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Premedication in paediatrics

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Introduction

Millions of children around the world undergo anaesthesia and surgery every year. Going to theatre is a stressful experience for children. Evidence suggests that more than 60% of children undergoing anaesthesia report anxiety and nearly 20% experience a high degree of anxiety.[1] The reasons for children's distress before anaesthesia are multifaceted and include anxiety about needles and cannulae, the anaesthetic or procedure itself, postoperative pain and recovery, as well as anxiety related to past experiences.[1] Preoperative anxiety is associated with adverse clinical and behavioural outcomes. Children who are highly anxious perioperatively have been found to have an increased incidence of the following negative outcomes after surgery:[2,3]

- A significantly higher incidence of postoperative pain
- A higher incidence of emergence delirium
- A delayed hospital discharge
- Sleep disturbances
- Other maladaptive behavioural changes lasting up to a few weeks following surgery
- Reluctance to seek medical care in the future

In addition, a negative experience could make the next clinical encounter much more problematic for all parties concerned.

Given these serious consequences, the development of strategies to decrease preoperative anxiety is essential. These strategies include various non-pharmacological techniques, sedative premedication or a combination of both. Non-pharmacological techniques should be employed for all children going for surgery and multiple techniques may be of value in managing preoperative anxiety. Possible strategies are listed in Table I.[4,5]

A recent study that specifically looked at children's own experiences and thoughts about being anaesthetised, highlights the fact that children experience being anaesthetised as being powerless and vulnerable, or even as a threat to their life.[6] Children respond by seeking security primarily from those whom they know well and with whom they feel safe. They often use various defence strategies to regain control. Viewpoints on the role of routine sedative premedication for children going for surgery vary considerably among healthcare professionals and parents, and often evoke strong emotions and opinions.[7]

In addition to the practicalities of sedative premedication varying among institutions and countries, the perioperative expectations of both parents and children vary greatly in different environments and cultures around the world. Multiple techniques may be of value in managing preoperative anxiety. There is 'no one size fits all' and an individualised approach is advocated.

Table I: Non-pharmacological techniques for managing preoperative anxiety in children[4,5]

Anxiolytic strategies	Practical examples
Pre-hospital information and preparation of both child and parent	Information in the form of printed pamphlets, children's books, operating theatre and hospital tours, videos, online resources, apps, or telephonic or in-person communication
Play therapy	Interaction with trained play therapists using visual aids and toys Child life therapists prepare children for surgery using techniques such as role-playing, managing expectations, and teaching coping strategies
Distraction	Blowing bubbles, toys, videos, games, humour and laughter Virtual reality is also being used with increasing frequency in some centres
Engagement with anaesthetic equipment	Handling and playing with the mask and anaesthetic circuit Practising 'blowing up the balloon'
Environmental adjustment	Lighting, music, tone and loudness of voices, fewest healthcare staff possible, positive language, and avoiding negative phrases
Actively involving parents/caregivers	Address and manage parental anxiety Parental presence for induction
Relaxation techniques	Breathing and relaxation exercises, hypnosis and immersive reality

Strategies to decrease preoperative anxiety include the following:

- Non-pharmacological techniques
- Pharmacological sedative premedication
- A combination of the above

Children who are at an increased risk of preoperative anxiety need to be identified and the use of sedative premedication needs to be considered. Is it possible to spot an anxious child? Several factors have been identified as increasing the risk for anxiety at induction of anaesthesia in children.[8] These include the following:

- A younger child (1–6 years of age) is associated with increased anxiety
- Multiple previous hospital admissions
- Previous behavioural problems at healthcare attendances
- Previous traumatic experiences with anaesthesia and surgery
- Children with special needs who have limited ability to cooperate (such as those with autism spectrum disorder, attention deficit disorder, attention deficit hyperactivity disorder or down's syndrome)
- Temperament of the child (i.e. shy, inhibited, dependent, withdrawn)
- Children going for major surgery
- Brief time for preoperative preparation
- Parental anxiety

The need for premedication and the identification of any potential contraindications should be part of every paediatric preoperative assessment. Parental input about whether premedication is needed or not may also be especially useful. A careful risk/benefit assessment should be done for each patient. Potential contraindications to sedative premedication are listed in Table II.[4]

Table II: Potential contraindications to sedative premedication[4]

