Prevention of Sevoflurane Delirium and Agitation With Propofol

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Emergence delirium and agitation (EAD) associated with sevoflurane general anesthesia are very commonly observed in young children. Such events pose a risk for injury as well as decreased parental satisfaction, especially in the ambulatory and office-based setting. This article reviews the different approaches described in the literature to reduce EAD. A novel approach using a Bispectral Index System (BIS)-guided anesthesia with propofol washout technique is proposed as a viable and effective approach to prevent EAD.

Key Words: Agitation; Delirium; Propofol; Sevoflurane.

Inhalation anesthesia has been known to cause emergence delirium and agitation, particularly in young children. Halothane was the induction agent of choice for children for 4 decades until the advent of sevoflurane, which offered better clinical outcomes in the pediatric patient. Sevoflurane is advantageous because it does not cause significant cardiac depression and dysrhythmias compared to halothane. Inhalation induction and maintenance are often necessary in children who are uncooperative and combative. There are numerous other advantages of sevoflurane inhalation and maintenance of general anesthesia in children. Inhalation anesthesia does not require intravenous access and patient cooperation during the initial stages of induction. Sevoflurane anesthesia is also easy to titrate for maintaining an adequate level of anesthesia, especially for the intubated and spontaneously breathing pediatric patient in a dental office. It also is a potent bronchodilator, which can offer an added benefit especially in children with a history of asthma. While sevoflurane has clearly become the inhalation induction agent of choice, it also presents a high incidence of emergence delirium and agitation compared to other inhalation anesthetic agents. This article will review the various agents investigated for the reduction of emer-

gence agitation and delirium (EAD), including the limitations of such techniques. Since Bispectral Index System (BIS)-guided anesthesia has been proven to be very useful in various aspects of ambulatory pediatric anesthesia, including reducing extubation, recovery, and discharge times, a novel technique employing the BIS-guided supplemental propofol anesthesia in the final stages of office-based pediatric sevoflurane general anesthesia is proposed to reduce the incidence of EAD.

DISCUSSION

All inhalation anesthetic agents are known to cause EAD. The incidence of postsevoflurane EAD has been described in the literature¹ to be as high as 58%, with an increased prevalence in toddlers and preschool-age children. The etiology of EAD is not clearly understood. Yasui et al² described an increase in noradrenaline release in the preoptic rat brains, especially in the locus coeruleus. It has been suggested that this also leads to disorientation in the early stages of recovery, which leads to the agitation component of EAD.

Cravero et al¹ described a 58% incidence of EAD in children undergoing sevoflurane anesthesia for bilateral myringotomy and insertion of ear tubes compared to 27% among children receiving halothane anesthesia. A

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longer postanesthesia discharge time was also documented among the sevoflurane group.

It is also understood that younger children have a significantly higher prevalence of EAD than older children do. Aono et al³ evaluated 2 groups of American Society of Anesthesiologists Physical Classification I (ASA PS I) children undergoing minor urologic procedures under halothane or sevoflurane anesthesia. Among 63 children of preschool age (3–5 years old), 40% of the sevoflurane group developed EAD compared to 10% of the halothane group. Among 53 children of school age (6–10 years old), 11.5% of the sevoflurane group developed EAD, while 15.4% of the halothane group had EAD. This implies that there is a possible behavioral and brain maturity component to EAD in addition to differences among anesthetic drugs administered.

Sikich and Lerman⁴ reported the development of a psychometric evaluation scale for assessment of pediatric anesthesia emergence delirium (PAED) by assigning a score of 1–4 to 5 different criteria.

- Criteria 1: Child makes eye contact with caregiver.
- Criteria 2: Child's actions are purposeful.
- Criteria 3: Child is aware of his/her surroundings.
- Criteria 4: Child is restless.
- Criteria 5: Child is inconsolable.

While earlier studies have assessed the EAD either subjectively or through simpler scoring methods, Sikich and Lerman⁴ provided a measureable psychometric tool to assess EAD with a higher level of objectivity.

