Premedication In Pediatrics: What Is Already Known And Recent Trends? A Review

D Malhotra

Citation

D Malhotra. *Premedication In Pediatrics: What Is Already Known And Recent Trends? A Review*. The Internet Journal of Anesthesiology. 2023 Volume 42 Number 1.

DOI: 10.5580/IJA.56856

Abstract

Perioperative anxiety has been associated with adverse clinical outcomes, such as emergence delirium, increased analgesic requirements, and negative post-operative behavioral changes, such as sleep disturbance, separation anxiety, eating problems, and new-onset enuresis. Preoperative anxiety has been identified and includes, among other factors, the age and temperament of the child. Multiple techniques may be valuable for managing preoperative anxiety. The need for sedative premedication should be considered during the preoperative assessment of each patient. Many factors may influence the choice of premedication, including the pharmacological profile, possible adverse effects, and the presence of comorbid conditions.

More work is required to clarify weight-based dosing in obese patients. The anesthetic plan must be individualized for special situations such as a child with a behavioral disorder or at risk of aspiration. This article details pharmacological and non-pharmacological methods to minimize preoperative anxiety and techniques of anesthetic induction in infants and children undergoing surgery.

The MEDLINE database was searched for this narrative review using keywords, including preoperative anxiety, child, premedication, pediatric, and anesthetic induction. The search was restricted to articles published in English; however, there were no publication date restrictions.

INTRODUCTION

Hospitalization and surgery can cause significant stress and anxiety among children. Induction of anesthesia may be the most distressing procedure a child experiences during the entire perioperative period.[1] Studies have shown that children who are extremely anxious and fearful during anesthesia induction are likely to develop adverse clinical outcomes such as emergence delirium, increased analgesic requirements, and negative postoperative behavioral changes such as sleep disturbance, separation anxiety, eating problems, new-onset enuresis, and aggression.[2,3] A stressful perioperative experience can also result in poor compliance with future medical therapies, including anesthesia. Minimizing distress is thus not only an ethical imperative, but also important for preventing long-term behavioral problems, as children react to the stress of surgery and anesthesia in an age-dependent manner. The predictors of preoperative anxiety are age between 1 and 3 years, inhibited, dependent temperament, anxious parents, and previous negative hospital experiences.[4] Infants aged <9 months will readily accept parental surrogates and are less likely to experience anxiety regarding separation from parents. They responded by soothing voices, gentle rocking, and being held. Maintaining fasting times to a minimum usually results in a calm child and smooth induction. Children aged one to three years are prone to separation anxiety. Between three and six years of age, children can have concerns about bodily mutilation. Simple explanations of surgical and anesthetic procedures are usually effective in reducing anxiety. Play therapy is particularly useful in this age group. Children between 7 and 12 years of age required more explanation and participation.

They may benefit from choosing an anesthetic facemask or being allowed to hold a mask during induction. Toys, storybooks, and videos are also useful. Adolescents have increased body awareness, independence, and need for privacy. Involving this age group in the anesthetic plan gives them a sense of control and can reduce their anxiety. Children with psychological, developmental, or behavioral

disorders are frequently fearful and suspicious of strangers, making rapport difficult. They are more likely to be aggressive and combative at induction of anesthesia, requiring sedation, restraint, or both.[5] Therefore, a successful plan for induction of anesthesia must consider the age and temperament of the child. Pre induction techniques for managing anxiety can be classified into sedative and non-pharmacological methods.

