28
Preschool children (aged < 7 yr)	2–4,13,14,17,18,20,21,26,27	1.88 (1.39–2.54)	0.0001	0.14
Pain-treated inguinal surgery	2,14,24,26,27	3.20 (1.65–6.22)	0.0006	0.76

CI = confidence interval; OR = odds ratio.

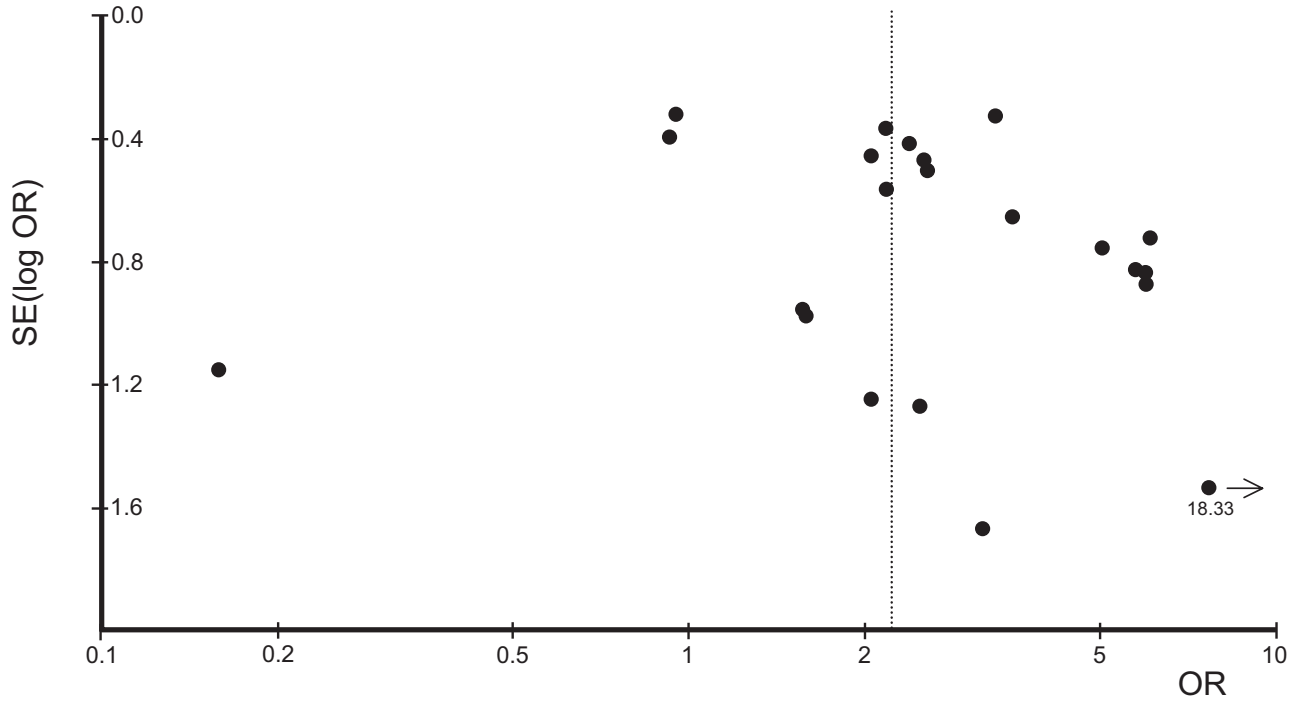

Fig. 3. Funnel plot of the selected trials to explore the publication bias. The pooled odds ratio (OR) is shown as the *vertical dotted line*. The *arrow* indicates the study data that lie outside the graph.

probability of emergence agitation than halothane, even if pain treatment strategy is provided. In addition, if we consider the fact that anesthesia for essentially pain-free procedural sedation can cause emergence agitation,[16] complete pain treatment does not guarantee a calm awakening after sevoflurane.

