Review Article

Premedication and Induction of Anaesthesia in paediatric patients

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ABSTRACT

Perioperative anxiety has been associated with adverse clinical outcomes such as emergence delirium, increased analgesic requirements and negative postoperative behavioural changes such as sleep disturbance, separation anxiety, eating problems and new-onset enuresis. Predictors of preoperative anxiety have been identified, and these include, among other factors, the age and temperament of the child. Any plan for anaesthetic induction in a child must take into account these factors. The anaesthetic plan must be individualised for special situations, for example, the child with behavioural disorder or at risk of aspiration. This article details the pharmacological and nonpharmacological methods to minimise preoperative anxiety and the techniques of anaesthetic induction in infants and children undergoing surgery. The benefits and limitations of inhalational and intravenous induction and the current status of rapid sequence induction in children are discussed. MEDLINE database was searched for this narrative review using the keywords including preoperative anxiety, child, premedication, paediatric and anaesthetic induction. Search was restricted to articles in English, but without any publication date restrictions.

Key words: Anaesthesia, anxiety, induction, paediatric, premedication

INTRODUCTION

Hospitalisation and surgery can provoke significant stress and anxiety in children. The induction of anaesthesia 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 anaesthetic induction are likely to develop adverse clinical outcomes such as emergence delirium, increased analgesic requirements and negative postoperative behavioural changes such as sleep disturbance, separation anxiety, eating problems, new-onset enuresis and aggression towards authority.[2,3] A stressful perioperative experience can also result in poor compliance with future medical therapy, including anaesthesia. Minimising distress is thus not only an ethical imperative but also important for preventing long-term behavioural problems.

Children react to the stress of surgery and anaesthesia 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 age <9 months will readily accept parental surrogates and are less likely to experience anxiety on separation from parents. They respond to soothing voices, gentle rocking and being held. Keeping fasting times to a minimum will usually result in a calm child and a smooth induction. Children age 1–3 years are prone to separation anxiety. Between 3 and 6 years, children can have concerns about bodily mutilation. Simple explanations of surgical and anaesthetic procedures are usually effective in reducing anxiety. Play therapy is especially useful in this age group. Children between 7 and 12 years need more explanation and participation. They may benefit from choosing an

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anaesthetic facemask or being allowed to hold the mask during induction. Toys, storybooks and videos can all be useful. Adolescents have increased body awareness, independence and need for privacy. Involving this age group in the anaesthetic plan gives them a sense of control and can reduce anxiety. Children with psychological, developmental or behavioural disorders are frequently fearful and suspicious of strangers, making rapport difficult. They are more likely to be aggressive and combative at induction of anaesthesia requiring sedation, restraint or both.[5]

A successful plan for induction of anaesthesia must therefore take into account the age and temperament of the child. Preinduction techniques to manage anxiety can be classified into sedative premedication and nonpharmacological methods.

SEDATIVE PREMEDICATION

The primary goal of premedication in children is anxiolysis, which helps facilitate smooth separation from the parents and ease the induction of anaesthesia. Other effects that may be achieved by premedication include amnesia, prevention of physiologic stress, vagolysis, reduction in total anaesthetic requirements, decreased probability of aspiration, decreased salivation and secretions, antiemesis and analgesia. All medications used have the potential to produce sedation and respiratory depression and should always be administered with caution under supervision and close monitoring. The tools for administration of supplemental oxygen, ventilation support and resuscitation should be readily available. Table 1 lists the commonly used drugs for premedication.

Midazolam

Midazolam is a water-soluble benzodiazepine and the most commonly used sedative premedicant in children. The benefits include a rapid and reliable onset and antegrade 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, available as 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 has been associated with this route secondary to local irritation. The rectal route is associated with erratic absorption and unpredictable action. 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, just before wheeling the child into the operating room.