PRACTICAL AND SAFETY CONSIDERATIONS

The need for premedication and identification of any potential contraindications should be part of every pediatric preanesthetic assessment, and a careful, individualized risk/benefit assessment must be made for each patient (Box 1). The expected effects of sedation should be explained when discussing the use of premedication with parents and children (where appropriate). If a child has previously received sedative premedication, it is useful to determine drugs and dose administered, its effectiveness, and any adverse events before or after surgery. The practicality of sedative premedication may vary among different patient groups, institutions, cultures, and countries. The timing of drug administration is key to optimizing its efficacy while minimizing potential delays in the operating theatre schedule. Clear communication with the preoperative nursing and operating theatre teams is required when premedication should be administered. Premedication should be withheld unless there is reasonable certainty that surgery will proceed, and the child's fasting status should be confirmed before dosing. Sedative drugs should only be administered in a safe environment where the patient can be observed appropriately, and resuscitation equipment is available. Ideally, a sedated child should be always monitored on a tilting trolley in the ward and should be transferred to the operating theatre complex with portable suction and a self-inflating bag-valve mask, accompanied by an appropriately trained staff member. In the event of respiratory depression or reduced consciousness, treatment should be supportive, providing airway protection and Ventilatory support, as required. The use of reversal agents, such as naloxone for opioids and flumazenil for benzodiazepines, should be carefully considered.

Box 1.

Conditions in which sedative premedication may be contraindicated.

- Anticipated difficult airway.

- Obstructive or central sleep apnea.

- Increased risk of aspiration.

- Severe renal or hepatic impairment.

- Altered conscious level or increased intracranial pressure.

- Acute systemic illness.

- New or unexplained reduction in oxygen saturations on air.

- Upper respiratory tract infection.

- Previous adverse or allergic reaction to proposed medication.

Parental Presence or Premedication.

Early studies suggested reduced anxiety and improved patient cooperation if parents were present during induction[5,6] The majority of parents prefer to be present during induction of anesthesia regardless of the child's age or previous surgical experience,[7] and also regardless of their experience with prior parental presence or premedication of their child in the case of repeated surgery.[8] Concerns regarding parental presence on the induction of anesthesia include a negative behavioral response to stress in some children when a parent is present and an upsetting experience to the parents, especially when watching their child go limp or when leaving their child after induction.[9,10] This has been demonstrated by an increase in heart rate and skin conductance levels in mothers.[11] If parental presence during induction is deemed to be in the child's best interest, a clear explanation that describes what the parent can expect to happen during the pre-induction period can significantly decrease parental anxiety and increase their satisfaction, which may be reflected in the child's behavior.[12,14] Predictive risk factors for children who would probably benefit from sedative premedication include children between the ages of two and six years, those who are shy and inhibited, those who have a history of prior stressful medical encounters, and those accompanied by an anxious parent.[15,16] In extremely anxious children, premedication would be indicated to avoid traumatic anesthetic induction, with the possibility of postoperative psychological disturbances.[17]

SEDATIVE PREMEDICATION

The primary goal of premedication in children is anxiolysis, which helps facilitate smooth separation from parents and eases the induction of anesthesia. Other effects that may be achieved by premedication include amnesia, prevention of

physiological stress, vagolysis, reduction in total anesthetic requirements, decreased probability, aspiration, decreased salivation, and secretion. All medications used have the potential to produce sedation and respiratory depression and should always be administered with caution under supervision and close monitoring. Tools for administration of supplemental oxygen, ventilation support, and resuscitation should be readily available.

Table 1

Drugs that are commonly used as premedication.

Benzodiazepines Midazolam Lorazepam Temazepam	PO: 0.5-0.75 mg/kg up to 20 mg max. IN: 0.3 mg/kg to 0.05-0.1 mg/kg. IV: 0.5 mg/kg. PR: 0.025-0.05 mg/kg (max. 4 mg). PO: 0.3-0.5 mg/kg (max. 20 mg).	20-30 min. 10 min. 2-3 min. 30 min. 60 min. 60 min.	Paradoxical agitation in some patients. Nasal midazolam causes stinging. Preferred in older children.
Alpha agonists Clonidine Dexmedetomidine	IN: 3-4 mcg/kg. PR: 2-4 mcg /kg. IN: 2.5-5 mcg /kg. PO: 1-2 mcg /kg.	60-90 min. 30-60 min.	Reduced need for rescue analgesia, reduced emergence agitation, PONV, and shivering.
NMDA antagonist Ketamine	PO: 5-8 mg/kg. IM: 4-6 mg/kg. IV: 0.5-1 mg/kg.	10 min. 3-5 min. 1 min.	Emergence reactions, increased secretions. IM ketamine is reserved for older, uncooperative children with developmental problems.
Others Chloral hydrate Melatonin	PO, PR: 20-75 mg/kg; maximum dose 2 g. PO: 0.5 mg/kg.	30-45 min. 20-30 min.	Long half-life, active metabolite can cause respiratory depression. PONV.

