Chapter

Ketamine for Anesthetic Premedication in Children: Pearls, Pitfalls and Review of Clinical Utility

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Abstract

Ketamine, since its difficult introduction into clinical practice nearly half a millennium ago, has now become widely utilized as an anesthetic agent, especially in adults. Its efficacy in procedural anesthesia and pain management, along with its safety, has been proven in several clinical studies. This book chapter reviews the clinical utility of ketamine when used in young individuals. Premedication is an essential component of anesthetic protocol for parents and children to overcome emotional or psychological distress. Preoperative anxiety, being associated with greater pain during postoperative recovery in children, calls for the effective use of premedicants. This chapter describes how the cognizance of perioperative pain and the use of ketamine in children has become especially popular over the past few decades. It also discusses how intramuscular ketamine as a premedicant in subanaesthetic doses has a special role in the management of highly uncooperative children. As a potent analgesic, ketamine has a complex mechanism of action, producing a state of sedation, immobility, analgesia, amnesia, and dissociation from the environment. Some institutions are using ketamine in infants over 7 months and toddlers as part of premedication protocols for preoperative sedation, prevention of response to separation and intravenous access, and postoperative pain control in infants. This chapter also discusses the pearls and pitfalls in using ketamine in these challenging populations.

Keywords: ketamine, procedural sedation, analgesia, dissociative anesthesia, preanesthetic drug, premedication

1. Introduction

Ketamine, since its difficult introduction into clinical practice nearly half a millennium ago, has now become widely utilized as an anesthetic agent, especially in adults. Its efficacy in procedural anesthesia and pain management, along with its safety, has been proven in several clinical studies. This book chapter reviews the clinical utility of ketamine when used in young individuals as a premedicant.

Surgical interventions are not merely physically stressful but are an emotionally distressful process for both children and their parents. In a scheduled surgical operation, the preoperative period is a traumatic and challenging experience for younger patients; which is often taken casually. This usually leads to preoperative anxiety,

postoperative distress, prolonged child illness, and hospitalization. Excessive preoperative anxiety has been reported to result in more pain, negative postoperative outcomes as fear of anesthesia, and long-term behavioral problems [1].

Approximately 70% of the children exhibit significant stress and anxiety before surgery [2]. Preanesthetic medications are highly required in pediatric surgical patients for the management of preoperative anxiety, to help in iv cannulation, mask acceptance, and prevent long-term psychological/behavioral disturbances.

Approximately 84–100% of anesthesiologists now use the premedicants [3]. As part of the anesthetic technique, these premedicant drugs are given before the administration of an anesthetic agent, to make anesthesia safer and more agreeable to the patient. To alleviate anxiety and fear of surgery and anesthesia a premedicant is usually required before anesthesia.

2. Criteria for selection of premedication

Various factors have to be considered while selecting the premedication. The premedicant must be able:

1. To provide sedation and hypnosis have an amnesiac effect
2. To allay anxiety and apprehension
3. Have an anticholinergic effect
4. Have anti-emetic effect
5. Have an additive or synergistic effect on induction, for instance, ensuring a smoother and more rapid induction of anesthesia
6. To inhibit the parasympathetic nervous system
7. Reducing the dosage of anesthetic agents
8. Counteract certain adverse effects of the anesthetic drug
9. To relieve pain

2.1 Choice of premedicant

It is found that if preoperative apprehension of the child is not relieved, leads to psychic trauma, struggling, prolonged stormy induction, sometimes hypoxemia, or even anoxia owing to inadequate induction and relaxation finally airway obstruction, thereby anesthetic risk is increased or multiply. It is an unforgettable situation for children and even adults and permanent psychological trauma. The choice of premedicant is usually individualized, chosen for a particular patient and technique of anesthesia. They should relieve anxiety and central nervous system (CNS) depressants are necessary for psychic sedation.

3. Commonly used premedicant and their comparison with ketamine

They are fentanyl, midazolam, promethazine pheniramine maleate and dexmedetomidine have their own merits and demerits. Narcotics and benzodiazepines

may produce respiratory depression and require close monitoring. Barbiturate, a hypnotic, is also used as a premedicant when basal narcotic doses are required. Such doses produce unconsciousness with respiratory and circulatory depression. Antisecretory agents, the anticholinergics are commonly used with premedicant drugs in children, considered mandatory in new-born and infants due to the following reasons: they suppress secretions or dry up secretion, prevent bradycardia, prevent laryngospasm (may produce due to excessive secretion), produce bronchodilatation and have an antiemetic effect. The most common method of administration of anticholinergic drugs in the past was the intramuscular route now they are used intravenously [4].

