Title: Nasal Midazolam for Sedation in Pediatric Patients Prior to Invasive Procedures: Clinical Safety and Effectiveness

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Context and policy issues:

Midazolam is a benzodiazepine and it has been used for pre-induction of anaesthesia in paediatric patients. It can be given by different routes, such as oral, rectal, intramuscular, and intravenous. Because of the issues around pain and co-operation, routes of administration that do not involve injection should be explored as alternatives. Oral and rectal application of midazolam are widely used in children; however, the first pass hepatic metabolism results in a low and unpredictable systemic availability, and furthermore, either spitting out or immediate defecation may prevent the use of oral or rectal routes.

There is an increasing interest in intranasal midazolam in children undergoing pre-anesthetic sedation and short surgical procedures. The nasal route provides direct access to the systemic circulation, and may be an attractive (needle-free) alternative to invasive administrations. The bioavailability of nasal midazolam is 60% higher than the oral route (15-45%) or the rectal route (40-50%). On the other hand, nasal administration may lead to unwanted systemic effects such as respiratory depression and anaphylactoid reaction, may irritate the mucosa or cause pain and be ineffective if secretions are abundant. Health Canada has approved the use of intravenous and intramuscular administrations of midazolam as a premedicant, sedative and anesthetic agent, but not the oral, rectal, or intranasal midazolam. In this report, the safety and clinical effectiveness of intranasal midazolam are examined in preschool children.

Research questions:

What is the clinical safety and effectiveness of using nasal midazolam for sedation prior to invasive procedures in pediatric patients?
Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 1, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and February 2008, and are limited to English language publications only. No filters were applied to limit the retrieval by study type.

Summary of findings:

Five randomized controlled trials (RCTs) and one non-randomized trial were identified. No health technology assessment report, systematic review or meta-analysis, or clinical practice guideline was identified on nasal midazolam as pre-medication in preschool children.

Intranasal midazolam was compared to oral midazolam in one RCT, compared to intramuscular midazolam in two RCTs and compared to ketamine in two RCTs. In addition, intranasal midazolam was compared to general anesthesia in one non-randomized trial. The dosage of intranasal midazolam was 0.2-0.3mg/kg body weight. Details of the five RCTs are summarized in Table 1.

All RCTs were small trials of poor quality. Although the five studies labeled themselves as a RCT, none of them provided details on how the participants were randomized. In addition, the operators who assessed patients’ status were blinded to the administration routes only in two studies; whereas in three others, this information was not reported, or the operator had prior knowledge of which premedication route had been used - this could have compromised the data accuracy since these were subjective ratings of the operator. Only one study recorded drug-related adverse events.

In Lee-Kim et al.’s study, intranasal midazolam was compared to oral midazolam in pediatric dental patients, to evaluate the drug effect on behavior, time of onset, maximum working time, efficacy and safety. The Houpt’s behavior rating scale was used to examine the patients’ behavior; a higher score represents a better outcome. The results showed that the mean onset time was approximately three times faster with intranasal administration compared to oral administration. Mean working time was approximately 10 minutes longer with the oral administration than it was with the intranasal administration. Overall behavior in the two groups was similar. However, more movement and less sleep were shown in patients with intranasal midazolam than those with oral midazolam toward the end of the dental session. All vital signs (oxygen saturation, heart rate, respiratory rate, blood pressure) were stable throughout the procedures and showed no significant differences between oral and intranasal administration.

Lam et al. conducted a randomized trial to compare intranasal versus intramuscular midazolam in children who received dental treatment. In their study, changes in behavior were evaluated by the modified Houpt’s rating scale. The mean ratings for the behavioral parameters of sedation level, degree of movement, and degree of crying were consistently higher, which means better sedative effect in the intramuscular midazolam group at all assessment timepoints. Intramuscular midazolam was found to be statistically more effective in providing a better sedation level and less movement at the time of venipuncture than intranasal administration. Their findings suggest a tendency for intramuscular midazolam to be more effective as a premedication.
The Gharde study\textsuperscript{11} compared intranasal midazolam with intranasal ketamine, and used a bispectral (BIS) index to quantify the hypnotic effects of anaesthetic drugs. The BIS ranged from 100 (awake) to 0 (isoelectric electroencephalogram). A 4-point scale to assess level of sedation and ease of separation from parents was used as well and higher scores indicated a better outcome. The authors found that sedation was good in patients who received midazolam as premedication, while the scores of sedation and separation were excellent in patients who received ketamine. Their conclusions were that intranasal ketamine is better than intranasal midazolam.

