KJA
Korean Journal of Anesthesiology

Emergence agitation: current knowledge and unresolved questions

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Review Article

Korean J Anesthesiol 2020;73(6):471-485
https://doi.org/10.4097/kja.20097
pISSN 2005-6419 • eISSN 2005-7563

Received: March 2, 2020
Revised: March 18, 2020
Accepted: March 23, 2020

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Emergence agitation (EA), also referred to as emergence delirium, can have clinically significant consequences. The mechanism of EA remains unclear. The proposed risk factors of EA include age, male sex, type of surgery, emergency operation, use of inhalational anesthetics with low blood–gas partition coefficients, long duration of surgery, anticholinergics, premedication with benzodiazepines, voiding urgency, postoperative pain, and the presence of invasive devices. If preoperative or intraoperative objective monitoring could predict the occurrence of agitation during emergence, this would help to reduce its adverse consequences. Several tools are available for assessing EA. However, there are no standardized clinical research practice guidelines and its incidence varies considerably with the assessment tool or definition used. Total intravenous anesthesia, propofol, μ-opioid agonists, N-methyl-D-aspartate receptor antagonists, nefopam, α_2-adrenoreceptor agonists, regional analgesia, multimodal analgesia, parent-present induction, and preoperative education for surgery may help in preventing of EA. However, it is difficult to identify patients at high risk and apply preventive measures in various clinical situations. The risk factors and outcomes of preventive strategies vary with the methodologies of studies and patients assessed. This review discusses important outcomes of research on EA and directions for future research.

Keywords: Anesthesia; Emergence agitation; Emergence delirium; Incidence; Practice guideline; Risk.

Introduction

Emergence agitation (EA) involves restlessness, disorientation, excitation, non-purposeful movement, inconsolability, thrashing, and incoherence during early recovery from general anesthesia [1]. The incidence of EA varies, from approximately 0.25% to 90.5%, with age, assessment tool used, definitions, anesthetic techniques, type of surgery, and time of EA assessment during recovery [2–6]. The clinical consequences of EA are similarly varied. It is typically short lived and resolves spontaneously, and its clinical consequences are often considered minimal [7,8]. However, it may have clinically significant consequences, such as injury to the affected patient or their medical staff, falling out of bed, bleeding at the surgical site, accidental removal of drains or intravenous catheters, unintended extubation, respiratory depression, and increasing medical care costs [9–11].

Emergence delirium (ED) is an acute confusion state during recovery from anesthesia; patients with ED may present with disorientation, hallucination, restlessness, and purposeless hyperactive physical behavior [8,12]. ED is not fully equivalent to EA; ED can involve hypoactive signs or mixed forms and hyperactive signs similar to agitation [13–15]. Nevertheless, the terms EA and ED have been used interchangeably in several studies [16,17]. Moreover, the same assessment tools (e.g., Riker Sedation-Agitation Scale or

Richmond Agitation-Sedation Scale) have been used for both conditions [18–21]. EA and ED should be differentiated from postoperative delirium. Postoperative delirium involves ED; ED represents the early onset of postoperative delirium in the operating room or on arrival at the postanesthesia care unit (PACU) immediately after the anesthesia period [18,21,22]. EA and ED in the PACU are strong predictors of postoperative delirium, which is associated with prolonged hospital stay and increased morbidity (e.g., pulmonary complications), mortality, and the need for institutionalization of adult patients [2,23]. The terms EA and ED are used interchangeably in this review, as in previous studies [16,17,24,25].

This review discusses the important themes of EA research, issues that remain unresolved, and future research directions.

Mechanism of emergence agitation

The precise pathophysiological mechanism of EA after general anesthesia is unknown [19,20]. In children, proposed causes of EA include high levels of anxiety regarding surgery, new environments, separation from parents, and encounters with unfamiliar medical staff [9,26]. These may lead to increased sympathetic tone and prolongation of the excited state during anesthesia recovery [27].

The advent of volatile agents with low blood solubility, such as sevoflurane and desflurane, has increased the incidence of EA in children [11,12,28]. A proposed explanation for this is that sevoflurane and desflurane cause differential recovery rates in brain function, due to differences in clearance of inhalational anesthetics from the central nervous system [12,29]; whereas audition and locomotion recover first, cognitive function recovers later, resulting in EA. In addition, elevated lactate and glucose concentrations in the parietal cortex due to sevoflurane anesthesia, and the occurrence of clinically silent sevoflurane-induced epileptogenic activity have been proposed to induce EA [16,30,31].

Functional magnetic resonance imaging has been used to study the mechanisms underlying the alteration of consciousness during anesthesia [32,33]. Studies have reported that alterations of brain network connectivity vary with the level of sedation. During emergence from general anesthesia, thalamocortical connectivity in sensory networks, and activated midbrain reticular formation are preserved. However, delayed recovery of impaired functionality of subcortical thalamoregulatory systems could contribute to defects in cortical integration of information, which could lead to confusion or an agitated state [33].