Postoperative sedation is a side effect, especially after short procedures. Oral midazolam may fail to produce sedation in 20% of patients. A small number of patients

Table 1: Commonly used medications for premedication in children

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

PONV – Postoperative nausea and vomiting; PO – Per oral; PR – Per rectal; IN – Intranasal; IM – Intramuscular; IV – Intravenous

can experience paradoxical reactions resulting in restlessness and agitation.[6]

In older children, lorazepam and temazepam are useful anxiolytics. Oral lorazepam tablet in the dose of 0.025–0.05 mg/kg administered 60 min prior has a duration of action of 12 h. Temazepam has been used orally in the dose of 0.3–0.5 mg/kg 1–2 h prior to induction. Diazepam is an unpopular choice as premedicant in children; its metabolite desmethyldiazepam has a pharmacologic activity similar to the parent compound. Immature liver function further prolongs the half-life.

Alpha 2–adrenergic agonists

Alpha 2–adrenergic agonists are being 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, reducing emergence agitation, postoperative nausea and vomiting (PONV) and shivering in the postoperative period.[7,8]

Clonidine is an alpha 2–adrenergic agonist, which can be administered orally (3–4 μg/kg) or intranasally (2 μg/kg). Nasal clonidine is not associated with nasal burning. Meta-analysis of published studies find premedication with clonidine superior to midazolam in terms of producing sedation, decreasing postoperative pain, PONV and emergence agitation.[9,10] Although it has a relatively long onset time (45 min), its analgesic and anaesthetic-sparing properties offer potential advantages especially in surgeries associated with significant postoperative pain. Larger 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) when compared with clonidine.

When compared with midazolam, dexmedetomidine produces more satisfactory sedation upon parent separation and mask acceptance.[11,12] Oral administration is associated with poor bioavailability. Intranasal dexmedetomidine has been used satisfactorily in the dose of 1 μg/kg administered 45–60 min prior to induction. The limitations for its use include long onset times (30 min), and bradycardia and hypotension with higher doses.

Ketamine

Ketamine, an NMDA receptor antagonist, has long been used as a premedicant. It can be administered by the oral (5–8 mg/kg), intramuscular (4–6 mg/kg), or iv (1–2 mg/kg) routes. The advantages include its analgesic properties and the ability to cause sedation without respiratory depression. Problems with its use include increased salivation, emergence delirium and prolongation of recovery. Due to the availability of newer agents with fewer side effects, its role is now often reserved for the older, developmentally delayed or autistic child who is uncooperative or combative. In these patients, a stun dose of intramuscular ketamine (injection into the deltoid acts within 2–3 min) may be given effectively.[13]

Fentanyl

Fentanyl is rapidly absorbed through the transmucosal route with a bioavailability of 33%. Fentanyl lollipop [oral transmucosal fentanyl citrate (OTFC)] in a dose of 15–20 μg 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.[13] OTFC is now primarily indicated for breakthrough cancer pain.

Other agents

Melatonin

The pineal hormone melatonin has several functions, including hypnosis, anxiolysis, sedation and anti-inflammatory actions. It produces a natural sleep and may reduce the incidence of emergence agitation. As a premedicant, it has been used in children in a dose of 0.25–0.5 mg/kg 60 min prior to induction with varying results.[14-16]

Chloral hydrate

Chloral hydrate is a nonbarbiturate, which can be administered orally or rectally (20–5 mg/kg) with an onset of sedation in 30–45 min. It has a slow onset and long elimination half-life. The active metabolite of chloral hydrate, trichloroethanol, has a long half-life with a 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 the potential accumulation of toxic metabolites.[17]

Triclofos

Triclofos syrup contains the monophosphate sodium salt of trichloroethanol, the pharmacologically

active metabolite of chloral hydrate. Triclofos has been commonly used as a sedative in view of better palatability and less gastric irritation when compared with chloral hydrate.

Topical anaesthetics

EMLA cream (eutectic mixture of local anaesthetic; Astra Zeneca, Wilmington, DE, USA) is a mixture of two local anaesthetics (2.5% lidocaine and 2.5% prilocaine). One-hour prior application of EMLA cream to intact skin with an occlusive dressing provides adequate topical anaesthesia for an iv catheter insertion. However, EMLA causes venoconstriction and skin blanching, making iv cannulation more difficult.

