⊞ ORAL MEDICINE

The effectiveness of topical lidocaine in relieving pain related to intranasal midazolam sedation: a randomized, placebo-controlled clinical trial

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Objective: Intranasal midazolam (INM) is an increasingly popular agent for sedation in the emergency department and outside the hospital in physician, imaging, and dental offices, to facilitate diagnostic and minor surgical procedures and avoid the need for an operating room and general anesthesia. The use of INM has been commonly associated with a burning sensation of the nasal mucosa. Despite its significance, this subject has received little adequate research focus. The objective of the current study was to evaluate the effectiveness of topical lidocaine in relieving pain related to INM administration. **Method and materials:** This was a blinded, randomized placebo-controlled trial. Sixty-three uncooperative children undergoing dental treatment, aged 4 to 11 years, were randomly assigned to one of three groups to receive the drug nasally via a precalibrated spray as per the following assignments: group A received 0.5 mg/kg midazolam, group B received lidocaine 2% prior to 0.5 mg/kg midazolam, and group C received saline 0.9% (placebo), 0.5 mg/kg. Children were asked to record the degree of pain using the Wong-Baker faces scale. Parental acceptance was also rated. **Results:** Topical lidocaine prior to INM administration reduced the burning sensation in the nasal mucosa and improved the drug acceptance. The median score of pain was 8, 1, and 4 in groups A, B, and C, respectively. The differences among the three groups were statistically significant ($P > .05$). The children's acceptance and parents' future acceptance regarding the intranasal drug administration was significantly higher in group B. **Conclusion:** INM administration results in burning sensation in the nasal mucosa with high levels of pain. Using topical lidocaine 2% counteracted the burning sensation and achieved a higher acceptance rate and lower pain scores. *(Quintessence Int 2020;51:162–167; doi: 10.3290/j.qi.a43223)*

Key words: burning sensation, children, intranasal, lidocaine, midazolam

Successful dental treatment is closely related to the degree of patient cooperation and acceptance of procedures without resistance, fear, or anxiety. Simple behavior management methods can be used in some cases, but that may not work with patients who are more anxious or need invasive procedures. Moderate sedation should be used in such cases to increase compliance of patients and alleviate procedural anxiety. Uncooperative and anxious patients tend to experience more pain and distress when undergoing dental procedures[1,2] due to their fear and negative expectations of the procedure.[3] This suggests the need for a method that may better achieve adequate sedation and anxiolysis.

Intranasal midazolam (INM) sedation has been prescribed as an effective and safe approach to reduce anxiety and emotional trauma, and facilitate completion of the procedure in both pediatric medicine and dentistry.[4,5] However, its administration causes a sensation of burning as well as irritation in the nasal mucosa.[6,7]

One descriptive study that examined the use of lidocaine with INM for procedural sedation in children showed that premedication with lidocaine spray counteracted the nasal discomfort resulting from INM administration, but this study was neither blinded nor had a control group.[8] In 2016, Smith et al[9] examined administrating lidocaine before INM administration;

their blinded placebo-controlled trial was performed in the emergency department (ED). It thus became necessary to perform such a study outside the ED relative to patients who needed dental procedures. To the authors' best knowledge, this is the first clinical, blinded, and controlled trial to date that has established administrating lidocaine 2% spray prior to INM to sedate uncooperative children receiving dental treatment.

Method and materials

Study design

This trial was randomized, parallel, and placebo-controlled. Written informed consent was obtained for all the participants.

This study involved 63 uncooperative children, aged 4 to 11, who visited the Department of Pediatric Dentistry from June 2017 to January 2018.

The current research protocol was approved by the Institutional Review Board (no. 1521) of Tishreen University.

The sample size was calculated for three independent groups using G*Power software (version 3.1.9.2-2014, Heinrich Heine University Düsseldorf), which showed that 63 children was a sufficient size to get an alpha error of 5% and a study power of 0.80.

Children were included in the study if they had been uncooperative and scored 1 or 2 on the Frankl scale.[10] All the study participants enjoyed good health and had no medical history of neurologic or cognitive alterations. Moreover, they did not suffer from any facial deformities, were deemed fit under ASA (American Society of Anesthesiologists) classification grade 1,[11] and required dental treatment under local anesthesia. Participants with a known allergy to midazolam or any other benzodiazepines, and those who suffered from upper respiratory tract infection with nasal discharge were excluded.

