PREOPERATIVE ORAL DEXTROMETHORPHAN VERSUS KETAMINE OR MIDAZOLAM FOR ATTENUATING SEVOFLURANE EMERGENCE AGITATION IN PRESCHOOL CHILDREN UNDERGOING ADENOTONSILLECTOMY

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Abstract

Background: Sevoflurane is a popular inhalational anesthetic agent used for induction and maintenance of anesthesia in pediatric patients. Because of its low blood solubility, it allows rapid induction and emergence from general anesthesia. However, when it is used as sole anesthetic agent, it is associated with a high incidence of emergence agitation (EA) that may be harmful to patients.

Objective: Our review Article aimed to discuss Preoperative Oral Dextromethorphan versus Ketamine or Midazolam for Attenuating Sevoflurane Emergence Agitation in Preschool Children Undergoing Adenotonsillectomy.

Methods: Relevant citations were extracted from Pubmed, Google scholar, Clinical key, Scopus, Med-line, and Cochrane to discuss Preoperative Oral Dextromethorphan versus Ketamine or Midazolam for Attenuating Sevoflurane Emergence Agitation in Preschool Children Undergoing Adenotonsillectomy

Review Article will cover the followings:

- Dextromethorphan
- Midazolam
- Ketamine
- Emergence agitation
- Effects of sevoflurane versus other general anaesthesia on emergence agitation in children

Conclusion: Premedication with ketamine is more effective than midazolam and dextromethorphan in preventing EA during the early emergence period after sevoflurane anaesthesia in children in comparison to placebo treated group in children undergoing adenotonsillectomy without reported side effects including (vomiting, hallucination, respiratory center depression except for nausea occurred and being lower in dextromethorphan group than other groups).

Keywords: Oral Dextromethorphan– Ketamine – Midazolam - Sevoflurane Emergence Agitation - Preschool Children – Adenotonsillectomy

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INTRODUCTION

Children account for approximately one-third of all patients undergoing ear, nose, and throat (ENT) surgery. Procedures range from simple day-case operations, such as myringotomy, to complex airway reconstruction surgery undertaken in specialist centers (1). Tonsillectomy with or without adenoidectomy is one of the most frequent surgical procedures that are carried out globally (2).

The plan of Anesthesia must to be general anesthesia. Intubation is facilitated by muscle relaxant with rocuronium, deep inhalational anesthesia or a propofol bolus (3).

Emergence from general anesthesia can be complicated by the presence of agitation in children and thus presents a challenging situation for post anesthesia care providers. Post anesthetic excitement, emergence delirium, and emergence agitation (EA) are terms used interchangeably to describe this acute phenomenon. This agitation is characterized by a change in perception of the environment with signs of disorientation, hypersensitivity to stimuli, and hyperactive motor behavior. In addition, paranoid ideas have been observed in combination with these abnormal emergence behaviors in the preschool age group. Although generally self-limiting, EA can be severe and may result in physical harm to the child. Severe EA may require pharmacological intervention, resulting in a prolonged stay in the post anesthesia care unit (PACU). In rare cases, agitation and restlessness associated with EA have lasted for longer than 2 days (4). The long-term psychological

implications of EA remain unknown (5). Early epidemiologic study demonstrated a 5.3% incidence of EA in all postoperative patients with a more frequent incidence in children (12%–13%). This phenomenon has been associated with specific anesthetics, in particular sevoflurane, a variety of perioperative medications, pain and patient related factors (4).

Sevoflurane is widely used in pediatric anesthesia because it is well tolerated by inhalation, gives fast induction and recovery, has lower level of hepatic toxicity and offers hemodynamic stability. Regardless of its advantages, there is a growing concern that sevoflurane causes post anesthesia agitation (PAA) in pediatric patients. Research shows that the incidence of agitation may be as high as 67% (6).

Dextromethorphan, the D-isomer of the codeine analog levorphanol, is another non competitive N-methyl-D-aspartate receptor (NMDA) antagonist which has been used for a long period as a central cough suppressant and analgesic adjuvant. The cough suppressant effect and the analgesic effect were attributed to its codeine analog structure and its NMDA receptor antagonistic action respectively (7). It is metabolised in the liver to active metabolite, dextrorphan, which is responsible for its side effects through acting on phencyclidine receptors (8).

Ketamine, a competitive (NMDA) receptor antagonist, has been reported in many studies to be effective in reducing the incidence of EA when administrated orally (9) or intravenously (10).

Midazolam is a short-acting hypnotic-sedative drug with anxiolytic, muscle relaxant, anticonvulsant, sedative, hypnotic, and amnesic properties. It belongs to a class of drugs called benzodiazepines. Midazolam acts on the benzodiazepine binding site of Gamma aminobutyric acid receptors type A(GABAA) receptors and results in inhibitory effects on the central nervous system (11).

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1. Dextromethorphan
2. Midazolam
3. Ketamine
4. Emergence agitation
5. Effects of sevoflurane versus other general anaesthesia on emergence agitation in children.

1. DEXTROMETHORPHAN

Mechanism of Action

Dextromethorphan has multi-faceted pharmacodynamic and pharmacokinetic properties. The drug is a lipophilic molecule with an ionizable amine at one end. It is structurally related to alkaloid opioids such as morphine but does not interact with the mu receptor. It derives from levorphanol, first designed as a morphine alternative. The main mechanism of action for its use in the cough suppressant is not completely understood. One proposed mechanism is that DM works on the nucleus tractus solitarius, the estimated site where the pulmonary vagal afferent fibers synapse in the central nervous system. This site in the brainstem functions as a gate for the cough reflex. DM is known to have many interactions with several different receptor sites (12).

DM is a synthetic analog of codeine and undergoes rapid metabolism upon initial absorption. Its metabolism is via cytochrome P450 2D6 (CYP2D6) into major O-demethylated metabolite, dextrorphan (DX). DX is further glucuronidated by uridine diphosphate-glucuronosyltransferase to form dextrorphan-o-glucuronide, the most prevalent form of DX present in the plasma (98%). Dextrorphan-o-glucuronide is permanently charged and has less permeability to the blood-brain barrier. DM also gets metabolized into 3-methoxymorphinan via cytochrome P450 3A4 (13).

DM has low oral bioavailability due to its extensive first-pass metabolism; however, this is also dependent on different metabolizers. People may fall under different metabolic groups: ultrarapid, extensive, intermediate, and poor metabolizers. Most of the population falls under the extensive metabolizer. A single oral dose of 30mg of DM showed a median half-life of 2.4 hours with an oral bioavailability of 1 to 2%. Approximately 9% of the population are poor metabolizers. The median half-life of DM after a single dose orally is 19.1 hours, with an oral bioavailability of 80%. Poor metabolizers have approximately four-fold higher plasma levels of DM (14).

Although structurally similar, DM does not have a direct action on the opioid receptors that produce classic CNS effects of opioid agonists. DM is known for its main site of action at N-methyl-D-aspartate (NMDA) receptors as a non-competitive antagonist. However, studies have found many sites of action with which DM and DX interact (12).

Other sites of action include:

- Sigma-1 receptors agonist
- Nicotinic receptors (a3b4, a4b2, a7) antagonists
- Serotonin transporters inhibitor
- Norepinephrine transporters inhibitor
- Voltage-gated calcium channels inhibitor

Indications

Dextromethorphan (DM) received FDA approval in 1958 for its use as a cough suppressant. It is one of the most common compounds found in the majority of the over-the-counter antitussives for the past 50 years (13).

In 2010, the FDA approved the use of DM for pseudobulbar affect (PBA) in combination with quinidine. Pseudobulbar affect (PBA) is a neurologic dysfunction of emotional expression characterized by outbursts of crying or laughing inappropriately and disproportionately to the mood. The pathology of PBA is still incompletely understood, but the leading hypothesis suggests that it is due to a loss of descending cortical control of brainstem motor nuclei and the cerebellum. This loss of control disrupts inhibitory mechanisms for motor control of emotional expression (15).

There are many other potential therapeutic uses for DM that are currently under investigation in clinical studies. Most of these use the property that DM has a neuroprotective agent. These indications include (14):

- Depression: DM has a fast-acting antidepressant activity for its similarity to ketamine
- Stroke: Studies have shown that DM has a role in the improvement of some neurological and psychiatric complications, however, not the overall functional outcomes
- Traumatic Brain Injury: Although the studies have shown limited effects, there are proposed mechanisms that confer the benefits of DM in TBI including its activity at NMDA and sigma-1 receptors.
- Seizure: Some clinical studies have shown that DM has efficacy in refractory seizures
- Pain: There are studies on the analgesic effects of DM for pain conditions such as cancer-related, post-operative, neuropathic and gastrointestinal pain
- Methotrexate Neurotoxicity: DM showed a complete resolution in neurologic deficits associated with MTX toxicity in 5 cases
- Parkinson's Disease: DM meliorated primary Parkinson's disease in 2 studies
- Autism: contradicting data regarding DM's role in behavioral improvement

Administration

Dosing and administration of dextromethorphan are mostly via the oral route. There are many formulations for administration:

- Combination liquid cough syrups; the common over-the-counter (OTC) formulation contains 15 mg/tsp of DM; recommended adult dosing is 2 tsp (10ml) every 4 hours
- Sustained-release cough syrup suspensions; another OTC product contains 30 mg/5mL
- Liquid filled capsules containing 15 or 30 mg of DM
- Oral strips containing 7.5 or 15mg of DM
- Lozenges containing 5, 7.5, 10 mg of DM

The recommended dosing for DM is 0.5 mg/kg up to 30 mg, administered three or four times a day.

