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Intranasal drug administration for procedural sedation in children admitted to pediatric Emergency Room

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Abstract. – OBJECTIVE: Pain relief is a very important aspect in Pediatrician's clinical practice. It is often thought that young children, particularly infants, do not perceive as much pain as adults because of their immature nervous system and that untreated pain would not have adverse long-term consequences. Instead, it has been demonstrated that infants and children experience pain in a similar manner to adults. Many factors, particularly emotional factors, can increase the child's pain perception. Children live with anxiety even minor procedures. This suggests the need for an adequate sedation and the way of sedation should be free of pain itself. We believe the route to be followed may be the intranasal (IN) administration of sedative drugs.

MATERIALS AND METHODS: We have conducted a brief review of the literature by Pubmed about the most commonly used sedative drugs: sufentanyl, fentanyl, midazolam, ketamine, nitrous oxide and dexmedetomidine. We have investigated in the literature the type of administration of IN drugs: drop instillation or by a mucosal atomizer device (MAD).

RESULTS: In our study, it was noted that IN drugs administration is an effective and safe method to reduce anxiety and to deliver analgesia because it is practical and non-invasive. Moreover, therapeutic levels of sedatives are low due to the presence of a rich vascular plexus in the nasal cavity, which communicates with the subarachnoid space via the olfactory nerve and reduce the time of medication delivery, that is, the onset of action. The use of MAD even gives as better bioavailability of drugs.

CONCLUSIONS: IN sedation via MAD is effective and safe and should be one of the first choices for procedural sedation in children.

Key Words:
Intranasal sedation, Procedures, Pain, Children.

Introduction

Pain relief is a very important aspect in Pediatrician's clinical practice, although it may sometimes be overlooked because pain is often underestimated in childhood. This is due to the common belief that young children, particularly infants, do not perceive as much pain as adults because of their immature nervous system and that untreated pain would not have adverse long-term consequences[1,2]. On the contrary, it has been shown that infants and children experience pain in a similar manner to adults[3]. Furthermore, high levels of pain in children may have significant neurophysiological and physiological effects[4,5]. Inadequately managed pain in children can also have detrimental psychological consequences, which can in turn lead to higher levels of pain during medical treatments. For example, emotional factors – such as elevated anxiety, distress, anger and low mood – can increase the child's pain perception and make subsequent medical procedures and pain management more difficult[6,7]. In addition, a large-scale early researche found that as many as one third of children who experienced medical procedures for diagnosis or treatment showed some evidence of subsequent psychological adjustment problems[8]. Moreover, reports of fear and pain experienced during medical procedures in childhood are predictive of fear and pain during medical procedures in young adulthood[9].

Children often live with many anxiety and anguish even minor procedures, most notably the placement of a venous access, and even more seizure control, laceration repair, dental and ophthalmologic procedures. Usually, children's fear and anticipatory anxiety increase the likelihood of experiencing more pain and distress during the actual procedures; in addition, children typically report having overly negative expectations prior to medical procedures, regardless of whether a pharmacologic or behavioral pain management intervention will be employed[10].

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This entails the need to propose not only adequate sedation but also a way of sedation free of pain itself as much as possible[11].

The benefits of providing adequate procedural sedation for children include decreasing patient anxiety and emotional trauma, decreasing parental emotional discomfort, and facilitating ease and/or completion of the procedure. A desirable sedating agent has a rapid onset with short duration of action; it is effective and safe[12].

In recent years, the use of intranasal (IN) administration of sedative drugs before performing the procedures has taken hold, because it is a practical and non-invasive route of administration. Therapeutic levels of sedatives can be reached via IN administration due to the rich vascular plexus cavity which communicates with the subarachnoid space via the olfactory nerve[13,14]. In the recent past many authors preferred IN midazolam administer by drop instillation; nowadays many studies investigate new methods such as the use of spray devices. A mucosal atomizer device (MAD, Figure 1) delivers drug via a fine spray over a broad surface area in the nasal cavity (Figure 2). It also reduces sneezing and coughing compared to other devices[15-17].

Different drugs have been used for IN sedation for procedural sedation in children; this review aims to re-evaluate this method of sedation and the drugs most commonly used for its usage.

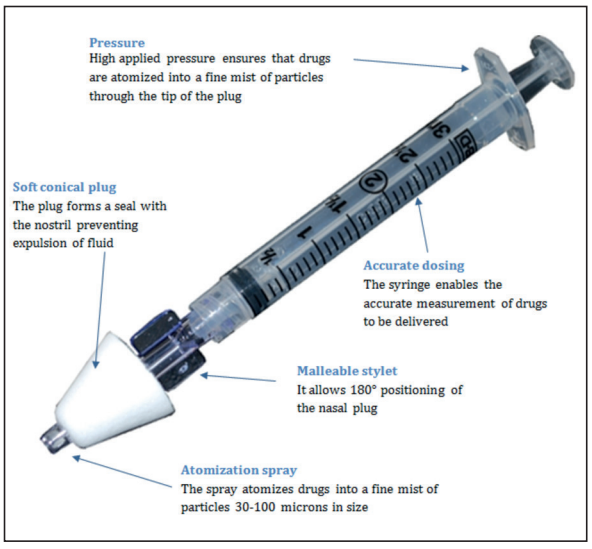

Figure 1. MAD (Mucosal Atomizer Device).