Anticipated difficult airway
Obstructive or central sleep apnoea
Increased risk of aspiration
Severe renal or hepatic impairment
Altered level of consciousness or raised intracranial pressure
Acute systemic illness (e.g. severe sepsis)
New or unexplained reduction in oxygen saturations
Upper respiratory tract infection
Previous adverse or allergic reaction to sedative premedication

Practical and safety considerations

A discussion with the parents and child (where appropriate) should include information on the options of medication and routes of administration, the expected effects of these agents, potential side effects and the possibility of sedation failure. If the child has received sedative premedication in the past, it is useful to determine the drug and dosage given, its effectiveness and any side effects or adverse events. Although the practicalities of sedative premedication may vary among institutions and cultures, the following safety considerations should always be adhered to:[4]

- Obtain informed consent from parents (and the child where appropriate)
- Confirm fasting status
- Chart the drug, route, dose and time when it should be administered
- Communicate clearly with the nurse responsible for the patient about when to administer the medication as the timing is key to optimising its efficacy
- Oral premedication can be given with a small volume (5–30 ml) of clear solution (apple juice, cordial or paracetamol mixture)
- Sedative drugs should only be given in a safe environment where the patient can be observed appropriately and where resuscitation equipment is available
- A sedated child should be monitored at all times, including when transferred from the ward to the preoperative holding area and through to theatre
- In the event of respiratory depression or reduced level of consciousness, treatment should be supportive, providing airway protection and ventilatory support as required, and consideration should be given to the use of reversal agents such as naloxone for opioids and flumazenil for benzodiazepines

Choice of premedication

There are various agents available to use as sedative premedication. A summary of the key characteristics of medications commonly used for preoperative sedation is presented in Table V.[4,9] The question of which drug or what combination of drugs to choose, is influenced by several factors. Availability and institutional culture might either limit or influence choices. Other factors include the drug formulation, pharmacological profile, contraindications, the degree of cooperation from the child, and information about what drug has worked well with a particular patient in the past. In the mid-1980s, midazolam was launched. It was considered to be a new 'wonder drug' which possessed a number of highly-desirable effects in the premedication setting. It became the gold standard drug for sedative premedication. While midazolam is still widely used for this purpose, it is regarded by some anaesthetists as a suboptimal choice for premedication in the paediatric population due to a number of undesirable characteristics in this setting.[7] Alternative drugs for sedative premedication include other benzodiazepines (diazepam and temazepam), alpha-2-adrenoceptor agonists (dexmedetomidine and clonidine), NMDA receptor antagonists (ketamine), opioids, trimeprazine and melatonin.

Midazolam

Midazolam has a lengthy track record of use for minimal and moderate sedation, and remains the most commonly used oral sedative for anxiolysis in children. A recent review found oral

midazolam to be an efficacious medication with an adequate safety profile for use in minimal or moderate sedation in children from 4 months to 18 years of age at doses of 0.25–1.5 mg/kg.[10] The incidence of adverse events such as paradoxical reactions, respiratory events and over-sedation increases with increasing doses.[10] According to critics of this drug, the effect of midazolam on memory is one of the most compelling arguments against its use in paediatric premedication.[11] Midazolam suppresses explicit memory but preserves implicit memory, thereby allowing the child to unconsciously memorise preoperative events of a negative and emotional nature, and be unable to report these events consciously in the postoperative period.[11] The limitations associated with its use for premedication in children are summarised in Table III.[4,7,11]

Table III: Limitations associated with the use of midazolam for premedication in children[4,7,11]

	Limitations associated with the use of midazolam in children
Oral administration	Bitter, unpleasant taste that is difficult to mask. Poor patient acceptance.
Intranasal administration	High incidence of burning and stinging due to the low pH of the formulation. May also cause bleeding. This route is best avoided.
Bioavailability	Low and unpredictable absorption when administered orally or rectally.
Pharmacokinetics	Not short-acting both in infants and in adolescents.
Pharmacodynamics	Causes loss of explicit memory but preserves implicit memory. May lead to increased anxiety and behavioural disturbances in the postoperative period. Risk of paradoxical reactions. High incidence of hiccups. Negative effect on respiratory drive and markedly potentiates the respiratory depression caused by opiates. Increased risk of emergence delirium.