Midazolam

Midazolam is a water-soluble benzodiazepine and the most used sedative pre-mendicant in children. The benefits include a rapid and reliable onset and ante grade amnesia with minimal respiratory depression. It is typically administered orally at a dose of 0.5-0.75 mg/kg, up to a maximum of 20 mg, after which sedation and anxiolysis are reliably achieved within 20 min. The injectable form of midazolam, which is available at a concentration of 5 mg/mL, has an extremely bitter taste. Various agents such as honey, pomegranate juice, and paracetamol syrup have been used to increase palatability and acceptance. In addition to the oral route, it can alternatively be administered by the intranasal (0.3 mg/kg), rectal (0.5 mg/kg), or sublingual (0.3 mg/kg) routes.

Peak plasma concentrations of midazolam after intranasal administration occur rapidly within 10 min; however, discomfort is associated with this route secondary to local irritation. The rectal route is associated with erratic absorption and an unpredictable activity. If parenteral administration is desired and there is an intravenous (IV) line in situ, midazolam 0.05-0.2 mg/kg can be administered in the preoperative holding area immediately before wheeling the child into the operating room. Postoperative sedation is a side effect, particularly after short procedures. Oral midazolam may fail to produce sedation in 20% of patients. A small number of patients experience paradoxical reactions that result in restlessness and agitation.[18] The dose of oral midazolam should be adjusted in children taking antidepressants or inducers of the cytochrome oxidase system such as anticonvulsants or barbiturates.

In addition, preservative-free midazolam is recommended when using this route of administration because intranasal midazolam with preservative has been shown to have neurotoxic effects in an animal model.[19]

There is synergism between propofol and midazolam on gamma-aminobutyric acid (GABA) receptors.[20] Oral midazolam decreases the infusion requirements of propofol by one-third during propofol-based anesthesia.[21] After premedication with oral midazolam (0.5 mg/kg) in children 1 to 3 years of age after adenoidectomy, emergence and early recovery were delayed with no change in discharge times after induction of anesthesia with propofol and maintenance with sevoflurane.[22] Spontaneous eye opening and discharge times were delayed compared to placebo after 25 min of sevoflurane anesthesia.[23,24] However, extubation, awakening, and discharge times were not affected by sevoflurane anesthesia in children aged 1-10 years who received the same dose of oral midazolam.[25]

Midazolam has the advantage of producing an anterograde amnesia. Memory usually becomes impaired within 10 min of the oral administration of midazolam.[26] This has a beneficial effect in children who require repetitive interventions. Midazolam, like other benzodiazepines, increases the threshold for central nervous system toxicity with seizures; however, the threshold for cardiovascular toxicity remains unchanged. Thus, after premedication with midazolam or benzodiazepine, cardiovascular collapse after regional anesthesia toxicity may occur unassociated with CNS symptoms of toxicity.

The secondary and adverse effects of midazolam may include paradoxical effects with behavioral changes, agitation, and hiccups. This may occur independent of the mode of administration, that is, rectal, nasal, or oral ketamine, 0.5 mg/kg, IV has been shown to reverse agitation.[27]

In older children, lorazepam and Temazepam are anxiolytics. Oral lorazepam tablets at a dose of 0.025-0.05 mg/kg administered 60 min prior had a duration of action of

12 h. Temazepam was administered orally at a dose of 0.3-0.5 mg/kg 1-2 mg/kg prior to induction. Diazepam is an unpopular pre medicant for children. Its metabolite desmethyldiazepam has pharmacological activity similar to that of its parent compound. Immature liver function further prolongs the half-life.