Some animal studies have suggested that to reach the potential neuroprotective effects requires the ingestion of doses higher than typically used for antitussive effects (60 to 120 mg/d) (16).

For PBA, the Food and Drug Administration (FDA) has approved the use of DM in combination with quinidine, a CYP2D6 inhibitor. The approved dose is 20/10mg (16).

Adverse Effects

Adverse effects from cough suppressants are rare. The most common are nausea and gastrointestinal discomfort, while drowsiness and dizziness can also occur. One study showed at high doses (greater than 4 mg/kg), up to 64% of patients felt euphoria, and some experienced various CNS effects such as visual hallucinations and persecutory delusions. These episodes were associated with agitation, leading to patient management difficulties. The most common side effects in this study were the sensation of a drunk feeling or a "high" (20%), nausea and vomiting (17%), nystagmus (15%), and dizziness (15%). Most side effects resolved within a day after the final dose, and no cardio-respiratory compromises were noted. Serum levels of DM exceeding 400 ng/ml presented in 87.5% of patients with these side effects. More than 60% of the patients who experienced side effects with DM had serum levels exceeding 120ng/ml and brain levels of 700 ng/g (17).

Contraindications

Dextromethorphan is contraindicated for patients with known or established hypersensitivity as well as those with an idiosyncratic reaction upon administration of the drug. (18).

Monitoring

Dextromethorphan is well tolerated and has a wide therapeutic window, which makes it an amenable drug for clinical use. (18).

Toxicity

One concern regards to dextromethorphan toxicity is its OTC misuse that has been increasing since the 2000s. DM misuse is known as "going pharming," "robotripping," and "dexing." In 2006, three different OTC product formulations accounted for 66% of reported instances of DM misuse in the USA. One life-threatening toxicity associated with DM abuse is serotonin syndrome. Due to its action on serotonin reuptake inhibition, if patients are already on common SSRI or MAOI antidepressants, DM toxicity potentiates excess serotonin in the body and produces a group of symptoms called serotonin syndrome. These include agitation, confusion, dilated pupils, headache, tachycardia, hypotension, high fevers, seizures, irregular heartbeat, and can lead to unconsciousness (19).

2. MIDAZOLAM

Mechanism of Action

Midazolam has poor oral absorption and has an elimination half-life of 1.5 to 2.5 hours. Midazolam converts into its active metabolite alpha-1 hydroxy midazolam, which contributes to 10% of drug action. Midazolam metabolism occurs via hepatic CYP450 enzymes and glucuronide conjugation. The mechanism of action of midazolam indirect and is related to GABA accumulation and its affinity to the benzodiazepine receptors. Two separate receptors for GABA and benzodiazepine couple to a common chloride channel. It increases the frequency of chloride channel opening. Occupation of both the receptors cause membrane hyperpolarization and neuronal inhibition. The anticonvulsant activity of midazolam is related to the excess GABA action on motor circuits in the brain. Midazolam acts on glycine receptors and produces muscle relaxation effect. Almost all the pharmacologic effects, including sedation, anxiolysis, anterograde amnesia, and anticonvulsant effect, can are explainable through its action on GABA receptors. Age-related deficits, hepatic, and renal insufficiency, also affect the pharmacokinetics of midazolam. Midazolam has both hydrophilic and lipophilic properties, depending upon the pH (20).

Indications

Intravenous midazolam is used for the induction of anesthesia and in the management of acute seizures. Because of its water-soluble nature, midazolam has a rapid onset of action and can be used to manage status epilepticus when intravenous administration of other medications is not feasible. Midazolam has a high rate of tolerance, and dose can be increased to maintain the therapeutic effect. Because of its easy mode of administration through the buccal and intranasal routes, it is a viable option in children for the management of seizures. For its use in anesthesia, the response to the induction dose is more variable compared to thiopental. Midazolam can be used for anxiolysis and hypnosis during the maintenance phase of general anesthesia and is also superior to thiopental in the maintenance of anesthesia because of the less need for adjunct medications. Midazolam is used as an adjunct medication to regional and local anesthesia for a wide range of diagnostic and therapeutic procedures and has greater patient and physician acceptance (21).

Administration

Midazolam administration can be through oral, intranasal, buccal, intravenous, and intramuscular routes. For the perioperative use of midazolam, the induction dose is 0.15 to 0.40 mg/kg via the intravenous route. For the premedication, the dose is 0.07 to 0.10 mg/kg with the intramuscular route. For intravenous sedation, the dose is titrated at 0.05 to 0.15 mg/kg. For children 1 to 5 months old, the recommended intranasal dose is 0.2mg/kg. For children six months and older, 0.2 to 0.3 mg/kg intranasal dose is the recommendation (22).

Adverse Effects

The common adverse effects associated with midazolam use are hiccoughs, cough, nausea, and vomiting. Thrombophlebitis, thrombosis, and pain on injection are other adverse effects. The incidence of thrombophlebitis is less than with diazepam but similar to that of thiopental. Midazolam causes anterograde amnesia, drowsiness, ataxia, falls, and confusion in the elderly. Residual hangover effect can happen with nighttime administration of midazolam, which can impair the cognitive and psychomotor abilities, which can result in falls in elderly and impaired coordination during driving. Hypotension and tachycardia can occur with rapid intravenous administration. A higher dose can result in midazolam infusion syndrome and respiratory depression. Instances of midazolam infusion syndrome require continuous ventilator support. Paradoxical effects of midazolam are possible in individuals with a history of alcohol abuse and aggressive behavior, potentially leading to involuntary movements, verbalization, uncontrollable crying, and aggressive behavior. Respiratory depression can happen with a dose of 0.15 mg/kg, and the risk increases when used along with fentanyl. Concomitant use of midazolam with other CNS depressants can result in severe respiratory depression and death even at therapeutic doses. (23).

Long-term use of midazolam is associated with lasting memory deficits, which are only partially reversible after the discontinuation of the drug. For pregnant women, the administration of the drug in third-trimester causes benzodiazepine withdrawal syndrome in the neonate resulting in hypotonia, cyanosis, and apnoeic spells. Neonates may suffer from diarrhea, tremors, and hyperexcitability. About one-third of individuals receiving midazolam can suffer from tolerance after using the drug for four weeks. Withdrawal syndrome can occur if the dose tapers too rapidly. Symptoms due to the withdrawal of benzodiazepine include irritability, clonus, hypertonicity, nausea, vomiting, diarrhea, tachycardia, and hypertension. Sudden discontinuation of midazolam can result in status epilepticus (24).

Contraindications

Contraindications for the use of midazolam include acute angle-closure glaucoma, hypotension, and shock. Careful dose adjustment is necessary in cases of kidney and liver diseases, alcohol, and drug-dependent individuals. Caution is necessary for pregnant individuals, children, and individuals with comorbid psychiatric conditions. Administration in elderly individuals and acutely ill patients requires caution to prevent the accumulation of active metabolites. Extra precautions should be taken in

critically ill individuals as dose accumulation can occur (25).

Monitoring

Frequent monitoring of blood levels of midazolam and its metabolites is a requirement during the treatment of midazolam overdose. Levels of midazolam and its metabolites can are measurable in blood, plasma, and serum. Monitoring is essential for elderly individuals and individuals with liver and kidney disease. The elimination of both the drug and its metabolite decreases with renal insufficiency. Monitoring is also necessary for drug interactions with erythromycin, clarithromycin, diltiazem, sertraline, protease inhibitors, rifampin, phenytoin, phenobarbital, carbamazepine, opioids, antipsychotics, and alcohol. Induction and inhibition of CYP450 3A4 play a role in decreased and increased levels of the drug in the circulation. Grapefruit juice reduces the activity of the CYP 450 enzyme and increases the level of the drug. St. John's wort induces the enzyme and reduces the blood level of midazolam (26).

Toxicity

Toxicity with midazolam is rare but can happen when combined with other CNS depressants like alcohol, opioids, and other tricyclic antidepressants. The risk increases with intravenous administration and in elderly individuals with COPD. Symptoms of overdose include ataxia, nystagmus, hypotension, slurred speech, slurred speech, impaired motor coordination, coma, and death. Impaired reflexes, impaired balance and dizziness, dysarthria, and vasomotor collapse can also occur. Flumazenil is the antidote for midazolam toxicity. Supportive treatment is the initial therapy course. Activated charcoal is an option within 1 hour of intoxication. In many instances, flumazenil is not prudent, as it can precipitate seizures when used in a mixed overdose of CNS depressants. Rapid intravenous infusion in elderly individuals having COPD can also result in an overdose (27).

3. KETAMINE

Mechanism of action

Its mechanism of action is mainly by noncompetitive antagonism of the N-methyl D-aspartic acid (NMDA) receptor. It also interacts with opioid receptors, monoamine, cholinergic, purinergic and adrenoreceptor systems as well as having local anesthetic effects (28).

