


## ORIGINAL RESEARCH

## Pediatrics

# Comparison of preadministered and coadministered lidocaine for treating pain and distress associated with intranasal midazolam administration in children: A randomized clinical trial

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**Meetings:** Pediatric Academic Societies, Balti-  
more, MD, April 2019.

Clinical Trials Registration Number:  
NCT03054844

**Funding and support:** By *JACEP Open* policy,  
all authors are required to disclose any and all  
commercial, financial, and other relationships  
in any way related to the subject of this article  
as per ICMJE conflict of interest guidelines (see  
[www.icmje.org](http://www.icmje.org)). The authors have stated that  
no such relationships exist.

## Abstract

**Objective:** Pain and distress associated with intranasal midazolam administration can be decreased by administering lidocaine before intranasal midazolam (preadministered lidocaine) or combining lidocaine with midazolam in a single solution (coadministered lidocaine). We hypothesized coadministered lidocaine is non-inferior to preadministered lidocaine for decreasing pain and distress associated with intranasal midazolam administration.

**Methods:** Randomized, outcome assessor-blinded, noninferiority trial. Children aged 6 months to 7 years undergoing laceration repair received intranasal midazolam with preadministered or coadministered lidocaine. Pain and distress were evaluated with the Observational Scale of Behavioral Distress—Revised (OSBD-R) (primary outcome; non-inferiority margin 1.8 units) and the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) and Faces, Legs, Activity, Cry, Consolability (FLACC) scales and cry duration (secondary outcomes). Secondary outcomes also included adverse events, clinician and caregiver satisfaction, and pain and distress associated with intranasal lidocaine administration.

**Results:** Fifty-one patients were analyzed. Mean OSBD-R scores associated with intranasal midazolam administration were 6.4 (95% confidence interval [CI] 5, 7.8) and 7 (95% CI 5.2, 8.9) units for preadministered and coadministered lidocaine,

Supervising Editor: Henry E. Wang, MD, MS.

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respectively. The difference of 0.6 (95% CI -1.7, 2.8) units represented an inconclusive non-inferiority determination. CHEOPS and FLACC scores and cry duration were similar between groups. OSBD-R, CHEOPS, and FLACC scores and cry duration associated with intranasal lidocaine administration were 3.8, 9.9, and 6 units, and 56 seconds, respectively. Clinicians considered coadministered lidocaine easier to administer.

**Conclusion:** Pain and distress associated with intranasal midazolam administration were similar when using coadministered or preadministered lidocaine, but our non-inferiority determination was inconclusive. Administration of intranasal lidocaine by itself was associated with a measurable degree of pain and distress.

**Keywords:** intranasal, midazolam, anxiolysis, sedation, emergency department, emergency medicine, pain, distress, pediatric, lidocaine, laceration

#### KEYWORDS

anxiolysis, distress, emergency department, emergency medicine, intranasal, laceration, lidocaine, midazolam, pain, pediatric, sedation

## 1 | INTRODUCTION

### 1.1 | Background

Intranasal midazolam is a sedative commonly used for children to facilitate distressing medical procedures in the pediatric emergency department.<sup>1-3</sup> It is safe and effective, but its administration is associated with a significant amount of nasal pain and burning.<sup>4-6</sup>

The pain and distress associated with intranasal midazolam administration can be decreased by using intranasal lidocaine.<sup>5-7</sup> One method involves medicating with intranasal lidocaine before intranasal midazolam administration (preadministered lidocaine), which requires 2 separate administrations.<sup>5-8</sup> A second method involves mixing the lidocaine and midazolam and administering the premixed solution (coadministered lidocaine), which requires only a single administration.<sup>8</sup> Both methods are effective in decreasing the pain associated with intranasal midazolam and other acidic solutions.<sup>6-8</sup> However, it is unknown whether the 2 methods produce comparable decreases in pain and distress associated with intranasal midazolam administration in children.

### 1.2 | Importance

To minimize pain and distress in children, it is necessary to determine whether preadministered and coadministered lidocaine are comparably effective in decreasing the pain and distress associated with intranasal midazolam administration. Children may find the 2 separate intranasal administrations required by preadministering lidocaine (ie, lidocaine followed by midazolam) to be more distressing than the single administration required when coadministering lidocaine. However, if coadministering lidocaine were not as effective as preadministering it, then the potential benefits of using only 1 instead of 2 administrations would be rendered moot.