Figure 2. With the use of MAD, the drug is delivered via a fine spray over a broad surface area in the nasal cavity, favoring its absorption.

Materials and Methods

Relevant studies were identified from two sources: a key word search including intranasal, drugs, sedation, children, medication, sufentanil, fentanyl, midazolam, ketamine, nitrous oxide, dexmedetomidine; a review of the references from each identified article. We included in this review only pediatric articles.

Results

Ketamine

Ketamine is usually administered intravenously (IV) or intramuscularly (IM), but it may also be administered nasally[18]. The dose required to achieve a state of dissociative sedation in children is typically 1.0 to 1.5 mg/kg IV or 3 to 4 mg/kg IM[19]. When used nasally, the recommended administration dose is 9 mg/kg[18].

In 2001, Acworth et al[20] compared IN midazolam *vs.* ketamine IV plus midazolam IV in children requiring minor procedures, such as laceration repair or foreign body removal, in the ambulatory setting, and concluded that the combination is higher to IN midazolam alone in terms of speed of onset and consistency of effect.

In 2013, Nielsen et al[21] studied the association of ketamine with sufentanil administered IN. They did not report any serious adverse events; oxygen saturation and heart rate remained stable. The reported adverse effects were mild and

mostly related to an unpleasant bitter taste immediately after the administration of the nasal spray, which disappeared after drinking.

Midazolam

The bioavailability of IN route ranges from 50-83%[22]. It can be administered orally, nasally, rectally, IV or IM. In a randomized, double-blind, placebo control study, Shapiro et al[11] showed that midazolam spray offers relief to children anxious about minor medical procedures, such as insertion of a needle in a subcutaneously implanted intravenous port, venous blood sampling and venous cannulation. A double-blind, randomized, controlled trial conducted by Rakaf et al[22] in 2011 reported a success rate of 91% to 100% for completing dental procedures following IN midazolam administration.

The dose of intranasal midazolam used in the different studies range between 0.2 mg/kg and 0.4 mg/kg or 0.5 mg/kg[11-15]. The most common adverse effects reported following IN midazolam are burning or irritation in the nose and a bitter taste in the mouth. It can determine respiratory and circulatory depression, but these side effects are unlikely when midazolam is used as a single drug, while they increase when it is used with opioids or other sedatives. In their work, Lane et al[12] had 1/205 children who received IN administration of midazolam with an adverse event. This was a minor desaturation episode following ketamine administration requiring brief blow by oxygen. They did not find any adverse events in patients who received midazolam alone.

Sufentanil

Sufentanil has been administered IV, epidural, intrathecal transdermal and nasally. Hronova et al[24] examined children in a randomized study to receive sufentanil *vs.* placebo. Sufentanil was given as drops and patients that received the drug had less anxiety in 10 min compared to those who were given placebo. Bayrak et al[25] demonstrated that children who received midazolam administration cried more compared with sufentanil administration. Concerning sufentanil, in the past the administration route was by drops, actually many authors prefer MAD for its simplicity and accuracy of dosing. The onset of sufentanil aerosol is about 5-10 min with a maximum sedative and analgesic effect at about 20-25 min. Doses used for procedural pain was usually 0.7-1 μg/kg. It was demonstrated that the children who received sufentanil had a marked decreased ventilatory compliance during the induction of anesthesia and had a higher incidence of vomiting during the first postoperative day[24].

Nitrous Oxide and Fentanyl

Seith et al[26] administered a continuous flow of nitrous oxide of 50 to 70% via a full-face mask in association with a pre-calculated dose of 1.5 μg/kg of IN fentanyl that was administered through MAD[26-30]. A nitrous oxide alone agent has been associated with higher levels of emesis; instead, according to Seith et al[26], the association with IN fentanyl reduces the incidence of vomiting. Fentanyl is an opiate analgesic with the most evidence to support IN route. It is most used for acute pain management like orthopedic fractures or burns because it controls at relatively high doses the pain. Its usage in pediatric patients has shown comparable effectiveness with the IV administration[31].

Dexmedetomidine

Recently, some Emergency Pediatric Departments have gained a useful experience of this IN medication for short procedures in pediatric outpatient. Intranasal route is more rapidly absorbed in blood stems compared to oral form and it preserves the airway reflexes and respiratory drive[32]. Generally, this drug is administered at dose of 2-4 μg/kg. Patel et al[33] described an 11-year-old girl sedated with 2.4 μg/kg of IN dexmedetomidine who reported symptomatic bradycardia precipitating vasovagal syncope.

