Intranasal Midazolam Sedation in a Pediatric Emergency Dental Clinic

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The purpose of this study was to compare the effectiveness and recovery times of 0.3 and 0.5 mg/kg intranasal midazolam (INM) administered with a mucosal atomizer device (MAD) in a pediatric emergency dental hospital clinic. One hundred eighteen children aged from 4 to 6 years were randomly administered either 0.3 or 0.5 mg/kg INM via an MAD in a triple-blinded randomized controlled trial. Sedation was achieved to some degree in 100% of the sample. The pulse rate and oxygen saturation were within the normal range in 99% of the patients. A burning sensation was reported in 9% of children. The recovery time of the 0.5 mg/kg group was statistically longer than that of the 0.3 mg/kg group (16.5 vs 18.8 minutes) but the difference was not clinically significant. The findings of this study show that 0.3 or 0.5 mg/kg doses of INM resulted in safe and effective sedation. The 0.5 mg/kg dose was more effective than the 0.3 mg/kg dose in reducing anxiety.

Key Words: Intranasal sedation; Midazolam; Pediatric emergency dental clinic.

Dental extraction is an invasive procedure, especially in young children at their preoperative stages.¹ These children tend to be anxious, and sedation can be useful to manage their anxiety such that the dental treatment required by these children can be completed in a less distressing manner.¹ In South Africa, advanced sedation techniques such as intravenous (IV) sedation require the skill of anesthetists or medical doctors trained in sedation, and they are a limited resource in Africa generally.

Consequently, most of the children who present for emergency extractions in the public service in South Africa are not offered sedation because of the lack of resources and may be inadvertently psychologically traumatized. This traumatic experience may lead to

poor cooperation if dental treatment is subsequently needed. This poor cooperation may result in the dental practitioner having to resort to the use of dental general anesthesia to complete the dental treatment required by the child. Dental general anesthesia is more expensive than sedation and is a limited resource that also carries greater risks than sedation. There is a need for a solution that will allow the operator-dentist to administer a sedation technique that is safe and effective in managing mildly to moderately anxious children in an emergency dental setting so as to avoid exposing the child to any unnecessary psychological trauma. The types of conscious sedation that an operator-dentist is allowed to administer in South Africa include oral sedation (OS), inhalation sedation, and intranasal sedation (INS).

Oral sedation (OS) is relatively inexpensive, is easy to administer, and does not require the use of injections as for IV sedation. It does not require the cooperation of the child as for inhalation sedation.² However, OS has a longer duration of onset and longer recovery than the

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other routes of sedation and carries a risk of oversedation because of the difficulty in determining the appropriate dose.² This risk of oversedation necessitates the presence of an anesthetist in South Africa in the event that cannulation is required to reverse the effect of the drug. OS is not the ideal sedation technique for a busy emergency clinic where time is of the essence.

A technique that is gaining popularity for patients who cannot cooperate with IV cannulation is intranasal midazolam (INM).³ INM delivered via a mucosal atomizer device (MAD) is rapidly absorbed through the nasal mucosa into the systemic circulation.³ One major advantage of INS is the fact that it has duration of onset that is 3 times faster than that of OS.² This is due to the rapid absorption of the drug, which bypasses first-pass hepatic portal metabolism.² There is also a reduced risk of the child spitting out the medication.² Intranasal sedation is increasingly being used by anesthetists in the United States as a premedication prior to general anesthesia.⁴

INS has not been recommended in the South African Society of Anaesthesiologists pediatric sedation guidelines because of the burning sensation and bitter taste experienced by children during INM administration.⁵ However, INM enables rapid onset of sedation and provides the shortest recovery period than any other route of sedation. INM may therefore prove to be a viable route of sedation for pediatric emergency dental extractions provided the burning sensation and bitter taste can be substantially reduced or eliminated.

Dentists and health care professionals who do not have full medical doctor training are allowed to administer single drugs for sedation via all routes except the IV route provided that they have the appropriate training in basic life support and/or pediatric advanced life support.^{6,7} The use of a single drug to provide moderate sedation provides a wide margin of safety⁵ so as to deliver optimal treatment to a large number of anxious children in a pediatric emergency dental setting.