Proposed risk factors for emergence agitation

The etiology of EA is multifactorial [3]. It is important to identify the causes and risk factors of EA, and modify them, when applicable, to reduce incidence and prevent adverse consequences. Results from previous studies have been inconsistent due to the application of different assessment tools, definitions, and study designs (e.g., prospective randomized controlled studies, prospective observational studies, or retrospective studies). In addition, proposed risk factors of EA have been different for children and adults. Potential risk factors for EA in children are as follows: preschool age (2–5 years), no previous surgery, hospitalization or high number of previous interventions, poor adaptability, attention-deficit hyperactivity disorder, patient pre-existing behavior, psychological immaturity, preoperative anxiety, parental anxiety, patient and parent interaction with healthcare providers, lack of premedication (with midazolam), paradoxical reaction to midazolam stated in child's medical history, type of surgery, use of inhalational anesthetics with low blood–gas partition coefficients (e.g., sevoflurane and desflurane), excessively rapid awakening (in a hostile environment), and pain [6,12,17,29,34–36].

The proposed risk factors for EA in adults are age, sex, obesity (body mass index ≥ 30 kg/m^2), African ethnicity, number of intubation attempts, type of surgery, emergency operation, method of anesthesia (inhalation anesthesia), duration of surgery or anesthesia, pre-existing mental health problems (e.g., psychiatric problems or cognitive impairment), chronic lung disease, recent smoking, history of social drinking, substance misuse, anticholinergics, doxapram, premedication with benzodiazepines, voiding urgency, postoperative pain, postoperative nausea and vomiting, and the presence of invasive devices (e.g., urine catheter, chest tube, or tracheal tube) [2,3,8,18,21,37–44] (Table 1). We review common risk factors and other related issues presented in literature.

Age

EA is more common in children than in adults [38,45,46]. In a study of children aged 2–12 years, the incidence of EA was inversely correlated with age [47]. In a prospective cohort study of children aged 3–10 years, younger age was associated with increased risk of preoperative anxiety [48]. The frequency of EA after surgery was higher in children with preoperative anxiety than those without [49].

In adults, the association between age and EA have varied among studies. Age was not associated with EA in a prospective observational study of 2000 patients, and in a case-controlled study [2,3]. Among studies that showed a relationship between

https://doi.org/10.4097/kja.20097

Table 1. Possible Risk Factors for Emergence Agitation

Risk factor	Children	Adult
Patient related	Preschool age (2–5 years)	Age
	No previous surgery	Sex
	Hospitalization or high number of previous interventions	Obesity (body mass index ≥ 30 kg/m^2)
	Poor adaptability	African ethnicity
	Attention-deficit hyperactivity disorder	Pre-existing mental health problems (e.g., psychiatric problems or cognitive impairment)
	Patient preexisting behavior	Chronic lung disease
	Psychological immaturity	Recent smoking
	Preoperative anxiety	History of social drinking
	Parental anxiety	History of substance dependence
	Patient and parent interaction with healthcare providers	Number of intubation attempts
Anesthesia related	Lack of premedication (with midazolam)	Method of anesthesia (inhalation anesthesia)
	Paradoxical reaction to midazolam stated in child's medical history	Duration of surgery or anesthesia
	Use of inhalational anesthetics with low blood–gas partition coefficients (e.g., sevoflurane and desflurane)	Premedication with benzodiazepines
	Excessively rapid awakening (in a hostile environment)	Neuromuscular blocking agents and anticholinergics
	Pain	Doxapram
		Voiding urgency
		Postoperative pain
		Postoperative nausea and vomiting
		Presence of invasive devices (e.g., urine catheter, chest tube, or tracheal tube)
Surgery related	Type of surgery	Type of surgery
		Emergency operation

age and EA, a variety of age groups were reported as risk factors. Kim et al. [39] reported that young age was a risk factor for EA. Rim et al. [41] and Rose [50] reported that old age was a risk factor for EA. Radtke et al. [21] reported that EA more frequently affected younger (18–39 years) and older (≥ 65 years) patients compared to middle-aged (40–64 years) patients. In a recent study on EA after sevoflurane anesthesia, age ≥ 65 years was significantly associated with EA [40]. Age-related changes in physiology can increase drug sensitivity and toxicity in elderly patients compared to young adults [51,52]. Adverse events caused by EA can also have more serious consequences in elderly patients. Further studies in elderly patients will facilitate better prevention of EA.

Sex

The effect of sex on EA in children is not well known [53]. However, in a prospective observational study of children, sex was not associated with the occurrence of EA [54]. Conversely, several studies have shown that male sex is associated with EA in adults [3,8,38,41,55,56].The higher rate of EA in men is explained by lower pain tolerance and a significant association between postoperative pain and the male sex [41,57]. In addition, male sex is a risk factor for catheter-related bladder discomfort, which is defined as voiding urgency. Voiding urgency is an independent risk factor for EA [42,58].