Alpha 2-adrenergic agonists

Alpha 2-adrenergic agonists are widely used preoperatively to reduce anxiety in uncooperative children. This group of drugs also provides clinically relevant benefits of reducing the need for rescue analgesia, emergence agitation, postoperative nausea and vomiting (PONV), and shivering in the postoperative period.[28,29]

Clonidine is an alpha 2-adrenergic agonist, that can be administered orally (3-4 mcg/kg) or intranasally (2 mcg/kg). Nasal clonidine is not associated with nasal burning. A meta-analysis of published studies found that premedication with clonidine is superior to midazolam in terms of producing sedation, decreasing postoperative pain, PONV, and emergence agitation.[30] Although it has a relatively long onset time (45 min), its analgesic and anesthetic□sparing properties offer potential advantages, especially in surgeries associated with significant postoperative pain. Higher doses are associated with postoperative sedation.

Dexmedetomidine is a potent, highly specific alpha 2-adrenoreceptor agonist (the alpha-2:alpha-1 affinity ratio of this drug is 1600:1) with a shorter terminal half-life (approximately 2 h in children) than clonidine.

Compared with midazolam, dexmedetomidine produces more satisfactory sedation upon parent separation and mask acceptance.[31,32] Oral administration is associated with poor bioavailability and has been used satisfactorily at a dose of 1 mcg/kg administered 45-60 min prior to induction. The limitations of its use include long onset times (30 min), bradycardia, and hypotension with higher doses.

Ketamine

Ketamine, an NMDA receptor antagonist, has long been used as a pre-medicant. It can be administered orally (5-8 mg/kg), intramuscularly (4-6 mg/kg) or intravenously (1-2 mg/kg). Advantages include analgesic properties and the ability to cause sedation without respiratory depression. Problems associated with its use include increased salivation, emergence delirium, and prolonged recovery. Owing to the availability of newer agents with fewer side effects, its role is now often reserved for older, developmentally delayed, or autistic children, who are uncooperative or combative. In these patients, a stun dose of intramuscular ketamine (injection into the deltoid within 2-3 min) may be given effectively.33 Nasal trans mucosal ketamine at a dose of 6 mg/kg is also effective in sedating children within 20 to 40 minutes before induction of anesthesia. Only preservative-free ketamine should be administered nasally to avoid neurotoxicity; a concentration of 100 mg/ml is preferable to minimize the volume administered in the nose.[34] Rectal ketamine has a bioavailability of 25% and can result in unpredictable effects.

Fentanyl

Fentanyl is rapidly absorbed through the trans mucosal route with a bioavailability of 33%. Fentanyl lollipop [oral trans mucosal fentanyl citrate (OTFC)] in a dose of 15-20 mcg/kg produces sedation in 20 min and has a peak effect at 30-45 min. Although it has been shown to be as effective as midazolam, it has unwanted side effects, such as vomiting, pruritus, and respiratory depression. OTFC are now primarily indicated for breakthrough cancer pain. Fentanyl may be administered via the parenteral, transdermal, nasal, and oral routes. A “lollipop” delivery system, oral trans mucosal fentanyl citrate (OTCF) is more accepted by children than other routes as a pre medicant. Fentanyl is strongly lipophilic and readily absorbed from the buccal mucosa, with an overall bioavailability of approximately 30-50%.[35] The optimal dose of preanesthetic medication with minimal desaturation and preoperative nausea appears to be 10-15 mcg/kg. Children begin to show signs of sedation within 10 min of receiving this dose. Recovery from anesthesia after premedication with 10-15 mcg/kg of oral fentanyl is similar to that after intravenous administration of 2 mcg/kg. Doses greater than 15 mcg/kg are not recommended because of opioid side effects, particularly occasional respiratory depression. The incidence of the opioid associated side effects is increased when the interval between completion of “lollipop” and induction of anesthesia is prolonged.[36,37] OTFC are now primarily indicated for the treatment of breakthrough cancer pain. Fentanyl has also been administered nasally (1-2 mcg/kg), but primarily after the induction of anesthesia, as a means of providing analgesia in children without intravenous access.

Sufentanil is 10 times more potent than fentanyl. Several instances of reduced chest wall compliance have been reported in children after nasal sufentanil, as well as a higher

incidence of nausea and vomiting and a prolonged discharge time when compared to nasally administered midazolam.[38] These potential side effects and prolonged hospital stay after nasal sufentanil administration make it an unpopular choice of premedication.