METHODS

Ethics

This study was conducted following approval by the University of Western Cape Senate Research and Ethics Committee. Parents were provided with written information sheets informing them of the scope and nature of the study and were required to provide written consent if

they agreed to allow their children to participate in this study.

Study Sample

One hundred eighteen mildly to moderately anxious children aged 4–6 years were randomly assigned into 2 groups, group A and group B, to receive INS with 0.5 mg/kg and 0.3 mg/kg midazolam respectively. All these children were healthy with a physical status classification of ASA I.

Children were not required to have fasted and were monitored with a pulse oximeter throughout the procedure.

Lidocaine 0.5% at a dose of 0.2 mg/kg was sprayed into each nostril using an insulin syringe with an MAD device. The lidocaine used for nasal anesthesia was included in the local anesthetic (LA) toxicity dose together with the lidocaine used prior to extractions.

The INM was administered into each nostril approximately 3–4 minutes later with an MAD device.

Safety

Appropriate safety equipment including suction catheters, supplemental oxygen source and ability to deliver positive pressure oxygen, oral and nasal airways, appropriate intubation equipment, emergency drugs and antagonists, vital signs monitors, and a defibrillator was immediately available.

Examiner Reliability

A pilot study with a sample of 10 patients was conducted to calibrate the examiners, and the proportion of agreement between examiners was 70%.

This randomized controlled trial and triple-blinded study involved 1 nurse who administered the INM, 1 dentist who performed the dental extractions, and 2 raters who recorded all data required.

Behavior and Anxiety Assessment

The level of sedation was assessed using the Wilson sedation scale (Table 1). The level of anxiety and behavior was rated using the Venham scale (Table 2). The Facial Image Scale (Figure 1) was used to assess

Table 1. Original Wilson Sedation Scale

Scale	Sedation Level
1	Fully awake and oriented
2	Drowsy
3	Eyes closed but rousable to command stimulation (earlobe tug)
4	Eyes closed but rousable to mild physical stimulation
5	Eyes closed but unrousable to mild physical stimulation

anxiety and mood of children before and after the extractions.

Statistical Analysis

The data were entered into Microsoft Excel and analyzed with the R program.

RESULTS

The mean body mass index of both groups was in a range of 14–16 and did not influence the effectiveness of either the 0.3 or the 0.5 mg/kg dose of INM ($P = .131$). Age and gender also did not affect the anxiety and behavior of the children in this study.

Pulse Rate

The pulse rates of both the 0.3 mg/kg and 0.5 mg/kg groups are illustrated in Figure 2. The final pulse rate was significantly different between groups ($P = .029$), with mean values of 115 in group A and 108 in group B respectively (Figure 2).

The oxygen saturation is also illustrated in Figure 2. Only 1 child presented with an oxygen saturation of 90% in the recovery stage, which was clinically significant (Figure 2). The final oxygen saturation rate was not significantly different ($P = .5$), with mean values of 98.53 in group A and 98.69 in group B.

Table 2. Venham Anxiety/Behavior Scale

Scale	Behavior
0	Total cooperation
1	Mild, soft verbal protest or (quiet) crying
2	Protest more prominent; both crying and hand signals
3	Protest presents real problem to dentist
4	Protest disrupts procedure
5	General protest, no compliance or cooperation

Sedation

The Wilson sedation scores revealed that 97% of children in the study presented with a sedation scale rating of 2 (patient drowsy) and only 4 children (3.4%) displayed a sedation scale rating of 3 (patient's eyes closed but rousable to command).

Anxiety

The level of anxiety experienced during the administration of INS is illustrated in Figures 3 and 4. A comparison of the anxiety levels between the 2 doses of INM administered showed that they were not statistically different.

Behavior Scores

Behavior scores during INS administration, LA, and extractions for 0.3 and 0.5 mg/kg INM are illustrated in Figures 5 and 6, respectively. The behavior scale scores between the 2 doses revealed a significant difference ($P = .04$) during the administration of the LA and when extractions were performed ($P = .03$). The higher dose of 0.5 mg/kg produced lower behavior scale scores than the 0.3 mg/kg dose for both the LA and extraction phases of treatment (Figures 5 and 6).

