

Paediatric Emergence Agitation: Management Options

Shikha Jain¹, Neha Garg², Puneet Khanna^{2*} and Sameer Sethi³

¹Department of Anaesthesiology, All India Institute of medical Science, Bhopal, India

²Department of Anaesthesiology, All India Institute of medical Science, New Delhi, India

³Department of Anaesthesiology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Abstract

Emergence Agitation (EA) is a common postoperative problem especially in children. It is more common in paediatric age group especially with low blood gas solubility inhalational agents like Sevoflurane and Desflurane. Other factors contributing to increase EA are head and neck surgeries, preoperative anxiety and pain. It increases the risk of postoperative physical trauma to patient like surgical site bleeding, psychological trauma to parents and delayed recovery. Various drugs have been described to decrease EA. In this review article, here we have discussed the management options of EA including non-pharmacological and pharmacological options.

Keywords: Emergence agitation; Dexmedetomidine

Introduction

Eckenhoff et al. [1] first described Emergence Agitation (EA) in early 1960s. Sikich and Lerman [2] have defined EA as “a disturbance in a child’s awareness of and attention to his/her environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behaviour in immediate postanesthesia period”. It is a common postoperative problem especially in children. Its incidence is reported to be from 10% -50%, may be as high as 80% [3].

Risk factors: Various risk factors are associated with EA including low blood soluble inhalational anaesthetics like Sevoflurane, Desflurane [4,5], paediatric age group, preoperative anxiety [6], eye or head and neck surgeries [7], pain, and rapid awakening. **Complications:** EA has been documented to increase postoperative complications like significantly increased risk for physical trauma to the patient like bleeding from surgical site, psychological trauma to the parents and delay in discharge from the Post Anesthesia Care Unit (PACU) [8].

Management of EA

Scales to Measure EA

Comparing studies have been difficult due to lack of a uniform definition of EA and the lack of a universal assessment scale. Sikich and Lerman [2] developed the Pediatric Anesthesia Emergence Delirium (PAED) scale consisting of five psychometric items for evaluating ED in pediatric patients. PAED scale consists of five psychometric items (1. the child makes eye contact with the caregiver 2. the child’s actions are purposeful 3. the child is aware of his/her surroundings 4. the child is restless 5. the child is inconsolable) (Table 1) incorporating cognitive and agitation assessments. They reported a sensitivity of 0.64, specificity

of 0.86 and area under ROC to be 0.77 at a PAED Score of 10. Recently, PAED score >12 has been shown to provide a greater sensitivity and specificity than a PAED Score ≥10 [9].

Non-Pharmacological Methods

Various non-pharmacological methods have been used to decrease EA. Parental presence is used to allay anxiety and regional anaesthetic blocks like sub-tenon blocks have been documented to decrease EA [7].

Pharmacological methods

various drugs are used for treatment of post operative EA.

Premedication

Midazolam

It is one of the most commonly and popularly used premedication. It possesses potent anxiolytic, amnestic, sedative-hypnotic, anticonvulsant, and skeletal muscle relaxant properties. Its anterograde amnesic property is useful for premedication before surgery to inhibit unpleasant memories. However, it is known to cause dose dependent side effects such as paradoxical reaction, amnesia, restlessness, cognitive impairment and respiratory depression [10].

Cox et al. [11] showed that children premedicated with 0.5 mg/kg oral midazolam 20-30 minutes before surgery is effective in reducing anxiety and facilitates parental separation, with minimal effects on recovery times.

Various routes of administration of midazolam premedication have been tried- oral, intranasal- drops and spray, rectal.

Lejus et al. [12] compared intranasal (0.2mg/kg) versus rectal midazolam (0.3mg/kg) in 95 children aged 8 months-12 years and concluded that intranasal drug should be reserved when there is no alternative, due to poor tolerance and rectal administration should not be used in older children.

In a study, Shrestha et al. [13] administered oral premedication with injectable midazolam mixed in syrup paracetamol, and concluded it as

1. The child makes eye contact with care giver	4 not at all
2. The child’s action are purpose full	3 just a little bit
3. The child is aware of his or her surrounding	2 Quite a bit
	1 Very much
	0 - Extremely
4. Child is restless	0 not at
5. Child is inconsolable	1 just a little bit
	2 Quite a bit
	3 Very much
	4 Extremely

Minimum score is 0, maximum is 20.