Newly found mechanisms of action with newer clinical applications

1. NMDA receptor interaction with ketamine plays a role in the opioid induced antihyperalgesic effects of ketamine (28).
2. Subanesthetic doses of ketamine via NMDA receptor blockade potentiate opioid analgesia (29).
3. Ketamine by suppressing the induction of NO synthase activity and protein expression by endotoxin exerts a protective antiinflammatory effect against sepsis process (30).
4. The hypnotic effects of ketamine are caused by a combination of immediate channel blockade of NMDA and hyperpolarization-activated cation channels
5. Its ant proinflammatory effects may be responsible for its antihyperalgesic effects (28).
6. Its immediate analgesic effects are mediated predominantly by a combination of opioid system sensitization and antinociception
7. Ketamine inhibits tumor necrosis factor-alpha and interleukin-6 gene expressions in macrophages. (28) NMDA receptor blockade by ketamine inhibits extracellular signal regulated kinase ½ pathway and proliferation of carcinoma cells by cell cycle arrest (29).
8. Downstream "postdrug" effects such as activity induced increase in structural synaptic connectivity lead to the prolonged antidepressant effects of ketamine.

Basic chemistry

Ketamine is a water-soluble phencyclidine derivative. The ketamine molecule contains an asymmetric carbon atom with two enantiomers: The S(+) isomer and the R(−) isomer (31).

Pharmacokinetics

Ketamine is highly lipid soluble and undergoes rapid breakdown and redistribution to peripheral tissues. It is metabolized extensively in the liver by N-demethylation and ring hydroxylation pathways. Norketamine is the main metabolite and is one-third to one-fifth as potent as ketamine as an anesthetic. Ketamine is excreted in urine and faeces as norketamine and as hydroxylated derivatives. It has a cumulative effect. Gradual resistance builds up on repeated administration (32).

Pharmacodynamics

Ketamine stimulates the cardiovascular system resulting in an increase in heart rate, blood pressure and increase in cardiac output, mediated principally through the sympathetic nervous system. It has minimal effects on central respiratory drive and produces airway relaxation by acting on various receptors and inflammatory cascades and bronchial smooth muscles. It increases salivation and muscle tone. It has cataleptic, amnestic, profound analgesic, and dose dependent anesthetic actions. The cataleptic state is an akinetic state with the loss of orthostatic reflexes, but without impairment of consciousness. The dissociative state produced by ketamine is unique in which the patient appears awake but is detached from the surroundings with eyes remaining open (31).

Current clinical applications of ketamine

Old well-established applications where the role of ketamine remains unchallenged.

1. As an IV induction agent in the emergency setting in shocked or hypotensive patients: The combination of rapid blood - cerebral transfer kinetics, sympathomimetic hemodynamic effects and absence of idiosyncratic adverse effects like impaired steroidogenesis all confer distinct advantages on ketamine when used for rapid sequence induction in hemodynamically compromised patients. A study showed that ketamine is a safe and valuable alternative to etomidate for endotracheal intubation in critically ill patients with sepsis. Its free radical scavenging property, neuroprotective effects against cerebral ischemia, anticonvulsant activity, potential to limit hypotension and hypotension related secondary brain injury are favorable in patients with traumatic brain injury. In patients with cardiac tamponade and restrictive pericarditis, ketamine provides excellent anesthetic induction, and maintenance (33).

2. For patients with reactive airways disease:

a. Ketamine by virtue of its bronchodilating property and profound analgesia allowing use of high oxygen concentration is considered to be the IV induction agent of choice in patients with active bronchospasm. Some researchers have found that ketamine not only protected against precipitation of asthma in asymptomatic surgical patients, but it also alleviated bronchospasm in patients with respiratory distress prior to induction of anesthesia (31)

b. Ketamine is considered to be the bronchodilator of choice in rescue therapy for refractory bronchospasm in OT and refractory status asthmaticus in the intensive care unit (ICU). A loading dose of 0.1-0.2 mg/kg followed by an infusion of 0.15-2.5 mg/kg/h can be used in these cases.

3. For induction of patients especially children with congenital heart disease with right to left shunt: Ketamine is the anesthetic drug of choice in these cases due to its beneficial cardiovascular effects of increasing systemic vascular resistance and the resulting decrease in right to left shunt. Furthermore, by increasing pulmonary blood flow, it improves oxygenation. In a study, IV or intramuscular (IM) ketamine as induction agents did not significantly affect SaO 2 % in patients with fallots tetralogy. Ketamine appears as a good alternative to sevoflurane for induction in patients with congenital heart disease where it preserves intra- and post-operative hemodynamic stability (34).

4. Burns: Ketamine has been widely used to provide analgesia in burn dressing changes, during excision and grafting and for sedation. It has a major role in repeated anesthetics for burns dressings. The major advantage of ketamine in burns is that unlike other agents, it usually preserves airway and spontaneous respiratory function in addition to providing good sedoanalgesia. It is the most desirable agent for IM administration in patients with extensive burns where there a difficulty in finding a suitable vein. A recent study has shown that ketamine is generally effective and well-tolerated in pediatric burns patients. Oral and IV ketamine have been used as an analgesic and sedative for wound care procedures in children with burns and provides improved analgesia and sedation. Ketamine in combination with midazolam/dexmedetomidine provides effective sedoanalgesia without causing any significant side-effects. Ketamine can be used in combination with propofol for burns dressings in adults and children. A recent study showed that ketamine therapy given 15 min after burns injury in rats improves survival in severe burns injury probably by eliciting heat-shock response as evidenced by the expression of heat-shock protein 70 in myocardial cells and cerebral tissues (35).

5. Prehospital and battlefield medicine: Ketamine is the anesthetic of choice when supplies of oxygen and monitoring and disposable equipment are limited. The United States Defense Health Board notes that morphine is the slipping gold standard in Tactical Combat Casualty Care pain management and recommends ketamine as a new alternative to battlefield analgesia. Ketamine is an effective agent in facilitating endotracheal intubation in the Helicopter Emergency Medical Services setting. In military practice, ketamine is currently used throughout the entire military chain of evacuation from the point of wounding, through the field hospital and on to the receiving hospital in the United Kingdom. All doctors joining the army are given training in the use of ketamine for the treatment of pain. Ketamine is added to opioids like morphine or transmucosal fentanyl to help the combat medic to control pain without the risk of opioid induced hypotension. Ketamine 50-100 mg IM or 50 mg intranasally using atomizer is given and repeated every 30 min to 1 h or until nystagmus appears. Ketamine is an invaluable agent for treatment of the trapped casualty or even in the mass casualty situation. It is used for sedation of the trapped casualty and also for pain control to facilitate extraction of the trapped casualty (36).

6. In low doses (IV 0.5 mg/kg) in combination with IV diazepam or midazolam as an IV supplement to local and regional anesthesia techniques including spinal anesthesia in adults and children. Low dose ketamine infusions (5-25 mg/kg/min) can be used for sedation and analgesia during local or regional anesthetic procedures. They can be used before the application of painful blocks but are more commonly used for sedation or supplemental anesthesia during long uncomplicated procedures or supplemental analgesia for inadequate blocks in combination with

IV diazepam. IV ketamine 0.5 mg/kg given prophylactically just before neuraxial blockade decreases the incidence of shivering, improves hemodynamic profile, provides good sedation and prevents recall. IV ketamine 1 mg/kg given before spinal anesthesia results in good hemodynamic stability in elderly patients undergoing transurethral resection of the prostate (37).

4. EMERGENCE AGITATION

Introduction

Emergence agitation (EA) involves restlessness, disorientation, excitation, non-purposeful movement, inconsolability, thrashing, and incoherence during early recovery from general anesthesia. 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. The clinical consequences of EA are similarly varied. It is typically short lived and resolves spontaneously, and its clinical consequences are often considered minimal. 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 (38).

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. ED is not fully equivalent to EA; ED can involve hypoactive signs or mixed forms and hyperactive signs similar to agitation. Nevertheless, the terms EA and ED have been used interchangeably in several studies. Moreover, the same assessment tools (e.g., Riker Sedation-Agitation Scale or Richmond Agitation-Sedation Scale) have been used for both conditions. 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. 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. The terms EA and ED are used interchangeably in this review, as in previous studies (39; 40).

Mechanism of emergence agitation

The precise pathophysiological mechanism of EA after general anesthesia is unknown. In children, proposed causes of EA include high levels of anxiety regarding surgery, new environments, separation from parents, and encounters with unfamiliar medical staff. These may lead to increased sympathetic tone and prolongation of the excited state during anesthesia recovery (41).

The advent of volatile agents with low blood solubility, such as sevoflurane and desflurane, has increased the incidence of EA in children. 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; 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 (42).

Functional magnetic resonance imaging has been used to study the mechanisms underlying the alteration of consciousness during anesthesia. 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 (43).

Proposed risk factors for emergence agitation.

The etiology of EA is multifactorial. 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 (44).

The proposed risk factors for EA in adults are age, sex, obesity (body mass index ≥ 30 kg/m2), 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) (Table 1). We review common risk factors and other related issues presented in literature (45).

Table (1). Possible Risk Factors for Emergence Agitation (45).

