



Cause analysis, prevention, and treatment of postoperative restlessness after general anesthesia in children with cleft palate

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Cleft palate is one of the most common congenital malformations of the oral and maxillofacial region, with an incidence rate of around 0.1%. Early surgical repair is the only method for treatment of a cleft lip and palate. However, because of the use of inhalation anesthesia in children and the physiological characteristics of the cleft palate itself combined with the particularities of cleft palate surgery, the incidence rate of postoperative emergence agitation (EA) in cleft palate surgery is significantly higher than in other types of interventions. The exact mechanism of EA is still unclear. Although restlessness after general anesthesia in children with cleft palate is self-limiting, its effects should be considered by clinicians. In this paper, the related literature on restlessness after surgery involving general anesthesia in recent years is summarized. This paper focuses on induction factors as well as prevention and treatment of postoperative restlessness in children with cleft palate after general anesthesia. The corresponding countermeasures to guide clinical practice are also presented in this paper.

Keywords: Cleft Palate; Emergence Agitation; General Anesthesia; Surgery.

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INTRODUCTION

Cleft palate is one of the most common congenital malformations in the oral and maxillofacial region, with an incidence rate of about 0.1% in China. Early surgical repair is the only way to treat a cleft lip and palate. At present, it is believed that the optimal age for surgery in children with cleft palate is between 12 and 18 months to reduce adverse physical and psychological effects [1].

However, due to the particularities of general anesthesia and the physiological characteristics of children combined with the specific nature of surgical repair of the cleft palate, the incidence of postoperative emergence agitation (EA) after general anesthesia in children is higher than that in adults. EA is a mental state characterized by disturbances in consciousness and behavior during the period of general anesthesia in children. Clinical manifestations that often appear include crying, nightmares, enuresis, separation anxiety, irritability, stubbornness, and

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uncooperative behavior postoperatively. Typically, the child will groan incoherently, have upper and low extremity movements that cannot be calmed, display thinking disorder and crying that cannot be appeased, have impaired performance with respect to the orientation of obstacles, and be unable to identify familiar people and objects. In addition, this restlessness can cause the infusion catheter and the monitor electrode pieces to become displaced; it can also induce circulatory system fluctuation, tracheal spasm, vomiting and aspiration, bleeding and infection of surgical wounds, as well as other risks [1]. Although EA is self-limiting, physicians should be vigilant in preventing it to avoid potential injury. Prevention and treatment of EA in children after cleft palate surgery is of great clinical significance.

EA-INDUCING FACTORS

A study has shown that the incidence rate of EA in children is about 12% to 13% [2], although Silva [3] reported an incidence of 10% to 67% [3]. In particular, the incidence rate of EA was higher after general anesthesia with sevoflurane, isoflurane, and halothane. A study of EA-induced factors showed that EA in children was mostly the result of a synergy of comprehensive factors and no single factor could fully explain its induction. Many studies have also shown that different types of surgical stimulation, individual differences, as well as the time and dosage of narcotic drugs have a certain impact on EA.

1. Postoperative adverse stimulation

At present, most children with cleft palate undergo surgery before the age of 2 to shift and then accurately connect the muscle fibers to reconstruct the correct anatomic morphology of the palate. Because the surgical area is in the palate, an iodine spinning strip and a protective plate on the palate is used to stop bleeding after the operation; however, there is small amount of bleeding to stimulate secretion and nausea. The narrowing

of the nasopharyngeal cavity leading to the respiratory tract may have a certain relationship with the occurrence of EA [4]. Research confirms that noxious stimulus after surgery is also considered a common cause of EA, of which 44.2% is with respect to tracheal catheter stimulation, and 35.4% with incision pain and hypoxemia, flatulence, urinary retention and postural discomfort [5].

2. Rapid awakening and pain stimulation

Many scholars believe that after inhalation anesthesia, the rapid withdrawal of anesthesia can cause awakening to occur too quickly, which can cause EA. Lai has shown that an intranasal dose of fentanyl (2.0-2.5 $\mu\text{g}/\text{kg}$) can effectively reduce the incidence of EA after general anesthesia induced with sevoflurane or desflurane. Normally, the stronger the pain stimulation, the higher the probability of EA, especially in cerebral, thoracic, and oral surgery in children with postoperative pain [6]. Postoperative pain is the main factor that induces EA; therefore, the application of analgesic drugs, especially the clinical application of opioid drugs, can significantly reduce the incidence of EA [7,8].