Surgery

In a prospective cohort study of 521 children aged 3–7 years, ophthalmological and otorhinolaryngological procedures were found to be associated with EA. In particular, otorhinolaryngological procedures were independent risk factors for EA [29]. Similarly, several studies have identified strabismus surgery and tonsillectomy as risk factors for EA in pediatric patients [54].

In a prospective observational cohort study of 1970 adult patients, the type of surgery was not a risk factor for EA [8]. However, the type of surgery was associated with EA in multiple other studies [3,18,21,42]. Spine surgery, musculoskeletal surgery, oral cavity surgery, otolaryngological surgery, breast surgery, and abdominal surgery have been associated with a high risk of EA in adult patients [3,18,21,41].

Conflicting results have been reported, depending on whether elective or emergency surgery was performed. In a 2006 study, Lepouse et al. [18] found that emergency surgery did not affect the incidence of EA. In a 2019 study, Ramroop et al. [40] found that emergency surgery increased the risk of postoperative EA

compared to elective surgery. The authors speculated that greater anxiety and uncorrected physiological derangements may have contributed to the increased incidence of EA in patients undergoing emergency surgery.

Duration of surgery/anesthesia

The duration of anesthesia changes with the duration of surgery. Caution is needed when interpreting studies that suggest a longer duration of surgery or anesthesia is a risk factor for EA; only one of these parameters (i.e., anesthesia time or surgery time) may have been measured and analyzed in the given study [18,40,41]. In a study that analyzed both surgery and anesthesia time, patients with EA had significantly longer surgery and anesthesia times than patients without EA [42]. Furthermore, in a prospective observational study of 1868 adult patients, a longer duration of surgery was identified as a risk factor for hypoactive ED [21].

Inhalational anesthetics

Halothane, isoflurane, desflurane, and sevoflurane can all serve as triggers of EA; however, EA is more common with inhalational anesthetics with low blood–gas solubility, such as sevoflurane and desflurane [8,9,28]. In a meta-analysis of pediatric patients performed in 2015, desflurane induced EA less frequently than sevoflurane [59]. Similarly, in a randomized controlled double-blind study of adult patients with orthognathic surgery, desflurane reduced the incidence of EA compared to sevoflurane (24% vs. 71%, respectively) [4].

Nitrous oxide is an inhalational anesthetic agent commonly used in general anesthesia as an adjunct to other inhalational anesthetics; its use is reportedly not associated with EA [21,40]. Nitrous oxide was shown to attenuate EA in pediatric patients [60,61], but few studies have investigated its effects in adult patients. Therefore, further studies are needed to determine the impact of nitrous oxide on EA in adult patients.

Rapid awakening from anesthesia

In studies of pediatric patients, rapid awakening by strange medical staff in unfamiliar environments has been identified as a potential risk factor for EA [29,62]. However, the rapid awakening process did not cause a higher incidence of EA after sevoflurane anesthesia in children [63]. Moreover, a study of adult patients revealed that desflurane was associated with a lower incidence of EA compared to sevoflurane, although desflurane was associated with a more rapid recovery time [4].

Neuromuscular blocking agents and reversal agents

Anticholinergics (e.g., atropine and scopolamine) are known risk factors for EA [51,64,65]. Neuromuscular blocking agents and reversal agents, such as anticholinergics (e.g., glycopyrrolate and atropine), cholinesterase inhibitors (e.g., pyridostigmine and neostigmine), and sugammadex, are commonly used for general anesthesia. However, only a few randomized controlled trials have been conducted to assess the effects of neuromuscular blocking agents and/or reversal agents on EA. In a prospective randomized controlled study, rocuronium-sugammadex reduced the incidence, severity, and duration of EA in patients undergoing closed reduction of nasal bone fracture compared to succinylcholine [5]. The authors speculated that elevated lactate and potassium concentrations, incomplete neuromuscular blockade during surgery, increased intraocular pressure, and histamine release due to administration of succinylcholine may have led to more negative effects on EA, relative to those caused by the use of rocuronium-sugammadex. Studies comparing the effects of sugammadex and cholinesterase inhibitors on EA have shown inconsistent results. In a retrospective study of children undergoing strabismus surgery, sugammadex showed no EA-preventive effect compared to pyridostigmine + glycopyrrolate [66]. In contrast, a prospective randomized controlled study of children undergoing adenotonsillectomy revealed that the use of sugammadex decreased the severity of EA resulted in less EA compared to the use of neostigmine + atropine [67]. Studies of EA-related drugs have mainly focused on sedatives and analgesics. Further studies are needed to investigate the effects of the depth of intraoperative neuromuscular blockade, sugammadex, and cholinesterase inhibitors on EA.