3.1 Comparison with phenothiazines

In comparison to ketamine the phenothiazine derivatives as chlorpromazine (the prototype), prochlorperazine, trimeprazine, and promethazine (phenergan), enhance the effects of other central nervous system depressants. They are neuroleptics and dopamine antagonists having antihistaminic, antiadrenergic, anticholinergic, and antiemetic activity.

Contrary to ketamine phenothiazines are sympatholytic and ganglioplegic, can cause hypotension due to alpha-1-adrenergic blockade and peripheral vasodilation; contraindicated in shock, hypotensive, or anemic patients. Phenothiazines possess antiarrhythmic properties, and promethazine of this group has the least side effects and is often recommended. In the past, trimeprazine and promethazine were the most commonly used premedicant in children. Furthermore, they lack any generalized hypnotic effect and do not produce analgesia, instead are ant analgesia. A large dose can depress ventilation, when combined with opioids and hypnotics, due to additive effects, thus respiratory depression may occur.

Contrarily, ketamine is sympathomimetic, a potent analgesic, and has anti-inflammatory, antidepressant, and antiemetic effects through its action centrally on the chemoreceptor trigger zone as well on the vomiting center of the CNS.

Metabolism of phenothiazine is by biotransformation in the liver with glucuronic acid. If overdosed, metabolites are excreted in the urine for several days, as no specific antagonist is available. Phenothiazines can be given, orally, subcutaneously, intramuscularly, or intravenously.

3.2 Comparison with benzodiazepines

The sedative-hypnotic drugs are usually essential premedicants in children, as a struggling child is often challenging to provide anesthesia to. A drowsy or sleepy child makes the process easier. The benzodiazepines are the most common premedicant in this group used in infants and children apart from adult patients because of their good anxiolytic properties coupled with fewer side effects. It was used approximately in 83% population to get smooth induction of anesthesia along with sedation and amnesia. In the past, temazepam or diazepam have been used in children when using ether-based or chloroform-based anesthetic protocols. Temazepam is most frequently used due to its short half-life as compared to diazepam [4]. Midazolam is a benzodiazepine believed to be a good choice for premedication due to its anxiolytic, sedative, anticonvulsant, antiemetic, rapid onset, and relatively short duration of action [5], but several studies have shown that satisfactory results are seen only in 60–80% of cases [6].

However, these drugs are less frequently used by some anesthetists probably due to concern of delayed recovery from anesthesia and respiratory depression following intravenous injection, which requires close monitoring.

The antagonist agent to benzodiazepines is flumazenil which is not frequently used in most parts of the world due to the high cost involved. Flumazenil injection is indicated for a complete or partial reversal of the sedative effects of benzodiazepines in conscious sedation and general anesthesia in both adult and pediatric populations.

3.3 Comparison with alpha 2 adrenergic agonists

In uncooperative children, clonidine or dexmedetomidine can also be used as a premedicant due to its anxiolytic property. They can reduce the need for rescue analgesics, reduce emergence agitation, postoperative nausea and vomiting, and postoperative shivering [7]. Dexmedetomidine being highly selective having sympatholytic properties provides sedation, analgesia, and anxiolysis without causing respiratory depression. It can be used as an adjunct for premedication, especially for those patients who are susceptible to preoperative stress [8].

Thus, children treated with dexmedetomidine are more adequately sedated at the time of arrival in the PACU and a less volatile anesthetic is required to achieve hemodynamic endpoints. This allows rapid recovery from anesthesia with greater overall cardiovascular stability and fewer episodes of tachycardia in the perioperative period [8].

4. Use of ketamine as a premedicant

Ketamine as a premedicant in children is not a very popular practice. It is a non-barbiturate anesthetic, meeting most of the criteria of ideal premedicant produces balanced sedation with intact airway reflexes, immobility, analgesia, amnesia, and dissociation from the environment. The incidence of agitation, anxiety at parental separation, and reaction to insertion of the intravenous catheter were very low while adverse side effects were seen rarely. There is less respiratory depression and no myocardial depression. The cardiovascular changes including changes in blood pressure (BP) or heart rate (HR) are significant when used alone. However, its effects on intracranial pressure and intraocular pressure have been concerning overtime.

5. Routes of administration of ketamine

The use of ketamine as a premedicant in children has not been a very popular practice historically. However, its oral preparations have been reported to be used by some authors in the past [5, 9–11].

Ketamine is rapidly absorbed after intravenous, intramuscular, or intranasal administrations. It was found that when it is given through the intranasal or intravenous routes, pharmacokinetic parameters were similar [12]. In general, drug absorption is mainly determined by its physicochemical properties. Ketamine's formulation as the ketamine is highly lipid-soluble which is five times higher than thiopentone. It has an extensive distribution in the body and has low binding to plasma proteins, being approximately 10–30% [13, 14].