3. Response during the recovery phase of inhalation anesthesia

Currently, the incidence of EA is significantly increased in children with cleft palate because of extensive clinical use of inhalation anesthesia. Clinical findings show that the incidence of EA is higher in children with cleft palate after the inhalation of high concentrations of enflurane; some even appear to twitch or have convulsions. There have been reports that the rate of EA after use of enflurane for anesthesia maintenance in open chest surgery is as high as 60.3% [9,10]. Van den Berg [11] reported that there was a close relationship between inhalation anesthesia with enflurane, isoflurane, or halothane and the incidence of EA. Sevoflurane has the characteristics of rapid induction and emergence, causing no irritation, low liver toxicity, and hemodynamic stability. However, the use of sevoflurane can lead to excitability in patients; the occurrence rate of excitability

in children after inhalation anesthesia is particularly high. Another study reported that in ear, nose, and throat surgery with anesthesia induction using inhaled sevoflurane and anesthesia maintenance using inhaled desflurane, the incidence of EA was significantly lower than that of simple anesthesia with sevoflurane inhalation alone. The use of most inhaled anesthetics has been reported to be related to the occurrence of EA. However, there are differences in the effects of various inhaled anesthetics in the literature perhaps because of the restlessness quantization criteria, measurement of the interval times, and different types and doses of preoperative medication [12].

4. Preoperative medication factors

Anticholinergic drugs, including atropine, penehyclidine hydrochloride, and scopolamine, are commonly used before anesthesia. There is a correlation between these anticholinergic drugs and the occurrence of EA [13]. Some scholars believe that preoperative elderly patients, after using penehyclidine hydrochloride, can suffer from blurred vision, delirium, visual hallucinations, auditory hallucinations, and disorientation.

5. Postoperative medication factors

A delayed postoperative recovery period in children with the use of drug reminders often increases the incidence of restlessness during general anesthesia. Research results show that using doxapram in the awakening period increases the incidence of restlessness in the recovery period. Doxapram is a nonspecific respiratory stimulant used for recovery from general anesthesia. It directly excites the medullary respiratory center, increases respiratory frequency and tidal volume, and causes sympathetic excitability. It is reported that the application of naloxone in the recovery period can also increase the incidence of EA; the mechanism may be the antagonism of naloxone on the analgesic effects of opioids, which induce active postoperative pain in children with EA [14].

6. Age factor

The incidence of EA in the clinic is usually higher in children and young adults than in elderly patients, and this may reflect a higher pain threshold and a decreased ability to react to the outside environment. However, in children, the incidence of EA is highest among preschool children [15]. One study confirmed that the incidence of restlessness in the recovery period after general anesthesia for preschool children (3–5 years old) was as high as 40.6%, while the incidence of EA in school-aged children (6–10 years old) was only 11.5%, which may be related to poor response ability with respect to the outside environment.

7. Psychological factors

Many studies have indicated that there is a certain relationship between postoperative restlessness and preoperative anxiety. Some studies found that children with more obvious preoperative anxiety have higher incidences of EA [16,17]. Although the relationship between preoperative anxiety and EA has not been reflected in all studies, the level of preoperative anxiety was closely related to the severity of EA.

8. Poor adaptability

Preoperatively, the adaptability of children to the sedative effect is usually poor after surgical repair of the cleft palate. One study on children who did not go to kindergarten and who did not have siblings found that a high proportion of them were impulsive, suffered from nightmares, and had anxiety, enuresis, and other undesirable behaviors in the 2–3 weeks after surgery. The mechanism of EA is still unclear, although it may be related to fear in children who are not familiar with a new environment, and the fact that the activity of the central nervous system is not consistent in different stages of awakening [18].

9. Other causes

Other possible causes of EA include [19]: (1) the

anxiety caused by the separation between the children and their parents and the fear of the unfamiliar environment; (2) a history of underlying diseases or central nervous system or mental illness; (3) hyponatremia, massive transfusion, hypoglycemia, and other metabolic disorders in children; (4) delayed recovery after surgery and use of antagonistic drugs to cause awakening, which incur a sudden onset of pain and other discomfort; (5) urinary retention, fecal and urinary incontinence, sputum suction, tracheal catheter, hypoxia and carbon dioxide retention, and other adverse stimuli; (6) Cardiac, cerebral, hepatic, renal, and other important organ dysfunction and severe infection, etc.; and (7) residual intravenous anesthesia with propofol, etomidate, ketamine, and muscle relaxants.

