Scientific Article

Reducing the Pain of Intranasal Drug Administration

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Abstract: ***Purpose:*** *The purpose of this research study was to develop a score to assess intranasal (IN) drug administration discomfort and then assess 3 different approaches to reduce the pain associated with the administration of an IN citrate study solution.* ***Methods:*** *After Institutional Review Board approval and with informed consent, volunteers intranasally received 0.3 M solution of citrate, on 4 different days. In stage 1, the citrate was administered via syringe or by aerosol. Stage 2 compared the IN citrate before and 60 seconds after 2% lidocaine was given. Stage 3 compared the IN citrate to an IN mixture of 2% lidocaine and citrate. A placebo of IN saline was also used on one occasion. The degree of pain, burning, and unpleasant taste was recorded using a scale of 1 to 10 to give an overall intranasal discomfort score (INDS).* ***Results:*** *The citrate proved significantly more unpleasant and painful than the placebo saline. The mean INDS was 12.1, which was significantly higher following IN citrate compared to saline. Lidocaine, both pretreatment and mixed, significantly reduced the INDS.* ***Conclusions:*** *The intranasal discomfort score appeared reproducible for assessing painful intranasal drug administration. The addition of lidocaine appeared to reduce the discomfort of intranasal citrate in adult volunteers. (Pediatr Dent 2011; 33:415-9) Received February 23, 2010 | Last Revision August 17, 2010 | Accepted August 25, 2010*

KEYWORDS: SEDATION, LOCAL ANESTHESIA, CLINICAL TRIALS, BIOSTATISTICS

For moderate sedation in pediatric dental patients, the oral administration route of sedative medicines is frequently used.[1-6] This is considered to be a safe method of sedation administration when used as part of a moderate sedation protocol. There are, however, several problems associated with this method. One of the most common problems encountered is compliance with the drug administration, due to the child's refusal to willingly take the medication. Children who present for sedation procedures in pediatric dentistry have usually already "failed" minimal sedation with nitrous oxide in the dental chair and also tend to be less cooperative.

Problems encountered with oral administration include the child either refusing to drink the sedation solution or spitting it out. In the former, no sedation occurs, and the latter can result in an unpredictable sedation due to the inability to assess how much sedative was actually swallowed, making additional safe dosing difficult to predict and, as such, not recommended.

Intranasal (**IN**) administration of a drug has many benefits for sedating the pediatric patient. Compared to drugs given orally, the doctor has more control over the amount of drugs the child actually receives intranasally. Minimal patient cooperation is required, and the onset of the drug is usually quicker due to a more rapid absorption through the mucous membranes of the nasal passages. This results in a lower dose of the sedative being used and a more rapid onset. There are several drugs routinely given via the IN route, such as desmopressin, sumatriptan, and inhaled steroids.[7]

One main disadvantage of using IN administration is that the child may experience IN and/or pharyngeal pain or discomfort after the solution has been sprayed into the nose. There are several sedative agents that have been used intranasally, such as midazolam,[8,9] sufentanil,[10] and dexmedetomidine.[11] Midazolam is the most commonly used IN sedative drug, and its use has been reported in pediatric dental patients.[12-14] Comparison studies between oral and IN midazolam suggest equal efficacy and a more rapid onset with the IN approach.[15,16] The use of IN midazolam has frequently been associated with pain on administration in both adults[17,18] and in up to 60% of children.[19-21] It has been shown that a citrate solution[22] with a pH similar to that of midazolam also causes a similar degree of burning on nasal administration.

To date, there appears to be no study evaluating methods of reducing the discomfort of intranasally administered medications. It would be useful if a simple method of attenuating this discomfort can be found. This would then allow for the painless use of IN midazolam, potentially facilitating a faster, more compliant, and predictable sedation in children. To assess these techniques, there must be a method for evaluating the nasal discomfort in a reliable manner. There is currently no published score for assessing discomfort from IN drug administration, which could make any evaluation unreliable.

The purposes of this study were, using citrate as an "inert" marker for painful intransal midazolam, to:

1. develop a reproducible score for assessing discomfort on IN drug administration; and

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2. assess 3 different approaches, including citrate aerosolization and the use of lidocaine to minimize the discomfort involved in administering a painful IN drug.

Methods

Institutional Review Board approval for this study was obtained from the Women & Childrens Hospital of Buffalo, and healthy 20- to 40-year-old volunteers were recruited from the Department of Pediatric Dentistry at the Women and Children's Hospital, Buffalo, NY. Informed consent was obtained from each of the subjects. Exclusion criteria were: inability or refusal to obtain informed consent, pregnancy, allergy to local anesthetic or citrate, upper respiratory tract infection, recent asthma attack (< 2 weeks), previous sinus surgery, recent sinus infection (< 2 weeks) and a history of nasal polyps.