### 1.3 | Goals of this investigation

The primary aim of this study was to determine whether coadministering lidocaine is non-inferior to preadministering it for decreasing pain and distress associated with intranasal midazolam administration. Our primary outcome was pain and distress associated with intranasal midazolam administration, measured with the Observational Scale of Behavioral Distress-Revised (OSBD-R).<sup>9</sup> Our secondary outcomes included pain and distress associated with intranasal midazolam administration, measured with the Faces, Legs, Activity, Cry, Consolability (FLACC) scale, Children's Hospital of Eastern Ontario Pain Scale (CHEOPS), and cry duration; pain and distress associated with intranasal lidocaine administration; adverse events; and clinician and caregiver satisfaction.<sup>4,10-12</sup> We hypothesized that administration of intranasal lidocaine as coadministered lidocaine would be non-inferior to preadministered lidocaine for decreasing pain and distress associated with intranasal midazolam administration.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and setting

We conducted a prospective, randomized, outcome assessor-blinded, non-inferiority clinical trial in the pediatric emergency department (ED) of New York-Presbyterian Morgan Stanley Children's Hospital, an academic tertiary care hospital in New York, New York with  $\approx 55,000$  annual visits. Care in this setting is provided by pediatric emergency medicine board certified attendings, general pediatricians, pediatric emergency medicine fellows, nurse practitioners, physician assistants, and pediatric and emergency medicine residents. Our institutional review board approved this study, and written informed consent was obtained from each participant's legal guardian.

## 2.2 | Selection of participants

Between April and October 2017, we enrolled a convenience sample of children aged 6 months to 7 years (ie, before their eighth birthday) who presented to the ED with a laceration and whose attending physician determined that intranasal midazolam was indicated to facilitate the repair. Patients were enrolled when a study team member was available (9 AM to 10 PM on weekdays; variable on overnights and weekends).

We excluded children for any of the following: weight <5 kg, known allergy to lidocaine or midazolam, inability to speak English or Spanish, known history of developmental delay or autism spectrum disorder, baseline motor neurologic abnormality (eg, cerebral palsy), illness associated with chronic pain, nasal injury precluding intranasal medication delivery, presence of intranasal obstruction that could not be readily cleared by suction or nose blowing, or in foster care or wards of the state.

## 2.3 | Interventions

Block randomization was used to achieve balance in the allocation of subjects to each study group. Patients were block randomized to receive either preadministered or coadministered lidocaine. Randomization was achieved with computer-generated, randomly varied blocks of 4 and 6 using a 1:1 ratio within blocks. Blocks were not defined by specific factors (eg, age). The random-allocation sequence was generated by a third party otherwise uninvolved with the study. Allocation was concealed by using sequentially numbered sealed opaque envelopes. Patients were enrolled and assigned to their respective interventions by a study team member who was not involved with the patient's outcome assessments (eg, scoring videos).

Patients assigned to receive preadministered lidocaine first received 20 mg of 4% lidocaine (0.5 mL), with 10 mg (0.25 mL) administered into each nostril. Five minutes later, intranasal midazolam (5 mg/mL) was administered at 0.5 mg/kg, with a maximum total dose of 10 mg (2 mL). Patients assigned to receive coadministered lidocaine received a single solution containing both 20 mg of 4% lidocaine and midazolam at 0.5 mg/kg (5 mg/mL), with a maximum total midazolam dose of 10 mg (2 mL). The maximum total volume in the coadministered lidocaine group was 2.5 mL.

Study medications were not stored or prepared in a blinded fashion because the outcome assessors were not present during study procedures and had access to only the video recordings to which they were blinded. All intranasal medications were administered with an LMA MAD Nasal (Teleflex, Morrisville, North Carolina) device attached to a 3-mL syringe with 0.1-mL scale markings. Medications were divided and administered into both nostrils, with a maximum volume of administration of 1 mL per nostril, either by alternating between both nostrils until the total volume was dispensed or by delivering simultaneously into both nostrils.<sup>1</sup> Administration of intranasal midazolam or the intranasal midazolam/lidocaine mixture was completed within a 15-second interval.

### The Bottom Line

In children, clinicians often temper the pain of intranasal midazolam with coadministered or preadministered lidocaine. In this randomized controlled trial of 51 children 6 months–7 years old undergoing laceration repair, the pain and distress of intranasal midazolam were similar with coadministered or preadministered lidocaine, but the non-inferiority design of the study precluded a definitive conclusion. This study provides important information to inform the design of future clinical trials.

## 2.4 | Methods of measurement and outcome measures

There were 3 phases during which outcome measures were assessed: baseline, intranasal lidocaine administration, and intranasal midazolam administration. The baseline phase was evaluated to determine whether the 2 groups were similar at the beginning of the trial in regard to baseline pain and distress. The intranasal lidocaine administration phase was applicable only to patients randomized to the preadministered lidocaine group and was evaluated to determine whether there was any pain and distress associated with intranasal lidocaine administration. The intranasal midazolam administration phase was when the outcomes for determining the primary aim were assessed. During this phase, patients in the preadministered lidocaine group received intranasal midazolam, and patients in the coadministered lidocaine group received the intranasal midazolam/lidocaine mixture.