Numerous drugs, including those listed below, have been tried to help prevent EAD as described.

MIDAZOLAM

In 2001, Kulka et al⁵ published a study in German describing a single-dose technique for children ages 2–7 years undergoing minor ambulatory surgery by administering midazolam, 0.1 mg/kg intravenously, at the end of the procedure. They reported this technique to be effective in the reduction mild EAD but ineffective in severe cases.

Utilizing the PAED scale, Breschan et al⁶ compared 2 intrarectal doses of midazolam, 0.5 mg/kg or 1 mg/kg, given to 115 children at the beginning of ambulatory surgical procedures. The first group had a 42.1% incidence of severe EAD compared to 36.2% in the second group. Advantages of the use of midazolam are summarized as follows:

- (a) it augments the amnesic effect during emergence;
- (b) it has mild muscle relaxant effects;
- (c) it has a relatively high therapeutic index; and

- (d) it has anxiolytic activity.

Unfortunately, the above-mentioned studies indicate that the use of midazolam intravenously and intrarectally seems to yield mixed results in terms of EAD prevention.

KETAMINE

Abu-Shahwan and Chowdary⁷ studied 85 children ages 4–7 years who were undergoing ambulatory dental rehabilitation under intubated sevoflurane general anesthesia. The study subjects were divided into 2 groups. Group 1 received an intravenous bolus of 0.25 mg/kg of ketamine during the procedure, while group 2 received a placebo saline injection. Group 1 had a 16.5% incidence of EAD compared to 34.2% for group 2. While the rate of EAD was reduced in half in the ketamine group compared to placebo, there was still a significant percentage occurring in the ketamine group. Although the reasoning behind the selection of the dose of ketamine was not clearly explained, one may speculate that this relatively low dose was intended to achieve the desired effect without prolonging recovery time or increasing the chance of ketamine-related psychogenetic side effects. As an N-methyl-D-aspartate receptor blocker, ketamine can provide a level of dissociative sedation that could be advantageous in the early stages of recovery when EAD is prevalent. Ketamine can also provide postoperative analgesia that can also reduce child anxiety. Unfortunately, ketamine tends to be unpopular with many anesthesiologists who are not experienced in using it due to its potential for causing emergence hallucinations and lowering the seizure threshold in highly seizure-prone individuals. However, both of these undesirable side effects have been linked to ketamine administration at much higher doses than what was reported in the literature to help eliminate EAD. Prolongation of recovery time often associated with higher doses of ketamine should not be a concern with the dose in the above-mentioned study. Nevertheless, 16.5% still represents a high incidence of EAD.

ALFENTANIL

Kim et al⁸ studied the administration of alfentanil in 105 children who were undergoing sevoflurane anesthesia for tonsillectomy and adenoidectomy. The study subjects were given 10 µg/kg or 20 µg/kg of alfentanil or a placebo control. Compared to the placebo group, the 2 alfentanil groups showed a statistically significant lower incidence of EAD. There was no statistically significant reduction in the 20 µg/kg group compared to the 10 µg/

kg group. Recovery time was not statistically different among all 3 groups. While alfentanil is effective in reducing EAD and useful in providing postoperative analgesia, many anesthesiologists prefer to provide narcotic-free anesthesia care in the office-based ambulatory setting to avoid increased recovery time, nausea, vomiting, and possible respiratory depression in small children.