The study was conducted in 4 visits on 4 different days for approximately 30 minutes per day. The volunteers were split into 2 groups: (1) Group 1; and (2) Group 2. The order and stages were randomized for the different groups. For each visit, the volunteers were not aware which drugs were used or in which order the drugs were being sprayed into either nares. The IN administration was performed in the following manner. The citrate was prepared fresh each morning of the study and stored in a drug refrigerator until its use. All mixing of drugs occurred just prior to drug administration.

Visit 1: Comparing placebo to citrate. In Group 1 subjects, the right nostril was sprayed with 1 ml of sterile saline solution using a mucosal aerosol device (MAD, Tory Wolfe Medical Inc, Murray, Utah). Then, each subject's left nostril was sprayed with 1 ml of 0.3 M citrate solution using the MAD.[23,24] In Group 2 subjects, using the MAD, the right and left nostrils, respectively, were sprayed with 1 ml of citrate solution and 1 ml of sterile saline.

Visit 2: Comparing MAD to the drop technique for delivering citrate. In Group 1 subjects, the right nostril was drop injected (using a 3 ml syringe) with 1 ml of citrate solution. Next, the subject's left nostril was sprayed with 1 ml of citrate solution using the MAD. In Group 2 subjects, the right nostril was sprayed with 1 ml of citrate solution using the MAD. Then, each subject's left nostril was drop injected (using 3 ml syringe) with 1 ml of citrate solution.

Visit 3: Predosing nares with lidocaine spray. In Group 1 subjects, the right nostril was sprayed with 0.5 ml of 2% lidocaine using the MAD. The research team then waited 60 seconds (timed using the second hand of a standard wristwatch). Each subject's right and left nostrils were then both sprayed with 1 ml of citrate using the MAD. In Group 2 subjects, using the MAD, the right and left nostrils, respectively, were sprayed with 1 ml of citrate and 0.5 ml of 2% lidocaine. The research team then waited 60 seconds (timed using the same wristwatch) before each subject's left nostril was sprayed with 1 ml of citrate using the MAD.

Visit 4: Mixing lidocaine with citrate. For Group 1 subjects, the research team mixed 1 ml of citrate with 0.5 ml of 2% lidocaine. Using the MAD, each subject's right and left nostrils, respectively, were sprayed with 1.5 ml of this mixture and 1 ml of the plain citrate solution. In Group 2 subjects, each right nostril was sprayed with 1 ml of the plain citrate solution using the MAD. Next, 1 ml of citrate was mixed with 0.5 ml of 2% lidocaine, and this 1.5 ml mixture was sprayed into each subject's left nostril using the MAD. A summary of the study visits is shown in Table 1.

Assessing the discomfort. The discomfort of the citrate administration was assessed in several ways—first, using a pain intensity scale scored from 1 to 10,[25] as proposed by the NIH Pain Consortium involved in researching pain and effective treatment. In both groups, the discomfort was assessed in the same manner. The volunteers were asked to assess pain, burning, and taste using a scale from 1 to 10 (minimal to maximum) for each sensation.

These 3 components were used to generate the intranasal discomfort score (**INDS**). This score was obtained on 2 occasions for each nasal administration: (1) immediately after administering; and (2) 5 minutes later. The volunteers were asked to assess the degree of numbness using a score from 1 to 10 (minimum to maximum) at these 2 times. The volunteers were then asked if they experienced any other symptoms after the IN administration. It was noted if the subject coughed or sneezed during the process. Statistical analysis included paired and unpaired *t* test as well as analysis of variance.

Results

Over a 1-year period, 18 volunteer adults were recruited for the study. The mean age was 27.7-years-old (±2.3 SD). The assessments used to evaluate the INDS are shown in Table 2. These are the scores derived from the citrate administration using the MAD on each separate visit for the study (Figure 1). For

Table 1. A SUMMARY OF THE 4 VISITS DURING THE STUDY*

Visit	Group 1		Group 2	
	Right nares	Left nares	Right nares	Left nares
1	Saline (spray)	Citrate (spray)	Citrate (spray)	Saline (spray)
2	Citrate (drop)	Citrate (spray)	Citrate (spray)	Citrate (drop)
3	Lidocaine then citrate (spray)	Citrate (spray)	Citrate (spray)	Lidocaine then citrate (spray)
4	Lidocaine then citrate (spray)	Citrate (spray)	Citrate (spray)	Lidocaine and citrate (spray)

* Spray administered using a mucosal aerosol device; saline=1 ml of sterile normal saline; lidocaine=0.5 ml of 2% lidocaine; citrate=1 ml of 0.3 M solution.