For the baseline phase, a study team member videotaped each patient for a 1-minute period before the administration of any intranasal medication. For the intranasal lidocaine administration phase, patients were videotaped for at least 1 minute and until either 30 seconds after they stopped crying or until 5 minutes had elapsed after intranasal lidocaine administration. This 5-minute limit was because our study protocol required intranasal midazolam to be administered 5 minutes after intranasal lidocaine administration. As a result, the maximum possible cry duration measured for this phase was 5 minutes, even if the patient had not stopped crying by that time. For the intranasal midazolam administration phase, patients were also videotaped for at least 1 minute and until 30 seconds after they stopped crying. There was no time limit on how long cry duration could be assessed for this phase.

Videos of the baseline assessment or administration of an intranasal medication were randomly assigned to 1 of 5 trained outcome assessors (N.C.O., H.A.W, P.L.F.-S, S.H.M., and M.I.), who independently scored each video. Assessors could score only 1 video for each patient to avoid unblinding that could result from seeing the same patient receive an intranasal medication in 2 separate videos and thereby inferring that the patient was assigned to receive preadministered lidocaine. Assessors did not score videos for patients they enrolled to

further maintain blinding. For videos in which an intranasal medication was administered (ie, lidocaine, midazolam, and lidocaine/midazolam), assessors were blinded to the type of medication administered.

The primary outcome was the pain and distress associated with administration of intranasal midazolam, measured with the OSBD-R.<sup>9</sup> The OSBD-R is a weighted observational scale based on 8 behaviors that identify intensity of pain and distress in children, which has been shown to have strong validity in children as young as 1 year.<sup>4,13</sup> Each of the 8 behaviors has a weighted score. Based on the frequency that each behavior is observed during a 15-second interval, a score from 0 to 23.5 units (0 = no pain or distress, 23.5 = maximum pain and distress) is assigned for that interval.<sup>9</sup> Four 15-second intervals were evaluated at the beginning of each of the 3 phases. Therefore, the maximum total OSBD-R score for each phase was 94 units. The OSBD-R scores obtained during the intranasal midazolam administration phase were compared to evaluate differences in pain and distress between the children who received preadministered or coadministered lidocaine.

The secondary outcomes included pain and distress associated with administration of an intranasal medication, measured with the FLACC, CHEOPS, and cry duration. Both the FLACC and CHEOPS have strong validity in young children.<sup>4,13</sup> The FLACC is composed of 5 criteria (Faces, Legs, Activity, Cry, Consolability), with a possible score of 0 to 2 for each criterion and a possible total score of 0 to 10 (0 = no pain, 10 = most pain).<sup>11</sup> The CHEOPS uses 6 observational factors (cry, facial, verbal, torso, touch, and legs) to evaluate pain in young children and can be used to monitor the effectiveness of interventions for reducing the pain and discomfort of an intervention. Each of the 6 factors is scored differently, with possible score ranges of 0 to 2, 1 to 2, or 1 to 3. The total score ranges from 4 to 13, with scores of 4 to 6 representing no pain.<sup>10</sup> FLACC and CHEOPS scores were assigned to the first 15 seconds after administration of an intranasal medication to capture the interval representing the maximal pain and distress experienced.<sup>4</sup> Cry duration was measured in seconds and defined as the time from onset of crying after administration of an intranasal medication until the cessation of crying sounds, tears, or both. If a patient did not cry, the cry duration was 0.<sup>4,12</sup>

Additional secondary outcomes included satisfaction of caregivers and clinicians associated with each study group. After completion of all intranasal medication administrations, a study team member obtained satisfaction scores from the child's caregiver and the clinician who administered the intranasal medication(s). Caregivers and clinicians used a 5-point Likert scale (strongly disagree, disagree, neither agree nor disagree, agree, or strongly agree) to answer questions related to their satisfaction with ease of intranasal administration and their perception of the discomfort experienced by the child during the procedure.

Adverse events were documented by a study team member who monitored the patient until he or she was discharged from the ED. Adverse events included vomiting, apnea (no respiratory effort for > 20 seconds), paradoxical reaction (ie, agitation precipitated by midazolam), and the need for supplemental oxygen, airway repositioning, or bag-valve-mask ventilation.

