

## Review article

# Ketamine and kids: an update

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### Introduction

The 'ketamine dart' is an old and trusted standby for pediatric anesthesiologists: in the uncooperative pediatric patient, the intramuscular administration of ketamine – if necessary straight through the clothes – has proven itself as an effective approach to induce a moderate level of anesthesia while maintaining blood pressure, breathing and airway reflexes. Ketamine also is used frequently for pediatric sedation and pain relief, by anesthesiologists and nonanesthesiologists, in the Emergency Department and Intensive Care Unit.

A number of developments have drawn renewed attention to ketamine for use in the adult population. The marketing in Europe of the S(+) isomer instead of the racemic mixture led to hopes that the at times troublesome side effects of ketamine could be reduced – hopes that appear to have faded (1), but that have led to the availability of a compound with a faster offset and allowing more easily titrated use in infusions. The profound analgesic properties of ketamine have been recognized anew, and a number of approaches for ketamine pain therapy in the perioperative period and for patients with chronic pain are being evaluated (2). Concerns about the use of ketamine in patients with head injury have been shown essentially unwarranted when used under appropriate conditions (3), and this has opened the

way to making use of its well-described cerebral protective properties, which seem to be even more pronounced in S(+) ketamine (4). Although ketamine can induce neuronal toxicity (5), further research will likely define an appropriate place of the compound in treatment of patients with intracranial pathology.

A number of these developments are applicable as much to the pediatric population as to adults, and a number of investigators have studied novel uses of ketamine in children. In this review we will, after a brief description of our current understanding of ketamine's pharmacology, discuss the recent literature on ketamine's use for three pediatric indications: anesthesia, sedation, and analgesia. We hope to demonstrate that there may be growing opportunities for improving patient care by using ketamine in children.

### Pharmacology

Ketamine's primary molecular target is the N-methyl-D-aspartate glutamate (NMDA) receptor (6). Other targets have been reported, but are probably not greatly relevant at plasma levels attained in the clinical setting. Glutamate is the major excitatory transmitter in the central nervous system, and inhibiting this receptor therefore decreases neuronal activity, which results in a state of anesthesia. In this action on the NMDA receptor, ketamine is very similar to nitrous oxide, a compound which therefore shares a number of clinical effects (such as profound analgesia) with ketamine.

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Ketamine has for many years been marketed as a racemic mixture of two isomers, S(+) and R(-). Since the inhibitory effect on the NMDA receptor of the S(+) isomer was shown to be approximately three times as great as that of R(-) (7), use of S(+) ketamine would require lower doses, and therefore, potentially, less side effects. In Europe, the compound is now available as a single isomer. Whereas early studies suggesting that S(+) ketamine would be associated with fewer psychotomimetic side effects have not been confirmed in subsequent trials (1), the compound has been found to be approximately twice as potent as racemic ketamine in the clinical setting. Importantly, S(+) ketamine has been shown to be significantly shorter acting than racemic ketamine, which allows a faster wake-up after use as an anesthetic, and easier titration when used for sedation and/or analgesia.

### Clinical applications

Ketamine is a remarkably versatile compound. Not only can it be administered by almost any route, it can be used for several different purposes. In low doses, ketamine causes analgesia and sedation; in high doses it produces general anesthesia.

#### *Ketamine for pediatric general anesthesia*

Induction of general anesthesia is the best-described use of the compound. Although newer anesthetics (in particular sevoflurane) have decreased the use of ketamine, it remains indicated in several specific situations. We already mentioned the use of intramuscular ketamine for induction of anesthesia in uncooperative pediatric patients. The compound can also be used effectively as an induction agent in trauma patients. Recent studies have addressed its use for anesthesia in patients with cardiac or neuromuscular disease.