Score ≥10 agitation.

Table 1: Pediatric Anesthesia Emergence Delirium Scale (PAEDS) [8].

*Corresponding author: Puneet Khanna, Department of Anaesthesiology, All India Institute of medical Science, New Delhi, India, Email: k.punit@yahoo.com

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a convenient and efficient method of premedicating children undergoing general anaesthesia. In contrast, a meta-analysis of pharmacological prevention of EA in children showed that midazolam was ineffective in prevention of completely reducing EA [14]. It can be explained due to short half life of midazolam, with no residual effect extending to the end of prolonged surgeries.

Hydroxyzine-midazolam premedication: Hydroxyzine is an H1, muscarinic and 5-HT₂ receptor antagonist [15]. It is used as a premedication drug in children and is also used to treat generalized anxiety disorders in adults [16]. The sedation success of oral hydroxyzine (3.7 mg kg⁻¹) premedication in paediatric dentistry is reported to be about 90% [17]. However, due to its prolonged onset time of action (30-60 min), it is not an appropriate premedication agent when used alone. But due to its anxiolytic properties and prolonged duration of action, it may help to reduce postoperative emergence agitation. Koner et al. [18] demonstrated that midazolam-hydroxyzine combination premedication had better reduction in EA than either midazolam or hydroxyzine alone in a study in eighty four children, 1-7 years, undergoing general anaesthesia with sevoflurane and caudal block.

Ketamine

Ketamine, N-methyl-D-aspartate receptor antagonist, with analgesic, amnesic and opioid sparing effects is shown to decrease EA. Karamaz et al. [19] showed that oral premedication with relatively high dose ketamine reduced the incidence of EA in children undergoing adenotonsillectomy after desflurane anaesthesia without delaying recovery. It was shown to have pre-emptive analgesic effects, reducing the incidence of EA [20]. In contrast, low-dose ketamine (0.5 mg/kg) was found to be ineffective to completely abolish EA, had no effect on postoperative pain, and it required additional analgesic requirement, during painful ophthalmic surgery [21].

Dexmedetomidine

It is a highly specific alpha 2 receptors ($\alpha_2:\alpha_1=1600:1$) than clonidine ($\alpha_2:\alpha_1=200:1$). It has anxiolytic, sympatholytic, and opioid sparing effect that can reduce the dose of hypnotics, opioids, analgesics, and anesthetics required without causing any clinical respiratory depression.

Various routes of administration of dexmedetomidine have been tried- oral, intranasal. Kamal et al. [22] compared Oral dexmedetomidine and oral midazolam for pre-anaesthetic sedation and postoperative recovery profile in children undergoing strabismus correction surgeries and found that premedication with 3 μ g/kg oral dexmedetomidine is superior to 0.5mg/kg oral midazolam. In another study, Cimen [23] showed that 1 μ g/kg intranasal dexmedetomidine is more effective than buccal administration and has better levels of sedation, parental separation and mask acceptance.

Gabapentin

Initially was developed as anticonvulsant. Recently, Salman et al. [24] conducted a randomized study in children undergoing tonsillectomy and adenoidectomy after sevoflurane anaesthesia using gabapentin as premedication at a dose of 15mg/kg orally. They concluded it decreases EA and also 24 hour analgesic requirement. It is shown to induce analgesia by binding and inhibiting presynaptic voltage dependent calcium channels, thereby decreasing calcium influx and inhibiting release of neurotransmitters, mainly glutamate, from primary afferent nerve fibers which synapse on and activate pain responsive neurons in spinal cord [25]. However, the beneficial effects of reduced opioid intake seem to be nullified by the side effects seen during 5 days after tonsillectomy in adult patients, but in this study very high dose of gabapentin was chosen [25].

Analgesics

Fentanyl

Fentanyl, a short acting opioid, with sedative and analgesic effects can decrease EA. Cohen et al. [26] reported a decrease in EA in thirty two children (2-7year) undergoing adenoidectomy, under desflurane anaesthesia following fentanyl. However, it was found to increase the extubation time, emergence time and time in PACU and a higher incidence of PONV.