Table 2. EARLY AND LATE COMPONENTS FOR THE INTRANASAL DISCOMFORT SCORE (INDS) USING CITRATE BY MUCOSAL AEROSOL DEVICE AND PLACEBO (VISIT 1 ONLY)

	Visit 1 Mean±(SD)	Visit 2 Mean±(SD)	Visit 3 Mean±(SD)	Visit 4 Mean±(SD)	Placebo Mean±(SD)
Early pain	3.3±2.2	3.1±2.5	3.7±2.3	3.2±2.0	1.1±0.2
Early taste	3.7±3.0	4.6±2.9	3.8±2.3	4.2±2.6	1.0±0.0
Early burning	5.1±2.6	4.6±2.6	4.8±2.4	4.4±2.8	1.7±1.2
Early INDS	12.2±6.5	12.3±7.0	12.3±5.8	11.9±6.5	3.8±1.6
Late pain	1.4±0.7	1.3±0.7	1.6±0.9	1.4±0.7	1.1±1.9
Late taste	2.7±2.0	2.6±1.9	3.3±1.9	2.8±1.8	1.1±0.3
Late burning	2.5±1.7	2.2±1.3	2.6±1.8	1.9±1.0	1.0±0.0
Late INDS	6.7±3.4	6.0 ±3.0	7.5±3.7	6.2±2.2	3.2±0.9

comparison, the normal saline scores from the first visit were used (placebo).

All component scores are based on a scale from 1 to 10. The minimum INDS score is 3 and the maximum INDS score is 30. There was no significant difference between the scores for each of the 3 different components (pain, taste, and burn) on the 4 different visits. This applied to both the early and late assessments. There was also no difference in the early and late INDS for each of the 4 visits. When both the early and late component scores, as well as the INDS, were compared to the scores obtained for the placebo (normal saline), all the scores for the MAD administered citrate were significantly higher than those for the placebo ($P<.01$). When the early and late component scores, as well as the early and late INDS, were compared, the early scores were all significantly higher than the late scores ($P<.01$), except for the taste scores, which were only significantly different on 2 visits.

Analysis of the component scores demonstrated that there was a significant difference between different volunteers for the different components of the INDS; however the overall score was similar. The contribution of each component of the INDS was also assessed, for both the early and late assessments. The most common complaints were burning and taste, respectively, during the early and late assessments ($P<.05$).

The first method used to reduce the discomfort of the IN citrate was the use of a MAD to administer the citrate compared to the syringe drop method that is often used (visit 2). The results are shown in Table 3. There was no difference shown between the 2 methods of IN citrate administration regarding pain, burning, taste, or the INDS. Both methods demonstrated a decrease in the INDS from early to later. There was also no difference between syringe and aerosol for the coughing or other complications such as sneezing, watery eyes, "runny nose,"or "scratchy" throat.

The results for the third visit, comparing the "pre-" IN administration of 0.5 ml 2% lidocaine using the MAD (followed 60 seconds later by 1 ml citrate) vs 1 ml of citrate alone, are shown in Table 4. The predosing use of lidocaine significantly reduced the early INDS ($P<.01$). The late INDS was not different between the 2 groups. Both groups showed a significant fall in the INDS from early to late ($P<.01$), as shown previously with other administering techniques. The predose lidocaine group also reported significantly more numbness compared to the other group ($P<.05$). This did not change between the early and late assessments. The differences in the INDS for both the early and late scores were due to significantly lower score for pain ($P<.05$) and burning ($P<.01$); taste was not different between the groups.

There was no difference found between the citrate and prelidocaine for coughing or any other complications noted either early or late. The sensation of numbness was noted to persist for between 15 and 30 minutes in most cases.