POSSIBLE MECHANISMS OF EA

The mechanism of EA is still not completely clear. The end stage of general anesthesia is not consistent with the early stage of the central nervous system; however, with the residual effect of general anesthesia drugs, EA may also be related to the changes in the levels of some hormones in the body. The main effect of general anesthesia is in the central nervous system, as anesthesia has an inhibitory action on the central nervous system after the disappearance of consciousness. While in partial recovery, there is still a small residual effect of the anesthesia's mild inhibition on the ascending reticular activating system; the transmissions from the cortex are not smooth, resulting in improper reaction to sensation and conduct in children, causing EA.

1. Central nervous system recovery is not consistent

General anesthesia acts on the central nervous system; however, inhibition of the central nervous system does not occur at the same rate for all functions, so the recovery time is not completely synchronized. Generally, in the recovery of consciousness after general anesthesia in children, the function of the advanced central nervous system has not yet fully recovered, which may affect

reactions and feelings in children. This lack of functional integrity can be expressed in many forms [20]. For example, the preoperative application of scopolamine can cause disorientation and restlessness after surgery, atropine can cause delirium after surgery, and inhaled anesthetics such as sevoflurane cause tracheal stimulation, increase in airway secretions, airway obstruction, etc.

2. Residual effects of anesthetics

Residual anesthetic can cause serious anxiety and restlessness in children possibly because respiratory function has not been fully recovered; the patient's irritability is often mistakenly thought to be caused by the tracheal catheter. If the tracheal catheter is withdrawn at this time, the child will be more irritable, unable to cough, glosso-coma, and have respiratory tract obstruction, SpO₂ drop, hypercapnia, severe uncoordinated motion, or obvious disorientation. Intravenous anesthetics such as propofol, vecuronium, midazolam, or fentanyl may lead to post-operative psychiatric symptoms [21].

3. Effect of inhaled anesthetics on gamma-aminobutyric acid (GABA) receptor

Some studies have indicated that low concentrations of sevoflurane can inhibit the GABA receptor-mediated postsynaptic inhibition of the current and this may be related to EA after general anesthesia. Studies have confirmed that the use of sevoflurane and propofol for induction can help stabilize recovery after general anesthesia, proving that through enhanced GABA-mediated postsynaptic inhibition of the current, recovery from sevoflurane-induced anesthesia can be improved. There are experiments that prove that midazolam also enhances the inhibitory effect of the GABA receptor, and can also reduce the incidence of EA after anesthesia with sevoflurane inhalation [21]. Clinical findings have shown that the incidence of EA in children under five years old was significantly higher than that in adults after anesthesia with sevoflurane inhalation. This may be because the excitatory effect of the GABA receptor in infants is dominant, while in the children, inhibition is

dominant. The change of GABA receptor excitability is related to the concentration of the nerve in the chloride. The difference in the development of the age-related neurotransmitter and neuromodulator requires further study.

PREVENTION AND TREATMENT MEASURES

The prevention and treatment of EA after general anesthesia in accordance with the principle of prevention is dominant and treatment is auxiliary.

1. Prevention

1.1. Eliminate psychological concerns

Children feel anxiety and fear before anesthesia because they are in a strange environment, with the surgical bed, lights, and medical staff. In the recovery period after general anesthesia, the perception of a variety of stimuli causes discomfort, increases fear, and results in twisting, struggling, and crying. Therefore, in the preoperative visit, anesthesiologists should carefully explain the types of discomfort that may arise during the perioperative period, explaining that this is temporary. This will allow families and children to be psychologically prepared, and encourage children to overcome their pain by eliminating concerns. Children are encouraged to actively cooperate with treatment to reduce their noise and fear levels to overcome the complications of the recovery period [22].

1.2. Improve the ability for anesthesia management

During the operation, medical staff should use timely communication and close observation of the progress of the operation to adjust medication and control the depth of anesthesia. Near the end of the operation, timely selection of short-acting drugs, such as remifentanyl and propofol, should be employed to maintain anesthesia. For inhalation anesthetics, which easily cause EA, early adjustments should occur so that children can have a high

degree of awareness after surgery, correctly judge the surrounding environment, and respond well. For the delayed recovery of children, analeptic drug treatment is not advocated, which is in line with the concept of agitation prevention. In the case of a lack of respiration inhibition, medium or long-acting anesthetics can be used to relieve postoperative pain. After removal of tracheal intubation, some children may have throat discomfort, for which atomization can be used to enhance the degree of tolerance [22].