Figure 1. Facial Image Scale.

Figure 2. The pulse rate and oxygen saturation of children sedated with 0.3 and 0.5 mg/kg intranasal midazolam.

INS Acceptability

The level of anxiety during INM is illustrated in Figure 7.

groups respectively. This was not statistically significant ($P = .34$).

Time of Procedure

The times of the procedure from the administration of the INM to the extraction(s) being performed were 35.21 and 36.45 minutes in the 0.3 mg/kg and 0.5 mg/kg

Recovery Time

The recovery time recorded from the end of the extraction procedure until the patient was discharged was 16.5 minutes in the 0.3 mg/kg dose group and 18.8 minutes in the 0.5 mg/kg dose group.

Figure 3. Anxiety scale scores during administration of 0.3 mg/kg intranasal midazolam.

Figure 4. Anxiety scale scores during administration of 0.5 mg/kg intranasal midazolam.

A small statistically significant difference exists between the 2 doses, as the Welch test produced a *P* value of .04 but the Wilcoxon rank sum test revealed a *P* value of .098.

A modified Aldrete discharge score was used to assess discharge time. In addition to the standard Aldrete scores, body temperature and pain were also assessed. A score of 12 out of 12 was required in order for the patient to be discharged, and the child was assessed every 15 minutes until this score was reached. A comparison between the 2 dose groups was analyzed using the chi-square and Fisher exact tests. The chi-square *P* value was .04 and the Fisher exact *P* value was .03, making this comparison statistically significant, with a higher proportion of patients achieving a discharge score of 12 sooner in the 0.3 mg/kg group.

Side Effects

The side effects experienced by patients due to the INS are as follows: none, 42%; swallowed drug, 30%; sneezing, 12%; burning sensation, 9%; coughing, 4%. One child experienced a dull aching pain in the head for a few minutes and 1 child presented with hiccups for a few seconds.

DISCUSSION

The results of this study revealed that all children who received either the 0.3 mg/kg or 0.5 mg/kg dose of midazolam displayed some level of sedation, although some children were less cooperative than others. Hence the use of the 0.3 mg/kg or 0.5 mg/kg dose of midazolam resulted in the safe and effective manage-

Figure 5. Behavior scores of children sedated with 0.3 mg/kg intranasal midazolam during the different phases of treatment.

Figure 6. Behavior scores of children sedated with 0.5 mg/kg intranasal midazolam during the different phases of treatment.

ment of anxiety levels in children aged 4–6 years, as evident from the results of anxiety and behavior levels. The sedative effect of the 0.3 and 0.5 mg/kg doses of midazolam effectively decreased the children's levels of anxiety and level of movement in order to allow for the extractions to be performed successfully. Midazolam was selected for use in the INS route because it provides some degree of amnesia, it has a short duration of action, and its sedative effect can be quickly and easily reversed.⁸

The amnestic property of midazolam allows the child to forget about the unpleasant experience so as to allow future dental treatment to be a positive experience, thereby allowing the child to achieve improved oral health.⁹ We did not study amnesia, but amnesia is a common effect of midazolam.⁸ Amnesia is preferable in young children undergoing unpleasant procedures such as dental extractions, as most extremely anxious children experience psychological trauma in their first dental appointment.^{8,10}

Figure 7. The level of anxiety during INM.

The level of sedation among children varied after INS administration. The reason for this variation could be the midazolam solution's either being swallowed or being expelled during sneezing after INS administration. It is possible that the bioavailability of the drug decreased during swallowing and sneezing and thus resulted in different onset times being recorded. The quick onset and rapid effectiveness of INM were due to the rapid absorption of the INM as it bypasses the hepatic portal circulation with rapid nasal mucosal absorption and probable absorption through the cribriform plate to the brain and cerebrospinal fluid.² INS allows for the highest bioavailability of the drug after the IV route. INS results in a quick onset of sedation and quick recovery more similar to IV sedation than to OS. This makes INS a preferred sedation technique for use in an emergency setting.¹¹

The lowest levels of anxiety (85%) and improved behavior (81%) were detected prior to LA and extractions, whereas the highest levels of anxiety and undesired behavior were detected during INS, LA, and extractions. The high levels of anxiety were probably due to the discomfort of the INM during the administration; the pain experienced during the LA injections, specifically the palatal injections; and the pressure experienced during the extraction procedure. Also, Salem et al¹⁰ reported that a previous painful experience such as an LA injection creates a negative memory associated with fear and psychological trauma, and this experience could possibly exacerbate pain sensations.