Pain

Pain is a major risk factor for EA in both children and adults, although EA has been reported in spite of pain-free procedures and may occur regardless of pain intensity [3,6,9,11,38,68]. These findings indicate that EA and postoperative pain are separate clinical phenomena; however, it is difficult to distinguish between EA and behavioral changes due to postoperative pain [69,70]. In adults, when postoperative pain was assessed with a numerical rating scale, a score ≥ 5 points was found to increase the risk of EA [21,38,39]. Nonetheless, EA may increase postoperative pain. Therefore, adequate perioperative pain control may influence onset of EA.

https://doi.org/10.4097/kja.20097

Presence of invasive devices

The presence of invasive devices (e.g., urine catheters, nasogastric tubes, chest tubes, and tracheal tubes) during emergence is a well-known risk factor for EA [2,3,8,39]. It can cause embarrassment, distress, discomfort, and pain in patients during emergence; it can also exacerbate delirium in the PACU by increasing the use of opioids and benzodiazepines [13,43].

Prediction of emergence agitation

Prevention is preferred over treatment, for EA; EA can have serious consequences for patients, and increase the patient care burden [16,71]. Recently, Hino et al. [54] developed and validated the EA risk scale (consisting of four domains—age, Pediatric Anesthesia Behavior score, operative procedure, and anesthesia time) for children receiving sevoflurane anesthesia in a single-center study. The EA risk scale showed excellent predictive performance. Therefore, the EA risk scale may be used to predict and prevent EA after sevoflurane anesthesia in pediatric patients. However, the EA risk scale is not validated for use in patients anesthetized with drugs other than sevoflurane. Further studies are needed to demonstrate external validity in other hospitals. In addition, for effective prevention of EA, it would be helpful to identify a biomarker that could predict the occurrence of EA, based on preoperative blood sample examination. In elderly patients undergoing gastrointestinal surgery, the plasma level of brain-derived neurotrophic factor (BDNF) collected at skin closure via blood sampling was significantly increased in patients with EA [72]. However, the study showed that the level of plasma BDNF collected before induction of anesthesia did not differ between patients who did and did not show EA. The study included only a limited number of well-selected patients. Thus, larger-scale clinical trials are needed to ensure the validity of BDNF as a predictive biomarker for EA. In addition, if the occurrence of postoperative EA can be predicted through objective monitoring during surgery, it may contribute to improved postoperative outcomes by preventing the occurrence of EA. In a prospective observational study published in 2019, the occurrence of specific electroencephalogram patterns (burst suppression and emergence trajectory) during anesthesia was associated with PACU delirium [73]. The authors could not provide information regarding agitation during emergence because all patients underwent assessment for PACU delirium after the return of consciousness. However, they suggested that EA could be predicted through intraoperative patient monitoring.

Assessment tools for emergence agitation

Although several scales and their variants have been proposed as tools for assessing EA in children, the most commonly used in pediatric EA studies is the Pediatric Anesthesia Emergence Delirium (PAED) scale developed in 2004 (Table 2). It provides a score from 0 to 20 and reportedly shows validity for assessment of EA in children [74]. However, the PAED scale has disadvantages of inherent subjectivity in assessing each behavior item and suboptimal interrater reliability [75]. In addition, the cutoff point for defining the presence of EA is controversial. Bong and Ng [76] suggested that PAED score ≥ 10 was the ideal cutoff for EA. In contrast, Bajwa et al. [69] reported that PAED score > 12 had greater sensitivity and specificity than PAED score ≥ 10 in the assessment of EA PAED. In another study, PAED score ≥ 16 was adopted as an indicator of EA without an obvious rationale [68].

In adults, the Riker Sedation-Agitation Scale (RSAS, 7-point scale with three levels of agitation) [71], Richmond Agitation-Sedation Scale (RASS, 10-point scale with four levels of agitation) [77], Aono's 4-point scale [78], Nurses Delirium scale [79], and the 3-point scale (graded as mild, moderate, or severe) [3] have been introduced for assessment of EA (Table 2). Although the RSAS and RASS have been commonly used, and show high interrater reliability in adult intensive care unit patients [80,81], none of the scales have been validated in the operating room and/or the PACU. There have been few studies of EA in intensive care unit patients [37]; the majority of EA studies have been performed in PACUs or operating rooms [19,20,82]. Consequently, the reported incidence of EA differed with the evaluation site (e.g., operating room vs. PACU), assessment tool (e.g., RSAS vs. RASS), and definition of EA (e.g., RASS ≥ +1 vs. ≥ +2 vs. ≥ +3). The reported incidence of EA was higher in the operating room when emerging from general anesthesia than in the PACU (e.g., 3.7% vs. 1.3% and 54.3% vs. 28.6%, respectively) [8,38,83]. The RSAS tended to show an incidence of EA that was similar to or higher than the incidence indicated by the RASS for the same patient group (13.8% by the RSAS vs. 11.2% by the RASS, respectively) [83] or same

