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REVIEW

Pain and anxiety management for pediatric dental procedures using various combinations of sedative drugs: A review

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Abstract For fearful and uncooperative children behavioral management techniques are used. In order to control the pain and anxiety in pedodontic patients, pharmacologic sedation, anesthesia and analgesia are commonly used. Midazolam is commonly used as an oral sedation agent in children; it has several features such as safety of use, quick onset and certain degree of amnesia that makes it a desirable sedation agent in children. This review paper discusses various aspects of oral midazolam, ketamine and their combinations in conscious sedation including, advantages of oral route of sedation, pharmacokinetics, range of oral doses, and antagonists for clinical dental treatment procedures.

Contents

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1. Introduction

Management of child patients for various dental procedures in dental office is very challenging. The behavioral problems are commonly seen in children under the age of 6 years due to various elements such as immature reasoning, restricted coping skills and anxiety/fear causing (Henry and Jerrell, 1990). Conscious sedation is a proven and well documented approach to assist in such a kind of situations. Conscious sedation is defined as a controlled state of low consciousness that conserves protective and unconditioned reflexes, permits continuance of a patient's airway impartially and allows the patient to communicate appropriately to physical and verbal stimuli (Kauffman et al., 1992). Hence, conscious sedation can be very supportive in allying anxiety, uneasiness, fear and minimizing an uncooperative child's attempt to resist treatment procedures (Lanza et al., 1988; Field et al., 1993). Procedural conscious sedation includes providing an adequate level/degree of sedation whereas decreasing pain and anxiety, maximizing amnesia, curtailing the potential for adverse drug-related events, monitoring and governing behavior, and sustaining a stable cardiovascular and respiratory status. Sedation drugs can be administered through various routes such as oral, inhalational, nasal, intramuscular, subcutaneous, and intravenous routes (Mistry and Nahata, 2005).

There are a variety of drugs available that can be used for conscious sedation for dental office procedures. Midazolam is an anxiolytic agent having a short acting time of action (Krauss and Green, 2006; Warncke et al., 1997) that limits its utilization to short dental strategies only (Kain et al., 2000; Kupietzky and Houpt, 1993; Dionne, 1999; Nathan and Vargas, 2002). Midazolam has likewise been demonstrated to upgrade anterograde amnesia when utilized preoperatively in young children (Al-Zahrani et al., 2009; Curran, 1986; Smith et al., 1998). Ketamine provides excellent amnesia and analgesia. It maintains muscle tone and ensures air route reflexes and spontaneous breathing (Krauss and Green, 2006; Warncke et al., 1997). Despite of its obvious advantages over other agents, many dental practitioners are hesitant to use ketamine alone secondary to its propensity to cause vivid and frightening emergent reactions (Green et al., 1998a,b). It has been suggested that merging these two agents for conscious sedation may preserve sedation efficacy while reducing their side effects. This is relatively due to the fact that many of the aforementioned potential unfriendly impacts are relying upon measurement dose, and when utilized in combination the reduction of dose has a beneficial role in reducing the unwanted effects. The objective of this review paper was to represent the recommendations for safety profiles of key sedative drugs for pediatric dental patients. In addition, it was aimed to explore the beneficial role of using ketamine and midazolam in various drug combinations for the intended applications.

2. Sedative drugs

The use of sedative drugs alongside local anesthetics is often appropriate to reduce anxiety and fear among patients. In certain studies (Kauffman et al., 1992; Al-Zahrani et al., 2009; Smith et al., 1998), patients preferred dental extractions and other dental procedures under local anesthesia with sedation to local anesthesia only.

There are a number of sedative drugs that can be used for dental procedures (Table 1). Midazolam belongs to benzodiazepine groups (Table 1) that is used as a short and fast acting drug prior to general anesthesia (GA) or several other medical diagnostic approaches (Golpayegani et al., 2012). On the other hand, several other studies (Sener et al., 2011; Chudnofsky et al., 2008; Warner et al., 2007; Karapinar et al., 2006; Shende et al., 2003), have looked at the sedative effects of similar drugs used along with midazolam with a synergic effect to reduce the required dose of midazolam. Ketamine and midazolam combination has already been used successfully for the surgical treatment of young fearful and anxious children (Golpayegani et al., 2012; Sener et al., 2011; Chudnofsky

Table 1 General mechanisms for sedation.