Bioavailability of ketamine depends largely on the route of administration as 20% oral; 93–90% intravenous or intramuscular; 25% rectal; 50% intranasal [15, 16].

After the intravenous route of administration, action is achieved within 1 min as it reaches the receptors very quickly with a transfer half-life of less than 1 min. On i.m. administration, the plasma peak concentration attained within 5 min. It is found that on intramuscular injection, the absorption occurs very fast in children as compared to adults. Children's muscles are not well developed as compared to adults and the regional flow is different.

Ketamine has a lipid-soluble structure, which diffuses more rapidly than non-lipid soluble drugs across cell membranes. On oral administration, it diffuses across a cell membrane from a region of high concentration such as gastrointestinal fluids to low concentration as blood. Apart from the flow following diffusion gradient and lipid solubility, it also depends on size, degree of ionization, and absorptive surface area. After oral administration, most of the ketamine is destroyed in the acidic media of the gastrointestinal tract, degraded by its secretions and enzymes. Despite the large surface area of the stomach, not much of the drug is absorbed from the stomach due to the thick mucus layer. Furthermore, owing to its parasympatholytic effect it has a short transit time hence gets less time for absorption. Thus, a large part of the drug gets destroyed on oral administration as compared to intramuscular or intravenous [3].

The intrarectal ketamine bioavailability is 25% while intranasal has 50%. It is found that nor ketamine plasma concentration achieved higher as compared to ketamine on identical dose [3].

5.1 Common clinical practice regarding the route of administration

Despite faster absorption by intravenous and intramuscular routes, it was most commonly used by the oral route in the past. Oral transmucosal ketamine (OTK) in the form of a lollipop was also used in the past.

In our hospital, we use ketamine as premedication either intravenous or intramuscular route.

Figure 1 summarizes the decision-making behind choosing between the two routes of ketamine.

The effectiveness of ketamine as premedication may be assessed based on Epstein et al. [17] scoring system, i.e. the Five Points-Sedation Score.

1. Asleep,

2. Not readily arousable,

3. Asleep, but arousable,

4. Calm but awake,

5. Restless, agitated

With ketamine, we should be getting a score of either 1 or 2 indicating the adequacy of sedation.

Regarding the score for acceptance of separation from parents (scoring = 1. easy, 2. slightly resistant, 3. markedly resistant) we get the score of 1 usually, representing competence of ketamine as premedication.

For mask acceptance (1. easy, 2. slightly resistant, 3. markedly resistant) again, the score with ketamine is usually 1, signifying the capability of ketamine as premedication.

	Ketamine IV	Ketamine IM
Dose	1-2 mg/kg slow IV push.	4-5 mg/kg IM
Onset	1-5 min	4-5 min
Duration	Approx. 20min	Approx. 25 min
Benefits	**1.** Provides Analgesia, Sedation and Amnesia **2.** Predictable onset and offset. **3.** Does not decrease respiratory drive.	Same as IV
Side-effects	Emesis Laryngospasm Emergence reaction	Similar IV but higher rate of emesis
Recovery	Approx. 60 min	Approx. 90-120 min

Figure 1.
Comparison of intravenous and intramuscular dosing of ketamine. Figure adapted from Emergency Medicine Cases website. Available from: https://emergencymedicinecases.com/pediatric-procedural-sedation/, Creative Commons License.

6. Standard protocol for ketamine as premedicant

Prerequisite for ketamine premedication includes the readily available all resuscitation equipment, emergency drugs anesthesia machine, or Ambu resuscitator for positive pressure ventilation and continuous oxygen source.

Preanesthetic evaluation to be done before ketamine administration. Children under 3 months of age are an absolute contraindication and age between 3 and 6 months is a relative contraindication to ketamine-based anesthesia. Pulmonary as current upper respiratory infection or neurologic disease as psychosis were not considered fit for ketamine premedication. Children with cardiovascular diseases where increased heart rate and cardiac workload is present as hypertension, ischaemic heart disease, cardiac failure are also cases where ketamine is contraindicated. Thyroid disease, and acute globe injury or glaucoma are considered as a contraindication to ketamine anesthesia.

The procedure should be explained to the parents including sedation and even about rare unpleasant emergence phenomena. Informed consent must be obtained before the use of ketamine premedication. Baseline vitals to be checked including

BP, HR, RR, and O_2 saturation. If the administration is planned apart from an oral route, then topical anesthetic cream should be applied approximately 45–60 min before the start of the intravenous line.