Table 2. Assessment Tools for Emergence Agitation

Children
Pediatric Anesthesia Emergence Delirium scale
Adults
Riker Sedation-Agitation Scale
Richmond Agitation-Sedation Scale
Aono's 4-point scale
Nurses Delirium scale
Three-point scale (graded as mild, moderate, or severe)

type of surgery (50% by the RSAS vs. 22% by the RASS, respectively) [39,82]. Fields et al. [2] used RASS ≥ +3 as an indicator of EA, while Jee et al. [20] and Ham et al. [84] adopted RASS ≥ +2 as an indicator of EA; most other groups defined RASS ≥ +1 as an indicator of EA [38,39,83].

Standardized clinical research practice guidelines are needed to reduce the variations of EA incidence with assessment tools and definitions among researchers. Furthermore, there is a need to develop a tool that can objectively evaluate the degree of agitation, in a manner similar to the bispectral index, which is an objective tool for assessing the depth of sedation during general anesthesia.

Strategies to prevent emergence agitation

In this section, we review strategies to prevent EA, classified into pharmacological and non-pharmacological methods (Table 3). Caution is needed when interpreting the results of studies comparing the preventive effects of drugs or agents on EA; the same drugs may not have identical effects depending on the dose, method of administration (e.g., continuous infusion or single bolus), timing of administration, or patients (e.g., children, adults, or elderly patients) [20,85].

Pharmacological methods

Choice of anesthesia methods: Total intravenous anesthesia, inhalational anesthesia, balanced anesthesia

Several types of anesthesia methods may be used—total intravenous anesthesia (TIVA), inhalational anesthesia, or balanced anesthesia. In a randomized controlled trial, TIVA with propofol and remifentanil reduced EA compared to volatile induction and maintenance of anesthesia with sevoflurane, in children aged 2–6 years, after strabismus surgery [86]. However, conflicting results have been reported regarding the effects of balanced anesthesia vs. inhalation anesthesia on EA in pediatric patients [47,87–89]. This was presumably due to differences in the types of surgery (i.e., fiberoptic bronchoscopy, adenotonsillectomy, or minor surface surgery), adjuvant analgesics (i.e., ketorolac and dexamethasone compared to none), regimens of balanced anesthesia (i.e., sevoflurane-remifentanil or sevoflurane-fentanyl), and tools for assessment of EA. In addition, the effects of balanced anesthesia on EA can differ with the doses of drugs that are administered, even with the same regimen [88,89]. Thus, further studies are needed to determine the optimal doses for effective EA prevention.

In adults, the effects of anesthetic techniques on EA showed diverse results; overall, TIVA showed no significant difference or lower incidence of EA compared to inhalational anesthesia [3,18,37,39,42,83]. In a prospective study of 1,359 patients, and a retrospective study of 488 patients, the incidence of EA did not differ with the anesthetic technique [18,42]. Conversely, EA was less frequent with TIVA than with inhalational anesthesia in both a prospective observational study of 2,000 patients, and a retrospective study of 792 patients [3,39]. Similarly, in a prospective cohort study, TIVA and a short duration (≤ 5.7 hours) of balanced anesthesia protected against EA [37]. In addition, a prospective randomized controlled clinical study showed that TIVA with propofol and remifentanil reduced the incidence of EA compared to volatile induction and maintenance of anesthesia with sevoflurane [83]. Therefore, TIVA may be appropriate for patients with a high risk of EA.

In a multicenter randomized controlled trial of adult patients undergoing elective craniotomy, the incidences of EA were similar in patients undergoing balanced anesthesia (sevoflurane-remifentanil and sevoflurane-fentanyl) and those undergoing TIVA (propofol-remifentanil) [90]. However, in that study, agitation was only evaluated as an adverse outcome; no specific definition of agitation was provided, and no tool for assessment of agitation was specified. Therefore, further well-designed prospective studies are needed to compare the effects of balanced anesthesia and TIVA on EA.

Propofol

Propofol is the preferred drug for the prevention and treatment

Table 3. Strategies to Prevent Emergence Agitation

Pharmacological methods
Total intravenous anesthesia
Propofol
Opioids
Ketamine
Magnesium sulfate
Tramadol
Nefopam
Dexmedetomidine
Regional analgesia
Multimodal analgesia
Avoidance of premedication with benzodiazepine (especially in adults)
Non-pharmacological methods
Informing the patient of predictable pain or discomfort prior to anesthesia
Removing indwelling invasive devices as early as possible
Parental presence during induction of anesthesia and recovery (in pediatric patients)
Family-centered behavioral preparation for surgery