Drugs group	Mode of action
Benzodiazepines	Potentiate GABA-mediated chloride ion influx
Barbiturates	Potentiate GABA and directly enhance chloride ion influx
Ketamine	Antagonize excitatory influences of glutamate
Antihistamines	Antagonize excitatory influences of histamine & acetylcholine
Opioids	Activate mu and kappa opioid receptors
Inhalation anesthetics	Potentiate inhibitory neurotransmission

(Al-Zahrani et al. (2009), Kauffman et al. (1992), Curran (1986), Mistry and Nahata (2005), Kupietzky and Houpt (1993) and Dionne (1999)).

Table 2 Comparison of various combinations of sedative drugs and outcome.

Researcher	Patient's age	Drugs/combination	Outcome
Treston (2004) (53) Prospective cohort Emergency	1–12 years	Ketamine No combination	Longer than 3 h: 15.7% patients vomited
Agrawal et al. (2003) Prospective case	5 days to 18 years	47% Ketamine 23% Fentanyl and midazolam	All adverse events were minor Emesis resulted in 15 (1.5%) patients
Mixed drugs	Median (5.4 years)	24% Chloral hydrate and pentobarbital	No signs of aspiration were observed
Roback et al. (2004) Prospective cohort Emergency ketamine, midazolam	19 days to 18 years Median: (6.7 year)	Ketamine, midazolam Used in combination	No significant adverse effects No patients experienced clinically apparent aspiration

et al., 2008; Karapinar et al., 2006; Shende et al., 2003). The development of pain pathways and anxiety reactions in the embryo, neonate, newborn child, kid and grown-up has been as of late clarified (Wolf et al., 1998). Based on ethical and moral grounds, it has been widely accepted that pain and anxiety should be managed securely and adequately regulated in all assemblies of age, step by step sedation and analgesia is a method of overseeing tranquilizers (midazolam, propofol, etomidate) or dissociative executors (ketamine) with or without opioid analgesics (fentanyl, morphine, meperidine) to get a condition that permits the patient to endure disagreeable techniques and still keeps up the cardio-respiratory functionality. According to Healy and Cohen (Wylie et al., 1995), chemical substances synthesized or released in response to tissue injury can be changed by systemic drugs which modify the peripheral nociceptor activity and improve patient's mood. Various combinations of drugs and their outcome for pediatric patients have been compared (Table 2).

2.1. Midazolam

Midazolam is a water-soluble imidazobenzodiazepine; presents as a clear, colorless solution of midazolam hydrochloride containing 2/5 mg/ml. The brief time of activity of midazolam is because of its high lipophilicity, high metabolic clearance and quick rate of elimination. However, this may not be the case after prolonged dosing on critical care. The utilization of midazolam in premedication diminishes the monitored anesthesia care (MAC) of volatile agents by approximately 15%. The clinical effects of the drug can be reversed using agents such as physostigmine, glycopyrronium and flumazenil (Sasada and Smith, 1997).

Midazolam is used (Sasada and Smith, 1997):

1- For induction of anesthesia,
2- For sedation during endoscopy and procedures performed under local anesthesia,
3- As a hypnotic agent,
4- For premedication prior to general anesthesia and may be of use,
5- In the treatment of chronic pain, including differentiation syndromes.

Thus, the main actions of midazolam are hypnosis, sedation, anxiolytics, anterograde amnesia, anticonvulsant and muscular relaxation.