The reasons for a higher incidence of emergence agitation after sevoflurane are not fully understood. Sevoflurane in particular situations may exert an irritating side effect on the central nervous system, because epileptiform seizure activity in previously nonepileptic patients has been observed with electroencephalography during sevoflurane anesthesia.[31,32] The mechanism of cortical epileptogenicity by sevoflurane is largely unknown.[33] Because volatile anesthetics with low blood solubility generally tend to cause a higher incidence of emergence agitation, rapid awakening has been posited as a cause for this phenomenon. However, rapid awakening after propofol has not been associated with emergence agitation.[34] Therefore, rapid awakening *per se* does not seem to be a factor in the causation of emergence agitation. Giving sedative premedication before anesthesia has been tried to ameliorate preoperative anxiety with hopes that it would decrease the incidence of emergency agitation. Although some studies[18,35] showed the usefulness of sedative premedication to reduce agitation, our subgroup analysis of the routine benzodiazepine administration group indicated that premedication does not reduce a higher incidence of emergence agitation to the same level as the incidence after halothane.

Our data demonstrate that sevoflurane in children has an increased risk of emergence agitation, and anesthesiologists treating children should be aware of the risk. Restless recovery after anesthesia is not absolutely harmless; rather, it may cause self-injury and the accidental removal of dressing or catheters. Parents feel extreme anxiety to see their child cry inconsolably. Although emergence agitation is typically self-limited and resolves spontaneously within 15 min, additional medications to address retractable excitation may delay recovery room discharge and add additional cost. Pediatric anesthesiologists should consider methods to reduce the risk of emergence agitation after sevoflurane anesthesia. Complete analgesia is an absolute requirement for comfortable emergence. A variety of medications, including opioids,[36] benzodiazepines,[18] and α_2 agonists,[37,38] were tried to reduce the incidence of emergence delirium with various success. Intravenous anesthesia using propofol reduces the risk of emergence agitation.[34,39] The efficacy of switching to isoflurane maintenance is debatable.[40,41,42] The strategies regarding prevention and treatment of emergence agitation were discussed in detail in a previous review.[43]

It is important to address some limitations of meta-analysis. First, each study has a different study protocol. This can elicit significant heterogeneity, although significant heterogeneity in our study was not suspected by statistical analysis. It is debatable whether it is justified to combine the results of different protocols in the calculation of the pooled OR and in drawing conclusions. Second, emergence agitation was the focus of this meta-analysis; however, measurement of emergence agitation

in each respective study was not always performed using a validated and reliable tool. This may preclude comparisons among the clinical trials. Most studies used a self-made, nonvalidated rating scale to evaluate emergence agitation, which focused more on behavioral than psychometric factors. None used a validated scoring system such as the Pediatric Anesthesia Emergence Delirium scale.[7] Furthermore, the emergence agitation was evaluated by a blinded specialist in some studies; in other studies, however, blindness was not warranted. These factors can cause serious errors in measurement of emergence agitation and significantly bias the results of this study. Third, because the meta-analysis is based on published articles, there is a possibility of publication bias. In this study, the number of unpublished, nonindexed, or non-English articles could affect our conclusions, although the funnel plot analysis showed no evidence of publication bias. Although we limited our analysis to the literature in English, the effect of excluding non-English trials on the results of a meta-analysis is equivocal. Some data suggest that exclusion of trials not published in English may actually result in a more conservative estimate of the treatment effect.[44] This may be related in part to the presence of publication bias where only positive findings are published, primarily in English-language journals.[45]

In summary, meta-analysis of the currently available randomized controlled trials that compared the incidence of emergence agitation in children after sevoflurane and halothane anesthesia indicates that sevoflurane results in a higher probability of emergence agitation than halothane, with a pooled OR of 2.21 (95% CI, 1.77–2.77; $P < 0.0001$). Various sensitivity analyses strengthened the reliability of the results. Anesthesiologists who care for children should be aware of the higher risk of excitatory emergence after sevoflurane anesthesia and should consider methods to prevent emergence agitation in order to provide high-quality anesthetic care for children.

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