Alpha-2 adrenoceptor agonists

Among the most interesting and useful alternatives to midazolam are the alpha-2 agonists clonidine and dexmedetomidine. Apart from their potential to produce sedation and anxiolysis, alpha-2 adrenoceptor agonists also have other beneficial effects within the anaesthetic context. These are listed in Table IV.[4,7] They do not affect memory and the sedation produced is very similar to normal tiredness/sleep. Potential disadvantages include quite a long onset time and prolonged postoperative sedation. These qualities may be advantageous in certain scenarios. Evidence shows that dexmedetomidine is at least as effective in decreasing preoperative anxiety and produces significantly lower anxiety in the postoperative period compared to midazolam.[12] Dexmedetomidine has been shown to have a shorter onset time and a faster elimination half-life compared to clonidine but cannot be administered orally due to limited absorption from the gastrointestinal tract. This can be circumvented by nasal or transmucosal administration. Clonidine is usually given orally. The intravenous preparation is suitable for oral administration as it is tasteless. A decrease in heart rate with accompanying decrease in blood pressure is a predictable response to alpha-2 agonists. Caution should be exercised in patients with severe ventricular dysfunction and advanced atrioventricular block, as well as those taking medications such as beta blockers or digoxin.

Table IV: Beneficial effects of alpha-2 adrenoceptor agonists in the anaesthetic setting[4,7]

	Beneficial effects of alpha-2 adrenoceptor agonists in the anaesthetic setting
Preoperative	Clonidine is a tasteless liquid and has a high and predictable bioavailability after oral and rectal administration with a long window of action. Dexmedetomidine given intranasally does not cause stinging or burning. Alpha-2 agonists produce anxiolysis and sedation with no effect on memory or cognitive function. Reduced salivation. Minimal effects on respiratory drive. No enhancement of the respiratory depression of opioids.
On induction	A reduced dose of induction agent is required. Attenuation of the stress response associated with intubation.
Intraoperative	Reduced anaesthetic requirements of volatiles and opioids.
Postoperative	Reduced risk of emergence delirium. Reduced postoperative pain.

NMDA receptor antagonists: Ketamine

Ketamine has sedative, anxiolytic and analgesic properties as well as a rapid onset of action. It may, however, have significant side effects such as hallucinations, increased secretions, random limb movements and significant emergence reactions, particularly when used as a sole agent where higher doses are required. It is also emetogenic and children who have been given ketamine should always be closely observed. The use of ketamine in combination with either midazolam or dexmedetomidine is preferable, allowing for lower doses of each drug to be given and, therefore, fewer side effects. The combination of intranasal dexmedetomidine (2 ug/kg) together with oral ketamine (3 mg/kg) was found to produce satisfactory sedation with minimal adverse effects.[13] When used in combination with midazolam the doses are reduced to oral midazolam (0.3 mg/kg) and oral ketamine (5 mg/kg). Ketamine is highly lipid soluble and is rapidly absorbed after intramuscular administration. This makes it a useful agent in cases where all other methods of sedation have failed, and the procedure is felt to be necessary. A 'ketamine dart' may be painful and traumatic for the child and physical restraint might be necessary. Parental counselling is required and the team needs to be prepared with a planned approach.

Opioids

If a rapid onset of sedation is warranted and close supervision is available, the use of nasal fentanyl or sufentanyl is a highly effective alternative, although ventilatory depression is a

significant risk.[14] The first formulation of oral transmucosal fentanyl citrate, tradename Oralet, was approved by the FDA in 1993 for preoperative sedation in children. After approval, it became evident that opioid-naive children who received it, could not tolerate the associated adverse effects of nausea and vomiting. Marketing of Oralet ceased in 2001. Opioids may be used in combination with midazolam, but this combination, in particular, is associated with an increased risk of respiratory depression and extreme caution is advised.[15]

Other agents

Trimeprazine

Trimeprazine (vallergan) is a long-acting phenothiazine derivative. It is an older drug which poses several unwanted anticholinergic side effects such as tachycardia, fever, dry mouth and, rarely, convulsions and coma. Paradoxical excitation has also been described. The very long duration of action makes it unsuitable in the ambulatory setting. It is available in oral form but has a variable onset time due to erratic absorption.[9]

Melatonin

Melatonin's safety profile makes it an appealing alternative to use for sedative premedication. While it may be effective in reducing preoperative anxiety in adults, trials assessing the effects of melatonin in paediatric patients have produced conflicting results. There is currently limited evidence to support the routine use of melatonin for premedication in children.[4]