2.1.1. Routes of administration and absorption

The resultant effects of midazolam in children under sedation for dental procedures have been studied in a number of projects, and midazolam is now the standard agent for conscious sedation during pedodontic treatments (Erlandsson et al., 2001; Jensen and Matsson, 2002; Jensen, 2002; Yanase et al., 1996; Lindh-Stromberg, 2001). Midazolam is a short-acting benzodiazepine with quick onset, shorter term of activity and negligible symptoms. The route of administration, the shorter holding up time and half-life, in combo with a level of sedation that permits medicines to be undertaken, are the primary focal points of conscious sedation with orally managed midazolam. After taken orally the peak plasma concentration is stretched within 20 min, quicker by means of the rectal course (10 min). The riddance half time is 2 h, sedative impact wears off around 45 min offering a quick recuperation (Erlandsson et al., 2001). Before the conscious sedation takes place, it is proposed, that the patient fasts as per the guidelines; no fluids 2–3 prior hours sedation and no solid sustenance or non-clear liquids 4 prior hours sedation.

The intramuscular prescribed amount (used for premedication) is 0.07–0.08 mg/kg; the intravenous measured quantity for tranquility is 0.07–0.1 mg/kg, titrated according to response; the oral amount for tranquility/drowsiness is 0.2 mg/kg. The end point for sedation is drowsiness and slurring of speech – response to commands is maintained. The bioavailability when administered by oral route is 44% and by intramuscular route is 80–100%. The drug is 96% protein-bound in the plasma; the V_D (volume of distribution) is 0.8–1.5 l/kg. The V_D may increase to 3.1 l/kg in the critically ill patients (Sasada and Smith, 1997; Butler, 2006).

2.1.2. Mode of action and effects

The mode of action of benzodiazepines (midazolam) is thought to act through specific benzodiazepine receptors found all around the central nervous system (CNS) and focal sensory system. Benzodiazepine receptors are completely joined with gamma amino butyric acid (GABA) receptors. It seems to encourage the action of the GABA initiated GABA receptors open chloride particle channels, which then either hyperpolarize or cut off synaptic film .When benzodiazepines tie to a particular site on a GABA receptor, they do not impact it straightforwardly. Rather, they make it more effective by expanding the recurrence with which the chlorine channel opens when GABA ties to its site on this receptor. The last

build in the levels of Cl-particles in the post-synaptic neuron promptly hyperpolarizes this neuron, thus, getting less edgy (Butler, 2006).

Midazolam decreases systolic blood pressure by 5% and diastolic pressure by 10% and the systemic vascular resistance falls by 15–33%; heart rate increases by 18%. Midazolam decreases the tidal volume but this is offset by an increase in respiratory rate; the minute volume is thus little changed. Apnea occurs in 10–77% when midazolam is used as an induction agent. The drug impairs the ventilation response to hypercapnia. The drug produces hypnosis, sedation and anterograde amnesia. The cerebral oxygen utilization and cerebral blood stream are diminished in a measurement related way, yet a typical relationship is kept up between the two. Midazolam decreases hepatic and renal blood flow as well (Sasada and Smith, 1997).

2.1.3. Metabolism and excretion

Midazolam is completely metabolized in the liver to hydroxylated derivatives which are then conjugated to glucuronides. Metabolites bind to CNS benzodiazepine receptors and are pharmacologically active. Excretion occurs in the urine, predominantly as the hydroxylated derivatives; renal impairment has little effect. The approval is 5.8–9 ml/kg and the elimination half-life is 1.5–3.5 h. The elimination half-life may increase to 5.4 h in the seriously critically ill patients (Sasada and Smith, 1997).

2.2. Ketamine

Ketamine is an N-methyl D-aspartate (NMDA) opponent which prompts a daze like sedation with few considerable impacts (Warner et al., 2007; Karapinar et al., 2006; Shende et al., 2003). Ketamine is a dissociative agent which makes a state of catalepsy that gives sedation, control of pain and amnesia (Rodriguez and Jordan, 2002). The significant focal points of ketamine lie in its amnestic and pain relieving activities, the relative cardiovascular steadiness and the restricted impact on the respiratory mechanics (Karapinar et al., 2006).