Ketamine is frequently chosen for anesthetic induction in patients with cyanotic conditions, as it increases systemic vascular resistance and cardiac output and does not worsen right to left shunting (8). A recent prospective, randomized study by Tugrul *et al.* (9) investigated the use of ketamine, as compared with isoflurane, for maintenance of anesthesia in 50 children (ages 3 months to 12 years) undergoing correction of tetralogy of Fallot. Patients

received one of two maintenance regimens, either up to 1% isoflurane and  $0.1 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  fentanyl, or up to  $5 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  ketamine and  $0.1 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  fentanyl. Hemodynamic and respiratory parameters were measured during four intervals: before induction, from induction to 10 min postintubation, from 10 min postintubation to poststernotomy, and from poststernotomy to completion of catheterization. Ketamine anesthesia was found to provide more stable precardiopulmonary bypass conditions than did isoflurane anesthesia. Arterial oxygen tension, oxygen saturation and mean arterial pressure were better maintained poststernotomy in those patients receiving ketamine. This study confirms older data that ketamine anesthesia can be a good alternative maintenance regimen in children undergoing correction of tetralogy of Fallot.

Another indication for ketamine is in pediatric patients with neuromuscular disorders, who are potentially at increased risk for the development of malignant hyperthermia. In such patients, both volatile anesthetics and muscle relaxants are best avoided, and ketamine may be an attractive alternative. Ramchandra *et al.* (10) reported the use of ketamine, administered either intravenously or intramuscularly, to 32 children (aged 3 months to 12 years) with floppy infant syndrome who required a diagnostic muscle biopsy under full general anesthesia. The children were divided into two groups, one group receiving  $2 \text{ mg}\cdot\text{kg}^{-1}$  of ketamine intravenously, followed by subsequent doses of  $1 \text{ mg}\cdot\text{kg}^{-1}$  if clinically indicated, and the other group receiving  $10 \text{ mg}\cdot\text{kg}^{-1}$  of ketamine intramuscularly. In both groups adequate anesthesia was obtained, suggesting that ketamine may be the agent of choice for children with neuromuscular disorders, since it is associated with cardiopulmonary stability and avoids the use of muscle relaxants and agents that may trigger malignant hyperthermia.

Thus, despite the advent of several new anesthetics, ketamine has maintained its niche as a general anesthetic for several specific procedures. Although it has not been investigated in children, ketamine's neuroprotective properties may make it an interesting compound for use in children with head trauma. In adults, ketamine has been conclusively shown not to increase ICP in head-injured patients, even when administered as a  $5 \text{ mg}\cdot\text{kg}^{-1}$  intravenous bolus, as long as ventilation is controlled and the patients are

sedated (11). However, this issue has not been studied in the pediatric population.

### *Ketamine for pediatric sedation*

Ketamine has been used extensively for pediatric procedures in and out of the operating room. The reasons for this popularity are clear: it provides effective analgesia and sedation with a low incidence of complications, such as the cardiorespiratory depression often seen after use of benzodiazepines or narcotics. Also, ketamine is cheap and easy to use. It can be administered orally, rectally, or intranasally, although it is most efficacious and predictable when given intravenously or intramuscularly. For this reason, these are the most commonly used routes of administration in pediatric anesthesia. Ketamine is pharmacologically quite predictable: its onset is within 1–2 min after intravenous use and 5 min after intramuscular use, and duration of action is approximately 45 min.

*Use for procedural sedation.* Ketamine sedation at times can be used instead of inhalational anesthesia for children undergoing fairly invasive procedures (12). Mason *et al.* (12) used intravenous or intramuscular ketamine in 38 children presenting for interventional radiology procedures, ranging from intravenous catheter placement and chest tube placement to renal and liver biopsies, percutaneous drainage catheters, and sclerotherapy. In all cases, sedation was successful and without adverse effects. Time to achieve sedation was usually less than 5 min. Time of sedation was on average 50 min and, not surprisingly, was longer for patients who received a ketamine infusion compared with a single intravenous bolus.

Similar results were obtained in a study reporting sedation in 211 children (all less than 10 years old) who presented for interventional radiological procedures. The patients received ketamine 2 mg·kg<sup>-1</sup> intravenously or 3 mg·kg<sup>-1</sup> intramuscularly. Only minimal respiratory depression and cardiovascular changes were noted in these patients (13).