OTHER AGENTS

Melatonin

The pineal hormone melatonin has several functions including hypnosis, anxiolysis, sedation, and anti-inflammatory actions. This leads to natural sleep and may reduce the incidence of agitation. As a premedication, it has been used in children at a dose of 0.25-0.5 mg/kg 60 min prior to induction with varying results.[39]

Chloral hydrate

Chloral hydrate is a non-barbiturate that can be administered orally or rectally (20-5 mg/kg) with an onset of sedation within 30-45 min. It has a slow onset and a long elimination half-life. The active metabolite of chloral hydrate, trichloroethanol, has a long half-life and the potential to cause prolonged sedation and respiratory depression. Its use is not recommended in neonates and patients with liver disease because of impaired metabolism and potential accumulation of toxic metabolites.[40]

Triclofos

Triclofos syrup contains the monophosphate sodium salt of trichloroethanol, which is a pharmacologically active metabolite of chloral hydrate. Triclofos is commonly used as a sedative because of its better palatability and lesser gastric irritation than chloral hydrate.

Topical anesthetics

The EMLA cream (eutectic mixture of local anesthetics; Astra Zeneca, Wilmington, DE, USA) is a mixture of two local anesthetics (2.5% lidocaine and 2.5% prilocaine). One hour prior to the application of EMLA cream to intact skin with an occlusive dressing provides adequate topical anesthesia for intravenous catheter insertion; however, EMLA causes vasoconstriction and skin blanching, making intravenous cannulation more difficult.

Lidocaine iontophoresis uses an impregnated electrode, current generator, and return pad to carry ionized lidocaine through the stratum corneum. It provides similar pain relief for insertion of IV catheters in children as EMLA cream but may cause stinging pain during current application and potential skin burns from the electrodes.[41]

ROUTES FOR ADMINISTERING PREMEDICANTS IN CHILDREN

The ideal route of premedication administration in children remains uncertain. The most used routes were the oral, nasal, and rectal routes in decreasing order of acceptability. Parenteral routes are generally avoided unless an intravenous cannula is placed. Oral administration is well accepted but has low bioavailability. Rectal administration often causes pain, can lead to expulsion in young children, and may not be appropriate for older children. An intramuscular approach is not recommended in children because it is invasive and painful. A more effective route for premedication could be trans mucosal administration, including intranasal, sublingual, and buccal administration, due to the high vascularization of the mucosa and its ability to bypass first-pass metabolism. In young children, compliance with nasal sedation may be easier to attain than compliance with oral sedation. The sensation of burning and nasal irritation is a disadvantage of the nasal route; sneezing or coughing caused by nasal irritation can reduce the effects of nasal premedication. A meta-analysis provided evidence that intranasal dexmedetomidine provides more satisfactory sedation at parent separation than other intranasal (midazolam, clonidine, ketamine) or oral pre medicants (midazolam), with reduced nasal irritation compared with midazolam.[42] Inhalation of nebulized drugs is an alternative method of administration that is relatively easy to set up, does not require venipuncture, and is associated with high bioavailability of the administered drug.[43] A recent study found that children premedicated with inhaled nebulized dexmedetomidine (2mcg/kg) had more satisfactory sedation scores, higher acceptance of the mask, and shorter recovery times than those who received nebulized ketamine (2 mg/kg) or midazolam (0.2 mg/kg). Dexmedetomidine premedication also lowered the incidence of postoperative agitation.

SPECIAL CONSIDERATIONS

Obstructive sleep apnea

Sedative premedication in children with obstructive sleep apnea (OSA) may cause pre- and post-operative airway obstruction and desaturation. However, safe and non-traumatic induction of anesthesia is not possible without premedication in some children. Thus, appropriate sedatives should be used with caution and, when indicated, with the support of anesthetists. Midazolam may increase supraglottic

airway resistance, induce central apneas and decrease the arousal response to hypoxia and hypercarbia.[44] Therefore, it should be used with caution to reduce the arousal response to hypoxia and hypercarbia. Dexmedetomidine causes a decrease in minute ventilation and increases arterial carbon dioxide; however, this occurs at a level similar to 'profound sleep,' suggesting a theoretical advantage over midazolam. Airway patency and tone are also maintained.[45] Ketamine may offer a theoretical advantage over midazolam as upper airway patency is maintained, although the associated hyper salivation may cause problems.