1.3. Prophylactic use of drugs

To reduce the occurrence of EA in the perioperative period, prophylactic use of clonidine, fentanyl, and midazolam can effectively prevent or reduce the severity of EA; the incidence rate of EA decreases by 70% and there are no obvious side effects. One study showed that oral midazolam syrup (0.2 mg/kg) could reduce the incidence of restlessness after general anesthesia prior to surgery. However, Cho [19] found that preoperative use of midazolam in children after halothane and isoflurane anesthesia increased the incidence of restlessness significantly (30%–40%); this causes a blank area of memory, so when the children wake up and find that they are a strange environment, in addition to being in pain and exposed to multiple stimuli, EA is easily induced. The study also reported that the application of fentanyl during surgery through intranasal instillation of 2.0–2.5 $\mu\text{g}/\text{kg}$ can effectively reduce the incidence of EA after sevoflurane or desflurane administration after general anesthesia.

2. Treatment measures

Once EA occurs, it must be handled quickly to avoid accidental injury or other serious complications. First, we should immediately eliminate (to the greatest extent possible) causes relating to medical treatment. For example, if the child does not tolerate the endotracheal catheter, the catheter should be removed as soon as possible after respiration is normalized to reduce or eliminate the occurrence of EA. If, after the removal of

such possible elements, EA continues or is due to an unknown cause, the child should remain under close monitoring to maintain smooth breathing. Appropriate sedative drug control can be used.

2.1. Propofol

In the operating room or recovery room, anesthesiologists can administer rapid-onset and short-acting sedatives and hypnotic such as propofol after general anesthesia. Firstly, a slow intravenous injection of 5–10 mg can be used to calm the child down; the dose can be increased to meet the desired effect. Adding a proper amount of lornoxicam, flurbiprofen, pentazocine, tramadol, or dexmedetomidine can also reduce EA, but close attention should be paid to changes in the circulatory and respiratory systems and stability should be maintained [9].

2.2. Midazolam

Midazolam has obvious effects as a sedative, anti-convulsant, or anti-restlessness medication, while causing some central muscle relaxation and anterograde amnesia. Studies have shown that midazolam, when used alone to reduce EA after anesthesia, is efficient with no side effects. Research shows that the application of 0.1 mg/kg midazolam through intravenous injection can quickly lead to a Ramsay sedation score greater than two points, allowing a good sedation state with a sedation time of more than 25 minutes [22].

2.3. Dexmedetomidine hydrochloride

The pharmacological action of dexmedetomidine is through activation of the presynaptic membrane α_2 receptors, inhibiting the release of norepinephrine and terminating the transmission of pain signals. Through activation of postsynaptic membrane receptors, dexmedetomidine inhibits sympathetic nerve activity, causing decreased blood pressure and heart rate. When combined with α_2 receptors in the spinal cord, analgesic effects are produced, leading to sedation and relief of anxiety. There are reports that the application of dexmedetomidine before induction of anesthesia (1 $\mu\text{g}/\text{kg}$ nasal drops) can

effectively alleviate preoperative anxiety in children, shortening the induction time of sevoflurane anesthesia and reducing the incidence of EA in the recovery period without prolonging recovery time. Studies have shown that after induction of anesthesia, a single dose of dexmedetomidine 0.3–0.5 $\mu\text{g}/\text{kg}$ can effectively prevent the occurrence of EA in the recovery period. A dose of 0.5 $\mu\text{g}/\text{kg}$ of dexmedetomidine is better, and does not affect hemodynamics during the recovery period [23,24].

2.4. Fentanyl and sufentanil

Fentanyl is an opioid receptor agonist, which is a potent narcotic analgesic. Its pharmacological action is similar to that of morphine, and its analgesic effect is about 80 times that of morphine. Sufentanil is a fentanyl derivative; its receptor binding force is 7.7 times that of fentanyl, and it has a lipid solubility twice that of fentanyl. Sufentanil has rapid onset, good controllability, a short half-life, and potential for long-term infusion without accumulation. It has been reported that inhalation of sevoflurane combined with a small dose of fentanyl for pediatric general anesthesia is better than the use of sevoflurane alone in reducing EA [25]. Another study showed that for children undergoing cleft palate surgery, intravenous injection of sufentanil at a dose of 0.15 $\mu\text{g}/\text{kg}$ at 15 min postoperatively did not prolong the recovery period and post-anesthesia care unit (PACU) time; it could effectively prevent EA, keeping the cardiovascular system stable during the awakening period and reducing the bleeding of the wound [26].

CONCLUSION

In summary, EA is a common complication after general anesthesia in children with cleft palate. In severe cases, children may suffer adverse effects with respect to physiological function and postoperative recovery. Because of its complex pathogenesis, the mechanism of EA is not clear. It is necessary to study EA and actively take effective measures to improve safety in the recovery

period after general anesthesia in children with cleft palate.

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