## 2.5 | Primary data analysis

For our primary outcome of pain and distress associated with intranasal midazolam administration, we compared the OSBD-R scores obtained during the intranasal midazolam administration phase, using the independent-samples *t* test. To determine non-inferiority of coadministered compared with preadministered lidocaine, we used a predetermined margin of non-inferiority ( $\Delta$ ) of 1.80 (SD 2.25). This margin was based on pooling effect estimates from previous randomized clinical trials of children undergoing painful procedures and selecting an estimate that represented a clinically significant difference.<sup>14-18</sup> To demonstrate non-inferiority with this  $\Delta$  with a 1-tailed  $\alpha$  of .025 and power of 80%, we required 25 patients in each arm, for a total of 50 patients. We enrolled an additional randomized block of 5 patients during the course of the study to account for patients excluded because of protocol violations, for a total of 55 patients enrolled. The interrater reliability of the 5 assessors was evaluated by determining the intraclass correlation coefficient for all 4 observational measures. All 5 assessors scored the same randomly selected 30 videos after all primary and secondary outcome assessments were completed. The intraclass correlation coefficients between reviewers for the OSBD-R, CHEOPS, FLACC, and cry duration were 0.90, 0.96, 0.98, and 0.92, respectively.

Satisfaction questionnaire responses were dichotomized into "satisfied" (ie, if respondent answered "agree" or "strongly agree") or "dissatisfied" (ie, if respondent answered "undecided," "disagree," or "strongly disagree") and compared between the groups with the  $\chi^2$  test. Statistical analyses were performed with SPSS (version 24; IBM Corporation, Armonk, New York, USA).

## 3 | RESULTS

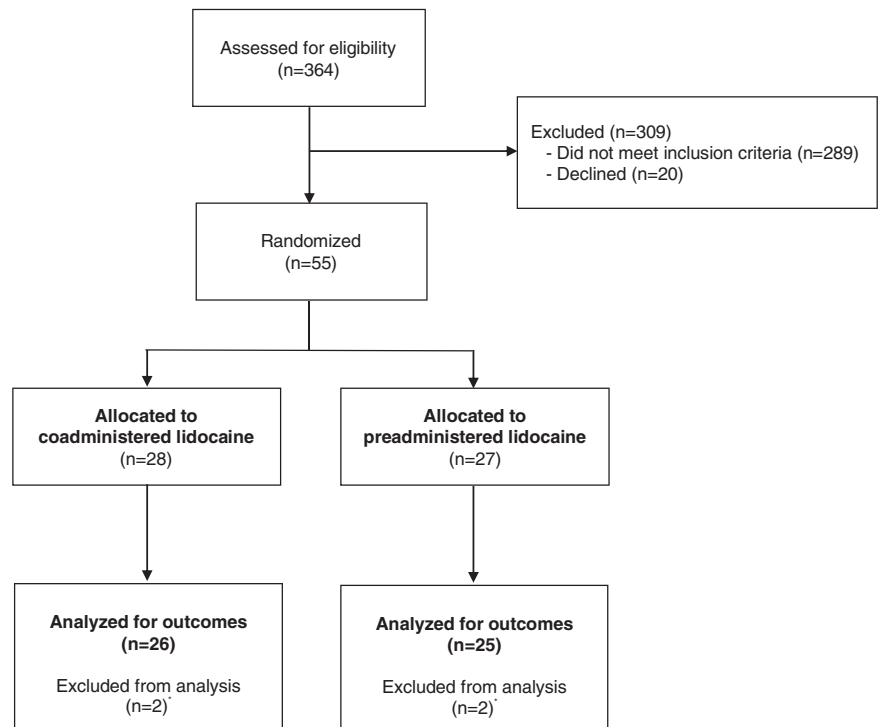
### 3.1 | Characteristics of study subjects

We enrolled 55 patients: 51 were evaluated for the primary and secondary outcomes, with 25 receiving coadministered lidocaine (Figure 1). The patient characteristics were similar between groups, except there were more patients whose primary language was Spanish who received coadministered lidocaine (Table 1). The baseline scores of pain and distress were similar in both groups (Table 2).