Ketorolac

Ketorolac, a Nonsteroidal Anti Inflammatory Drug (NSAID), has been an alternative analgesic to decrease EA. It has been postulated that EA is more with low blood gas soluble agents like sevoflurane, desflurane. It was found that rapid emergence from general anaesthesia along with inadequate pain control could have attributed to EA. This was supported by Davis et al. [27], who conducted a double blinded prospective study to see the effects of ketorolac on EA in children premedicated with nasal midazolam (0.2 mg/kg) undergoing bilateral myringotomy. It showed that ketorolac reduced the incidence of EA three to fourfold after myringotomy under sevoflurane or halothane anaesthesia. However, recently Kim et al. [28] found that 1mg/kg ketorolac was not effective in decreasing the incidence of EA in children, 3-7 years of age, undergoing sevoflurane anaesthesia. Therefore, they postulated that in high risk children other interventions are required for prevention of EA.

Intravenous

Ketamine

Ketamine, with analgesic, amnesic and opioid sparing effects is shown to decrease EA. Won Ju Jeong et al. [29] studied the effect of Ketamine in ophthalmic surgery in sixty children (2-8years), following Desflurane anaesthesia. They concluded that 1mg/kg Ketamine effectively reduces anxiety, postoperative pain and scores of EA without delay in discharge. Recently, Lee et al. [30] compared iv ketamine 0.25 mg/kg and 0.5 mg/kg and reported the similar decrease in incidence of EA due to combined analgesic and sedative effect. However, less pain score was noted with the higher dose of ketamine, that suggested that an increase in ketamine dose was effective in analgesic action, but increasing its dose did not affect the incidence of EA.

Propofol

Propofol is a short acting sedative- hypnotic agent. It has also been used to decrease EA with decreased nausea and vomiting. Aoud et al. [31] conducted a study in 80 children (2-6yr) receiving 1mg/kg propofol at end of surgery for prevention of EA undergoing strabismus surgery during sevoflurane anaesthesia. They concluded that single dose of propofol at end of surgery after sevoflurane discontinuation decrease incidence of EA without delaying patients discharge. However, Cohen et al. [32] reported that propofol 2mg/kg when used at the beginning of surgery did not decrease EA, probably due to its shorter duration of action and reduced serum level post-operatively, insufficient to effectively decrease EA.

Ketofol

Propofol is a sedative-hypnotic agent and ketamine, a phencyclidine derivative, provides analgesia and amnesia. So combining low dose ketamine offsets the cardiorespiratory depression caused by propofol while providing adequate analgesia, sedation and better haemodynamics [33]. Sherry et al. [34] used ketofol in a randomized study to assess its efficacy and safety to control EA in 90 children (3-6 years) undergoing adenotonsillectomy after sevoflurane based anaesthesia. They were randomly assigned to receive 10 ml normal saline, 1mg/kg propofol in 10 ml saline or ketofol as 1mg/kg propofol and 0.25mg/kg ketamine in

10 ml saline. They found lower pain scores in ketofol group with better postoperative and analgesic effect.

Alpha 2 agonists

Presently, α_2 agonists like Clonidine and Dexmedetomidine are being explored.

Clonidine

Clonidine provides both sedation and analgesia. Kulka et al. [35] found a reduction of post sevoflurane agitation with clonidine 2 μ g/kg IV administered 5 minutes after the start of surgery from 80% to 10% in a randomized trial in children aged 2-7 years undergoing circumcision under sevoflurane anesthesia. However, it was associated with increased time to awakening, prolonged PACU stay and sleepiness post-operatively.

Ghai et al. [36] conducted a study on 75 midazolam premedicated children 1-6 years old undergoing cataract surgery. The children were randomly assigned to three groups which received normal saline (group NS), clonidine 1 μ g/kg (groupC1) and 2 μ g/kg (groupC2) intraoperatively. Postoperative agitation was assessed by Pain / Discomfort Score. A PDS \geq 3 was an indicator of EA and a score > 6 was used to define severe agitation. They reported a significant lower agitation scores with the incidence of 5.1% in clonidine 1 μ g/kg group as compared to 27.5% in NS group and none in Clonidine 2 μ g/kg group (p<0.001). The time to discharge was also significantly shorter in Clonidine 1 μ g/kg group (p<0.001).