Ketamine is used (Sasada and Smith, 1997):

1- For the induction of anesthesia, especially in high risk patients with hypotension or asthma,
2- For short procedures it is the fundamental technique, for instance; intra-visual examinations, burns dressings and radiological and radiotherapy procedures in children,
3- As an agent for mass casualties in the field,
4- For analgesia both post-operatively and in patients receiving intensive care,
5- For pain relief from chronic pain for patients,
6- For the reversal of severe un-responsive asthma.

It portrays a white crystalline powder (a phencyclidine derivative) which is diluted in water prior to use to yielding a color-less solution that contains 10/50/100 mg/ml of racemic ketamine hydrochloride. The 50 and 100 mg/ml preparations contain 1 in 10,000 benzethoniumchloride as a preservative (Karapinar et al., 2006).

2.2.1. Routes of administration and absorption

The intramuscular dose is 10 mg/kg; the onset of action is 2–8 min and the duration of action is 10–20 min. The corresponding intravenous dose is 1.5–2 mg/kg administered over a period of 60 s; the onset of action occurs within 30 s and the duration of action is 5–10 min. Ketamine may be infused intravenously at the rate of 50 mcg/kg/min. The drug is also effective when administered orally, extradural (in an adult dose of 10 mg) or intrathecally. Ketamine is well absorbed after oral or intramuscular administration; the oral bioavailability is 20%. Ketamine is 20–50% protein-bound in the plasma; the V_D is 31/kg. The distribution half-life is 11 min; recovery is primarily due to redistribution from brain to peripheral tissues (Sasada and Smith, 1997; Malinovsky et al., 1996).

2.2.2. Mode of action and effects

Ketamine is a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptors Ca^{2+} channel pore and also inhibits NMDA receptor activity by interaction with phencyclidine binding site. It may also modulate opioid and muscarinic receptor activity. Ketamine causes tachycardia, an increase in the blood pressure, central venous pressure and cardiac output secondary to enhance sympathetic tone. It causes mild stimulation of respiration with relative reservation of airway reflexes. Bronchodilation is a feature of the action of the drug. The state of dissociative anesthesia is produced by ketamine. The cerebral blood flow, cerebral metabolic rate, intraocular pressure increased; amnesia is a marked feature. The EEG demonstrates dominant theta activity and loss of alpha rhythm. At high doses, ketamine exhibits local anesthetic properties. Post-operative nausea and vomiting are common; salivation is increased following the administration of the drug. Ketamine increases uterine tone (Sasada and Smith, 1997; Nagdeve et al., 2006).

2.2.3. Metabolism and excretion

Ketamine is converted in the liver by NDE methylation and hydroxylation of the cyclohexylamine ring. Some of the metabolites are pharmacologically active. The conjugated metabolites are excreted in the urine. The clearance is 17 ml/kg/min and elimination half-life is 2.5 h (Adamowicz and Kala, 2005).

3. Midazolam in combination with ketamine

Ketamine and midazolam have been utilized independently to encourage the sedation of painful techniques for pediatric patients (Tobias et al., 1992; Sievers et al., 1991). However, benzodiazepine sedation does not give a pain relieving impact and is deficient to anticipate suffering/distress/pain emulated by additional combative techniques for example central venous catheter insertion or bone marrow biopsy. It was demonstrated that the combo of ketamine with midazolam gave speedier onset of absence of pain and much proficient amnesia diminishing the obliged dosage of ketamine and the occurrence of delusions/deliriums/illusions and ecstasy (Beebe et al., 1992; Okamoto et al., 1992). Midazolam or more ketamine was discovered having the greatest adequacy of a blending, giving quick and satisfactory analog of sedation in edge and truculent, difficult and belligerent patients (Koirala et al., 2006).

A study (Roelofse et al., 1998) involved 100 children, aged 2–7 years, undergoing minor oral surgical procedures under the influence of anesthesia to investigate the safety and efficacy of oral trimeprazine–methadone and ketamine–midazolam for sedation. These patients were randomly assigned to two groups to receive either, a combination of midazolam (0.35 mg/kg) and ketamine (5 mg/kg) (Group A), or a combination of trimeprazine (3 mg/kg) and methadone (0.2 mg/kg) (Group B) 30 min preoperatively. Hemodynamic parameters were seen, adverse reactions were observed, and post-operative recovery and behavior were evaluated. The findings of this study proved that the number of children who were asleep, still arouse to verbal commands, 30 min. after drug administration which was more in Group A (40%) than that it was in Group B (8%).