Lidocaine iontophoresis uses an impregnated electrode, current generator and a return pad to carry ionised lidocaine through the stratum corneum. It provides similar pain relief for insertion of iv catheters in children as EMLA cream, but may cause a stinging pain during current application and potential skin burns from the electrodes.[18]

ROUTES FOR ADMINISTERING PREMEDICANTS IN CHILDREN

The ideal route of administration for premedication in children remains uncertain. The most commonly used routes are the oral, nasal, and rectal routes in decreasing order of acceptability. Parenteral routes are generally avoided unless an iv cannula has previously been sited. Oral administration is well-accepted but has low bioavailability. Rectal administration often causes pain, could lead to expulsion in young children and might not be appropriate for older children. An intramuscular approach is not recommended for children because it is invasive and painful. A more effective route for premedication could be transmucosal, including intranasal, sublingual and buccal administration due to the high vascularisation of mucosa and its ability to bypass first-pass metabolism. In young children, compliance with nasal sedation may be more easily attained than oral sedation. The sensation of burning and nasal irritation is a disadvantage of the nasal route, and sneezing or coughing caused by the nasal irritation could reduce the effects of nasal premedication. A meta-analysis has provided evidence that intranasal dexmedetomidine provides more satisfactory sedation at parent separation than other intranasal (midazolam, clonidine, ketamine) or oral premedicants (midazolam) with reduced nasal irritation compared with midazolam.[19]

Inhalation of nebulised drug 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.[20] A recent study found that children premedicated with inhaled nebulised dexmedetomidine (2 μg/kg) had more satisfactory sedation scores, higher acceptance of the mask and shorter recovery times than those who received nebulised ketamine (2 mg/kg) or midazolam (0.2 mg/kg).[21] Dexmedetomidine premedication also lowered the incidence of postoperative agitation.

NONPHARMACOLOGICAL MANAGEMENT OF ANXIETY AT INDUCTION OF ANAESTHESIA

Family-centered approach and parental presence at induction of anaesthesia

The preoperative visit is an opportunity both to assess the child's fitness for anaesthesia and to create a personal connection with the child and family prior to the induction of anaesthesia. A family-centered approach involves providing information not only to the children but also to the parents as part of preparing the entire family in the preoperative period. Information provided is delivered in a developmentally appropriate manner and describes procedural (what will happen) and sensory (what the child will feel) aspects. The child is also taught coping mechanisms. Parental presence at induction is an integral part of respecting the parent's wishes and engaging the parents in decision-making processes.

Parental presence at induction of anaesthesia (PPIA) remains a controversial strategy in reducing preoperative anxiety. It was initially introduced as a technique to decrease anxiety and increase cooperation in children, with the additional benefit of reduced need for premedication, thus preventing potential side effects and increased monitoring required for pharmacologic anxiolysis.[22] Concerns regarding parental presence include disruption of operating room (OR) routine, need for additional support staff to escort parents, stress on the anaesthesia providers and the possibility of legal implications if the parent faints and sustains injury. Current evidence shows that for the most part, parental presence does not seem to benefit parents and children's anxiety.[23] Certain children, for example, those with calm parents, those undergoing repeated procedures may possibly benefit from PPIA.[24] The decision to permit PPIA depends on hospital policy and the discretion of the attending anaesthesiologist.

Behavioural interventions[25]

Prehospital-based programmes such as hospital tours, videos, leaflets and interactive books can help develop coping skills and reduce anxiety. Play therapy–trained therapists using visual aids such as videos, interactive books and dolls can be useful in children with previous negative anaesthetic experiences. Hypnosis, music and lighting can be used to provide a calm and soothing environment for the child in the anaesthetic room. Distraction methods (blowing bubbles, toys) or engagement with the anaesthetic process itself (choosing and handling the face mask, blowing up the 'balloon') can be used in young children.

A Cochrane review that included 28 trials (2681 patients) investigated nonpharmacologic interventions to reduce anxiety. The presence of parents during induction of general anaesthesia did not diminish anxiety. Effective interventions included parental acupuncture, clowns and hypnosis, playing videos of the child's choice during induction, low sensory stimulation and hand-held video games.[26] While these behavioural interventions diminished anxiety, they did not provide superior anxiolysis to the use of a sedative premedication.