### 3.2 | Main results

Figure 2 presents the OSBD-R scores associated with the administration of intranasal midazolam in children who received preadministered and coadministered lidocaine. The mean OSBD-R scores associated with intranasal midazolam administration were similar in both groups. However, the upper limit of the 95% confidence interval (CI) of the difference in OSBD-R scores between coadministered and preadministered lidocaine was greater than our predetermined margin of

**FIGURE 1** Patient enrollment flow diagram.\*Patients excluded from analysis because of protocol violations



**TABLE 1** Patient characteristics

	Coadministered Lidocaine (n = 26)	Preadministered Lidocaine (n = 25)
Age, median (IQR), years	2 (2–4)	2 (2–3.5)
Male patients, No. (%)	16 (61.5)	13 (52)
Weight, mean (SD), kg	16.4 (5.1)	15.7 (2.9)
Dose of IN midazolam administered, mean (SD), mg	7.7 (1.6)	7.9 (1.4)
<b>Ethnicity/race, No. (%)</b>		
Hispanic	21 (80.8)	16 (64)
White	1 (3.8)	3 (12)
Black	2 (7.7)	2 (8)
>1	2 (7.7)	4 (16)
<b>Primary language of child, No. (%)</b>		
English	13 (50)	18 (72)
Spanish	13 (50)	7 (28)
<b>Received IN midazolam in the past, No. (%)</b>		
No	26 (100)	0
Yes	0	25 (100)
<b>Received any IN medication or spray in the past, No. (%)</b>		
No	21 (80.8)	19 (76)
Yes	5 (19.2)	6 (24)

IQR, Interquartile range; IN, intranasal.

non-inferiority, and the lower limit of the 95% CI was less than zero (Table 2, Figure 3). This means that we could not determine if one group was non-inferior to the other (ie, inconclusive). The FLACC and CHEOPS scores and cry duration were similar between groups (Table 2). The pain and distress associated with intranasal lidocaine administration by itself measured with the OSBD-R, CHEOPS, FLACC, and cry duration were 3.8 units (95% CI 2.5 to 5.1 units), 9.9 units (95% CI 9 to 10 units), 6 units (95% CI 4.4 to 7.7 units), and 56 seconds (95% CI 25 to 87 seconds), respectively. Cry duration was truncated at 5 minutes for only 1 patient after receipt of intranasal lidocaine; the patient was in the preadministered lidocaine group.

Table 3 presents caregiver and clinician satisfaction. There was no difference between the 2 groups in caregiver or clinician satisfaction in regard to the perceived nasal pain or burning experienced by children. More clinicians were satisfied with the ease of administration of intranasal midazolam when using coadministered lidocaine, and more clinicians who used coadministered lidocaine would use the same method again.

There were no paradoxical reactions and no serious adverse events. Of patients who received preadministered lidocaine, 3 (12%) vomited and 1 (4%) had an “other” adverse event (nosebleed). There were no adverse events in children who received coadministered lidocaine. The frequency of vomiting was similar between the 2 groups.

#### 4 | LIMITATIONS

We enrolled a convenience sample in accordance with study team availability, which could have introduced sampling bias. The subjective nature of certain outcomes (eg, observational measures of pain and

**TABLE 2** Pain and distress associated with intranasal midazolam administration

	Coadministered Lidocaine (n = 26)	Preadministered Lidocaine (n = 25)	Difference (95% CI)	Margin of Non-inferiority <sup>a</sup>
<b>OSBD-R score, mean (95% CI), units<sup>b</sup></b>				
Baseline	0.1 (0 to 0.2)	0.1 (0 to 0.2)	0 (-0.2 to 0.1)	
Administration of IN midazolam	7.0 (5.2 to 8.9)	6.4 (5.0 to 7.8)	0.6 (-1.7 to 2.8)	1.8
<b>CHEOPS score, mean (95% CI), units<sup>c</sup></b>				
Baseline	6.1 (5.7 to 6.5)	6.0 (5.5 to 6.5)	0.1 (-0.5 to 0.7)	N/A
Administration of IN midazolam	10.5 (9.5 to 11.4)	10.6 (9.7 to 11.4)	-0.1 (-1.4 to 1.2)	
<b>FLACC score, mean (95% CI), units<sup>d</sup></b>				
Baseline	0.1 (-0.1 to 0.4)	0.2 (-0.3 to 0.7)	-0.1 (-0.7 to 0.4)	
Administration of IN midazolam	7.0 (5.4 to 8.6)	6.7 (5.3 to 8.1)	0.3 (-1.8 to 2.4)	N/A
<b>Cry duration, mean (95% CI), s<sup>e</sup></b>				
	73 (45 to 102)	84 (58 to 109)	-11 (-48 to 27)	N/A

CHEOPS, Children's Hospital of Eastern Ontario Pain Scale; CI, confidence interval; FLACC, Faces, Legs, Activity, Cry, Consolability; IN, intranasal; N/A, not applicable; OSBD-R, Observational Scale of Behavioral Distress-Revised.

<sup>a</sup> Coadministered lidocaine is noninferior to preadministered lidocaine if the upper limit of the 95% CI of the difference between the 2 groups is less than the margin of noninferiority.