Two children (4%) in Group A vomited. Ten (20%) children in Group A hallucinated contrasted with none in Group B. A blinded observer rated the procedure as worthy or excellent in 94% of children in Group A contrasted with 78% in Group B. Outcomes of this study strongly suggested that the mixture of midazolam and ketamine, when directed orally, is a protected, powerful, and viable methodology for the administration in youngsters for minor oral surgical procedures under the influence of local anesthesia. Both midazolam and oral ketamine fulfill a considerable lot of qualities of great predicaments. A synthesis of the two pills has been examined at different dosages successfully (Warner et al., 2007). Shende et al. (2003) conducted a twofold blind randomized clinical trial to assess adequacy of this combination in low measurement (MKL) and contrast it and the synthesis of these 2 drugs in high dosage. With the proposition of looking after the anxiolytic response to midazolam, the calming and pain relieving characteristics of ketamine with controlled side effects were observed.

Seventy two children planned to undergo ophthalmic surgery were arbitrarily doled out to one of three aggregations. Group MKH received and admixture of 0.5 mg/kg midazolam and 6 mg/kg ketamine, Group MKL accepted a mixture of midazolam (0.5 mg/kg) and ketamine (6 mg/kg), Group MKL gained midazolam 0.25 mg/kg and ketamine 3 mg/kg; control gathering accepted midazolam 0.5 mg/kg orally. Premedication was administered 30 min prior to the surgery. The blood pressure, heart rate and SpO_2 were recorded every 5 min and postoperatively. Sedation and parental detachment score were noted 10 min by doling out 1–5 focuses for nature of sedation and 1–4 focuses for parental partition. The children were watched for reaction to instigation of anesthesia, on recuperation and any antagonistic occasions related to medication post operatively. There were no critical changes in patient's blood pressure, heart rate and SpO_2.The best parental partition time was essentially lower in mixture amasses as contrasted with midazolam ($p < 0.001$). There were no noteworthy contrasts in intra-operative pethidine prerequisite, reaction to impelling of anesthesia, emergency score and postoperative sedation. The onset of preoperative sedation, and recuperation by Aldrete (Scoring System for Conscious Sedation), were fundamentally promptly in the MKL Group ($P < 0.001$). The occurrence of exorbitant salivation was essentially greater in the MKH Group ($p < 0.05$). It was observed that the consolidation of oral ketamine and midazolam in low dosages is superior to high measurements blend for preanesthetic prescription as it has a potent and quick onset of action when prescribed for pediatric patients. The overall consequence of this study suggested that oral ketamine and midazolam combination shows a synergistic impact and early recuperation.

A study by Chudnofsky et al. (2008) was conducted to assess a combination of intravenous midazolam (0.07 mg/kg) and ketamine (2 mg/kg) for procedural sedation in mature ED patients. Signs for procedural sedation included abscess (66%), fractures (26%), and others (8%). There were no instances of delirium, hallucinations, or different emergence reactions. However, eighteen (25%) patients dreamed, 12 (17%) had pleasant feelings, 2 (3%) upsetting, 3 (4%) both pleasant and offensive, and 1 (1%) not average or unsavoury. There were 3 instances of respiratory dejections, a couple of scenes of emesis, and one case of myoclonus and laryngospasm. These conditions were transient and mellow in nature, and not found to affect the disposition. No patients encountered a clinically critical ascent in pulse or B.P. rise or chest torment. A few patients (1%) did not encounter any genuine emerging responses or unfavorable impacts were unsatisfied with the sedation treatment. The normal time to achieve release criteria was 64 ± 24 min. Authors inferred that midazolam and ketamine is an excellent mixture for the purpose of procedural sedation for dental procedures in pedodontic patients.