INDUCTION OF ANAESTHESIA

In infants and children, the technique of induction of anaesthesia demands careful consideration. Inhalation and iv inductions are used in paediatric anaesthesia, and many factors influence the choice of induction method. Inhalation induction has traditionally been the preferred technique, since most children are needle-phobic. Inhalation induction is the choice in children with difficult venous access. In patients with a difficult airway, inhalation anaesthesia allows for continuous maintenance of spontaneous ventilation, with a slow induction and easy, rapid reversibility. IV induction is rapid and smooth and is appropriate if a venous cannula is already *in situ*. IV induction is the method of choice in patients with high risk of aspiration.

The choice of agent and the technique depends on the individuality of the child. As early as 1948, Dr. Smith roughly classified patients into groups that have definite characteristics. Infants under 1 year of age have no apprehension of the impending procedure and are amenable to inhalational induction. In children 1–3 years old, there will usually be resistance to any method of induction. Their small veins are not easy to cannulate, so inhalational induction may be most appropriate in the absence of any contraindications. In children 3 years of age and over, fear, imagination and previous experiences can influence behaviour in the immediate preoperative period. The older child may be encouraged to choose between inhalational and iv methods for induction.[27]

Inhalational induction

Sevoflurane induction is safe, reliable, quick and well-accepted by patients and is the agent of choice for inhalation induction. Halothane was once used extensively for induction, but it sensitises myocardium to catecholamines resulting in arrhythmias, bradycardia and cardiovascular compromise.

Techniques of inhalational induction

Incremental induction can be performed with 6 L fresh gas flow (FGF) and the sevoflurane dial set at 1% in a 2:1 mixture of N_2O and O_2. The dial setting is increased by 1% every 2–3 breaths until loss of eyelash reflex, with a mean induction time of 1–2 minutes. This technique is useful in calm children, who will easily accept the mask.

In healthy children, induction times can be significantly shortened (mean 42 s) using a high-concentration primed circuit technique without increase in the frequency of respiratory complications or haemodynamic compromise.[28] The anaesthesia circuit is primed using high FGF 6 L/min of N_2O: O_2 in a 2:1 concentration with the sevoflurane dial set at 8% and the patient end occluded. In approximately 3 min, priming is completed, confirmed by end-tidal sevoflurane concentration which should approximate 8%. The facemask is then gently applied on the face, with the same settings for FGF and sevoflurane until loss of eyelash reflex.

A Cochrane review showed that a high initial concentration sevoflurane technique results in a more rapid induction of anaesthesia with a similar rate of complications as the incremental technique, with the exception of apnoea which is more common with high initial concentration.[29]

Hyperventilation increases the speed of induction by causing faster equilibration of the inspired anaesthetic concentration with the alveolar concentration compared with normal tidal volume breathing.

The single breath vital capacity technique of inhalation induction consists of exhaling to residual volume,

and then with the anaesthetic system and the mask gently applied to the face inhaling to vital capacity followed by a breath hold. This technique is suitable for children 5 years and older, with faster induction times compared with the conventional tidal volume technique.[30] The effectiveness and success of the vital capacity technique increase with age. For children unable to hold a vital capacity breath, a double-breath vital capacity induction is a suitable alternative.[31]

Steal induction

Steal induction is a type of inhalational induction where the child comes to the operating room already asleep undergoing anaesthesia induction without being awakened. No force or physical restraint is used and the child transgresses from natural to anaesthesia-induced sleep. The principle of steal induction was first described by Meyers in 1977 which used intramuscular droperidol to induce sleep.[32] Subsequently, a number of agents have been used, including ketamine, clonidine and, more recently, melatonin.[33,34]

Intravenous induction

IV inductions are faster; there is no pungent gas to irritate the airway, and the child rapidly progresses through the excitement phases of light anaesthesia. In children at risk for developing perioperative respiratory complications, iv induction is found to be safer (10.7% vs 26% incidence of respiratory complications).[35] Patients at risk for developing respiratory complications include children with upper respiratory tract infection (URI) within previous 2 weeks, more than three episodes of wheezing in the past 12 months, wheezing at exercise, nocturnal dry cough, history of eczema, passive smoking and two members of the family with atopic symptoms.[36]