Study protocol

Prior to the procedure, parents were provided with information about the risks and benefits involved in having their children take part in the study, as well as the possible burning sensation that may occur in the nasal mucosa following administration, and they were required to sign an informed consent form. Children who met the inclusion criteria were enrolled in the study.

Before the administration of the drug/drugs, the Wong-Baker faces scale (WBFS)[12] was explained by the first assistant to ensure that the participants understood how to use the scale well to describe the pain they experienced.

Patients were randomly assigned to one of three groups (21 children in each group) to receive the study drugs nasally via a precalibrated spray of 0.2 mL per puff:

- group A received 0.5 mg/kg midazolam, with a maximum dose of 10 mg
- group B received a puff of lidocaine 2% in each nostril; after 60 seconds, they received 0.5 mg/kg midazolam, with a maximum dose of 10 mg
- group C received saline 0.9% (placebo), 0.5 mg/kg, with a maximum dose of 10 mg.

The drugs were administered in a similar fashion within the three groups, alternating between the two nostrils of the child.

The midazolam used in the current study was in formulation of 5 mg/mL for intravenous and intramuscular injection in a dosage of 0.5 mg/kg with a maximum dose of 10 mg (2 mL). Lidocaine spray was used topically due to its low toxicity profile and rapid onset,[13] in light of the British Thoracic Society's recommendation to use 1% to 4% lidocaine spray as a topical upper airway anesthesia,[14,15] and lidocaine 2% was used proportionally to how much an extra dosage of the drug might have been required to perform local anesthesia during the dental procedure. The latter's toxicity was calculated and factored in as well.

For randomization, the 63 patients were assigned to the three groups as per a randomization chart. In order to conceal the allocation sequence, group identifiers were included in sealed envelopes with session numbers identical to those assigned to patients by the randomization chart. The envelopes were kept at the Department of Family and Community Medicine. On session day, the envelope corresponding to a patient number was handed to the second assistant, who calibrated the identified drug(s) proportional to the child's weight before drug administration.

The drug was given in the presence and with the assistance of the participants' parents, so if the child was not willing to accept the drug, physical restraint could be exercised by the parent if necessary. Immediately following the administration, the first assistant, who was blinded to the drug and did not participate in the administration, asked the child to record the score of pain on WBFS.

Ten minutes after drug administration, the child was moved to the dental chair, and the clinician started dental treatment under local anesthesia using rubber dam.

Since the clinician was also blinded to the drug and not aware whether the patient was sedated or not (placebo), non-pharmacologic behavior management techniques were applied with all patients.

Fig 1 Wong-Baker faces pain rating scale.[16,17] ©1983 Wong-Baker FACES Foundation. Used with permission from www.WongBakerFACES. org. Originally published in Whaley and Wong,[31] © Elsevier.

Patients whose treatment was not completed due to lack of cooperation were scheduled to another dental appointment to provide treatment under sedation out of the study scope.

The child's acceptance of the drug was rated as follows:

- Good: when the drug was administered without any resistance or rejection
- Adequate: when the drug was administered with some verbal resistance
- Poor: when the drug was administered with mild crying and controllable movement
- Worse: when the child showed a violent movement and crying, and drug administration was possible only after physical restraint by parents.

After the dental treatment was finished, the parents were asked to answer a yes/no question: would they like to have a similar experience if their uncooperative child needed dental treatment in the future?

Measures

Children were asked to record the degree of pain associated with the process using the WBFS (Fig 1).[16,17]

Data analysis

Statistical analysis of the data was performed using SPSS (IBM, version 25). A P value < .05 was considered significant. For pain assessment, the ordinal scale WBFS was used. The median score of pain on WBFS was compared among the three groups and between pairs of groups. The acceptance of the drug administration and the parents' attitude towards intranasal sedation were also compared among the groups. Kruskal-Wallis and Mann-Whitney tests were used to compare differences.