<sup>b</sup> OSBD-R minimum score = 0; maximum score = 94. Mean of total scores obtained during 1-minute baseline and administration phases for each patient.

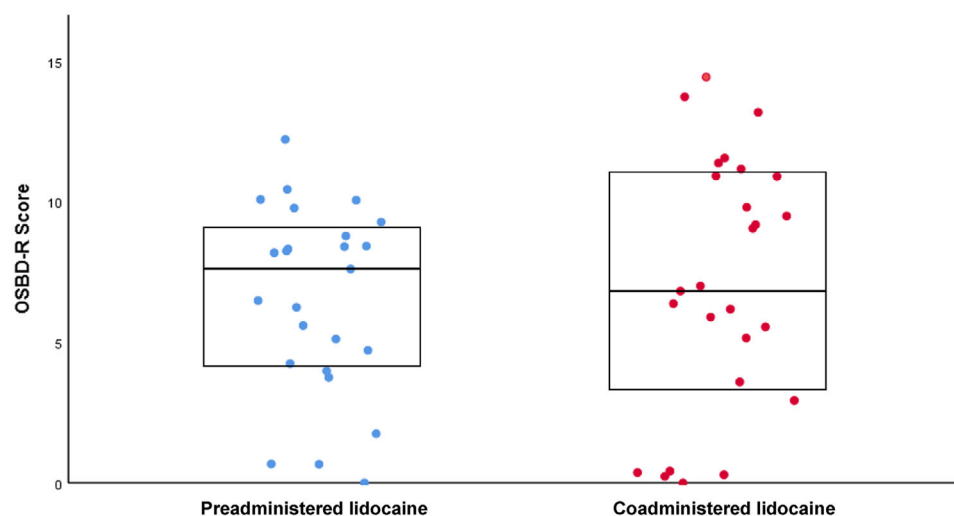
<sup>c</sup> CHEOPS minimum score = 4 (4 to 6 = no pain); maximum score = 13. Mean of maximum scores obtained during baseline and administration of first 15 seconds of IN midazolam for each patient.

<sup>d</sup> FLACC minimum score = 0; maximum score = 10. Mean of maximum scores obtained during baseline and administration of the first 15 seconds of IN midazolam for each patient.

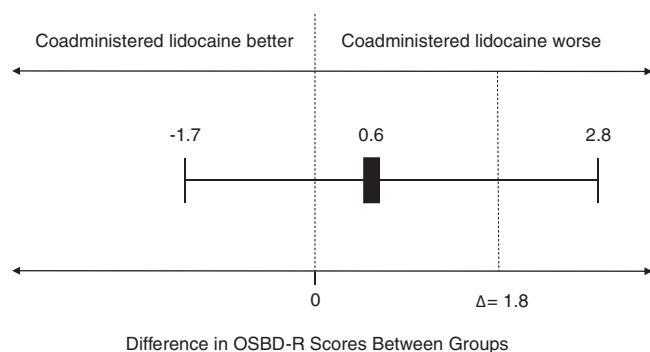
<sup>e</sup> Cry duration measured from administration of intranasal medication to cessation of crying.

distress) may have the potential for bias, although we demonstrated high interrater reliability among our 5 outcome assessors. There were 4 patients enrolled but excluded because of protocol violations. Although these patients were assigned to a study group, we could conduct only a modified intention-to-treat analysis because none of the excluded patients had outcome data collected. We used cry duration as a secondary outcome, which has been shown to have poor to moderate convergent validity when used in children receiving intranasal

midazolam.<sup>4</sup> However, we were able to demonstrate similar OSBD-R, CHEOPS, and FLACC scores between groups, which are all observational measures of pain and distress that have been shown to have strong validity in this context.<sup>4,13</sup> Our study enrolled a small sample size, which may have been less successful in balancing baseline risk factors than a larger trial would have been. Our study was a single-center trial, which may limit the generalizability of our findings. Finally, we were unable to evaluate for differences based on whether intranasal



**FIGURE 2** Pain and distress associated with administration of intranasal midazolam in children who received preadministered and coadministered lidocaine. Pain and distress were measured with the Observational Scale of Behavioral Distress-Revised (OSBD-R), for which the minimum score is 0 units and the maximum score is 94 units. Boxes represent median (middle line), 25th percentile (bottom line), and 75th percentile (top line)



**FIGURE 3** Difference in Observational Scale of Behavioral Distress–Revised (OSBD-R) scores between children who received preadministered and coadministered lidocaine. The upper limit of the 95% confidence interval (2.8) of the difference in scores was greater than the margin of non-inferiority ( $\Delta$ ) of 1.8, and the lower limit of the 95% confidence interval (–1.7) was less than zero, representing an inconclusive result

midazolam was administered sequentially or simultaneously into the nostrils. However, we aimed to minimize any potential differences in observed pain and distress caused by this variation by ensuring that the total dose was administered within a 15-second interval for all patients.