The most frequently used iv induction agent today is propofol, a short-acting hypnotic and amnestic agent. The former most common iv induction agent thiopental is currently less used, one major reason being longer residual sedation compared with propofol. One specific adverse effect of propofol is injection pain, with a reported incidence of 30%–90%. Various strategies, the most common being the addition of the local anaesthetic lignocaine, have been used to reduce the incidence. Etomidate is an imidazole derivate with the same favourable properties as propofol: fast onset and quick recovery. It does not affect myocardial function or sympathetic tone, and therefore maintains very stable haemodynamics. It is the agent of choice when haemodynamic stability is a concern. Problems with its use are the inhibition of corticosteroid synthesis and occurrence of myoclonic movements during induction.

INDUCTION IN CHILDREN AT RISK OF PULMONARY ASPIRATION

Rapid sequence induction of anaesthesia (RSI) and intubation have been advocated for reducing the risk of regurgitation and subsequent pulmonary aspiration. The 'classic' RSI, as described in adults, involves preoxygenation, followed by iv induction, administration of a rapid acting muscle relaxant, concomitant application of cricoid pressure and suspending ventilation until the trachea is rapidly secured with the endotracheal tube. There are several problems while adopting this technique in infants and children.

Neonates, infants and small children have a reduced apnoea tolerance compared with o adults due to small FRC, high closing capacity that approximates FRC upon induction of anaesthesia and a high metabolic oxygen demand. Optimal preoxygenation can be difficult to achieve. Cessation of spontaneous or assisted ventilation can thus quickly lead to hypoxaemia, bradycardia and cardiovascular compromise.[37]

Gentle, pressure-limited mask ventilation with 100% oxygen after induction of anaesthesia allows oxygenation, prevents hypercarbia and keeps small airways open without increasing gastric insufflations.[38]

The cricoid cartilage in small children is smaller and more cephalad in position, making it difficult to locate. A study examining computed tomography scans of the neck showed that 45% of children less than 8 years of age had lateral displacement of the oesophagus at the level of the trachea, which raises questions regarding efficacy of cricoid pressure in this age group.[39] More often than not, cricoid pressure is applied at the incorrect site, without knowledge of the appropriate force for a particular age group.[40] The resultant distortion of the airway can make intubation and even mask ventilation difficult. When applied too early during anaesthetic induction, children can react by straining vigorously interfering with a smooth induction. The pressure on the cricoid causes lowering of the lower oesophageal sphincter tone, further increasing the risk of regurgitation.

In children, controlled RSI without the use of cricoid pressure offers a safer alternative to the classic RSI.[41] The controlled RSI sequence involves preoxygenation, titrated administration of the induction agent followed by muscle relaxant, usually atracurium. Any muscle relaxant can be used, but it is recommended to confirm optimal muscle relaxation using neuromuscular monitoring. Gentle bag mask ventilation keeping insufflation pressures <12 cm H_2O is continued up to laryngoscopy. This technique may reduce the risks of hypoxaemia, without increasing the incidence of pulmonary aspiration.

As an alternative technique, heated humidified high flow nasal oxygen can be used to preoxygenate, limit the risk of desaturation during intubation and reduce the potential of gastric insufflation associated with mask ventilation. In the author's practice, ultra modified RSI (UMRSI) using Airvo® Fisher Packel, Auckland, New Zealand is useful during induction of neonates and infants where the pulmonary compliance is very low and even small insufflation pressures are likely to distend the stomach, for example, tracheoesophageal fistula and congenital diaphragmatic hernia.[42]

Pharmacological regimens to increase gastric pH and reduce the volume of stomach contents are routinely used in adults at risk of aspiration. In contrast, only mechanical methods such as aspiration of an indwelling nasogastric tube and cricoid pressure are popular in children. The usage of drugs with unknown or unproven benefit may be a major factor for their avoidance in children.

SUMMARY

In summary, induction of anaesthesia is as much an art as it is a science. Preinduction anxiety and stormy anaesthetic inductions have long-term behavioural consequences. The anaesthesiologist must understand child psychology and promote child-friendly practices. Sedative premedication and behavioural techniques must be tailored to the age and temperament of the child. In children at risk of aspiration, a controlled RSI is safer than the classic RSI sequence.

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