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A randomized clinical trial comparing oral, aerosolized intranasal, and aerosolized buccal midazolam

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Abstract

Study Objective—To determine whether aerosolized intranasal or buccal midazolam reduces the distress of pediatric laceration repair compared to oral midazolam.

Methods—Children 0.5–7 years old needing non-parenteral sedation for laceration repair were randomized to receive oral, aerosolized intranasal, or aerosolized buccal midazolam. Patient distress was rated by blinded review of videotapes using the Children's Hospital of Eastern Ontario Pain Score. Secondary outcomes included activity scores, sedation adequacy, sedation onset, satisfaction, and adverse events.

Results—For the 169 subjects (median age 3.1 years) evaluated for the primary outcome, we found significantly less distress in the buccal midazolam group compared to oral route (p=0.04; difference −2, 95% CI −4, 0), and a corresponding non-significant trend for the intranasal route (p=0.08; difference −1, 95% CI −3, 1). Secondary outcomes (177 subjects) favored the intranasal group, including a greater proportion with an optimal activity score (74%), a greater proportion of parents wanting this sedation in the future, and faster sedation onset. Intranasal was the route least tolerated at the time of administration. Adverse events were similar between groups.

Conclusions—When comparing the administration of midazolam by 3 routes to facilitate pediatric laceration repair, we noted slightly less distress in the aerosolized buccal group. The intranasal route demonstrated a greater proportion with optimal activity scores, greater proportions of parents wanting similar sedation in the future and faster onset, but was also the most poorly tolerated at the time of administration. Aerosolized buccal or intranasal midazolam represent effective and useful alternatives to oral midazolam for sedation for laceration repair.

Introduction

Background

Adequate sedation of children can provide superior conditions for laceration repair and improve the experience for the patient, caregiver and family.[1] Oral midazolam is one of the

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most commonly used sedative agents in the ED for minor procedures[2,3], and is effective approximately 60–76% of the time.[4,5] Intranasal midazolam dripped into the nares has not been well tolerated due to its acidity and the resulting pain of administration.[6–10]

Importance

Aerosolized administration of midazolam on mucosal surfaces may enhance drug delivery.[11] Aerosolized, rather than drip, administration of nasal midazolam may decrease discomfort and improve tolerance of this route.[11]

Goal

We sought to determine if using an atomizer device to aerosolize midazolam (either intranasal or buccal) would decrease procedural distress during pediatric laceration repair compared to standard oral delivery of midazolam. As secondary outcomes, we compared activity scores, sedation adequacy, time to sedation, provider and parental satisfaction, and drug tolerability.

Methods

Design and Setting

This randomized controlled trial was performed at Seattle Children's Hospital Emergency Department, an urban ED treating nearly 40,000 children annually. Historically, children at our institution requiring sedation for laceration repair have been given oral midazolam while parenteral agents such as ketamine are reserved for those with very large or complex lacerations, or inadequate sedation with oral midazolam. This study was approved by our Institutional Review Board with informed consent, and was registered at ClinicalTrials.Gov (#NCT00675909).

Participants

Between November 2006 and December 2009 ED clinical research associates enrolled children 6 months to <7 years old requiring laceration repair who were NPO for solids and liquids for at least two hours, had English-speaking parents, and for whom the parents and ED physician agreed that sedation was needed but that parenteral sedatives were not warranted. We excluded children with oral or nasal wounds (which could impede drug delivery); closed head injury with loss of consciousness; an abnormal neurologic exam; significant developmental delay or baseline neurologic deficits; severe trauma with suspected internal injuries; acute or chronic respiratory, renal, cardiac, or hepatic abnormalities; known allergy or previous adverse reaction to benzodiazepines; use of an erythromycin containing antibiotic (which could impact benzodiazepine metabolism); or prior enrollment.