https://doi.org/10.4097/kja.20097

of EA in pediatric patients [36,91]. In a meta-analysis of pediatric patients, propofol showed a prophylactic effect against EA, depending on the timing of administration [85]. An intravenous bolus of 2 mg/kg propofol, administered immediately after induction of anesthesia, did not reduce EA after desflurane anesthesia [92]. In contrast, continuous infusion of propofol during maintenance of anesthesia, or addition of a bolus of propofol at the end of surgery showed a preventive effect against EA in pediatric patients undergoing general anesthesia [93–95]. These effects can be explained mainly by the rapid pharmacokinetics of propofol [85]. As observed in pediatric patients, continuous infusion of propofol alone during maintenance of anesthesia reduced the incidence of EA in adult patients undergoing closed reduction of nasal bone fracture compared to sevoflurane anesthesia [96]. However, to the best of our knowledge, there are no studies on the effects of a single bolus injection of propofol at the end of surgery on EA in adult patients. Therefore, further research is needed on this aspect of propofol usage.

Opioids

In a meta-analysis of 19 randomized controlled trials with 1528 children, prophylactic administration of μ-opioid agonists (i.e., fentanyl, sufentanil, alfentanil, or remifentanil) was found to reduce the incidence of EA following sevoflurane anesthesia [97]. In addition, in a meta-analysis of 37 studies with 3,172 children, fentanyl had a prophylactic effect in the prevention of sevoflurane- and desflurane-related EA [85]. In contrast to children, only a few studies assessed the effects of opioids on EA in adult patients. In a prospective double-blind randomized trial of 60 adult patients, maintenance of low-dose remifentanil (range 0.01–0.05 μg/kg/min) infusion during the emergence phase reduced the incidence of non-purposeful movement [98]. In a randomized double-blind placebo-controlled study of 34 adult patients undergoing an oral surgical procedure, intravenous injection of alfentanil (15 μg/kg) during emergence suppressed EA after isoflurane anesthesia compared to placebo [99]. In a randomized controlled trial comparing pre-anesthesia use of fentanyl and oxycodone, an intravenous bolus of oxycodone (0.2 mg/kg) reduced the incidence of EA compared to a bolus of fentanyl (2 μg/kg); however, it resulted in delayed awakening in patients undergoing closed reduction of nasal bone fracture under desflurane anesthesia [100].

Ketamine

Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, which has sedative, amnestic, and analgesic properties. Ketamine (0.25 mg/kg and 0.5 mg/kg) administered 10 minutes before the end of surgery contributed to EA prevention without delayed recovery in children after sevoflurane anesthesia [101,102]. At the dose of 0.5 mg/kg, ketamine did not show a significant difference in the incidence of EA compared to 0.25 mg/kg; however, patients' pain scores decreased as the dose of ketamine increased [102]. In adult patients undergoing anesthesia with sevoflurane, 0.5 mg/kg of ketamine injected 20 minutes before the end of surgery contributed to EA prevention after rhinoplasty; however, it prolonged the anesthesia time due to delayed recovery [38].

Magnesium sulfate

Magnesium sulfate is a noncompetitive NMDA receptor antagonist, which has central sedative, neuroprotective, and analgesic-sparing effects [103,104]. In a study of pediatric patients (3–16 years old), magnesium sulfate (30 mg/kg) administered 10 minutes prior to the end of surgery did not reduce EA after sevoflurane anesthesia [105]. In contrast, a 30 mg/kg bolus with continuous infusion of 10 mg/kg/h (from the start of surgery to the end of surgery) reduced the incidence and severity of EA in pediatric patients (4–7 years) undergoing the same surgery (adenotonsillectomy) under sevoflurane anesthesia [53]. The authors speculated that the neuroprotective and anticonvulsant properties of magnesium sulfate may have reduced the incidence of EA. Similarly, in a randomized double-blind placebo-controlled trial in adult patients (20–60 years old) undergoing endoscopic sinus surgery, magnesium sulfate administered throughout the surgery was effective in preventing EA [104].

Tramadol

Tramadol is an atypical centrally acting opioid that inhibits M1 and M3 muscarinic acetylcholine and nicotinic acetylcholine as well as NMDA receptors [106–108]. In a retrospective cohort study, a single dose (2 mg/kg) of tramadol administered intravenously at the start of surgery was found to reduce the incidence of EA after sevoflurane anesthesia in adult patients undergoing nasal surgery [19]. The authors speculated that the analgesic, antitussive, and anti-shivering effects of tramadol, as well as its ability to reduce voiding urgency, may have resulted in the prevention of EA. In a prospective randomized controlled study of children undergoing adenotonsillectomy with sevoflurane anesthesia, 2 mg/kg of tramadol intravenous infusion after tracheal intubation for 10 minutes was found to show a similar protective effect against EA compared to 1 μg/kg of dexmedetomidine administered in the same manner [109].