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	
	Psychological immaturity	
	Preoperative anxiety	Chronic lung disease
	Parental anxiety	Recent smoking
	Patient and parent interaction with healthcare providers	History of social drinking
		History of substance dependence
Anesthesia related	Lack of premedication (with midazolam)	Number of intubation attempts
	Paradoxical reaction to midazolam stated in child's medical history	Method of anesthesia (inhalation anesthesia)
		Duration of surgery or anesthesia
	Use of inhalational anesthetics with low blood–gas partition coefficients (e.g., sevoflurane and desflurane)	Premedication with benzodiazepines
		Neuromuscular blocking agents and anticholinergics
	Excessively rapid awakening (in a hostile environment)	Doxapram
		Voiding urgency
	Pain	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

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. In a study that analyzed both surgery and anesthesia time, patients with EA had significantly longer surgery and anesthesia times than patients without EA. Furthermore, in a prospective observational study of 1868 adult patients, a longer duration of surgery was identified as a risk factor for hypoactive ED (46).

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. In a meta-analysis of pediatric patients performed in 2015, desflurane induced EA less frequently than sevoflurane. 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) (47).

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. Nitrous oxide was shown to attenuate EA in pediatric patients, 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 (48).

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. However, the rapid awakening process did not cause a higher incidence of EA after sevoflurane anesthesia in children. 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 (49).

Neuromuscular blocking agents and reversal agents

Anticholinergics (e.g., atropine and scopolamine) are known risk factors for EA. 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. 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. 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. 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 (50).

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. 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. In adults, when postoperative pain was assessed with a numerical rating scale, a score ≥ 5 points was found to increase the risk of EA. Nonetheless, EA may increase postoperative pain. Therefore, adequate perioperative pain control may influence onset of EA (51). **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. 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 (52).

Prediction of emergence agitation

Prevention is preferred over treatment, for EA; EA can have serious consequences for patients, and increase the patient care burden. Recently, Hino et al. (53) 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. 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. 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 (54).

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. However, the PAED scale has disadvantages of inherent subjectivity in assessing each behavior item and suboptimal interrater reliability. In addition, the cutoff point for defining the presence of EA is controversial (55).

Bong and Ng (56) suggested that PAED score ≥ 10 was the ideal cutoff for EA. In contrast, Bajwa et al. (51) 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.

Table 2. Assessment Tools for Emergence Agitation (55).

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)

In adults, the Riker Sedation-Agitation Scale (RSAS, 7-point scale with three levels of agitation), Richmond Agitation-Sedation Scale (RASS, 10-point scale with four levels of agitation), Aono's 4-point scale, Nurses Delirium scale, and the 3-point scale (graded as mild, moderate, or severe) 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, 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; the majority of EA studies have been performed in PACUs or operating rooms. 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 $\geq$ +1 vs. $\geq$ +2 vs. $\geq$ +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). 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) or same type of surgery (50% by the RSAS vs. 22% by the RASS, respectively). Fields et al. (57) used RASS $\geq$ +3 as an indicator of EA, while Jee et al. (41) and Ham et al. (58) adopted RASS $\geq$ +2 as an indicator of EA; most other groups defined RASS $\geq$ +1 as an indicator of EA.

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) (41).

Table (3). Strategies to Prevent Emergence Agitation (41).

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

Effects of ketamine and midazolam on emergence agitation after sevoflurane anaesthesia in children receiving caudal block

Emergence agitation (EA) is a common postanaesthetic problem in children after sevoflurane anaesthesia. However, the aetiology of EA has not yet been identified clearly. The predisposing factors are preschool age, preoperative anxiety, lack of premedication, type of surgery, awakening in a strange environment. The incidence of EA had been reported between 10% and 80% in different studies. Although EA is also seen in pain-free procedures, pain is thought to be the major contributing factor for EA. In addition to pain treatment, benzodiazepines, opioids, ketamine, alpha-2 agonists and propofol have also been used to prevent EA. (59).

Pain, rapid emergence in an unknown environment, separation from parents, and preoperative anxiety are major factors contributing to EA (59).

Different definitions and scales exist for evaluation of EA, but PAED scale is preferred in most of the studies. A score of 10/20 on the PAED scale was reported as the best threshold point for determining the presence of EA. (61) However, Bajwa et al. (51) reported that a PAED score greater than 12 had greater sensitivity than a score of ≥10. In our study, we used a score of ≥10 on PAED scale for the assessment of EA.

Pain is thought to be the major factor that contributes to EA. In previous studies several analgesics including acetaminophen, ketorolac, fentanyl were administered to prevent EA after sevoflurane anaesthesia. In most of these studies, addition of analgesics reduced the incidence of EA. (60) Caudal block is another preferred technique for pain relief in children. Aouad et al. (61) had shown that the incidence of EA and pain scores in patients receiving caudal block were significantly lower compared to those receiving intravenous fentanyl under sevoflurane anaesthesia for inguinal hernia repair. However, Aono et al. (62) reported EA in 40% of children with caudal block following sevoflurane anaesthesia for minor urologic surgery. We used modificada Children's Hospital of Eastern Ontario Pain Scale (mCHEOPS) scoring system to evaluate and to exclude pain as a contributing factor of EA.

Although pain is thought to be important in aetiology, EA is also seen in pain free procedures. (63; 64) This may due to rapid emergence in an unknown environment with altered cognitive function which is another risk factor for EA. It is difficult for the children to cooperate to a strange environment upon rapid emergence following anaesthesia. Therefore, agents that provide sedation at the time of emergence may be helpful in prevention of EA. (65; 66) This point was one of the reasons to establish this study.

Low doses of midazolam and ketamine are safely used for sedation. Chen et al. (66) found that 0.05 mg kg−1 midazolam in combination with 0.5 μg kg−1 of fentanyl at the end of surgery was effective in reducing the incidence and severity of EA. Ozcengiz et al. (67) found 0.5 mg kg−1 oral midazolam, given for premedication, very effective in reducing EA. Kararmaz et al. (9) had shown that oral ketamine reduced the incidence of EA after desflurane anaesthesia without delaying recovery. Abu-Shahwan and Chowdary (68) showed that administration of 0.25 mg kg−1 iv ketamine at the end of anaesthesia reduced significantly the incidence and severity of EA in children undergoing dental repair. Dalens et al. (69) administered 0.25 mg kg−1 ketamine, 0.1 mg kg−1 nalbuphine and saline in three groups of patients, and they found significantly lower EA in ketamine and nalbuphine groups compared to control without a delay in awakening and discharge. In contrary to literature, ketamine and midazolam did not affect EA in children in whom pain was relieved by caudal block in the present study.

Parental presence may be another important factor that influences the incidence of EA. Arai et al. (70) studied the effect of parental presence on EA and found that parental presence during induction of anaesthesia enhanced the effect of oral midazolam on EA of children compared with midazolam and parental presence alone groups. In our study, parents were present at the arrival to PACU.

6. Effects of sevoflurane versus other general anaesthesia on emergence agitation in children

Sevoflurane is an inhaled volatile anaesthetic that is widely used in paediatric anaesthetic practice. First described in 1975 (71), its use commenced in Japan in 1992 and became widespread in 1995 (72).

Sevoflurane is a non- pungent, insoluble agent that facilitates smooth, rapid induction and emergence. However, since its introduction, postoperative behavioural disturbance, observed predominantly in the paediatric population (73), has become an important clinical issue.

Some studies suggest that sevoflurane is associated with the highest risk of behavioural disturbance of all current general anaesthetics, while others show conflicting results (74).

These behavioural changes have been described in the literature using a variety of descriptive terms, such as emergence agitation (EA), emergence delirium (ED) and postanaesthetic excitation. No consensus has been reached regarding a definition; however the condition has been described as a mental disturbance during recovery from general anaesthesia that may consist of hallucinations, delusions and confusion manifested by moaning, restlessness, involuntary physical activity and thrashing about in the bed (75).

Emergence delirium appears to represent a subset of EA, as not all agitated children are truly delirious (76).

The term 'emergence agitation' will be used to encompass this clinical entity. Until recently, no reliable and validated scale has been available to measure EA. Concern has been expressed as to the reliability of research results and the ease of comparing studies; this probably played a part in the development in 2004 of the Pediatric Anesthesia Emergence Delirium (PAED) scale (77).

Although the PAED scale is now the most frequently used scale in research studies, at least one investigator has described a PAED scale modification, and some study authors are now reporting EA by using two scales simultaneously—typically PAED plus one other scale (78).

In addition, some trial authors are using different PAED scores as cutoffs for the presence of EA . This suggests that no one scale currently fulfils all relevant requirements in determination of EA (51).

The potential adverse effects of EA are mostly short lived. It would be unusual for children with EA to be discharged from the postanaesthetic care unit (PACU), as a restless child may cause self- injury, the dressing or surgical site may be disrupted and indwelling devices have the potential to become dislodged. To prevent such outcomes, the child may require pharmacological or physical restraint. Pharmacological management provides the disadvantage of exposing the child to medications such as opioids and sedatives. These drugs themselves could have adverse effects, and their administration could delay discharge from the PACU or hospital. The psychological and long- term consequences of EA are largely unknown, but it has been suggested that maladaptive behaviours, for example, withdrawal, sleeping and eating problems, may be associated with EA. Extra care is required to manage a patient with EA, and this might strain already limited nursing resources. Caregivers are at risk of injury when managing these children and may feel dissatisfied with the quality of available anaesthetic care. Parents who witness EA may become concerned regarding future anaesthetic experiences for their child. Additional costs and potential delays to discharge may be significant (79).

The exact aetiology of EA remains unclear; however research to date suggests numerous predisposing factors. Anaesthetic factors may include rapid emergence and the intrinsic characteristics of the anaesthetic. The newer volatile anaesthetic agents, such as sevoflurane, allow faster emergence, which potentially results in early manifestation of acute pain and anxiety. Some authors have suggested that sevoflurane exerts a stimulating or even neurotoxic effect on the central nervous system (80).