DEXMEDETOMIDINE

Dexmedetomidine is a fairly new drug. Because it possesses α_2 receptor agonist and α_1 receptor antagonist effects, it provides several clinical advantages, including sedation, analgesia, and reduction of blood pressure. It has been studied extensively as a sedative agent in dental office-based sedation as well as an adjunctive agent in general anesthesia. Forty-two children ages 18 months to 10 years who were undergoing diagnostic magnetic resonance imaging with sevoflurane anesthesia were studied by Isik et al⁹ based on the PAED scale described by Sikich and Lerman. Group 1 was given 1 $\mu\text{g}/\text{kg}$ of dexmedetomidine, while group 2 received a placebo injection. An EAD incidence of 4.8% was reported in group 1 versus 47.6% in group 2 without significantly increasing recovery time. This study demonstrated the most remarkable desirable EAD prevention effect of all of the above listed techniques. A study by Shukry et al¹⁰ evaluated a different approach by administering 0.2 $\mu\text{g}/\text{kg}/\text{h}$ of dexmedetomidine over the duration of the procedure in 50 children ages 1–10 years under sevoflurane anesthesia. The dexmedetomidine group had a 26% incidence of EAD compared to 60.8% in the placebo group. This approach with dexmedetomidine was not nearly as successful as the technique described by Isik et al⁹, but nevertheless demonstrated significant preventative activity. Unfortunately, dexmedetomidine (Precedex) is still under patent, which makes it a cost-prohibitive option, especially in the office-based environment.

PHYSOSTIGMINE

Physostigmine, a parasympathomimetic alkaloid, has been used often in the past to treat postanesthesia delirium. In a study involving 211 children ages 1–5 years who underwent sevoflurane anesthesia with midazolam oral premedication and various analgesic regimens, some of which included remifentanyl, Funk et al¹¹ evaluated the intravenous administration of physostigmine to highly agitated children in the postoperative period. Half of the group was given physostigmine, 30

$\mu\text{g}/\text{kg}$, and the other half was given placebo. Severe agitation was still present in 10 of 20 patients in the physostigmine group versus 16 of 20 in the placebo group. The difference was not statistically significant. This study included so many variables in the anesthesia protocols that validating the outcome is difficult. The use of physostigmine has been based on the assumption that the agitation was caused by central anticholinergic syndrome, a point that may not be applicable in the case of sevoflurane-induced delirium and agitation. This particular study did not support the routine use of physostigmine for that purpose.

ACUPUNCTURE

Lin et al¹² studied the use of acupuncture in the reduction of postsevoflurane EAD in 60 children ages 1–6 years undergoing insertion of bilateral myringotomy ventilation tubes. This prospective randomized controlled trial was designed to evaluate the effectiveness of acupuncture to control pain and agitation after placement of the tubes in 60 unpremedicated children. Acupuncture was applied at points LI-4 (he gu) and HT-7 (shen men) immediately after induction of anesthesia. A single-blinded assessor evaluated postoperative pain and agitation using Children's Hospital Eastern Ontario Pain Scale (CHEOPS) and emergence agitation scale. Pain and agitation scores were significantly lower in the acupuncture group compared to those in the control group at the time of arrival in the postanesthesia care unit and during the subsequent 30 minutes. This suggests that acupuncture could be useful in reducing EAD in children. Acupuncture is a technique that requires specialized training and in some locations, separate licensure or certification.

PROPOFOL

Propofol is an anesthetic that is utilized very commonly as a sedative as well as an induction agent for general anesthesia. Aouad et al¹³ studied 80 healthy children ages 2–6 years undergoing strabismus surgery under sevoflurane general anesthesia. The PAED score of 10 or below was deemed acceptable in this study. Group 1, which was given intravenous propofol 1 mg/kg at the end of surgery, had a 19.5% incidence of EAD compared to 47.2% in the placebo group. While the propofol group at that dose had a significantly lower percentage, it is still far from ideal. Recovery time was also increased in the propofol group compared to the placebo group. When setting the PAED acceptable score at 16, Abu-Shahwan¹⁴ reported a 4.8% incidence of

EAD in the propofol 1 mg/kg group compared to 26.8% in the placebo group. One can speculate that setting the bar lower with regard to the acceptable PAED score could be partially responsible for their significantly better outcome compared to the Aouad study.

Propofol offers several advantages:

- (a) it has a shorter recovery time without persistent residual anesthetic effects;
- (b) it has an antiemetic effect at general anesthesia levels; and
- (c) it is cost-effective and easy to administer and titrate by steady-state infusion devices.