A higher percentage of children (22%) achieved a relaxed and calm state and cooperated well during all stages of treatment with the 0.5 mg/kg dose, whereas only 9% of children achieved a relaxed and calm state with the 0.3 mg/kg dose of INM. This confirms that the 0.5 mg/kg dose produced greater anxiolysis than the 0.3

mg/kg dose. The duration of the treatment between the 2 groups is comparable to those of similar studies.^{11,12}

The recovery time recorded for the children who were administered the 0.5 mg/kg dose was statistically significantly longer, with a difference of 2.3 minutes (16.5 vs 18.8 minutes, $P = .03$) in comparison to the 0.3 mg/kg dose. This, however, was not considered as being clinically significant, as the difference of a few minutes with the 0.5 mg/kg dose did not slow the flow of patients in the emergency clinic. In light of the fact that the 0.5 mg/kg dose resulted in a decreased level of anxiety and better behavior scores than the 0.3 mg/kg dose, it can be considered as being the more suitable dose in a pediatric emergency dental clinic.

Safety

Safety is the primary goal in sedation, and the use of a pulse oximeter is compulsory to monitor the pulse rate and oxygen saturation.⁶ The pulse rates of the children in this study were monitored throughout the procedure and charted before and after sedation, with both dose groups being within the normal range.

The mean pulse rate was lower in the 0.5 mg/kg group (108) in comparison to the 0.3 mg/kg group (115). However, the mean values of pulse rates of both groups were within a normal range for children aged 4–6 years.¹³ The pulse-oximeter readings revealed oxygen saturation levels above 95% at baseline and after treatment. Only 1 child desaturated briefly for 3 minutes with an oxygen saturation value of 90% and presented with snoring. The initial management of this event of desaturation was to stimulate and rouse the child in order to increase the muscle tone and prompt breathing.⁶ This maneuver normalized the oxygen saturation immediately to above 95%. There were no cases that required respiratory support or emergency intervention. However, in the event that emergency intervention is required, the majority of sedation complications can be managed with simple maneuvers, such as supplemental oxygen, opening the airway, suctioning, and bag-mask-valve ventilation.⁶

It is mandatory for operator-sedationists using INS to have the appropriate basic life support or pediatric advanced life support certification in order to provide the appropriate resuscitation intervention if required.⁵ Operator-sedationists in emergency dental clinics can safely and effectively administer single-drug INS for children between the ages of 4 and 6 years, particularly if this type of sedation is administered in a hospital setting.⁶ Furthermore, it is compulsory that the sedated patient's pulse rate and

oxygen saturation are monitored with a pulse oximeter and all appropriate resources are available for patient recovery.⁶

In the event that an adverse event occurs and reversal of INM is required, the benzodiazepine antagonist flumazenil is recommended.¹⁴ Although flumazenil is currently registered for use as an IV preparation,¹⁵ it may also be utilized as an intranasal preparation via an MAD at a recommended dose regimen of $40 \mu\text{g} \cdot \text{kg}^{-1}$.¹⁴ Scheepers et al¹⁴ reported that the mean plasma concentrations of flumazenil administered via a syringe intranasally were similar to plasma concentrations of flumazenil administered IV. This dose regimen was also used by Heard et al,¹⁶ who administered 1 mL ($100 \text{ mcg} \cdot \text{mL}^{-1}$) per opening of the nares to effectively reverse the effect of midazolam. The patients in the study by Heard et al¹⁶ were then required to be observed for at least a 2-hour period following the administration of intranasal flumazenil in order to observe for any episodes of re-sedation. A 2-hour period of observation is recommended following the administration of intranasal flumazenil.¹⁶ The use of intranasal flumazenil allows for delivery of the benzodiazepine antagonist in a quick and easy manner resulting in a successful outcome.^{14,16} The intranasal form of flumazenil can be administered by the operator-sedationist. The use of intranasal flumazenil will, however, be dependent on regulations governing the use of intranasal flumazenil in each specific country. Irritation of the nasal mucosa is possible.