Discussion

IN drugs were studied to light procedural sedation and anxiety and their use include laceration repair, MRI, computed tomography scan, burn-dressing changes, dental extractions, endoscopies and accessing central venous port[34-36]. Procedural sedation is now being used in a variety of conditions, both for diagnostic purposes, such as urine sampling and lumbar punctures, and therapeutic purposes, such as intravenous insertion, wound care and orthopedic trauma[37]. Each of these medical situations deserves focused research and clinical attention, and each could serve as a referral source for assistance in reducing children's pain and suffering. Health care professionals strive to provide medical treatment while avoiding any undue pain and

suffering by the patient. Children almost always have fear even of minor procedures and their pain relief is important both for their comfort and for the success of the procedure. Furthermore, we have to consider that children who have experienced procedural pain are more likely to have increased pain during future painful procedures[10]. It can be often difficult even the use of an intravenous sedation as it involves the use of needles. For that reason, in recent years the use of the IN route is becoming more widespread as it is essentially painless and effective. In fact, without the need of finding a venous access, it allows a rapid absorption through nasal mucosa directly into the systemic circulation, avoiding fist-pass metabolism[18]. Successful IN medication delivery requires a basic understanding of delivery techniques that include minimizing drug volume and maximizing drug concentration with adequate dose of drug, with the usage of both nostrils to double the absorptive mucosal surface, with the use of MAD to enhance medication absorption[35]. Talon et al[32] and Pandey et al[38] compare the use of MAD with droplets in the nasal cavity. It was noted that drops into the nose are primarily deposited on the ciliary surface with excess runoff down the throat. In comparison, atomized particles cover more surface area and they are better distributed into the nasal mucosa, resulting in better bioavailability[39]. The advantages of atomized delivery include less drug being lost to the oropharynx, higher cerebrospinal fluid drug levels, better patient acceptability and improved sedative effects[38,40]. IN midazolam is the most commonly studied although there are many data also about fentanyl, ketamine, and sufentanil. Atomized IN midazolam and ketamine are useful also to make gastric aspirates more acceptable and easy to perform in children[41]. Midazolam at dose route of 0.4-0.5 mg/kg was demonstrated to have advantageous properties like amnesia and anxiety[12,15]. Sufentanil and nitrous oxide have a similar action of midazolam; in fact, these drugs do not control the pain but they have a sedation effect[24]. On the contrary, ketamine and fentanyl are used for their pain controlling action at the administration dose of respectively 5-9 mg/kg and 1.5-2.0 μg/kg (Table I)[18]. In literature, many authors recommend the usage of IN drugs in children to low adverse effects; in fact at recommended doses these drugs are effective and safe[33]. Recently, there is growing interest in the use of IN dexmedetomidine and several studies are showing its valuable utility for pediatric sedation in the Emergency Room[42-43].

Conclusions

IN drug administration is an effective method for delivering analgesia; in fact, it can reduce the time of medication delivery, the onset of action, the pain due to the injection, and patients' and parents' anxiety. This review has shown that the use of these drugs is effective and safe if they are administered by personnel with expertise and equipment necessary to monitor patients during and after administration (Table II). Therefore, we believe these drugs may be inserted in standard protocols to an adequate use in pediatric Emergency Department.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Table I. Drug characteristics for intranasal administration or inhalation.

Drug	Dose	Characteristics
Ketamine	5-9 mg/kg	Pain control like laceration repair. No serious side effects
Midazolam	0.4-1 mg/kg	Sedation. Adverse event is burning o irritation of mucosa
Sufentanil	0.7-1.0 μg/kg	Sedation. Decreased ventilatory compliance and increased vomiting
Nitrous oxide	Continous flow of 0-70% with mask	Sedation. Increased vomiting
Fentanyl	1.5-2.0 μg/kg	Pain control like orthopedic fractures. No serious side effects
Dexmedetomidine	2.0-4.0 μg/kg	Sedation. Symptomatic bradycardia

Table II. Comparison of the main literature.

References	Drug	Conclusions
Acworth et al[20]	Intranasal midazolam *vs.* intravenous ketamine with intravenous midazolam	The combination is higher
Nielsen et al[21]	Ketamine with sufentanil administered intranasally	Good level of sedation without serious adverse effects
Shapiro et al[11]	Intranasal midazolam	Good effectiveness in minor procedures
Rakaf et al[22]	Intranasal midazolam	Good effectiveness in dental procedures
Lane et al[12]	Intranasal midazolam spray	Good effectiveness in minor procedures in Pediatric Emergency Department
Hronova et al[24]	Sufentanil intranasal drops	Reduced anxiety compared to placebo
Bayrak et al[25]	Midazolam vs. sufentanil	Sufentanil was more effective than midazolam in reducing babies crying
Borland et al[31]	Intranasal fentanyl *vs.* intravenous morphine	Intranasal fentanyl is an effective analgesic in children with an acute fracture

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