## 5 | DISCUSSION

We demonstrated that the pain and distress associated with intranasal midazolam administration in children undergoing laceration repair was similar between groups of children who received coadministered

and preadministered lidocaine, with a small difference in OSBD-R, CHEOPS, and FLACC scores between groups (ie, 0.6, 0.1, and 0.3 units, respectively). However, our non-inferiority determination was inconclusive and does not indicate whether there is a difference in decreasing pain and distress associated with intranasal midazolam administration between groups. Coadministered lidocaine was preferred by clinicians in several domains. We also demonstrated that the administration of intranasal lidocaine by itself was associated with a measurable degree of pain and distress.

The paradox of administering intranasal midazolam to facilitate distressing medical procedures in children is that its administration itself causes pain and distress.<sup>1,4-6</sup> Rather than abandon the use of this effective sedative and forgo its favorable properties (eg, rapid onset, needle-free administration, reliable anxiolysis), the use of intranasal lidocaine has been explored to ameliorate this problem. Both preadministered and coadministered lidocaine have been shown to be effective in decreasing the pain and distress associated with intranasal midazolam or similarly acidic solutions.<sup>6-8</sup> However, to our knowledge there are no previous studies comparing the effectiveness of both methods, and it is unknown whether one might be a suitable alternative to the other. This is important in the context of providing care to children in the ED because the ability to achieve a comparable decrease in pain and distress with coadministered lidocaine would both streamline ED work flow and spare a child the exposure to an additional potentially noxious stimulus (ie, administration of intranasal lidocaine). Although we did not demonstrate non-inferiority, the similar scores of pain and distress observed in both groups suggests that coadministered lidocaine may potentially be a suitable alternative to preadministered lidocaine for decreasing the pain and distress associated with intranasal midazolam

**TABLE 3** Caregiver and clinician satisfaction

	Coadministered Lidocaine (n = 26)	Preadministered Lidocaine (n = 25)	Difference in proportions (95% CI)
<b>Caregiver satisfaction</b>			
My child did not have any burning or pain in the nose when receiving intranasal midazolam spray, No. (% [95% CI]) <sup>a</sup>	12 (46 [27 to 67])	10 (40 [21 to 61])	6 (–20 to 31)
If my child needed medications to stay calm for a procedure, I would like to use the same ones again, No. (% [95% CI]) <sup>a</sup>	25 (96 [80 to 100])	20 (80 [59 to 93])	16 (–3 to 36)
<b>Clinician satisfaction<sup>a</sup></b>			
It was easy to administer the intranasal midazolam, No. (% [95% CI]) <sup>a</sup>	26 (100 [87 to 100])	16 (64 [43 to 82])	36 (16 to 56)
I would like to use this method of administering intranasal midazolam and lidocaine again, No. (% [95% CI]) <sup>a</sup>	24 (92 [75 to 99])	8 (32 [15 to 54])	60 (35 to 76)
Using lidocaine decreased the patient's burning or pain in the nose caused by the intranasal midazolam, No. (% [95% CI]) <sup>a</sup>	18 (69 [48 to 86])	13 (52 [31 to 72])	17 (–9 to 41)
This method of giving the intranasal midazolam and lidocaine is more difficult compared with giving only intranasal midazolam without lidocaine, No. (% [95% CI]) <sup>a</sup>	2 (8 [1 to 25])	16 (64 [43 to 82])	–56 (–73 to –31)

CI, confidence interval.

<sup>a</sup>Number of individuals who answered “agree” or “strongly agree” to the statements posed.

<sup>b</sup>Clinician is the individual who administered the intranasal medication(s). Physicians and nurses performed administrations in a standardized fashion for 45 and 6 patients, respectively.

administration in children, although future study with larger sample sizes are needed to make this conclusion. In addition to streamlining ED work flow by removing the need to separately administer an additional medication, coadministered lidocaine spares a child the need to undergo a separate administration of intranasal lidocaine, which we found is associated with a measurable degree of pain and distress.