PROPOSED TECHNIQUE TO MINIMIZE THE INCIDENCE OF SEVOFLURANE-ASSOCIATED EAD

While sevoflurane carries the risk of malignant hyperthermia (estimated at 1 : 13,000) and a significantly high incidence of EAD, it is still a very valuable anesthetic agent for children. The availability of sophisticated physiologic monitors to quickly diagnose malignant hyperthermia and the immediate availability of intravenous dantrolene to effectively treat it has markedly increased the margin of safety of sevoflurane general anesthesia. It offers a needleless mask induction alternative for highly anxious healthy children without adversely affecting their hemodynamic stability. The ability to initiate mask induction without having to forcefully insert an intravenous catheter in a highly anxious or combative child is extremely valuable. During the propofol and fentanyl shortage that was experienced in the United States recently, sevoflurane certainly provided a safe and effective anesthetic option for practitioners to provide general anesthesia for fearful children as well as for children and adults with special needs undergoing dental rehabilitation in the office or ambulatory setting. Since sevoflurane is such a valuable anesthetic in pediatric ambulatory procedures, an effective method to reduce its undesirable EAD effects is necessary. The above-referenced propofol studies showed a high percentage of PAED when the acceptable threshold was 10 and a much lower percentage when the acceptable threshold was 16. It is obvious that a different approach needs to be evaluated.

BIS is a valuable monitoring modality in ambulatory pediatric anesthesia. Messieha et al^{15,16} reported the reduction of extubation, recovery, and discharge times when anesthesia is titrated based on the BIS number in children undergoing dental rehabilitation in an ambulatory setting. Thus, the use of BIS is likely to be of value when combining propofol with sevoflurane in attempting to reduce the incidence of EAD.

Oberer et al¹⁷ compared the laryngeal response to rigid laryngoscopy manipulation in children under sevoflurane anesthesia versus propofol. The incidence of laryngospasm in the first group was 26% versus 4% in the propofol group. Thus, during the emergence phase of sevoflurane anesthesia when laryngospasm typically occurs, the presence of propofol may offer protection from that complication.

Given the evidence-based data presented above, the propofol technique can be utilized to conduct a sevoflurane washout in the spontaneously breathing intubated child. In the final 30 minutes of the procedure, the dentist anesthesiologist discontinues the administration of the sevoflurane and maintains the anesthetic state with a propofol infusion using an infusion pump guided by the BIS number as well as by the usual standard patient vital signs. As the procedure nears its conclusion, the depth of propofol anesthesia is reduced to facilitate rapid extubation and recovery. Postoperative analgesia with intravenous ketorolac, 0.5–0.7 mg/kg, is administered at the same time the propofol is initiated, and the intravenous antiemetic ondansetron 0.15 mg/kg is also administered, provided there are no patient contraindications for either. At the end of the procedure, extubation is conducted with the BIS value in the upper 60s or low 70s with a low possibility of postextubation laryngospasm, yet the patient is usually sedated enough not to be combative or agitated during extubation. The patient is subsequently allowed to recover with the effects of the propofol infusion completely gone within 15–20 minutes. While the young child patients might still cry, they are usually lucid and responsive and able to articulate their desire to go home or to drink water. This is in contrast to the EAD profile where the child is generally disoriented, delirious, and often nonconsolable. By limiting the infusion of propofol to only 30 minutes, the recovery time is usually under 30 minutes from extubation time to discharge. The use of the BIS-guided technique enhances the ability to titrate the anesthetic to its desired level.

CONCLUSION

The administration of intubated sevoflurane general anesthesia by a dentist anesthesiologist for children having dental rehabilitation in the ambulatory office setting is very safe and cost-effective. Using the BIS-guided propofol washout technique in the final 30 minutes seems to offer an effective technique for significant reduction of EAD without compromising extubation and recovery times. The author has conducted over 300 cases utilizing the above-mentioned

technique with a significant limitation of EAD in over 90% of the cases. Large double-blinded studies are needed to assess the validity and effectiveness of this technique in an evidence-based fashion.

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