Dexmedetomidine

Recently, Dexmedetomidine has been evaluated by different routes to prevent agitation. It is a highly specific alpha 2 receptors ($\alpha_2:\alpha_1=1600:1$) than Clonidine($\alpha_2:\alpha_1=200:1$).

Ibacache et al. [37] studied two doses of Dexmedetomidine in unpremedicated children undergoing circumcision, orchiopexy or inguinal hernia with caudal analgesia to determine the appropriate dose to prevent Sevoflurane agitation following anesthesia. He administered a single dose of 0.15 μ g/kg Dexmedetomidine (N=30), 0.3 μ g/kg Dexmedetomidine (N=30), or normal saline (N=30). He found decreased incidence of EA in 0.3 μ g/kg without significant changes in haemodynamics.

Jeongmin Kim et al. [38] conducted a randomized trial in 96 children aged 1-5 year undergoing strabismus surgery following Desflurane anaesthesia. They were randomly allocated in two groups – Dexmedetomidine (Group FD, n =47) with a continuous infusion of 0.2 μ g/kg/h or normal saline (Group F, n=47). Anaesthesia was induced with Propofol and maintained with Desflurane. All children received 1 μ g/kg Fentanyl after induction. Postoperative Objective Pain Score (OPS) [39], Paediatric Agitation and Emergence Delirium (PAED) scale [2], and EA score [40] were documented every 10 minutes in PACU.

Premedication	Midazolam
	Hydroxyzine-Midazolam
	Ketamine
	Dexmedetomidine
	Gabapentin
Analgesics	Fentanyl
	Ketorolac
Intravenous	Ketamine
	Propofol
	Ketofol
Alpha2 Agonists	Clonidine
	Dexmedetomidine

Table 2: Various drugs used in EA are given below.

The OPS scale includes haemodynamic change, emotional factors (crying, agitation, and movement), and localisation of pain. Sikich and Lerman [2] developed the Pediatric Anesthesia Emergence Delirium (PAED) scale consisting of five psychometric items for evaluating ED in pediatric patients. PAED scale consists of five psychometric items (1.the child makes eye contact with the caregiver 2. the child's actions are purposeful 3. the child is aware of his/her surroundings 4. the child is restless 5. the child is inconsolable) incorporating cognitive and agitation assessments. The EA scale consists of five grades (1=sleeping, 2=awake and calm, 3=irritable and crying, 4=inconsolable and crying, and 5=severe restlessness and thrashing). Severe EA cut-off points were defined as a 5-point EA score of 4 and above, PAED score 11 and above and 6 for OPS. They observed that the mean values of maximum EA, maximum PAED, and maximum OPS score were significantly lower in Group FD than in Group F at all time intervals up to 20 minutes with p<0.001. The severity of EA (FD- 12.8% VS F-74.5%, p<0.01) and frequency of rescue analgesia was significantly lower in group FD than group F (p<0.001) (12.8% vs. 74.5%, p<0.001). They concluded that intraoperative low dose infusion of Dexmedetomidine effectively reduces EA in children undergoing strabismus surgery following anaesthesia with Desflurane.

In another randomized, placebo-controlled study, by Guler et al. [41] iv dexmedetomidine (0.5 μ g/kg) and placebo were compared for the reduction of emergence agitation following sevoflurane used for anesthesia in 60 unpremedicated patients (3-7 years) undergoing adenotonsillectomy. Agitation behaviour and pain postoperatively were assessed using a 5-point scale (1=sleeping, 2=awake/calm, 3=irritable, 4=inconsolable, crying, 5=severe disorientation, thrashing, restlessness). Pain and agitation scores were better among patients in the dexmedetomidine group (p<0.05). However, emergence time and time to extubation were significantly long in the group, along with lower heart rate and blood pressure (p<0.005) upon extubation and recovery compared with placebo.

Conclusion

EA is a common postoperative problem with EA ranging upto 80% [4,5]. Various strategies have been used to decrease its incidence, such as pharmacological or non pharmacological methods. However, the most convenient and efficacious method and drug is still debatable.

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