Patient- related factors include age, preoperative anxiety and the temperament of the child. The risk of EA is highest in preschoolers, potentially because of psychological immaturity in this age group (71). Surgery- related factors include pain and type of surgery. Pain may increase the risk of EA, and the behaviour of a child in pain may mimic EA. Otorhinolaryngology and ophthalmological procedures carry an increased risk of EA; however this phenomenon has been observed even after non-painful imaging procedures (71).

Sevoflurane may be a major contributor to the development of EA. Therefore, an evidence- based understanding of the risk/benefit profile regarding sevoflurane compared with other general anaesthetic (GA) agents and adjuncts would facilitate its rational and optimal use.

- **Sevoflurane versus halothane**

All studies (34 trials) for this comparison reported risk of EA and show that halothane has a lower risk

of EA when compared with sevoflurane (RR 0.51, 95% CI 0.41 to 0.63).

- **Sevoflurane versus isoflurane**

All six studies investigating this comparison reported risk of EA. No difference in EA was found (82).

- **Sevoflurane versus desflurane**

Six studies investigating this comparison reported risk of EA. No difference in EA was found. One study used a five- point scale and reported no difference in agitation scores (82).

- **Sevoflurane versus propofol induction and maintenance (including total intravenous anaesthesia [TIVA])**

Fourteen studies investigated risk of EA for this comparison and found that propofol anaesthesia reduced risk of EA (RR 0.35, 95% CI 0.25 to 0.51). It should be noted that in one of these studies, the TIVA arm included ketamine 1.5 mg/kg at induction of anaesthesia, and that another study compared TIVA with sevoflurane anaesthesia with 1 mg/kg of propofol at the end of anaesthesia, yet showed TIVA propofol to be superior in reducing EA (83).

One additional study reported lower mean PAED scores in the propofol group.

- **Sevoflurane versus propofol maintenance (after sevoflurane induction)**

Some studies reported risk of EA and found that the propofol group had a lower risk of EA (RR 0.59, 95% CI 0.46 to 0.76). Two further studies found lower EA scores in the propofol group. One study used a five- point scale, and another small study reported that PAED scores indicated a greater frequency of EA in the sevoflurane group without reporting the risk (71).

- **Sevoflurane versus ketamine anaesthesia**

One small study included only 20 participants and showed no difference in risk of EA (80).

- **Sevoflurane versus midazolam anaesthesia**

One study found lower risk of EA, although it should be noted that the outcome assessor was not blinded (84).

- **Sevoflurane versus other GA combinations**

Two further comparisons were reported in one small study (85).

Comparison 2. Adjuncts to sevoflurane anaesthesia

Studies investigating the effectiveness of an adjunct for EA while sevoflurane anaesthesia was administered. Results of different individual adjuncts compared with no adjunct or placebo are reported below.

- **Propofol bolus**

At induction

One study investigated propofol 3 mg/kg induction and showed no effect on risk of EA, whilst another study investigated 2 to 2.5 mg/kg propofol induction with no difference in EA scores between groups (80). Two studies investigated 1 mg/kg of propofol just after sevoflurane induction. The former showed no difference in scores for EA whilst the latter showed no effect on risk of EA (80).

At the end of anaesthesia

Five studies investigating the effect of 1 mg/kg of propofol administered at the end of anaesthesia showed decreased risk of EA (RR 0.58, 95% CI 0.38 to 0.89) (58).

Two further studies reported only EA scores. They gave propofol 1 mg/kg and found lower PAED scores, whilst they compared propofol 1 mg/kg versus 2 mg/kg vs intralipid placebo and found no difference in mean EA scores across the three groups (86).

In view of I2 > 40%, we investigated heterogeneity and found that when we removed the trial with an MRI setting, I2 decreased from 62% to 49%, and EA was still significantly reduced (RR 0.66, 95% CI 0.46 to 0.93). When only the two studies of adenotonsillectomy were analysed, the reduction in EA was no longer evident (RR 0.74, 95% CI 0.42 to 1.32) (I2 = 52%).

- **Thiopentone**

One study reported no difference in risk of EA following thiopentone induction, and another study administered 2 to 3 mg/kg thiopentone after sevoflurane induction and found reduced risk of EA and lower PAED scores in children undergoing MRI scans with mean duration of less than 20 minutes (87).

- **Clonidine**

Some studies investigated risk of EA and showed an overall reduction in risk of EA (RR 0.45, 95% CI 0.31 to 0.66) (I2 = 61%) (88).

Bergendahl (89) compared midazolam and clonidine premedication and showed reduced EA scores in children younger than five years of age receiving clonidine. Mikawa (90) investigated oral clonidine premedication 4 mcg/kg and found that it was more effective when compared with clonidine 2 mcg/kg, midazolam 0.5 mg/kg, diazepam 0.4 mg/kg or placebo, without influencing discharge readiness.

In view of I2 > 40%, we investigated heterogeneity with respect to studies with regional block analgesia versus systemic analgesia and route of administration (IV vs caudal). I2 for these analyses remained unaffected, as did the effectiveness of this

intervention. When clonidine (all routes) was used in conjunction with a regional block (seven studies), it was effective in reducing EA (RR 0.37, 95% CI 0.23 to 0.59) (I2 = 55%), whereas in the two systemic analgesia studies (one of which was an adenoidectomy study), this effect was no longer evident (RR 0.74, 95% CI 0.49 to 1.12) (I2 = 19%).

- **Dexmedotomidine**

Some studies investigating this intervention found a large overall reduction in risk of EA, with I2 = 0 (RR 0.37, 95% CI 0.29 to 0.47). An additional four studies reported lower EA scores for this intervention (91).

- **Ketamine**

Oral premedication

Two studies have shown this to be an effective intervention with an overall reduction in risk of EA (92; 93).

Ketamine 0.25 mg/kg bolus at end of anaesthesia

Three studies show an overall reduction in risk of EA (RR 0.30, 95% CI 0.13 to 0.69) (66).

In view of I2 > 40%, we investigated heterogeneity with respect to potentially inadequate analgesia for painful surgery versus any other setting such as MRI, or painful surgery with analgesia. When the study in which no analgesia was reported to be administered to the control group undergoing adenotonsillectomy was removed, I2 decreased from 44% to 0%, yielding RRs of 0.30 (95% CI 0.13 to 0.69) and 0.43 (95% CI 0.22 to 0.81), respectively (10).

- **Fentanyl**

Fifteen included studies showed an overall decrease in risk of EA (RR 0.37, 95% CI 0.27 to 0.50) (I2 = 54%). One further study investigating intranasal fentanyl 1 mcg/kg reported no difference in risk of EA (but did not present the risk data) or mean EA scores (data were reported) (94).

In view of I2 > 40%, we investigated heterogeneity with respect to potentially inadequate analgesia for painful surgery versus any other setting such as MRI, or painful surgery with analgesia or route of administration.

When the three studies of adenotonsillectomy/adenoidectomy in which limited (rectal paracetamol only) or no analgesia was reported to be administered to the control group were removed, I2 remained high at 61% but still showed fentanyl to be an effective means of decreasing EA (RR 0.34, 95% CI 0.23 to 0.49) (95).

Analysis of IV fentanyl versus non- IV fentanyl (intranasal, transmucosal) studies showed that this intervention was still effective in the 12 IV fentanyl studies (RR 0.35, 95% CI 0.24 to 0.51) (I2 = 55%) had an RR of 0.42 (95% CI 0.22 to 0.77) (I2 = 59%) (96).

- **Other opioids (including tramadol)**

Five studies show an overall reduction in risk of EA when remifentanil is administered (RR 0.50, 95% CI 0.30 to 0.85) (97).

Two studies show no overall reduction in risk of EA when sufentanil is administered (98).

One study administered alfentanil and reduced the risk of EA (99).

One study found nalbuphine to be effective in reducing the risk of EA (74).

One study administered dextromethorphan and found it to be effective in reducing the risk of EA (90).

One study found that oxycodone premedication was ineffective in reducing the risk of EA (100).

Two studies investigated tramadol. One showed reduced risk of EA, and the other found lower PAED scores (101).

- **Midazolam**

Oral midazolam premedication

Some studies showed no overall reduction in risk of EA (RR 0.81, 95% CI 0.59 to 1.12) (I2 = 50%) (102).

One study compared 0.5 mg/kg versus 1 mg/kg oral premedication and found no difference in the risk of EA (70).

In view of I2 > 40%, we investigated heterogeneity with respect to midazolam dose; studies with regional block analgesia versus systemic or no analgesia and adenoidectomy versus other procedures. The only difference was found when the two adenoidectomy studies were removed, resulting in I2 = 4% and an overall reduction in EA (RR 0.68, 95% CI 0.53 to 0.87).

- **Non- steroidal anti- inflammatory drugs (NSAIDs)**

Three studies were suitable for meta- analysis. Two investigated ketorolac, and one, ibuprofen premedication; these studies showed a decrease in risk of EA (RR 0.43, 95% CI 0.26 to 0.73). One further study investigating ketorolac reported no difference in risk of EA (but did not present the risk data) nor mean EA scores (data were reported), and another, investigating diclofenac, showed lower PAED scores (12).