Obesity

Obesity is associated with several conditions that must be considered when prescribing sedative premedication, including OSA and gastroesophageal reflux. Achieving optimal drug dosing in obese children is challenging. The physiological changes that occur can affect the pharmacokinetics of many drugs, and failure to adjust drug dosing appropriately may result in inadvertent toxicity or therapeutic failure. The available evidence is complicated by variations in BMI percentile thresholds used to define obesity. Drug dosing guidance (where available) is typically provided derived from the data of obese adults. Several key pharmacokinetic principles have been proposed.

(I) Absorption appears unaltered (based on limited data from adults with obesity).

(II) Drug distribution changes as both fat mass and lean body mass increase but not proportionally.

(III) Dose adjustments were made based on the physicochemical properties of the drug.

(a) Ideal body weight should be used for a relatively hydrophilic drug (e.g., morphine).

(b) Adjusted body weight may be used for medications that are partially distributed to adipose tissue (e.g., dexmedetomidine and clonidine).

(c) The initial doses of lipophilic drugs may need to be increased to achieve an adequate response and should be based on the total body weight (e.g., benzodiazepines and ketamine).

(IV) Changes in protein binding are not clinically significant.

(V) The effect of obesity on drug metabolism may differ depending on the metabolic pathway and drug. Applying these principles in practice is challenging. For example, in obese adult patients, the Volume of distribution of midazolam is increased, and it is suggested that the loading or initial dose be based on the total body weight, with maintenance doses calculated based on the ideal body weight. As clearance remains unchanged, prolonged sedation may occur from the larger dose required to achieve an initial adequate plasma concentration. Information regarding its dosing in obese pediatric patients is limited. Although dosing on an ideal body weight may result in a reduced clinical response, this approach has been advocated to minimize the risk of significant respiratory depression. The paucity of evidence and guidance means that the experience and judgement of clinicians in managing these patients is vital. The necessity to achieve a therapeutic effect must be balanced against the risks posed by over dosage. Previous experience with inadequate premedication: For some children, preoperative sedation may not have been adequate or effective. Factors that may lead to inadequate sedation include the timing of administration relative to the induction of anesthesia, the agent used, the route, the dose, and the possibility of paradoxical agitation, especially with midazolam. If a child previously spats out oral medication, administering the drug via the intranasal route may ensure better drug delivery. When a low dose was previously used unsuccessfully, a higher dose of the same agent or a combination of synergistic agents can be effective. The useful combinations include the following.

(I) Benzodiazepines (e.g., midazolam) and ketamine.

(II) Benzodiazepines and a-2 agonists (clonidine or dexmedetomidine).

(III) Benzodiazepines, a-2 agonists, and opioids.

The common practice at our institution is to use buccal or oral midazolam in combination with intranasal dexmedetomidine. Caution should be exercised when using combined agents in patients at risk of airway obstruction or respiratory depression as the combination of synergistic medications may increase the risk of overdosage. In particular, the combination of midazolam and opioids is associated with an increased risk of respiratory depression.[45]

CONCLUSION

In summary, the primary goal of premedication in children is to ease the induction of anesthesia by facilitating smooth separation from parents. Other pharmacological effects

(amnesia, prevention of physiological stress, reduction of total anesthetic requirements, decreased risk of aspiration, acidic stomach contents, and analgesia) may also be achieved. Special considerations for patients with deteriorating mental status, airway obstruction, hemodynamic instability/intolerance to hypercapnia (such as those with significant increases in pulmonary artery pressure/pulmonary arteriolar resistance), or systemic organ failure should be considered before the administration of premedication. In such cases, parental presence may be a preferred choice. The major effect of premedication is to allay anxiety. However, it has the potential to produce sedation and should always be administered with caution under supervision and close monitoring. Tools for administration of supplemental oxygen, ventilation support, and resuscitation should be readily available.