Combinations of drugs

Various combinations of drugs given via different routes may be advantageous in certain situations. Caution is advised in

Table V: Summary of the key characteristics of sedative premedication[4,9]

Drug and route of administration	Dose when given as a sole agent	Max dose	Onset in minutes	Duration of action dose dep	Advantages	Limitations and adverse effects
Midazolam					Reduced PONV	See Table III
Oral	0.25–0.5 mg/kg	7.5 mg	10–30	60 minutes		Bitter taste
Sublingual	0.25–0.3 mg/kg	0.3 mg/kg	10–15	20–60 minutes	Quick onset Better compliance	
Intravenous	0.025–0.1 mg/kg	1 mg	3–5	20–60 minutes		
Rectal	0.5–0.75 mg/kg	1 mg/kg	10–20	60 minutes		
Intranasal	0.2–0.3 mg/kg	0.3 mg/kg	10–15	60–120 minutes		Burning and stinging
Dexmedetomidine					See Table IV	Caution in CVS instability
Intranasal or buccal	1–4 µg/kg	200 µg	15–30	40–135 minutes	Intranasal option; shorter half-life than clonidine	Intranasal by mucosal atomisation device
Intravenous	0.5–1 µg/kg slowly		5–10	60–120 minutes		
Clonidine						Caution in CVS instability
Oral	1–5 µg/kg	200 µg	45–60	45–90 minutes	Tasteless, long 'window' of action	
Intramuscular	2–4 µg/kg		30–60		Alternative in non-compliant child	Painful, traumatic
Intranasal	2 µg/kg		30–60			
Ketamine					Quick onset; useful in combination with midazolam	Salivation, hallucinations, emergence delirium, PONV
Oral	5–8 mg/kg		10–15	3 hours		
Intramuscular	4–5 mg/kg		2–5	30–120 min	Alternative in non-compliant child	Painful, traumatic
Rectal	4–6 mg/kg		> 5 min	30–120 min		
Intranasal	5 mg/kg		5–10	20–120 min		
Opioids					Analgesic properties, useful in combination	Significant potential for respiratory depression
Fentanyl intranasal	1–2 µg/kg		10	1–2 hours		
Morphine orally	0.2 mg/kg	10 mg	20–30	1–2 hours		
Trimeprazine						Long duration, anticholinergic side effects
Orally	1–2 mg/kg		60–90	5–8 hours		

patients at risk of airway obstruction or respiratory depression. The combination of midazolam and opioids in particular is associated with an increased risk of respiratory depression.

Special considerations

Obstructive sleep apnoea

Children with obstructive sleep apnoea (OSA) are at increased risk of airway obstruction and desaturation as a result of sedative premedication. It should be used with due caution and only if indicated. Extra vigilance from the anaesthetist is warranted. Midazolam should be used with caution as it may increase supraglottic airway resistance, induce central apnoeas and decrease the arousal response to hypoxia and hypercarbia. Dexmedetomidine maintains airway patency and tone and offers a theoretical advantage over midazolam. It does decrease minute ventilation and increases arterial carbon dioxide, but this occurs at a level similar to profound sleep. Ketamine maintains upper airway patency but hypersalivation may cause problems.

Obesity

Obesity is associated with OSA and gastro-oesophageal reflux. These comorbidities need to be taken into consideration when prescribing sedative premedication. Optimal drug dosing in obese children is challenging and there is a paucity of evidence to guide clinicians. Dosing based on ideal body weight is advocated to minimise the risk of significant respiratory depression.[16] This, however, may result in a reduced clinical response.

Conclusion

Children experience being anaesthetised as stressful. More than 60% of all children undergoing anaesthesia experience anxiety. The reasons for perioperative anxiety are multifaceted and multidimensional. The consequences of untreated and poorly-managed preoperative anxiety are adverse clinical and behavioural outcomes. Multiple techniques are of value in managing preoperative anxiety. Non-pharmacological techniques should be employed in all paediatric patients going to the operating room. These techniques vary according to institution, culture and resource availability. Children who are at increased risk of preoperative anxiety need to be identified and the use of sedative premedication considered. Many factors influence the choice of drug and the route of administration. There is no 'one size fits all' and the management of preoperative anxiety needs to be individualised and tailored to each specific child and their parents.

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