Although there are some published reports on the effective use of intranasal flumazenil, more research is required before this technique can be recommended without reservation.

Preoperative fasting cannot be planned in emergency medical and dental settings.⁶ In order to ensure the safety of those who are unable to fast, a balance is required between depth of sedation and the possible risk.⁶ Sedation that does not require the child to fast is appropriate for these types of settings.⁶ The guidelines of countries might differ on fasting requirements for INS, and it is imperative that the appropriate guidelines be followed for the region in which the dentist practices. In this study there was minimal risk of aspiration, as the children's protective reflexes were maintained throughout the treatment as moderate sedation was the achieved level of sedation in all participants. This level of sedation was acceptable to carry out the treatment required based on our ability to complete treatment on all patients with reasonable behavior. The INS, with doses of 0.3 and 0.5 mg/kg midazolam, is a suitable technique for use in an emergency medical or dental hospital setting.

Side Effects

The only drawback of the administration of INS is that a burning sensation of the nasal mucosa has been reported in children.² Midazolam is an anxiolytic but does not have analgesic properties, so LA to anesthetize the nasal mucosa prior to INS is beneficial. Chiaretti et al¹⁷ conducted a study using INS with midazolam with prior administration of an LA spray (lidocaine) in order to anesthetize the nasal mucosa prior to INM administration and reported that there was no burning sensation experienced in 100% of their sample. This motivated the researchers in this study to include an LA (lidocaine) to anesthetize the nasal mucosa prior to INS in order to avoid the unpleasant burning sensation. According to the findings by Wood,¹¹ 43% of children experienced a burning sensation, in comparison to 9% in this study. The lidocaine used in the study by Wood¹¹ was given with the midazolam, as opposed to this study, where lidocaine was given 3–4 minutes prior to INS so as to anesthetize the nasal mucosa and avoid the burning sensation. The low concentration of midazolam (5 mg/mL) used in this study results in a larger volume, which inadvertently passes through the oropharynx and makes contact with the tongue, causing the bitter taste.¹¹ The concentrated formulation of 4 g/mL used in the study by Wood¹¹ effectively decreased the likelihood of midazolam being swallowed through the nasopharynx and resulted in 57% acceptability, in comparison to the 35% acceptability of INM in this study. Hence, a concentrated dose of midazolam such as 25 mg/mL or 40 mg/mL with lidocaine may avoid the burning sensation and bitter taste produced with the INM. It may also preferable to use a more concentrated 10 mg/mL lidocaine rather than the 5 mg/mL prior to INS to avoid the experience of a burning sensation.

Limitations of the Study

A control group was not included in this study, and therefore the researchers could not assess how many children would have displayed minimal or no anxiety without INS.

The use of the diluted dose of 5 mg/mL INM may have decreased the effectiveness of the midazolam, as more may have been swallowed rather than absorbed through the nasal mucosa than had a higher concentration/lower volume been used. The use of a low concentration of 0.2 mg/kg intranasal lidocaine may have also contributed to 9% of children experiencing a burning nasal sensation that was not associated with INM.

CONCLUSION

The operator-sedationist model using INS with 0.3 mg/kg or 0.5 mg/kg midazolam resulted in safe and effective anxiolysis for emergency dental extractions in children between 4 and 6 years old who did not fast. The 0.5 mg/kg dose was more effective than the 0.3 mg/kg dose in reducing anxiety and improving the child's behavior. The recovery time of the 0.5 mg/kg dose was slightly more than that for the 0.3 mg/kg dose, but this did not impede the patient flow in the pediatric emergency dental clinic and is recommended for use in emergency medical and dental hospital settings.

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