Results

Sixty-three children were enrolled in the study over an 8-month period beginning in June 2017. Table 1 displays the characteristics of the participants. The distribution of participants within the three groups was equivalent in terms of age, sex, and weight.
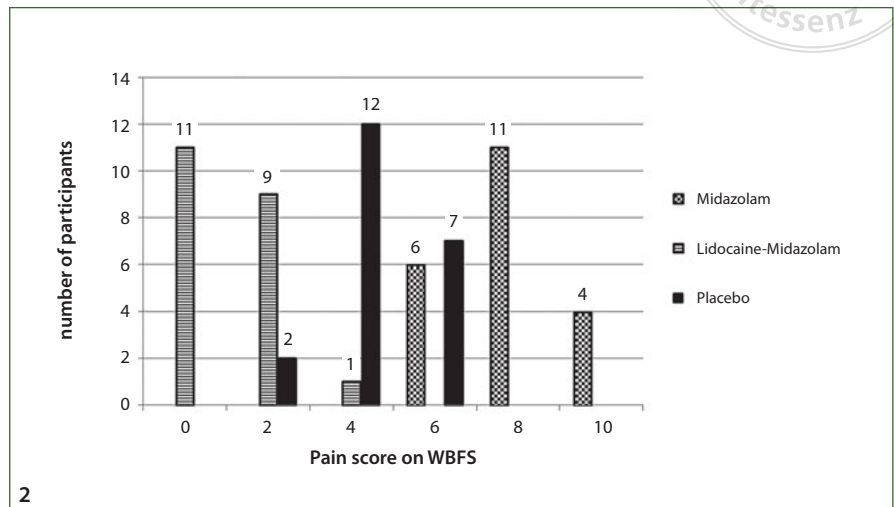
Patients in group A, who received INM only, reported a median WBFS score of 8 (6 to 10) compared with a median score of 1 (0 to 4) for children in group B, who received lidocaine prior to midazolam administration. Children in the placebo group reported a median score of 4 (2 to 6) (Fig 2).

Table 1 Characteristics of the study sample

Characteristic		Group A: midazolam	Group B: lidocaine-midazolam	Group C: saline (placebo)
Patients (n)		21	21	21
Mean age, y (SD)		7.62 (2.27)	7.95 (1.96)	6.62 (1.99)
Gender, n (%)	Male	9 (42.9)	9 (42.9)	8 (38.1)
	Female	12 (57.1)	12 (57.1)	13 (61.9)
Mean weight, kg (SD)		24 (6.41)	23 (6.08)	21 (5.62)

SD, standard deviation.

Fig 2 Pain score (Wong-Baker faces scale, WBFS) according to the treatment.

The differences in median pain scores among the three groups were statistically significant ($P > .05$). Differences between the compared pairs of groups (A/B, A/C, B/C) were also statistically significant ($P > .05$).

When comparing the children's acceptance of the intranasal drug administration, there were statistically significant differences ($P > .05$). Table 2 shows the percentage of drug acceptance in groups A, B, and C. Parents' acceptance of their children having INM sedation in the future was 85.7%, 100%, and 14.3% in groups A, B, and C, respectively. The differences were statistically significant ($P > .05$).

Discussion

Intranasal sedation is increasingly popular in dentistry due to its simple and fast administration, lack of needle, minimization of spread of infectious diseases, lack of need for intravenous access, and relatively easy route of administration in patients who are combative or seizing. This route is especially good for patients who are fearful of needles.[18]

Midazolam is an excellent candidate for intranasal sedation because it has a rapid onset of action, and has sedative, anxiolytic, hypnotic, muscle relaxant, and anterograde amnesic effects, as well as its anticonvulsant activity.[19] Discomfort or feeling a burning sensation in the nasal mucosa is the most frequently reported side effect with INM administration,[20,21] and this is a result of the alcohol content and low pH of the midazolam solution.[22]

Pain and anxiety are related in a circular fashion, and therefore there is a real need for a sedation method with no pain or discomfort, hence the reason for the present study, which may lead to a successful and effective sedation method.[23]

In the current study, pain related to INM administration was evaluated and compared when dispensed alone, following

Table 2 Drug acceptance in groups A, B, and C

Drug acceptance	Group A: midazolam	Group B: lidocaine-midazolam	Group C: saline (placebo)
Good	4.76%	95.24%	0.00%
Adequate	9.52%	4.76%	28.57%
Poor	38.10%	0.00%	47.63%
Worse	47.62%	0.00%	23.80%

lidocaine 2% topically, or placebo alone in uncooperative pediatric patients aged between 4 and 11.