- **5- HT3 antagonists**

Three studies investigated this intervention—two with ondansetron and one with tropisetron—with no overall effect in EA (103). Erden (103) reported no difference in agitation scores but did not report the

risk of EA, so this study does not appear in Analysis 2.1.25.

- **Hydroxyzine**

One study, which added this intervention to a midazolam premedication, showed reduced risk of EA (104).

- **Melatonin**

One study showed no reduction in risk of EA with melatonin compared with placebo (Analysis 2.1.28), although study authors reported lower risk of EA (72).

- **Magnesium sulphate**

One study showed no effect on risk of EA or PAED scores (105), whilst Apan (106) also showed no difference in agitation scores.

- **Gradual cessation of sevoflurane**

One study showed no difference in risk of EA when compared with rapid cessation of sevoflurane (107).

- **Sevoflurane concentration**

One study showed no difference in PAED scores with lower concentrations of sevoflurane titrated to BIS (Bispectral Index) (108).

- **Nitrous oxide washout**

One study showed lower agitation scores when inhaled nitrous oxide concentration was maintained at the end of surgery until BIS had reached 80 to wash out sevoflurane (109).

- **Diazepam**

Diazepam 0.25 mg/kg added to midazolam 0.25 mg/kg for premedication showed decreased EA scores compared with midazolam 0.5 mg/kg alone and placebo (110).

- **Sufentanil + clonidine (multi- modal)**

One study investigated a multi- modal approach to EA and found that sufentanil and clonidine in combination (four of 20 participants experienced EA) decreased the risk of EA further than when either drug was used alone (eight of 20 with EA) or against placebo (13 of 19 with EA) (111).

- **Acupuncture**

One study reported lower EA scores with acupuncture after induction of anaesthesia for children undergoing bilateral myringotomy and tympanostomy tube insertion (112).

- **Parental presence at induction of anaesthesia (PPIA)**

PPIA showed lower EA scores when all participants were premedicated with midazolam. Another study (Kazak 2010) using a lower dose of midazolam premedication (0.25 mg/kg) in the PPIA group compared with the non- PPIA group, which received 0.5 mg/kg midazolam, showed no effect on EA scores (110).

- **Airway management**

One study showed lower risk of EA when a laryngeal mask airway (LMA) was removed deep compared with an endotracheal tube (ETT) removed awake. No difference between ETT deep versus LMA deep extubation was reported. However no LMA awake group was included; therefore no comparison was performed with ETT awake versus LMA awake or LMA deep versus LMA awake (113).

CONCLUSION:

Premedication with ketamine is more effective than midazolam and dextromethorphan in preventing EA during the early emergence period after sevoflurane anaesthesia in children in comparison to placebo treated group in children undergoing adenotonsillectomy without reported side effects including (vomiting, hallucination, respiratory center depression except for nausea occurred and being lower in dextromethorphan group than other groups).

7. REFERENCES

1. Roberts S, Thornington RE. Paediatric bronchoscopy. Contin Educ Anaesth Crit Care Pain 2005; 5: 41–4.
2. Strauss L. Anaesthetic management of paediatric adenotonsillectomy,S Afr Fam Pract 2012;54(3)(Suppl 1):S17-20.
3. Anniko M, Bernal-Sprekelsen M, Bonkowsky V, Bradley P, Lurato S. Otorhinolaryngolgy, Head and Neck surgery (European Manual of Medicine)2010:717.
4. Mamuda A, Gudaji MI. Effect of oral midazolam in preventing postoperative emergence agitation in children. Sahel Med J 2019;22:1-7.
5. Veyckemans F. Excitation phenomena during sevoflurane anaesthesia in children. Curr Opin Anaesthesiol 2001;14:339‑43.
6. Gani H, Beqiri V, Prifti P, NacoM, Domi R, Janushaj O, et al. Oral midazolam plus ketamine compared to midazolam only to reduce agitation in children undergoing urological surgery after sevoflurane anesthesia. Anaesth Pain & Intensive Care 2014;18(3):237-40.
7. McCartney CJ, Sinha A, Katz J. A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. Anesth Analg 2004;98(5):1385–400.
8. Butkovic D, Kralik S, Matolic M, Zganjer M, Toljan S, Jakobovic J,et al. Pre-emptive dextromethorphan compared with midazolam for premedication in children. Anest Pediatr Neonat 2007;5:1–10.
9. Kararmaz A, Kaya S, Turhanoglu S, et al. Oral ketamine pre-medication can prevent emergence agitation in children after desflurane anesthesia. Paediatr Anaesth. 2004;14:477-82.
10. Lee YS, Kim WY, Choi JH, Son JH, Kim JH, Park YC. The effect of ketamine on the incidence of emergence agitation in children undergoing tonsillectomy and adenoidectomy under sevoflurane general anesthesia. Korean J Anesthesiol 2010;58(5):440–5.

11. Griffin CE 3rd, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner J. 2013 Summer;13(2):214-23.
12. Rachel Homer J, Elwood T, Peterson D, Rampersad S. Risk factors for adverse events in children with colds emerging from anesthesia: a logistic regression. Paediatr Anaesth. 2007;17(2): 154-161.
13. Chen R, Zheng X and Hu P (2017) CYP2D6 Phenotyping Using Urine, Plasma, and Saliva Metabolic Ratios to Assess the Impact of CYP2D6∗10 on Interindividual Variation in a Chinese Population. Front. Pharmacol. 8:239.
14. Corado CR, McKemie DS, Knych HK. Pharmacokinetics of dextromethorphan and its metabolites in horses following a single oral administration. Drug Test Anal. 2017 Jun;9(6):880-887.
15. Taylor CP, Traynelis SF, Siffert J, Pope LE, Matsumoto RR. Pharmacology of dextromethorphan: Relevance to dextromethorphan/quinidine (Nuedexta®) clinical use. Pharmacol Ther. 2016 Aug;164:170-82.
16. Nguyen L, Thomas KL, Lucke-Wold BP, Cavendish JZ, Crowe MS, Matsumoto RR. Dextromethorphan: An update on its utility for neurological and neuropsychiatric disorders. Pharmacol Ther. 2016 Mar;159:1-22.
17. Patatanian E, Casselman J. Dextromethorphan/quinidine for the treatment of pseudobulbar affect. Consult Pharm. 2014 Apr;29(4):264-9.
18. Pioro EP. Review of Dextromethorphan 20 mg/Quinidine 10 mg (NUEDEXTA(®)) for Pseudobulbar Affect. Neurol Ther. 2014 Jun;3(1):15-28.
19. Lauterbach EC. An extension of hypotheses regarding rapid-acting, treatment-refractory, and conventional antidepressant activity of dextromethorphan and dextrorphan. Med Hypotheses. 2012 Jun;78(6):693-702.
20. Oh S, Agrawal S, Sabir S, Taylor A. Dextromethorphan. 2021 May 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 30855804.
21. Ganetsky M, Babu KM, Boyer EW. Serotonin syndrome in dextromethorphan ingestion responsive to propofol therapy. Pediatr Emerg Care. 2007 Nov;23(11):829-31.
22. Olkkola KT, Ahonen J. Midazolam and other benzodiazepines. Handb Exp Pharmacol. 2008;(182):335-60.
23. Appleton R, Macleod S, Martland T. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database Syst Rev. 2008 Jul 16;(3):CD001905.
24. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. Anesthesiology. 1985 Mar;62(3):310-24.
25. Lingamchetty TN, Hosseini SA, Saadabadi A. Midazolam. 2020 Jun 22. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 30726006.
26. Mencía SB, López-Herce JC, Freddi N. Analgesia and sedation in children: practical approach for the most frequent situations. J Pediatr (Rio J). 2007 May;83(2 Suppl):S71-82.
27. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol. 2008 Dec;64(12):1147-61.
28. Bushra R, Aslam N, Khan AY. Food-drug interactions. Oman Med J. 2011 Mar;26(2):77-83.
29. Persson J. Wherefore ketamine? Curr Opin Anaesthesiol 2010;23:455-60.
30. Hirota K, Lambert DG. Ketamine: New uses for an old drug? Br J Anaesth 2011;107:123-6.
31. Yoon SH. Concerns of the anesthesiologist: Anesthetic induction in severe sepsis or septic shock patients. Korean J Anesthesiol 2012;63:3-10.
32. Goel S, Agrawal A. Ketamine in status asthmaticus: A review. Indian J Crit Care 2013;1793:154-61.
33. Reves JG, Glass P, Lubarsky DA, et al. Intravenous anesthetics. In: Miller RD (ed). Miller's anesthesia, 17th ed. Philadelphia: Churchill Livingstone Elsevier, 2010, pp. 742–747.
34. Sih K, Campbell SG, Tallon JM, Magee K, Zed PJ. Ketamine in adult emergency medicine: Controversies and recent advances. Ann Pharmacother 2011;45:1525-34.
35. Goyal R, Singh S, Bangi A, Singh SK. Case series: Dexmedetomidine and ketamine for anesthesia in patients with uncorrected congenital cyanotic heart disease presenting for non-cardiac surgery. J Anaesthesiol Clin Pharmacol 2013;29:543-6.
36. O'Hara D, Ganeshalingam K, Gerrish H, Richardson P. A 2 year experience of nurse led conscious sedation in paediatric burns. Burns 2014;40:48-53.
37. US Defence Health Board. Pre Hospital Use of Ketamine in Battlefield Analgesia in Tactical Combat Casualty Care Pain Guidelines, 2012-03.
38. Wason R, Jain N, Gupta P, Gogia AR. Randomized double-blind comparison of prophylactic ketamine, clonidine and tramadol for the control of shivering under neuraxial anaesthesia. Indian J Anaesth 2012;56:370-5.
39. Lee SJ, Choi SJ, In CB, Sung TY. Effects of tramadol on emergence agitation after general anesthesia for nasal surgery: a retrospective cohort study. Medicine (Baltimore) 2019; 98: e14763.
40. Mason KP. Paediatric emergence delirium: a comprehensive review and interpretation of the literature. Br J Anaesth 2017; 118: 335-43.
41. Jee YS, You HJ, Sung TY, Cho CK. Effects of nefopam on emergence agitation after general anesthesia for nasal surgery: a prospective, randomized, and controlled trial. Medicine (Baltimore) 2017; 96: e8843.
42. Dahmani, S, Delivet, H, Hilly, J. Emergence delirium in children: an update. Curr Opin Anaesthesiol 2014; 27: 309–315.
43. Bonhomme V, Boveroux P, Brichant JF, Laureys S, Boly M. Neural correlates of consciousness during general anesthesia using functional magnetic resonance imaging (fMRI). Arch Ital Biol 2012; 150: 155-63.
44. Huett C, Baehner T, Erdfelder F, Hoehne C, Bode C, Hoeft A, et al. Prevention and therapy of pediatric emergence delirium: a national survey. Paediatr Drugs 2017; 19: 147-53.
45. Makarem J, Larijani AH, Eslami B, Jafarzadeh A, Karvandian K, Mireskandari SM. Risk factors of inadequate emergence following general anesthesia with an emphasis on patients with substance dependence history. Korean J Anesthesiol 2020; 73: 302-10.
46. Radtke FM, Franck M, Hagemann L, Seeling M, Wernecke KD, Spies CD. Risk factors for inadequate emergence after anesthesia: emergence delirium and hypoactive emergence. Minerva Anestesiol 2010; 76: 394-403.
47. He J, Zhang Y, Xue R, Lv J, Ding X, Zhang Z. Effect of desflurane versus sevoflurane in pediatric anesthesia: a meta-analysis. J Pharm Pharm Sci 2015; 18: 199-206.
48. Park JH, Lim BG, Kim HZ, Kong MH, Lim SH, Kim NS, et al. Comparison of emergence agitation between sevoflurane/nitrous oxide administration and sevoflurane administration alone in children undergoing adenotonsillectomy with preemptive ketorolac. Korean J Anesthesiol 2014; 66: 34-8.
49. Choi GJ, Baek CW, Kang H, Park YH, Yang SY, Shin HY, et al. Emergence agitation after orthognathic surgery: a randomised controlled comparison between sevoflurane and desflurane. Acta Anaesthesiol Scand 2015; 59: 224-31.
50. Korkmaz MO, Sayhan H, Guven M. Does sugammadex decrease the severity of agitation and complications in pediatric patients undergoing adenotonsillectomy? Saudi Med J 2019; 40: 907-13.
51. Bajwa SA, Costi D, Cyna AM. A comparison of emergence delirium scales following general anesthesia in children. Paediatr Anaesth. 2010;20:704-11.
52. Kim HJ, Kim DK, Kim HY, Kim JK, Choi SW. Risk factors of emergence agitation in adults undergoing general anesthesia for nasal surgery. Clin Exp Otorhinolaryngol 2015; 8: 46-51.
53. Hino M, Mihara T, Miyazaki S, Hijikata T, Miwa T, Goto T, et al. Development and validation of a risk scale for