Our study does not address whether the degree of pain and distress observed in children receiving preadministered and coadministered lidocaine is significantly different from that experienced by children receiving intranasal midazolam without any lidocaine. Although not a direct comparison, our previous work showed that in a similar population of children, OSBD-R, CHEOPS, and FLACC scores associated with intranasal midazolam administration (27.1, 11.5, and 8.9 units, respectively) were higher than the scores observed in the current study.<sup>4</sup> Additionally, previous studies have shown that preadministered and coadministered lidocaine are more effective than placebo in decreasing pain and distress associated with intranasal administration of midazolam or acidic solutions in both children and adults.<sup>7,8</sup>

The mean scores of pain and distress associated with intranasal midazolam administration observed in both groups of children who received preadministered and coadministered lidocaine were not scores that typically represent no pain or mild pain.<sup>9-12</sup> This differs from a previous study of children aged 5 to 50 months who received intranasal lidocaine before intranasal midazolam and whose parents assigned pain scores associated with intranasal midazolam administration that were no >2 out of 10.<sup>6</sup> A separate study showed that children aged 6 to 12 years who received intranasal lidocaine had a greater decrease in pain associated with intranasal midazolam compared with placebo and reported a median pain score associated with intranasal midazolam administration of 3 out of 10 (interquartile range 0 to 6).<sup>7</sup> One possible explanation for the higher scores of pain and distress associated with intranasal midazolam administration observed in our study is that although intranasal lidocaine may be effective in decreasing the pain associated with midazolam, it may not completely ameliorate the distress associated with intranasal administration in general. In addition, the distress related to intranasal administration may be more pronounced in younger children (ie, ≤7 years), who composed the entirety of the cohort in our study. However, the posited distress associated with intranasal administration should not automatically preclude the use of intranasal medications in younger children. Some may consider the transient distress an acceptable tradeoff, considering the benefits associated with intranasal administration.<sup>2</sup> The decision to use intranasal medications in younger children should, therefore, be made in conjunction with families with these factors taken into consideration.

The results of our study were inconclusive. This meant we could not determine if one group was non-inferior to the other, although an inconclusive result does not mean that one group was better or worse than the other. This inconclusive result could have been due in part to the observed standard deviations of the primary outcome in the coadministered and preadministered groups (ie, 4.5 and 3.5, respectively) being larger than our estimated standard deviation (ie,

2.25) upon which our sample size was based. A future effort with a larger sample size could overcome this limitation and provide updated insights.

In conclusion, our study shows that pain and distress associated with intranasal midazolam administration in children undergoing laceration repair are similar when using either coadministered lidocaine or preadministered lidocaine. However, our non-inferiority determination was inconclusive, and our findings do not indicate whether there is a difference in decreasing pain and distress associated with intranasal midazolam administration between groups. Future study with a sample size based on a larger SD is required to determine non-inferiority of one method compared with the other and to evaluate the comparative feasibility and acceptability of both methods in the ED setting.

#### ACKNOWLEDGMENTS

The authors acknowledge Maria Kwok, Lauren Chernick, Lorraine Ng, and Kara Gross Margolis for serving on the Scholarly Oversight Committee for this study; Cindy Roskind and Nazreen Jamal for their advocacy and support; Cheng-Shiun Leu for his statistical review; and the research coordinators, nurses, child life specialists, attending physicians, fellows, and residents of the Morgan Stanley Children's Hospital Pediatric Emergency Department, without whom this study would not have been possible. All authors attest to meeting the 4 ICMJE.org authorship criteria: (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) drafting the work or revising it critically for important intellectual content; AND (3) final approval of the version to be published; AND (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately *investigated and resolved*.

#### CONFLICT OF INTEREST

None of the authors have any conflicts of interest to disclose.

#### AUTHORS' CONTRIBUTIONS

Nicole C. O'Connell and Daniel S. Tsze conceptualized the study, designed the trial, supervised the conduct of the trial and data collection, and conducted the statistical analyses for the study. Nicole C. O'Connell, Daniel S. Tsze, Hilary A. Woodward, Pamela L. Flores-Sanchez, Son H. McLaren, Maria Ieni, Kenneth W. McKinley, and SriPriya T. Shen undertook recruitment of participating patients. Nicole C. O'Connell, Hilary A. Woodward, Pamela L. Flores-Sanchez, Son H. McLaren, and Maria Ieni analyzed and scored the video recordings. Nicole C. O'Connell, Daniel S. Tsze, and Peter S. Dayan provided substantial contributions to the analysis and interpretation of the data. Nicole C. O'Connell drafted the manuscript, and all authors contributed substantially to its revision. Daniel S. Tsze takes responsibility for the paper as a whole.

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**How to cite this article:** O'Connell NC, Woodward HA, Flores-Sanchez PL et al. Comparison of preadministered and coadministered lidocaine for treating pain and distress associated with intranasal midazolam administration in children: A randomized clinical trial. *JACEP Open.* 2020;1:1562-1570. <https://doi.org/10.1002/emp2.12227>