In previous studies, 45% to 77% of children reported nasal irritation.[21-24] To overcome such a drawback, Lugo et al[25] suggested premedication with lidocaine.

Smith et al[9] compared the pain related to INM administration between two groups: one received sodium chloride as placebo prior to INM, while the other received lidocaine prior to INM. As nasal delivery of any medication may cause discomfort for some patients,[26] their study may not have been able to provide an accurate assessment of the pain related to midazolam when dispensed alone, as the administration of saline (placebo) prior to INM may affect the WBFS score recorded by the child.

In the current study, children in the placebo group reported a median score of 4 on WBFS; 67% of them had mild discomfort reflected by scores between 2 and 4 on WBFS, and 23% recorded a score of 6 on the same scale. For the children who received midazolam alone, a median score of 8 (6 to 10) was recorded on WBFS; 71% had scores between 8 and 10 on WBFS, ie, intense burning in the nasal mucosa. Consequently, the differences among groups were statistically significant ($P > .05$).

Administering lidocaine 2% spray counteracted the burning sensation and helped to avoid discomfort resulting from INM administration. Of the children who received lidocaine prior to INM, 20/21 (95%) reported a median score of 1 (0 to 2) on WBFS, and only 1/21 reported a score of 4. The increased pain in group C may be due to the "nocebo" effect.[27]

The present findings did not correspond to those of Musani et al.[28] In their study, 100% of the participants reported no pain after INM administration. This may be because they used an extra sedative agent, nitrous oxide, which has analgesic effects,[29] and could have contributed to reducing the pain perception. In contrast, 43% of participants in the study by Lugo et al[25] reported discomfort and nasal irritation after the administration of INM and intranasal lidocaine. The authors likely did not provide enough time for lidocaine to anesthetize the nasal mucosa before contact with midazolam.

For pain evaluation, the present study used the WBFS pain rating scale, as both children and medical staff prefer WBFS to other self-report scales.[30]

When the administration of a nasal drug causes pain and discomfort, a child's response will probably be negative, as in groups A and C. Lidocaine prior to INM improved the acceptability of the intranasal drug, because the local anesthesia of the nasal mucosa reduces the burning sensation, as in group B.

The parents reported higher degrees of satisfaction with INM sedation when the child was sedated without pain and had the dental treatment completed. ▦
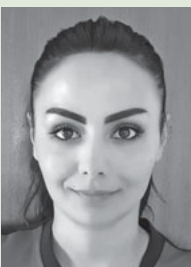
Conclusion

INM administration is associated with burning sensation and high levels of pain in the nasal mucosa. Using lidocaine 2% prior to INM administration overcomes this disadvantage and improves the position of the child as well as the parents towards the INM sedation. As pain triggers and increases anxiety, the lidocaine group achieved greater acceptability of INM administration than the other groups. Sedation should be pain-free, and therefore this study is significant, as INM becomes a pain-free method with the use of lidocaine. These findings can be applied in clinical practice.

Declaration

There are no conflicts of interest related to this study. All authors have made substantial contributions and approved the final manuscript.

References

1. Oliveira NC, Santos JL, Linhares MB. Audiovisual distraction for pain relief in paediatric patients: a crossover study. Eur J Pain 2017;21:178–187.

2. Dufresne A, Dugas MA, Samson Y, Barré P, Turcot L, Marc I. Do children undergoing cancer procedures under pharmacological sedation still report pain and anxiety? A preliminary study. Pain Med 2010;11:215–223.

3. Duchicela SI, Meltzer JA, Cunningham SJ. A randomized controlled study in reducing procedural pain and anxiety using high concentration nitrous oxide. Am J Emerg Med 2017;35:1612–1616.

4. Gilchrist F, Cairns AM, Leitch JA. The use of intranasal midazolam in the treatment of paediatric dental patients. Anaesthesia 2007;62:1262–1265.

5. Shanmugaavel AK, Asokan SH, John B, Priya G, Devi G. Comparison of behavior and dental anxiety during intranasal and sublingual midazolam sedation: a randomized controlled trial. J Clin Pediatr Dent 2016;40:81–87.

6. Fantacci C, Fabrizio G, Ferrara C, Francesch P, Chiaretti A. Intranasal drug administration for procedural sedation in children admitted to pediatric emergency room. Eur Rev Med Pharmacol Sci 2018;22:217–222.