emergence agitation after general anesthesia in children: a prospective observational study. Anesth Analg 2017; 125: 550-5.
54. Hesse S, Kreuzer M, Hight D, Gaskell A, Devari P, Singh D, et al. Association of electroencephalogram trajectories during emergence from anaesthesia with delirium in the postanaesthesia care unit: an early sign of postoperative complications. Br J Anaesth 2019; 122: 622-34.
55. Lee SJ, Sung TY. Emergence agitation: current knowledge and unresolved questions. Korean J Anesthesiol. 2020 Dec;73(6):471-485.
56. Bong CL, Ng AS. Evaluation of emergence delirium in Asian children using the Pediatric Anesthesia Emergence Delirium Scale. Paediatr Anaesth. 2009;19:593-600.
57. Fields A, Huang J, Schroeder D, Sprung J, Weingarten T. Agitation in adults in the post-anaesthesia care unit after general anaesthesia. Br J Anaesth 2018; 121: 1052-8.
58. Ham SY, Kim JE, Park C, Shin MJ, Shim YH. Dexmedetomidine does not reduce emergence agitation in adults following orthognathic surgery. Acta Anaesthesiol Scand 2014; 58: 955-60.
59. Dahmani S, Stany I, Brasher C, et al. Pharmacological prevention of sevoflurane- and desflurane-related emergence agitation in children: a meta-analysis of published studies. Br J Anaesth 2010; 104: 216–223.
60. Galinkin JL, Fazi LM, Cuy RM, et al. Use of intranasal fentanyl in children undergoing myringotomy and tube placement during halothane and sevoflurane anesthesia. Anesthesiology. 2000;93:1378-83.
61. Aouad MT, Kanazi GE, Siddik-Sayyid SM, et al. Preoperative caudal block prevents emergence agitation in children following sevoflurane anesthesia. Acta Anaesthesiol Scand. 2005;49:300-4.
62. Aono J, Ueda W, Mamiya K, et al. Greater incidence of delirium during recovery from sevoflurane anesthesia in preschool boys. Anesthesiology. 1997;87:1298-300.
63. Uezono S, Goto T Terui K, et al. Emergence agitation after sevoflurane versus propofol in pediatric patients. Anesth Analg. 2000;91:563-6.
64. Cravero J, Surgenor S, Whalen K. Emergence agitation in pae-diatric patients after sevoflurane anaesthesia and no surgery: a comparison with halothane. Paediatr Anaesth. 2000;10:419-24.
65. Breschan C, Platzer M, Jost R, Settener H, Likard R. Midazolam does not reduce emergence delirium after sevoflurane anesthesia in children. Paediatr Anaesth 2007; 17:347–352.
66. Chen J, Li W, Hu X, et al. Emergence agitation after cataract surgery in children: a comparison of midazolam, propofol and ketamine. Pediatr Anesth. 2010;20:873-9.
67. Ozcengiz D, Gunes Y, Ozmete O. Oral melatonin, dexmedetomi-dine, and midazolam for prevention of postoperative agitation in children. J Anesth. 2011;25:184-8.
68. Abu-Shahwan I, Chowdary K. Ketamine is effective in decreasing the incidence of emergence agitation in children undergoing dental repair under sevoflurane general anesthesia. Pediatr Anesth. 2007;17:846-50.
69. Dalens BJ, Pinard AM, Letourneau DR, et al. Prevention of emergence agitation after sevoflurane anesthesia for pediatric cerebra magnetic resonance imaging by small doses of ketamine or nalbuphine administered just before discontinuing anesthesia. Anesth Analg. 2006;102:1056-61.
70. Arai YC, Ito H, Kandatsu N, et al. Parental presence during induction enhances the effect of oral midazolam on emergence behavior of children undergoing general anesthesia. Acta Anaes-thesiol Scand. 2007;51:858-61.
71. Wallin 1975 Wallin R, Regan B, Napoli M, Stern I. Sevoflurane: a new inhalational anesthetic agent. Anesthesia and Analgesia 1975; 54 (6):758–66
72. Holzki 1999 Holzki J, Kretz F. Changing aspects of sevoflurane inpaediatric anaesthesia: 1975-99. Paediatric Anaesthesia 1999; 9 :283–6
73. Voepel-Lewis T, Malviya S, Tait AR. A prospective cohort study of emergence agitation in the pediatric postanesthesia care unit. Anesth Analg. 2003;96:1625–1630.
74. De Hert S, Moerman A. Sevoflurane. F1000Res. 2015 Aug 25;4(F1000 Faculty Rev):626.
75. Sikich, N, Lerman, J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. Anesthesiology 2004; 100: 1138–1145.
76. Malarbi S, Stargatt R, Howard K, Davidson A. Characterizing the behavior of children emerging with delirium from general anesthesia. Paediatr Anaesth. 2011 Sep;21(9):942-50.
77. Russell PSS, Mammen PM, Shankar SR, Viswanathan SA, Rebekah G, Russell S, Earnest R, Chikkala SM. Pediatric Anesthesia Emergence Delirium Scale: A diagnostic meta-analysis. World J Clin Pediatr. 2022 Mar 9;11(2):196-205.
78. Bal HS, Sen S, Karl S, Mathai J, Thomas RJ. An assessment of quality of life of operated cases of esophageal atresia in the community. J Indian Assoc Pediatr Surg. 2016 Jul-Sep;21(3):131-8.
79. Cohen IT, Finkel JC, Hannallah RS, Hummer KA, Patel KM. Rapid emergence does not explain agitation following sevoflurane anaesthesia in infants and children: a comparison with propofol. Pediatric Anesthesia. 2003 Jan;13(1):63-7.
80. Singh H, Kundra S, Singh RM, Grewal A, Kaul TK, Sood D. Preemptive analgesia with ketamine for laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol 2013;29:478-84.
81. Miller D, Lewis SR, Pritchard MW, Schofield-Robinson OJ, Shelton CL, Alderson P, Smith AF. Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery. Cochrane Database Syst Rev. 2018 Aug 21;8(8):CD012317.
82. Welborn LG, Hannallah RS, Norden JM, Ruttimann UE, Callan CM. Comparison of emergence and recovery characteristics of sevoflurane and halothane in pediatric ambulatory patients. Anesth Analg 1996;83:917-20.
83. Xiao Y, Jin X, Zhang Y, Huang T, Zhou L, Gao J. Efficacy of propofol for the prevention of emergence agitation after sevoflurane anaesthesia in children: A meta-analysis. Front Surg. 2022 Oct 3;9:1031010.
84. Jung HJ, Kim JB, Im KS, Oh SH, Lee JM. Effect of ketamine versus thiopental sodium anesthetic induction and a small dose of fentanyl on emergence agitation after sevoflurane anesthesia in children undergoing brief ophthalmic surgery. Korean J Anesthesiol. 2010 Feb;58(2):148-52.
85. Jones, P.M., Bainbridge, D., Chu, M.W.A. et al. Comparison of isoflurane and sevoflurane in cardiac surgery: a randomized non-inferiority comparative effectiveness trial. Can J Anesth/J Can Anesth 63, 1128–1139 (2016).
86. Zhou Z, Ying M, Zhao R. Efficacy and safety of sevoflurane vs propofol in combination with remifentanil for anesthesia maintenance during craniotomy: A meta-analysis. Medicine (Baltimore). 2021 Dec 23;100(51):e28400. doi: 10.1097/MD.0000000000028400. PMID: 34941178; PMCID: PMC8702137.
87. Brioni, J.D., Varughese, S., Ahmed, R. et al. A clinical review of inhalation anesthesia with sevoflurane: from early research to emerging topics. J Anesth 31, 764–778 (2017).
88. Costi D, Cyna AM, Ahmed S, Stephens K, Strickland P, Ellwood J, Larsson JN, Chooi C, Burgoyne LL, Middleton P. Effects of sevoflurane versus other general anaesthesia on emergence agitation in children. Cochrane Database of Systematic Reviews. 2014(9).
89. Bergendahl 2004 {published data only} Bergendahl HTG, Lonnqvist PA, Eksborg S, RuthstromE, Nordenberg L, Zetterqvist H, et al.Clonidine vs.midazolam as premedication in children undergoing adeno-tonsillectomy: a prospective, randomized, controlledclinical trial. Acta Anaesthesiologica Scandinavica 2004; 48 (10):1292–300. [PUBMED: 15504191
90. Mikawa 2002 {published data only} Mikawa K, Nishina K, Shiga M. Prevention of sevoflurane-induced agitation with