4. Potential side effects of the sedative drugs

A study (Karapinar et al., 2006) was led to assess the levels of sedation and absence of pain acquired by ketamine–midazolam fusion in 227 pediatric patients. The patients were experiencing frightful and uncomfortable procedures outside the operating room. Sedation was started with midazolam at the measurements of 0.05 mg/kg (greatest 2.5 mg) IV to minimize the frequency of hallucinatory development responses that may be initiated by ketamine. After a 2 min perception period, sedation was further preceded with ketamine (1 mg/kg, IV introductory dosage). The effects of this study indicated that for ketamine and midazolam-based sedation absence of pain when regulated by an expert in an overall regulated setting, is protected and successful for children experiencing tormenting procedures. In spite of the fact that, conceivably serious respiratory complications happened in 4.8%, all such occasions were immediately distinguished and adequately treated by pediatric personals trained in airways management. The authors encountered apnea scenes in three patients. While apnea scenes determined with transient bag valve-mask ventilation in two kids, the other youngster required unplanned intubation. Since the presence of anesthesiologist and operation room is not obliged, this system is more savvy and proficient than general anesthesia.

4.1. Side effects of midazolam

Side effects are confined to occasional discomfort at the site of injection. Withdrawal phenomena may occur in children after prolonged infusion (Kain et al., 2000). In case of any unwanted event, antidote for midazolam (Flumazenil) can be administered intravenously (0.01 mg/kg/dose).The dose can be repeated for up to four times with an interval of one minute each (Adams and Dervay, 2012; Khalid et al., 2011).

4.2. Side effects of ketamine

Transient rashes occurred in 15% of patients receiving this drug. Emergence delirium, unpleasant dreams and hallucinations are much notable complications of the use of ketamine (VI). The hyper tonus produced by ketamine may require positioning of the patient prior to induction. Pain on injection may be alleviated by combination with lignocaine (Sasada and Smith, 1997; Webster and Walker, 2006). Transitory depression of breath and apnea was accounted for after administration of ketamine either IM or IV (Green et al., 1998a,b; Zsigmond et al., 1976). It was expressed that respiratory despondency and apnea were because of expanded concentrations of ketamine in Central Nerves system after IV bolus administration and fast assimilation of ketamine (Green et al., 1998a,b). Administration of ketamine invigorates salivary, tracheal and bronchial discharges, prompts a potential airway route hindrance, laryngospasm and tracheal aspiration of secretions. The overabundance secretions can adequately be counteracted by prior administration of an anti-sialagogue, for example, atropine or glycopyrrolate (Karapinar et al., 2006). Ketamine is a sympathomimetic agent acting by repressing re-usage of catechol amines and, consequently, can result in gentle to mild increase in blood pressure, heart rate, cardiovascular output and myocardial oxygen utilization (Krauss, 1999).

In studies examining the fusion of ketamine and midazolam (Slonim and Ognibene, 1998; Parker et al., 1997), the occurrence of serious tachycardia and hypertension was 0% and 0.6%, separately. Not with standing this favorable conclusion, ketamine ought to be utilized with extreme alert and ought to be avoided in people having uncontrolled hypertension. No reversal agents exist for sedative and dissociative agents, for example, Ketamine and patients experiencing cardiopulmonary antagnostic impacts ought to be screened and dealt with supportive care (Adams and Dervay, 2012).

5. Recommendations

Ketamine and midazolam have parallel safety profiles in the emergency setting for pediatric patients. Administration of conscious sedation was ought to be directed in a suitable setting that takes into account persistent supervision of the patient via expert and trained medical staff. Ketamine causes all the more vomiting but instead still, it is the favored agent for some dental and medical practitioners. There is a lot of data in the emergency literature to show adequacy and well-being for both agents. Ketamine–midazolam consolidations likewise may be more viable and secure than fentanyl midazolam mixes for procedural sedation and analgesia. As the evaluated studies are little, reporting of adverse events is often limited; the literary works is not strong enough to authoritatively reason and conclude that midazolam and ketamine are superior to either agent alone or used in combination with a different agent.

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