One can argue whether this dosage scheme can still be considered sedation, or whether it constitutes a light general anesthetic. Green *et al.* (14) investigated the optimal dose of intramuscular ketamine for procedural sedation in the emergency depart-

ment, and found that 4–5 mg·kg<sup>-1</sup> intramuscularly provided effective 'sedation' in 93–100% of children. No differences in time to discharge or side effects were noted between lower and higher doses (14).

A few studies have showed effective use of ketamine administered orally for sedation in children undergoing painful minor procedures (15,16). However, oral administration is associated with high hepatic first pass effect; only 16% of a given dose is bioavailable. In addition, it takes approximately 20 min for full sedation to occur. Alderson & Lerman (17) used either oral ketamine or midazolam in 40 healthy children scheduled for ambulatory dental surgery. The dose of ketamine used in this study was 5.0 mg·kg<sup>-1</sup>. Ketamine was found to be as effective as midazolam in sedating the children within 20 min, and was without notable side effects.

*Side effects.* Side effects of ketamine are of concern, particularly when the drug is being used by non-anesthesiologists. Reports from developing countries indicate a complication rate of less than 0.2% for apnea, laryngospasm, emergence reactions, aspiration, and death (18). In fact, ketamine appears to be one of the safest approaches to sedation in children. However, side effects are real, the most common being increased salivation, purposeless movements, agitation, and emergence reactions (19). In one study involving oral ketamine as preanesthetic medication, 3 mg·kg<sup>-1</sup> and 6 mg·kg<sup>-1</sup> were used. The authors observed excess salivation in 13–33%, nystagmus in 7–20%, vomiting in 13–20%, and crying in 87% cases (20). Atropine given orally or intramuscularly can prevent increased secretions. Concerns over increased tracheobronchial secretions and salivation have prompted antisialogogues such as atropine (0.01 mg·kg<sup>-1</sup>, maximum 0.5 mg) or glycopyrrolate (0.005 mg·kg<sup>-1</sup>, maximum 0.25 mg) to be given prior to or in combination with ketamine (21). However, atropine pretreatment is unpleasant and not very effective because oral atropine has a bitter taste and takes as long as 2 h to be active. Atropine can be administered i.m., but this defeats the very purpose of avoiding injections in patients given oral ketamine.

Recovery from the dissociative anesthesia of ketamine can result in an agitated, confused, and combative child: the well-known emergence reaction (22). Risk factors for emergence reactions have

classically been described as: age over 15 years, female gender, a history of vivid dreams, and personality or psychiatric problems. Emergence reactions are rare in children, with rates around 2% being reported, compared with 30% in adults. However, these findings have recently been challenged in a study suggesting no effects of age on the incidence of emergence phenomena when ketamine was used for pediatric sedation in the emergency department (23). Hence, it is probably most appropriate to consider all children receiving ketamine at risk.

Anesthesiologists have coadministered propofol, midazolam, or other sedatives to decrease the risk of emergence phenomena (24). Low-dose midazolam can be given at 0.05–0.1 mg·kg<sup>-1</sup>. However, use of midazolam may prolong the recovery time. More importantly, recent studies suggest that benzodiazepines, in general, do not reduce postoperative agitation and emergence reactions. Sherwin *et al.* (25) determined whether midazolam reduces recovery agitation after ketamine sedation in children treated in the emergency department. A total of 104 children, aged 12 months to 15 years, were randomized to receive either intravenous midazolam, 0.05 mg·kg<sup>-1</sup> up to 2 mg, or placebo, after prior intravenous administration of ketamine, 1.5 mg·kg<sup>-1</sup>. Crying, hallucinations, and nightmares were used as indicators of emergence reaction during the postoperative period and graded using a 100-mm visual analog scale. Median recovery agitation was 4 mm (range 2–19) in the midazolam group and 5 mm (range 3–14) in the placebo group. The authors concluded that recovery agitation is common but generally of very low magnitude after ketamine sedation in children in the emergency department. Importantly, the data indicate that concurrent midazolam did not reduce such agitation. These data are confirmed by a study of Wathen *et al.* (26). These authors randomized 266 children (up to 16 years old) sedated with ketamine 1 mg·kg<sup>-1</sup> in the emergency department to receive either midazolam 0.1 mg·kg<sup>-1</sup> or placebo. No effect on emergence reactions was noted. However, the group receiving midazolam had an increased rate of respiratory depression (7.3% Vs 1.6%) and children over 10 years receiving midazolam had a greater incidence of agitation (35.7% Vs 5.7%). Midazolam reduced the incidence of nausea from 19.4 to 9.6%.