STATEMENTS

Statement of Ethics

No ethics approval required as per institutional ethics committee, Research Medical affairs.

Disclosure Statement

The authors declare no conflicts of interest.

Funding Sources: None.

Author Contributions

DM: Design, manuscript drafting, critical analysis, and final approval.

References

1. Chorney JM, Kain ZN. Behavioral analysis of children’s responses to anesthesia induction Anesth Analg 2009;109:1434-40.
2. Watson AT, Visram A. Children’s preoperative anxiety and postoperative behavior. Pediatr Anaesth. 2003;13(3):188-204.
3. McCann ME, Kain ZN. The management of preoperative anxiety in children: an update. Anesth Analg. 2001;93(1):98-105.
4. Barends CR, Absalom A. Dexmedetomidine versus Midazolam in procedural sedation. A systematic review of efficacy and safety. PLoS One. 2017;12(1):e0169525.
5. Bergendahl H, Lönnqvist P-A. Clonidine in paediatric anaesthesia: review of the literature and comparison with benzodiazepines for premedication. Acta Anaesth Scand. 2006;50(2):135-143.
6. Schulman Jl, Foley Jm. A study of the effect of the mother's presence during anesthesia induction. Pediatrics; 1967;39:111-114.
7. Hannallah Rs, Rosales Jk. Experience with parents' presence during anesthesia induction in children. Can Anaesth Soc J 1983;30:286-289.
8. Ryder I, Spargo P. Parents in the anesthetic room: A questionnaire survey of parents' reactions. Anaesthesia 1991;46:977-979.
9. Kain Zn, Caldwell-Andrews Aa. Parental intervention choices for children undergoing repeated surgeries. Anesth Analg; 2003;96:970-975.
10. Kain Zn, Caldwell-Andrews Aa. Trends in the practice of parental presence during induction of anesthesia and of preoperative sedative premedication in the United States, 1995-2002: results of a follow-up national survey. Anesth Analg; 2004;98:1252-1259.
11. Shaw Eg, Routh Dk. Effect of mother’s presence on children's reactions to aversive procedures. J Pediatr Psychol 1982;7:33-42.
12. Bowie Jr. Parents in the operating room. Anesthesiology 1993;78:1192-1193.
13. American Academy of Pediatrics: Child life programs. Pediatrics 1993;91:671-672.
14. Kain Zn, Caldwell-Andrews Aa. Family-centered preparation for surgery improves perioperative outcomes in children: a randomized controlled trial. Anesthesiology 2007;106:65-74.
15. Melamed Bg, Dearborn M. Necessary considerations for surgery preparation: Age and previous experience. Psychosom Med 1983;45:517-525.
16. Kain Zn, Mayes Lc. Preoperative preparation in children: a cross-sectional study. J Clin Anesthesia 1996;8:508-514.
17. Ryder I, Spargo P. Parents in the anesthetic room: A questionnaire survey of parents' reactions. Anaesthesia 1991;46:977-979.
18. O'byrne K, Peterson L. Survey of pediatric hospitals' preparation programs: Evidence of the impact of health psychology research. Health Psychol 1997;16:147-154.
19. Rosenbaum A, Kain ZN. The place of premedication in pediatric practice. Paediatr Anaesth 2009;19:817-28.
20. Brosius Kk, Bannister Cf. Effect of oral midazolam premedication on the awakening concentration of sevoflurane, recovery times and bispectral index in children. Paediatr Anaesth; 2001, 11:585-590.
21. Martlew Ra, Meakin G. Dose of propofol for laryngeal mask airway insertion in children: effect of premedication with midazolam. Br J Anaesth 1996;76:308-309.
22. Viitanen H, Annila P. Midazolam premedication delays recovery from Propofol-induced sevoflurane anesthesia in children 1-3 yr. Can J Anaesth 1999;46:766-771.
23. Viitanen H, Annila P. Premedication with midazolam delays recovery after ambulatory sevoflurane anesthesia in children. Anesth Analg 1999;89:75.
24. Brosius Kk, Bannister Cf. Effect of oral midazolam premedication on the awakening concentration of sevoflurane, recovery times and bispectral index in children. Paediatr Anaesth 2001;11:585-590.
25. Kain Zn, Hofstadter Mb. Midazolam: effects on amnesia and anxiety in children. Anesthesiology 2000;93:676-684.
26. Golparvar M, Saghaei M. Paradoxical reaction following intravenous midazolam premedication in pediatric patients-a randomized placebo-controlled trial of ketamine for rapid tranquilization. Paediatr Anaesth 2004;14:924-930.
27. Nishina K, Mikawa K. Clonidine in paediatric anaesthesia.Curr Opin Anaesthesiol 2002;15:309-16.
28. Kulka PJ, Bressem M. Clonidine prevents sevoflurane induced agitation in children. Anesth Analg 2001;93:335-8.
29. Almenrader N, Passariello M. Premedication in children: comparison of oral midazolam and oral clonidine. Paediatr Anaesth 2007;17:1143-49
30. Pasin L, Febres D. Dexmedetomidine vs midazolam as preanesthetic medication in children: A meta analysis of randomized controlled trials. Paediatr Anaesth 2015;25:468-76