Table 3. INTRANASAL DISCOMFORT SCORE (INDS) AND OTHER SYMPTOMS DURING CITRATE IN ADMINISTRATION USING EITHER A MUCOSAL AEROSOL DEVICE (MAD) OR DROP SYRINGE METHOD

	Early INDS Mean±(SD)	Late INDS Mean±(SD)	Cough (N)	Other (N)	Any side effect (N)
MAD	12.2±6.5	6.7±3.4	4	8	11
Drop syringe	11.9±6.3	6.8±3.1	6	8	10

For the fourth and final visit in the study, the aerosol mixture of 1 ml citrate and 2% lidocaine vs 1 ml of citrate alone were compared (results are shown in Table 5). The results were very similar to those with the predosed lidocaine (Figure 2). The early INDS was significantly lower in the lido mix group ($P<.01$); however, it was also significantly lower for the late INDS also ($P<.05$). The effects on numbness were also similar, with significantly more numbness in the lidocaine mix group. There was no significant difference in the numbness between the predose lidocaine and the lidocaine mix groups. Reduction in the scores for pain and burning were the main contributors to the reduction in the INDS. No difference was observed between the citrate and the mixture for the complications early or late.

When the INDS scores for visits 3 and 4 were compared for IN citrate, there was no significant difference between both early and late INDS, suggesting that both techniques may be equally effective.

Table 4. EFFECTS OF PREDOSING 1 NARES WITH LIDOCAINE PRIOR TO ADMINISTERING IN IN CITRATE (MEAN±SD)

	Early intranasal discomfort scale Mean±(SD)	Late intranasal discomfort scale Mean±(SD)	Numb early Mean±(SD)	Numb late Mean±(SD)	Cough (N)	Other (N)	Any side effect (N)
Predose lidocaine	8.9±6.0*	5.3±3.2†	3.3±2.4‡	3.4±3.0	3	3	6
No lidocaine	12.3±7.0	6.0±3.0†	1.7±1.5	1.4±0.9	4	7	8

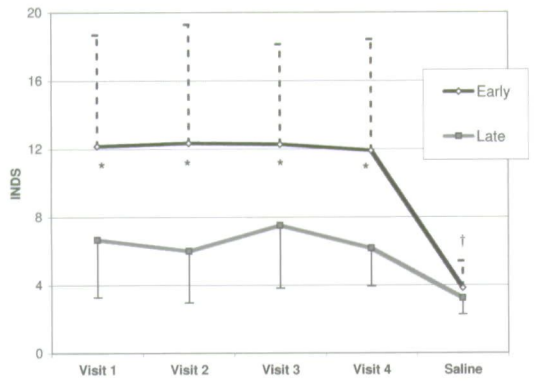
* $P<.01$ between the 2 groups. † $P<.01$ between early and late. ‡ $P<.05$ between the 2 groups.

Table 5. EFFECTS OF MIXING LIDOCAINE WITH CITRATE ON THE INDS

	Early intranasal discomfort score Mean±(SD)	Late intranasal discomfort score Mean±(SD)	Numb early Mean±(SD)	Numb late Mean±(SD)	Cough (N)	Other (N)	Any side effect (N)
MIxed lidocaine	8.6±6.4*	5.2±3.2†‡	2.2±1.4‡	2.9±2.0‡	4	8	8
No lidocaine	12.3±6.0	7.5±3.7†	1.7±1.7	1.5±1.3	3	7	9

* $P<.01$ between the 2 groups. † $P<.01$ between early and late. ‡ $P<.05$ between the 2 groups.

Figure 1. Assessment of citrate and saline intranasal discomfort (Mean±SD)*†

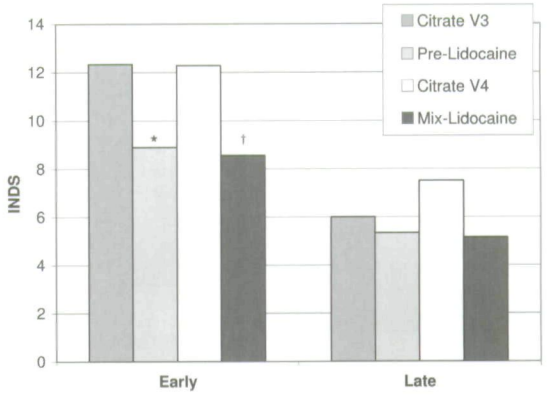


No significant difference was found between citrate intranasal discomfort score for all 4 visits;

* $P<.01$ compared to late intranasal discomfort score.

† $P<.01$ compared to both early and late citrate intranasal discomfort score.

Figure 2. The effects of predosed and mixed lidocaine on intranasal discomfort*†



All of the late intranasal discomfort scores (INDS) were significantly lower ($P<.05$) than the corresponding early INDS;

* $P<.01$ compared to citrate V3.

† $P<.05$ compared to citrate V4.