Hence, it is unclear if coadministration of midazolam is necessarily of benefit.

In summary, ketamine is an excellent choice for pediatric procedural sedation. Its analgesic properties (see below) allow use as a sole agent for relatively painful procedures in a variety of settings, and its cardiovascular and respiratory profile make the drug safer than most other compounds under consideration. Emergence reactions are probably not affected by midazolam in children, but their incidence is, luckily, low. Although it has not been studied in detail in children, the shorter half-life of S(+) ketamine might make it an interesting compound in this setting.

### *Ketamine for analgesia*

The use of NMDA receptor antagonists in general, and ketamine in particular, is being actively investigated as a modality for prevention of postoperative pain. A consensus is slowly being reached that the compound is effective, but that a single-shot administration is insufficient to provide long-lasting pain relief. Hence, ketamine infusion, or coadministration of morphine and ketamine for patient-controlled analgesia, appears a more promising approach. However, there are conflicting results concerning its efficacy as an analgesic agent. Some studies in adults have failed to demonstrate pain improvement after ketamine.

*Intravenous or intramuscular ketamine.* Few studies have been undertaken in children. The procedure considered most frequently is tonsillectomy, which is common in the pediatric population, and associated with significant pain. In addition, the depression of respiration by opioids is a potential risk factor after airway surgery. This is particularly so since 2% of children who present for adenotonsillectomy have obstructive sleep apnea. A prospective randomized controlled study compared ketamine with morphine for postoperative pain relief in children after adenotonsillectomy (27). The study group included 50 children, ages 1–16 years, presenting for routine adenotonsillectomy. Patients were randomized to receive either iv morphine 0.1 mg·kg<sup>-1</sup>, or ketamine 0.5 mg·kg<sup>-1</sup> at induction. Time to supplementary analgesia, defined as achieving a pain score of 4 or more, was used to compare the two groups. There was

no difference in the time to supplementary analgesia, suggesting that ketamine can provide similar postoperative analgesia as morphine. In another, similarly designed study, Marcus *et al.* (28) compared the effects of intramuscular ketamine with morphine for postoperative analgesia in children undergoing tonsillectomy. Eighty children, aged 6–15 years, were randomized to receive either intramuscular morphine 0.1–0.15 mg·kg<sup>-1</sup>, or intramuscular ketamine 0.5–0.6 mg·kg<sup>-1</sup>, after induction. Thirty minutes after extubation pain scores were greater in the ketamine group, but thereafter they were similar to the morphine group. Mean times to recovery from anesthesia were similar between the two groups. There were no differences in supplemental analgesia requirements or side effects between the groups. Elhakim *et al.* (29) showed in a randomized, placebo controlled trial that premedication with low dose ketamine (0.1 mg·kg<sup>-1</sup> intramuscularly) before tonsillectomy improved postoperative analgesia, swallowing and oral intake during the first postoperative day. However, these data have not been universally supported. O'Flaherty & Lin (30) did not demonstrate a decrease in pain or analgesic consumption in pediatric patients undergoing tonsillectomy when pretreated with a single dose of 0.15 mg·kg<sup>-1</sup> ketamine and/or 30 mg·kg<sup>-1</sup> magnesium sulfate. The reasons for this different outcome cannot be determined at this time.