Nefopam

Nefopam is a centrally acting nonnarcotic analgesic drug. Nefo-

pam modulates glutaminergic transmission via inhibition of postsynaptic NMDA receptors, while inhibiting serotonin and noradrenaline reuptake; thus, it has anticonvulsant, antidepressant, anti-shivering, and opioid-sparing effects [110,111]. In a prospective randomized controlled trial, 20 mg of nefopam infusion for 20 minutes immediately after induction of anesthesia was found to be effective in reducing the incidence and severity of EA after desflurane anesthesia in adult patients undergoing nasal surgery [20].

α_2-adrenoreceptor agonists

α_2-adrenoreceptor agonists (clonidine and dexmedetomidine) possess sympatholytic, analgesic, and sedative properties [112–114]. In a double-blind trial, 2 μg/kg of clonidine injected intravenously after induction of anesthesia was found to effectively reduce the incidence and severity of sevoflurane-induced EA in male children [115]. In addition, in a meta-analysis that examined clonidine as a premedication agent in children, premedication with clonidine was found to be superior to premedication with midazolam for attenuation of EA [112].

Dexmedetomidine is a highly selective α_2-adrenoreceptor agonist with 7 to 8-fold greater affinity for the α_2-adrenoreceptor compared to clonidine [116]. In a meta-analysis of the effects of dexmedetomidine on EA after sevoflurane anesthesia in children, dexmedetomidine was found to reduce the incidence of EA compared to placebo; however, it was associated with a delay in recovery [117]. Nonetheless, in a network meta-analysis study of the effects on EA, of anesthetic adjuvants for sevoflurane anesthesia in children, dexmedetomidine was found to be the most effective drug for prevention of EA compared to ketamine, propofol, clonidine, midazolam, fentanyl, and sufentanil [118]. Furthermore, in adult patients undergoing nasal surgery, an intraoperative dexmedetomidine infusion (0.4 μg/kg/h) provided hemodynamically stable emergence and an EA reduction effect, without a delay in extubation [82]. In contrast, in adult patients undergoing microvascular free flap surgery, preoperative and postoperative dexmedetomidine infusions did not affect the overall incidence of EA [119]. In addition, in adult patients undergoing orthognathic surgery, the addition of a single dose of dexmedetomidine (1 μg/kg) to postoperative remifentanil infusion (0.02 μg/kg/min) did not reduce the incidence of EA compared with remifentanil infusion alone [84]. In adult patients undergoing nasal surgery with desflurane anesthesia, dexmedetomidine infusion (0.04 μg/kg/h) from the induction of anesthesia to extubation showed a better EA preventive effect than placebo (saline) infusion; however, it was inferior to remifentanil infusion (0.05 μg/kg/min) [120].

Benzodiazepines

Benzodiazepines, especially midazolam, are commonly used as premedication agents to provide anxiolysis, sedation, and amnesia in adults and children [36,121,122]. The effects of preoperative administration of midazolam on EA in pediatric patients were inconsistent [86,123]. Specifically, in a meta-analysis published in 2010 [85], prophylactic administration of midazolam showed no preventive effect against EA in children anesthetized with sevoflurane, desflurane, or both. In contrast, another meta-analysis (published in 2013) indicated that prophylactic administration of midazolam reduced sevoflurane-induced EA [123]. In adults, premedication with benzodiazepines or a patient history of long-term benzodiazepine use increased the risk of EA [18,21,37]. Avoidance of benzodiazepine premedication can be helpful for preventing EA in adults [124].

Interestingly, in contrast with the effects of benzodiazepine premedication, perioperative administration of midazolam reduced EA in both children and adults. Intravenous injection of 0.03 mg/kg of midazolam immediately before the end of the operation reduced EA in children undergoing strabismus surgery with sevoflurane anesthesia [125]. In addition, infusion of midazolam from 15 minutes before anesthesia induction to the end of surgery provided an EA reduction effect similar to that of dexmedetomidine infusion in adult patients undergoing nasal surgery with sevoflurane anesthesia [126].

Regional analgesic techniques

Because postoperative pain is a major risk factor for EA, several studies have been conducted to investigate whether effective pain control through regional blockade can reduce the incidence and/or severity of EA, while reducing the side effects of systemic analgesics. In a prospective randomized double-blind study of 2 to 6-year-old children undergoing inguinal hernia repair under sevoflurane anesthesia, preoperative caudal block was found to reduce the incidence of EA compared to intraoperative intravenous fentanyl (4.5% vs. 59%, respectively) [35]. Peripheral nerve blockade also reduced the incidence or severity of EA in pediatric patients following sevoflurane anesthesia [127,128]. Infraorbital nerve block reduced the incidence and duration of EA in children undergoing cleft lip repair surgery [127], while fascia iliaca compartment block reduced the severity of EA in children undergoing orthopedic surgery that involved the anterior or lateral thigh [128]. Wang et al. [127] speculated that EA may have been reduced as a result of reduction in the amount of intraoperative sevoflurane, as well as reduction in pain caused by the infraorbital nerve block performed at the start of surgery. However, a randomized controlled trial involving different concentrations of

https://doi.org/10.4097/kja.20097

sevoflurane did not show significant reduction of EA in children [24]. Further studies are needed to determine the mechanism by which regional analgesia reduces EA.