oral clonidine premedication. Anesthesia and Analgesia 2002; 94 (6):1675–6. [PUBMED:12032063]
91. Mizrak 2013 {published data only} Mizrak A, Karatas E, Saruhan R, Kara F, Oner U, Saricicek V, et al.Does dexmedetomidine affect intraoperative bloodloss and clotting tests in pediatric adenotonsillectomy patients?. The Journal of Surgical Research 2013; 179 (1):94–8. [PUBMED: 23122669]
92. Abdelmawgoud A, Mohy A. Effect of oral dextromethorphan versus oral ketamine on sevoflurane related emergence agitation in children undergoing adenotonsillectomy, Egyptian Journal of Anaesthesia 2012; 28:4, 243-8,
93. Khattab A.M. Z.A.El-Seify. Sevoflurane-emergence agitation: effect of supplementary low-dose oral ketamine premedication in preschool children undergoing dental surgerySaudi J Anaesth3220096166
94. Lee A, Chan SK, Fan LT. Stimulation of the wrist acupuncture point PC6 for preventing postoperative nausea and vomiting. Cochrane database of systematic reviews. 2015(11).
95. Murphy A, O'Sullivan R, Wakai A, Grant TS, Barrett MJ, Cronin J, McCoy SC, Hom J, Kandamany N. Intranasal fentanyl for the management of acute pain in children. Cochrane Database Syst Rev. 2014 Oct 10;2014(10):CD009942.
96. Haddadi S, Marzban S, Karami MS, Heidarzadeh A, Parvizi A, Naderi Nabi B. Comparing the duration of the analgesic effects of intravenous and rectal acetaminophen following tonsillectomy in children. Anesth Pain Med. 2014 Feb 6;4(1):e13175.
97. Tan Y, Shi Y, Ding H, Kong X, Zhou H, Tian J. μ- Opioid agonists for preventing emergence agitation under sevoflurane anesthesia in children: a meta- analysis of randomized controlled trials. Pediatric anesthesia. 2016 Feb;26(2):139-50.
98. Weibel S, Jelting Y, Afshari A, Pace NL, Eberhart LH, Jokinen J, Artmann T, Kranke P. Patient- controlled analgesia with remifentanil versus alternative parenteral methods for pain management in labour. Cochrane Database of Systematic Reviews. 2017(4).
99. Mugabure Bujedo B. A clinical approach to neuraxial morphine for the treatment of postoperative pain. Pain research and treatment. 2012;2012.
100. Cole JW, Murray DJ, McAllister JD and Hirshberg GE. Emergence behaviour in children: defining the incidence of excitement and agitation following anaesthesia. Paediatr Anaesth. 2002;12(5):442-7.
101. Schnabel A, Reichl SU, Meyer-Frießem C, Zahn PK, Pogatzki-Zahn E. Tramadol for postoperative pain treatment in children. Cochrane Database Syst Rev. 2015 Mar 18;2015(3):CD009574.
102. Gao W, Zhang QR, Jiang L, Geng JY. Comparison of local and intravenous dexamethasone for postoperative pain and recovery after tonsillectomy. Otolaryngol Head Neck Surg. 2015;152(3):530-535.
103. Erden 2012 {published data only} Erden O, Koner O, Temur S, Menda F, Bilgen S. Effects of ondansetron on sevoflurane induced paediatric emergenceagitation. British Journal of Anaesthesia 2012; 108(Suppl 2) :ii301
104. Koner 2011 {published data only} Koner O, Ture H, Mercan A, Menda F, Sozubir S. Effectsof hydroxyzine-midazolam premedication on sevoflurane-induced paediatric emergence agitation: a prospectiverandomised clinical trial. European Journal of Anaesthesiology 2011; 28 (9):640–5. [PUBMED: 21822077]
105. Yucel 2012 {published data only} Yucel A, Begec Z, Ozgul U, Aydogan MS, Gulhas N, Ersoy MO. The effect of magnesium on emergence agitation inchildren undergoing adenotonsillectomy under sevofluranegeneral anesthesia: a prospective randomised clinical trial. HealthMED 2012; 6 :1605–10
106. Apan 2010 {published data only} Apan A, Aykaç E, Kazkayasi M, Doganci N, TahranFD. Magnesium sulphate infusion is not effective ondiscomfort or emergence phenomenon in paediatricadenoidectomy/tonsillectomy. International Journal of Pediatric Otorhinolaryngology 2010; 74 (12):1367–71.[PUBMED: 20880596]
107. Ou 2011 {published data only} Ou M, Zhang XY, Wang JP, Li KH, Du Z. Application of sevoflurane inhalation anesthesia on strabismus operation inchildren. Internationational Journal of Ophthalmology 2011; 11 :1853–5
108. Liao 2011 {published data only} Liao WW, Wang JJ, Wu GJ, Kuo CD. The effect of cerebralmonitoring on recovery after sevoflurane anesthesia inambulatory setting in children: a comparison among bispectral index, A-line autoregressive index, and standardpractice. Journal of the Chinese Medical Association 2011; 74 (1):28–36. [PUBMED: 21292200
109. Shibata 2005 {published data only} Shibata S, Shigeomi S, Sato W, Enzan K. Nitrous oxideadministration during washout of sevoflurane improvespostanesthetic agitation in children. Journal of Anesthesia 2005; 19 (2):160–3. [PUBMED: 15875135
110. Araki 2005 {published data only} Araki H, Fujiwara Y, Shimada Y. Effect of flumazenilon recovery from sevoflurane anesthesia in childrenpremedicated with oral midazolam before undergoing herniorrhaphy with or without caudal analgesia. Journal of Anesthesia 2005; 19 (3):204–7. [PUBMED: 16032
111. De Kort 2007 {published data only} DeKort R,Vandevelde A,LauwersM,Camu F.Comparisonof sufentanil and clonidine in the prevention of agitation in children after sevoflurane anesthesia. Acta Anaesthesiologica Belgica 2007; 58 (2):148.
112. Lin 2009 {published data only} Lin YC, Tassone RF, Jahng S, Rahbar R, Holzman RS,Zurakowski D, et al.Acupuncture management of pain andemergence agitation in children after bilateral myringotomy and tympanostomy tube insertion. Paediatric Anaesthesia 2009; 19 (11):1096–101. [PUBMED: 197093
113. Lee 2011 {published data only} Lee YC, Kim JM, Ko HB, Lee SR. Use of laryngeal mask airway and its removal in a deeply anaesthetized statereduces emergence agitation after sevoflurane anaesthesia in children. The Journal of International Medical Research 2011; 39 (6):2385–92.