In the Shashikiran’s trial,\textsuperscript{10} 40 uncooperative children aged 2-5 years were enrolled. The efficacy and safety of intranasal midazolam and intramuscular midazolam were compared in these young patients attending a dental clinic. A modified Houpt’s rating scale was used to assess the changes in behavior; five self-designed, dichotomized scales were used to record any adverse reactions. Both groups matched each other in their efficacy and safety profiles, however, the intranasal route showed a significantly faster pharmacodynamic profile in terms of faster onset, peak and recovery times. The authors concluded that midazolam could be safely and successfully employed by intranasal and intramuscular routes for pediatric conscious sedation in a routine dental setup at a dose of 0.2mg/kg body weight, and the intranasal route is preferable when the clinical situation warrants a faster action, peak and recovery time.

Gautam and coworkers evaluated the efficacy of intranasal midazolam against ketamine in 50 children scheduled for elective surgery.\textsuperscript{12} There were significant differences between time of separation from a parent in two groups, but no difference in sedation scores at intravenous insertion between groups. This study indicated that in 1-6 year old children, intranasal ketamine (5mg/kg) was more effective than intranasal midazolam (0.2mg/kg) for easier separation of children from their parents, and the two drugs were both effective in obtunding children’s response to intravenous line insertion.

Finally, the effectiveness of intranasal midazolam was compared to general anesthesia among 74 children with congenital nasolacrimal duct obstruction undergoing probing.\textsuperscript{13} Their ages ranged from six to 48 months. Thirty-three patients in the general anesthesia group were given oxygen-nitrous oxide and sevoflurane via a face mask, while a dose of 0.3mg/kg of intranasal midazolam was given to another 44 patients. The success of the probing was determined by asking the parents whether the symptoms resolved. Results showed that for children aged six to 36 months, the success rates were 80% in the general anesthesia group and 88.9% in the midazolam groups (p>0.05); for children aged 36 to 48 months, the success rates were 20% and 25% in the two groups, respectively (p>0.05). There was no significant difference between the two groups with respect to the success rates when the two age groups were combined, 60% in the general anesthesia group and 77% in the midazolam group (p>0.05). The authors did not observe any instances of respiratory depression or oxygen desaturation below 96%. None of the patients required supplemental oxygen and there were no other complications. Their conclusions were that probing under topical anesthesia with intranasal midazolam was safe and comparable in effectiveness to probing under general anesthesia but with less risk.
Table 1: Details and results of randomized controlled trials on nasal midazolam in children

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<tr>
<th>Study</th>
<th>Population, Intervention/comparators, number of patients</th>
<th>Results</th>
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| Lee-Kim et al., 2004⁸  | Children 24-72 months with early childhood caries, ASA I (medically healthy) or II (well-controlled systemic disease), and in need of 1 or more dental visits for comprehensive dental care | Onset time (mean±sd): Oral MID: 15.5±5min
IN MID: 5.55±2.2min
p=0.000
Working times (mean±sd): Oral MID: 38.1±7.58min
IN MID: 29.3±11.6
p = 0.007
No statistical difference for overall behavior (p=0.749); however, more movement (p=0.038) and less sleep (p=0.019) were shown in subjects with IN MID than those with oral MID toward the end of the dental session.
No significant differences in vital signs, p=0.595. |
| Lam et al., 2005⁹       | Children aged 2-9 ys scheduled for restorative dental treatment under intravenous sedation, ASA I | Sedation level (at 10min after drug administration, parental separation, papoose board, nitrous oxide nasal hood, local anesthetic, or initial venipuncture): IM MID: 2.00, 2.08, 2.08, 2.00, 1.92, 2.00; IN MID: 1.82, 1.64, 1.64, 1.64, 1.54, 1.45. (p<0.05 for the last two timepoints)
Degree of movement at the above six timepoints:
IM MID:3.08, 3.17, 3.17, 3.17, 3.17, 3.17;
IN MID: 3.00, 3.00, 2.91, 3.00, 2.82, 2.55. (p<0.05 for the last timepoint)
Degree of crying at the above six timepoints:
IM MID: 4.00, 3.90, 3.80, 3.67, 3.42, 3.42;
IN MID: 3.80, 3.55, 3.40, 3.18, 2.63, 2.73. (no significant difference between groups, p value not provided) |
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<td>Gharde et al., 2006&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Children aged 1-10ys with tetralogy of Fallot, and scheduled for elective corrective surgery</td>
<td>BIS (mean±sd): KET: from 98.2±0.4 at baseline to 96.7±0.7 at 30min (p&lt;0.05) MID: from 98.4±0.5 at baseline to 87.3±1.1 at 30min (p&lt;0.05) Significant differences between groups (p&lt;0.05). Sedation score (mean±sd) at 30min (1=agitated; 2=awake; 3=drowsy; 4=asleep): KET: 3.75±0.44 MID: 3.25±0.44 Significant differences between groups (p&lt;0.05) Separation score (mean±sd) at 30min (1=poor; 2=fair; 3=good; 4=awake excellent): KET: 3.90±0.28 MID: 2.90±0.31 Significant differences between groups (p&lt;0.05)</td>
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<td>Shashikiran et al., 2006&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Uncooperative children aged 2-5 ys attending a pediatric dental clinic and whose treatment necessitated the administration of a local analgesic injection.</td>
<td>Both groups showed highly significant decrease in the crying levels, motor movements and sensory perception levels, and a highly significant improvement in the overall behavior between the pre-sedation and post-sedation scores (p&lt;0.001). No statistical significant differences were found between IM MID and IN MID regarding the post-sedation outcomes and overall improvement in behavior. Onset, peak and recovery times: IN MID consistently proved to be faster than IM MID (p&lt;0.001) IM MID: 2 (10%) showed sneezing/coughing/hiccoughs; IN MID: 6 (30%) showed sneezing/coughing/hiccoughs. (no significant difference between groups, p value not provided) The cardio-respiratory profiles of both groups showed good stability and no significant</td>
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Nasal Midazolam for Sedation