31. Sun Y, Lu Y. Is dexmedetomidine superior to midazolam as premedication in children? Meta-analysis of randomized controlled trials. Paediatr Anaesth 2014;24:863-74.
32. Bozkurt P. Premedication of the pediatric patient—Anesthesia for the uncooperative child. Curr Opin Anaesthesiol 2007;20:211-5.
33. Weksler N, Ovadia L. Nasal ketamine for pediatric premedication. Can J Anaesth 1993;40:119-121.
34. Egan Td, Sharma A. Multiple dose pharmacokinetics of oral transmucosal fentanyl citrate in healthy volunteers. Anesthesiology 2000;92:665- 673.
35. Dsida Rm, Wheeler M. Premedication of pediatric tonsillectomy patients with oral transmucosal fentanyl citrate. Anesth Analg 1998;6:66-70.
36. Epstein Rh, Mendel Hg. The safety and efficacy of oral transmucosal fentanyl citrate for preoperative sedation in young children. Anesth Analg 1996;83:1200-1205.
37. Binstock W, Rubin R. The effect of premedication with OTFC, with or without ondansetron, on postoperative agitation, and nausea and vomiting in pediatric ambulatory patients. Paediatr Anaesth 2004;14:759-767.
38. Isik B, Baygin O. Premedication with melatonin versus midazolam in anxious children. Paediatr Anaesth 2008;18:635-41.
39. Malviya S. Prolonged recovery and delayed side effects of sedation for diagnostic imaging studies in children. Pediatrics 2000;105:E42.
40. Galinkin JL, Rose JB. Lidocaine iontophoresis versus eutectic mixture of local anesthetics (EMLA) for IV placement in children. Anesth Analg 2002;94:1484-8.
41. Jun JH, Kim KN. The effects of dexmedetomidine premedication in children: A systematic review and metaanalysis. Can J Anesth 2017;64:947.
42. McCormick ASM, Thomas VL. Plasma concentrations and sedation scores after nebulized and intranasal midazolam in healthy volunteers. Br J Anaesth 2008;100:631-6.
43. Faghihian R, Eshghi A. Comparison of oral melatonin and midazolam as premedication in children undergoing general anesthesia for dental treatment. Anesth Pain Med 2018;8:e64236.
44. Abdel Ghaffar HS, Kamal SM. Comparison of nebulized dexmedetomidine, ketamine, or midazolam for premedication in preschool children. Br Jour Anaesth 2018;121:445 52.
45. Kennedy RM, Porter FL. Comparison of fentanyl/midazolam with ketamine/midazolam in pediatric orthopedic emergencies. Pediatrics 1998;102:956e63.

Author Information

Dinesh Malhotra
Department of Anesthesia. Al Jalila Children Specialty Hospital, Dubai Academic Health Corporation
Dubai, UAE