Multimodal analgesia

Ketamine, magnesium, tramadol, nefopam, α_2-adrenoreceptor agonists (e.g., clonidine or dexmedetomidine), acetaminophen, nonsteroidal anti-inflammatory drugs (e.g., ketorolac), dexamethasone, gabapentinoids, and regional analgesia are included in multimodal analgesia [129]. However, only a few studies have evaluated the effects of multimodal analgesic regimens on EA. In a prospective randomized double-blind controlled study, administration of low-dose ketamine (0.15 mg/kg) followed by dexmedetomidine (0.3 μg/kg), both administered intravenously approximately 10 minutes before the end of surgery, was found to reduce the incidence and severity of EA in pediatric patients undergoing adenotonsillectomy using sevoflurane anesthesia compared to the administration of volume-matched saline [130]. Notably, ketamine administration at the end of surgery in children undergoing sevoflurane anesthesia (after performing caudal block prior to surgery) could not further reduce EA compared to the placebo group [131]. In children aged 2–10 years, who received preemptive analgesia using acetaminophen and ketorolac, intravenous administration of clonidine (2 μg/kg) reduced the incidence of EA, but lengthened the duration of PACU stay and frequency of postoperative sleepiness compared to children who received preemptive analgesia alone [132].

Further prospective randomized controlled studies with multimodal analgesic regimens are needed to identify drug combinations with better EA preventive effects and fewer adverse effects.

Non-pharmacological methods

Informing patients of predictable surgical pain or discomfort from the presence of invasive devices during emergence, prior to the induction of anesthesia, is expected to aid in prevention of EA by reducing sudden embarrassment. Early removal of indwelling invasive devices is expected to aid in relief of EA [3,39]. However, there remains a lack of scientific evidence for the EA reduction effects of these methods in adult patients.

In pediatric patients, preoperative anxiety is a risk factor for EA; recovery in strange environments can also cause EA [63]. Parental presence during induction of anesthesia was found to improve the effect of oral midazolam on EA in children aged 1–3 years undergoing sevoflurane anesthesia [133]; parental presence upon the patient's arrival in the PACU is also expected to help reduce EA in pediatric patients [131]. In addition, family-centered behavioral preparation for surgery, which includes preoperative education and training of children and their parents, was found to reduce the incidence of EA in pediatric patients aged 2–10 years compared to administration of oral midazolam (0.5 mg/kg) at 30 minutes prior to surgery [134].

Management of emergence agitation

EA is a self-limiting phenomenon, which lasts for only a short period (1–15 minutes) [5,11]. The elimination of causative factors (e.g., pain, anxiety, presence of invasive devices) is the mainstay of EA management [3,39]. Differential diagnosis and prompt treatment should also be performed for conditions that can lead to disorientation, such as increased intracranial pressure, bladder distention, upper airway obstruction, hypo- and hyperglycemia, hypotension, hypoxia, and hypercarbia [11]. Two web-based surveys conducted by pediatric anesthesiologists in Canada and Germany [36,91] revealed that sedatives (e.g., propofol and midazolam) and opioids (e.g., fentanyl and morphine) were preferred therapeutic pharmacological treatments for EA. Rarely, some anesthesiologists chose "wait for spontaneous resolution" and/or "parental presence" as the first choice of therapy for EA [36]. To the best of our knowledge, there has only been one randomized controlled trial to evaluate the effects of therapeutic strategies on EA, which compared physostigmine and placebo as its treatments [135]. Further studies are needed to determine the efficacy of pharmacological or non-pharmaceutical interventions (e.g., parental presence) for treatment of established EA.

There have been few EA-related studies in adults compared to studies performed in children. Since the results of the studies in children cannot be extrapolated to adults, it is necessary to verify the consistency of the results for children by performing randomized controlled trials in adults. The establishment of standardized clinical research practice guidelines and the development of objective assessment tools for EA are needed to reduce the discrepancies of EA incidence among various studies, and facilitate better interpretation of the results from published studies. Effective EA prevention involves the identification of risk factors, elimination of correctable risk factors, and the application of pharmacological and non-pharmacological strategies on patients or during surgeries with high risks of EA. Strategies to reduce EA may vary with patient age (i.e., children vs. adults). Considerations for the dosage, timing, and method (e.g., bolus or continuous infusion) of administration of the agent should be made before applying pharmacological methods. In the future, prediction through objective indicators (before or during surgery) is expected to aid in preventing EA.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Seok-Jin Lee (Conceptualization; Writing – original draft; Writing – review & editing)
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