*Ketamine for regional anesthesia.* The ability of racemic ketamine to provide intra- and postoperative analgesia after caudal or epidural administration has been demonstrated in pediatric patients. For example, Lee & Sanders (31) studied 32 children, aged 18 months to 12 years, presenting for circumcision under general anesthesia. They were randomly allocated to receive either caudal ropivacaine 0.2% 1 ml·kg<sup>-1</sup> or caudal ropivacaine 0.2% 1 ml·kg<sup>-1</sup> plus caudal ketamine 0.25 mg·kg<sup>-1</sup>. The median duration of analgesia was 12 h in the ketamine/ropivacaine group and 3 h in the ropivacaine group. Patients in the ropivacaine group required more doses of pain medication in recovery than those in the ketamine/ropivacaine group. No differences were found between the groups in the terms of side effects, such as postoperative nausea, vomiting, sedation, and emergence reactions.

However, the safety of this approach is still being debated, and because of potential neurotoxicity of

preservatives added to the ketamine mixture, neuraxial ketamine is not recommended at this time (32). However, a study using ketamine with the preservative benzethonium chloride, administered epidurally, did not show any neurotoxicity in patients being followed up for a year (33).

More recent studies have investigated the effects of S(+) ketamine for neuraxial analgesia. In comparison with racemic ketamine, S(+) ketamine is twice as potent as an analgesic agent (34). The pharmacological properties and hemodynamic responses are comparable between the S(+) and the racemic ketamine. Marhofer *et al.* (35) compared the analgesic efficacy of preservative-free S(+)-ketamine with that of bupivacaine for caudal block in children undergoing hernia repair. Forty-nine children were given caudal S(+)-ketamine at 0.5 mg·kg<sup>-1</sup> (group K1) or 1.0 mg·kg<sup>-1</sup> (group K2) or 0.25% bupivacaine with epinephrine 1:200 000 (group B). Duration of analgesia in groups B, K2 and K1 was 300 ± 96, 273 ± 123, and 203 ± 117 min, respectively. Groups B and K2 required fewer analgesics during recovery compared with group K1 (30% and 33% Vs 72%). The authors conclude that caudal block with S(+)-ketamine at 1.0 mg·kg<sup>-1</sup> provides intra- and postoperative analgesia similar to that of bupivacaine. Koinig *et al.* (36) reported that despite similar plasma concentrations during most of the postoperative period, caudal S(+) ketamine provided more effective analgesia than intramuscular S(+) ketamine. The authors concluded that the prolonged analgesic effect of caudal block is because of the drug concentration in the epidural tissue and not to that of the plasma. This suggests a local analgesic effect of S(+) ketamine.

In summary, the potential for low-dose ketamine to be used as an adjunct for analgesia in pediatric patients seems real, but the most effective and safe methodologies remain to be determined. Single-dose application will, at most, have a short-term effect. If the compound is to be used after major surgery, a prolonged infusion approach may be more valuable. However, this has not been studied in the pediatric population. Neuraxial ketamine, and particularly S(+) ketamine, appears a promising approach, but conclusive safety studies will be required before this technique can be recommended for clinical practice.

Despite the introduction into clinical practice of several new anesthetic compounds, the roles for

ketamine in pediatric patients seem to be expanding rather than diminishing. The compound still has a defined place in pediatric anesthesia, in particular for trauma victims and children with major cardiac disorders. It may also be an appropriate choice for patients at potential risk for malignant hyperthermia, and recent data in adults suggest that the compound could play a major role in patients with cerebral injury. Further studies in this area are necessary, however.

Ketamine is an excellent choice for procedural sedation in children, as its profound anesthesia is associated with few respiratory and hemodynamic side effects. The many potential administration modalities add flexibility. Recent evidence indicates that the incidence of psychotomimetic emergence reactions in children is low, but that addition of benzodiazepines has little beneficial effects.

The role for ketamine in perioperative pain management requires further clarification. Systemic as well as neuraxial administration have been shown effective in a number of studies. However, it is becoming clear that single-shot systemic administration has a short-term effect only. Alternative modes may be necessary. Although caudal and epidural ketamine have been shown effective approaches to providing postoperative pain relief, further safety studies are required before these techniques can be used in clinical practice.

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