Anticholinergics as glycopyrrolate or atropine are necessary with ketamine premedication to prevent the excessive salivation associated with ketamine use, which may lead to blockage of the endotracheal tube due to drooling of saliva. However, in oral or intramuscular ketamine premedication, anticholinergic is usually given after sedation, following the start of the intravenous line. Intravenous ketamine premedication is started with anticholinergic as glycopyrrolate/atropine depending upon pediatric age, infants, or grown-up child. Benzodiazepines such as midazolam are usually given simultaneously in a low dose with ketamine via i.v. or i.m. route to prevent its psychomimetic effects like agitation, hypertension, hyperthermia, and seizures [18].

Anesthetic adjunctive agent as ondansetron may be considered before the start of ketamine sedation, in children over 8 years of age [19].

Standard monitoring includes pulse oximetry, non-invasive blood pressure, heart rate and respiratory rates (RR) along with close observation of the airway and chest movements are required. The intravenous line usually sets in after achieving sedation and analgesia.

The oral ketamine dose is 4–6 mg/kg, usually, 5 mg/kg is adequate. Intravenous dose is 1–2 mg/kg, usually, 1.5 mg/kg, given slowly (over 1–2 min) as rapid administration may lead to respiratory depression, clinical onset is 1–2 min. The intramuscular dose is 2–4 mg/kg, clinical onset 3–4 min, effective sedation is achieved within 5 min. Intranasal is 3–5 mg/kg onset 10–15 min and buccal/transmucosal is 5–6 mg/kg onset is also 10–15 min. Per-rectal ketamine usually 5–10 mg/kg is given. 10 mg/kg may lead to delayed emergence from anesthesia [20].

In our institution, we prefer the intramuscular route for ketamine premedication in an uncooperative or frightened child or when it is difficult to put IV line or where no intravenous access has been secured before the transfer of the child to the preoperative preparation room. If there is already an IV line then it is a reasonable approach to administer ketamine intravenously. However, rapid injection through the intravenous route has also been associated with respiratory depression [21].

7. Side effects of ketamine premedication

Ketamine does have side effects. Most commonly these are seen as vocalization, random purposeless movements, muscle twitching, and hypersalivation, and transient tachycardia and/or hypertension.

Hypersalivation needs essential anticholinergic in premedication and may require oral suctioning. Excessive salivation and bronchial secretions may sometimes lead to occasional laryngospasm (incidence of 0.3%) which needed immediate positive pressure ventilation, or rapid sequence intubation (RSI) [22]. Respiratory depression (0.4%) or even transient apnoea may occur, assisted mask ventilation may be needed. Vomiting is common in older children usually over 8 years of age. In short surgical procedures where oral ketamine is used as premedicant unpleasant emergence, phenomena may be seen beyond mid-adolescence, which resolve after some time in a calm and quiet environment with minimal or no stimulation.

Generally, the side effects are related to doses, larger doses take less onset time but longer time for metabolism and excretion, finally more chances of residual effects as hallucination, emergence, and vomiting. Orally administered ketamine of 6 mg/kg have an onset of action to produce sedation 10 min as compared to 3 mg/kg takes 20 min [23, 24].

8. Use of co-medication with ketamine

The combination of ketamine with other drugs has also been used in several studies, with the co-medication helping to overcome the side effects and increases bioavailability by affecting the drug disposition and its pharmacokinetics [12].

8.1 Combination of ketamine with midazolam

It is reported that when a combination of ketamine and midazolam administered orally produces 90% successful anxiolysis as compared to <75% when either drug is given alone. This oral mixture produces a better quality of sedation and amnesia and requires less IV propofol as compared to intramuscular meperidine, promethazine, and chlorpromazine for pediatric cardiac catheterization [25].

8.2 Combination of ketamine with dexmedetomidine

The combination of dexmedetomidine with ketamine reduces its cardiovascular effects and slower the elimination, as dexmedetomidine is a strong inhibitor of the N-demethylation of ketamine to norketamine.

9. Conclusions

As a potent analgesic, ketamine has a complex mechanism of action, producing a state of sedation, immobility, analgesia, amnesia, and dissociation from the environment. Ketamine as a premedicant especially in subanaesthetic doses and in combination with midazolam produces prompt sedation. Some institutions are using ketamine in infants over 7 months and toddlers as part of premedication protocols for preoperative sedation, prevention of response to separation and intravenous access, and postoperative pain control in infants. This helps in smooth separation from parents and the child accepts the face mask easily, is immobile, is dissociated from the environment. There is little incidence of emergence phenomenon on recovery. The patient is somewhat sedated without any respiratory depression or suppression of protective reflexes or any other untoward side effects with good postoperative analgesia. Intramuscular ketamine as a premedicant in subanaesthetic doses has a special role in the management of uncooperative children.

Conflict of interest

The authors declare no conflict of interest.

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