Discussion

In this study, the first aim was to develop a scoring system to assess IN discomfort. The evaluation of the INDS found it to be both reliable and repeatable, as is required for a clinically useful tool. The results supporting the INDS as being useful were taken from the evaluation of the IN discomfort that was associated with the administration of IN citrate using the MAD on the 4 different study visits, often weeks apart. The overall INDS, as well as its 3 base components, were reproducible on the 4 different visits. The score decreased reliably with time after the IN administration. The INDS derived from the IN citrate was also significantly higher when compared to the INDS derived from the placebo (normal saline) on the first visit. The placebo INDS was almost equal to the lowest score (3) possible with the INDS, confirming that the score changed significantly with the uncomfortable IN citrate administration.

Three different sensations for evaluating the IN discomfort were chosen, because different people perceive stimuli in a different manner. It was noticeable during the study that there were large differences between different volunteers and the way they described the IN administration; what may have been very painful for one was more of a burning sensation or unpleasant taste to another. All 3 components appeared to contribute to the score, and this changed with time. Taste appeared to be the longest lasting of the unpleasant experiences. The INDS as described should serve as a useful tool for evaluating the discomfort of IN drug administration during research studies.

This INDS was then used in the second part of our study to evaluate 3 different techniques to reduce the discomfort of IN drug administration. The MAD, which attaches onto a syringe, provides a fine spray when used and has been used to administer several different medications intranasally, including midazolam.[26] This device has been used extensively in clinical practice for the administration of both local anesthetics and other medications. There was a report that its use reduced the discomfort of IN midazolam when compared to the drop syringe technique.[27] Our evaluation of the MAD, using citrate during visit 2, was unable to support this benefit. The MAD is used to provide a fine aerosolized mist that should improve mucosal distribution and absorption of a drug. This might actually increase the discomfort from the acidic drug, as it is better dispersed throughout the nasal passages. There was no detectable increase in the associated complications when comparing these 2 techniques. Fifty percent of the subjects experienced symptoms such as coughing, watery eyes, and runny nose.

The second method to reduce IN discomfort was to topically anesthetize the nasal mucosa with a predose IN spray of 2% lidocaine using the MAD. This method was able to demonstrate a significant reduction in the INDS. The predose with lidocaine did result in a mild sensation of numbness that was short lived. The lidocaine did not result in any increase in taste discomfort, despite having an unpleasant taste itself. Due to the rapid onset of lidocaine administered topically to mucosa, 60 seconds between the lidocaine and citrate appears to have been appropriate. The reduction in the early INDS as well as increased early numbness supports this rapid onset.

The third method, mixing lidocaine with the citrate, was tried because it is unlikely that a young child will willingly undergo 2 IN drug administrations in the same nostril without complaining. The pharmacy did not find any stability or precipitation risk with the combination, which was always prepared just prior to administration. The benefits of this technique appeared to be very similar to that of the predose lidocaine.

Both of the techniques using lidocaine include the addition of another drug to a sedation regimen. The routine use of lidocaine for either infiltration or nerve blocks by the dentist must be considered. This is most important regarding the maximum safe dose of lidocaine that can be used. In this study, 10 mg of lidocaine was used for either the predosing or mixed techniques. For a child of 20 kg whose maximum recommended dose of lidocaine is 4.4 mg/kg, 90 mg total,[28] this represents about 10% of the dose available.

Although the use of IN drug administration is widespread, it must be noted that some states restrict dentists from using it. In these states, IN administration is considered a parenteral route and, as such, requires additional training and the appropriate permit from a dentist's state board.

There are several limitations to the study. The number of volunteers was small, however, in spite of this, the results appeared to be fairly reproducible. Adult volunteers only were used, resulting in a more reliable degree of self-reporting. The degree of discomfort, however, may be different in children vs adults. Although the use of citrate rather than midazolam did allow for the use of volunteers in this initial evaluation, the benefits of using lidocaine may not be transferable between citrate and midazolam. A study evaluating the mixing of lidocaine with midazolam is probably now warranted to assess the clinical significance of these findings.

Although there were significant differences in the INDS between volunteers (as expected), the INDS was not significantly different between the 4 different assessments. Also, the other common complaints noted, such as watery eyes and coughing, were not reduced by any of the techniques used and may still be an issue with a child during IN drug administration.

Conclusions

1. The intranasal discomfort score appears to be a reliable and repeatable assessment tool that can be utilized in determining the discomfort of intranasal drug administration.
2. The benefit noted from mixing lidocaine with citrate may provide a useful technique, if employed with other intranasal drugs, to reduce the discomfort of intranasal medication administration.

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