7. Klein EJ, Brown JC, Kobayashi A, Osincup D, Seidel K. A randomized clinical trial comparing oral, aerosolized intranasal, and aerosolized buccal midazolam. Ann Emerg Med 2011;58:323–329.

8. Chiaretti A, Barone G, Rigante D, et al. intranasal lidocaine and midazolam for procedural sedation in children. Arch Dis Child 2011;96:160–163.

9. Smith D, Cheek H, Denson B, et al. Lidocaine pretreatment reduces the discomfort of intranasal midazolam administration: a randomized, double-blind, placebo-controlled trial. Acad Emerg Med 2016;2:161–167.

10. Frankl S, Shiere F, Fogels H. Should the parent remains with the child in the dental operatory? J Dent Child 1962;29:150–163.

11. American Society of Anesthesiologist Classification. Guidelines for the elective use of conscious sedation, deep sedation and general anesthesia in pediatric patients. Pediatr Dent 1985;7:334–337.

12. Wong DL, Baker CM. Smiling faces as anchor for pain intensity scales. Pain 2001;89:295–300.

13. Cox B, Durieux ME, Marcus MA. Toxicity of local anaesthetics. Best Pract Res Clin Anaesthesiol 2003;17:111–136.

14. Du Rand IA, Blaikley J, Booton R, et al. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. Thorax 2013;68:1–44.

15. Pani N, Kumar Rath S. Regional and topical anaesthesia of upper airways. Indian J Anaesth 2009;53:641–648.

16. Savino F, Vagliano L, Ceratto S, Viviani F, Miniero R, Ricceri F. Pain assessment in children undergoing venipuncture: the Wong–Baker faces scale versus skin conductance fluctuations. PeerJ 2013;1:E37:1–15.

17. Xue FS, Yang QY, Liao X, Liu JH, Tong SY. Topical anesthesia of the airway using fibreoptic bronchoscope and the madgic atomizer in patients with predicted difficult intubation. Can J Anesth 2007;54:951–952.

18. McBride DL. Emergency departments increasingly administering medications through the nose. J Pediatr Nurs 2017;37:132–133.

19. Wermeling DP. Intranasal delivery of antiepileptic medications for treatment of seizures. Neurotherapeutics 2009;6:352–358.

20. Bhakta P, Ghosh BR, Roy M, Mukherjee G. Evaluation of intranasal midazolam for preanaesthetic sedation in paediatric patients. Indian J Anaesth 2007;51:111–116.

21. Ljungman G, Kreuger A, Andreasson S, Gordh T, Sorensen S. Midazolam nasal spray reduces procedural anxiety in children. Pediatrics 2000;105:73–77.

22. Dallman JA, Ignelzi MA, Briskie DM. Comparing the safety, efficacy and recovery of intranasal midazolam vs. oral chloral hydrate and promethazine. Pediatr Dent 2001;23:424–437.

23. Schottstraedt WW. Psychophysiologic approach in medical practice. Chicago: Year Book Medical, 1960.

24. Kogan A, Katz J, Efrat R, Eidelman LA. Premedication with midazolam in young children: a comparison of four routes of administration. Paediatr Anaesth 2002;12:685–689.

25. Lugo RA, Fishbein M, Nahata MC, et al. Complication of intranasal midazolam. Pediatrics 1993;92:638.

26. Del Pizzo J, Callahan JM. Intranasal medications in pediatric emergency medicine. Pediatr Emerg Care 2014;30:496–501.

27. Eliav E. Editorial: Placebo analgesia in dentistry. Quintessence Int 2018;49:605.

28. Musani IE, Chandan NV. A comparison of the sedative effect of oral versus nasal midazolam combined with nitrous oxide in uncooperative children. Eur Arch Paediatr Dent 2015;16:417–424.

29. Dong T, Liu M, Lv K. Inhaled nitrous oxide can reduce the pain perception in post Caldwell-Luc operation patients: a randomized trial. Sci Rep 2017;7:17760.

30. Garra G, Singer AJ, Domingo A, Thode HC Jr. The Wong-Baker pain FACES scale measures pain, not fear. Pediatr Emerg Care 2013;29:17–20.

31. Whaley LF, Wong DL. Nursing Care of Infants and Children, 2nd edition. St Louis: Mosby, 1983.

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