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<td>Gautam et al., 2007¹²</td>
<td>Children aged 1-6 ys scheduled for elective surgery, ASA I and II</td>
<td>Sedation score assessed at the time of separation from parent and insertion of intravenous line: MID: G₀ 3(12%), G₁ 6(24%), G₂ 16(64%) KET: G₀ 3(12%), G₁ 7(28%), G₂ 15(60%) p=0.332 Time of separation from parent (mean±sd): MID: 17.12±4.12min KET: 15.68±11.62min p&lt;0.001 *G₀ – no sedation; G₁ – mild sedation; G₂ – good sedation</td>
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ASA – American Society of Anesthesiologists; IN – intranasal; IM – intramuscular; MID – midazolam; KET – ketamine; y – year; mon – month; min – minute; BIS – bispectral; SD – standard deviation

Limitations

- The available evidence regarding effectiveness of intranasal midazolam as compared to the alternatives is limited. No health technology report, systematic review, or clinical practice guideline was identified.
- The included RCTs were of poor quality, in that the method of randomization was unclear. In addition, the operators were not blinded to the administration routes in the majority of these studies.
- Patients’ characteristics (except age) in the two groups were not reported in the non-randomized trial, so it’s uncertain that patients in the two comparison groups were with similar baseline conditions.
- Adverse events were poorly reported in the included studies. This does not allow us to sufficiently examine the drug-related adverse events.
- Only English-language studies were included in this report.

Conclusions and implications for decision or policy making:

When comparing intranasal midazolam to intramuscular midazolam, results from the two studies were not consistent. One stated that intramuscular routes was significantly more effective in providing a better sedation level and less movement at the time of venipuncture, while another stated that all the efficacy and safety profiles were similar between groups, but the intranasal route had faster onset, peak and recovery times. The effectiveness of intranasal midazolam as compared to intramuscular midazolam is uncertain.
When comparing intranasal route to oral route, results from one study indicated faster onset time in the intranasal midazolam group, but longer working time in the oral midazolam group. Patients in the intranasal midazolam group showed significantly more movement and less sleep during the procedures.

When comparing intranasal midazolam to ketamine, results from the two studies both favored ketamine, showing a higher level of sedation and ease of separation from parent, and shorter time of separation.

When comparing intranasal midazolam to general anesthesia, results from one non-randomized trial concluded that midazolam was safe and had comparable effectiveness as general anesthesia in inducing sedation.

Severe adverse reactions related to the use of intranasal midazolam, such as respiratory depression, respiratory arrest, cardiac arrest, bradycardia and ataxia, and minor adverse reactions such as urticaria, nausea, vomiting and local reactions (burning and irritation) were reported in other reports, however, these adverse events were not assessed, or not reported in the five studies that were included in this report. One of the included studies that reported on the adverse events of midazolam found that the intranasal route of administration of midazolam was not related to serious adverse events and only minor adverse events were reported. This could be attributed to the inclusion criteria of these studies – the majority of the participants were healthy children that were scheduled for elective surgery. All the patients had stable vital signs and good cardio-pulmonary functions. Intranasal midazolam appears to be a safe drug when used as premedication in this study population.

In conclusion, intranasal midazolam is effective in pre-induction of anaesthesia in preschool children, and it appears to be safe, when compared to the available alternatives. Each route of administration of midazolam has some drawbacks. When choosing the optimal routes for pediatric patients, several factors are under consideration: ease of use, reliable administration, minimal adverse effect, the patient’s age, history of underlying illness, and length of the procedure.

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