Intervention

We randomized children into three study groups using a permuted block randomization schedule in a ratio of 1:1:1. Those assigned to the first group received oral midazolam (0.5 mg/kg, oral preparation; maximum dose 15 mg, Roxane Laboratories Inc, Columbus, OH) mixed in cherry syrup. Children in the other groups received midazolam (0.3 mg/kg parenteral solution; maximum dose 10 mg, Baxter Healthcare Corporation, Deerfield, IL) aerosolized with an atomization device, either intranasal (group 2) or buccal (group 3). ED nurses administered all study drugs. Treating physicians remained blinded to study group. Although the parents, children, ED nurses, and research staff were not blinded, they were asked not to reveal the assignment to the treating physicians.

Methods of Measurement and Data Collection

Children were video recorded prior to study drug administration, and from immediately after administration of the study drug until discharge from the ED. The ED nurse recorded tolerance of study drug administration. Research staff recorded demographic information, vital signs (oxygen saturation, respiratory rate, heart rate), and the occurrence of any adverse events including vomiting, oxygen saturation less than 93%, and need for oxygen or airway repositioning. At the conclusion of sedation, the treating physician and ED nurse scored their satisfaction with the child's sedation on a 10-cm Likert scale.

Within two weeks of ED discharge, a research staff member contacted parents by telephone and asked about delayed complications and their satisfaction with the sedation.

Video recordings were scored by one of two trained nurse evaluators, who were blinded to treatment group and the purpose of the study. At five minute intervals they recorded the child's distress using the modified CHEOPS (Children's Hospital of Eastern Ontario Pain Scale)[3,12] and an activity score. The CHEOPS is a 4- to 13-point scale that measures cry, facial expression, verbal expression, torso movement, leg movement, and reaching toward the wound. The activity score is a 5-point scale indicating level of sedation (1=asleep, not readily arousable, 2=asleep, slowly responds, 3= drowsy, readily responds, 4=awake, calm, 5= awake, active). We defined a score of 3 or 4 as optimal for sedation for minor procedures. In addition, the evaluator recorded their subjective assessment of the time at which the child appeared to be adequately sedated.

Data Analysis

Our primary outcome was the first CHEOPS score after the laceration repair procedure began, comparing each of the two aerosolized midazolam groups (buccal and intranasal) individually relative to the standard oral midazolam group. These comparisons were made with the Wilcoxon rank sum test, with p-values doubled as a Bonferroni adjustment for the two comparisons such that an adjusted p-value of <0.05 was considered statistically significant.

We designed the study to have 80% power to detect a 2-point reduction in the median CHEOPS score for buccal or nasal midazolam relative to oral midazolam, assuming $\alpha=0.05$. To achieve these design characteristics, 180 subjects (60 per treatment group) were required.

We supplemented the primary analysis above with calculations of differences between groups, and the 95% confidence intervals of these differences (for medians using the Bonett-Price method[13–15]). Time to adequate sedation was depicted with Kaplan-Meier methodology.

Results

Characteristics of Study Subjects

Of 180 subjects enrolled, 169 were evaluable for the primary outcome, and 177 for the secondary outcomes (Figure 1). Children in the buccal midazolam group were slightly older; however other baseline characteristics were similar between groups (Table 1).

Results

The CHEOPS score at the beginning of the procedure demonstrated significantly less distress in the buccal group compared to oral (p=0.04; difference −2, 95% CI –4, 0), and exhibited a non-significant trend in the intranasal group (p=0.08; difference −1, 95% CI −3, 1) (Table 2). These distributions are shown in Figure 2.

Despite this primary outcome, secondary outcomes did not favor the buccal group (Table 2). The intranasal route demonstrated faster sedation onset (Figure 3), a greater proportion achieving adequate sedation, a greater proportion with optimal activity scores, and a higher rate of parents choosing the same regimen again in the future (Table 2). The intranasal route, however, demonstrated the most irritation and the smallest proportion of patients who accepted the medication easily (difference −20% 95% CI −38%, −2% compared to oral midazolam) (Table 3).

Adverse events were similar between groups. One patient in the oral midazolam group was deeply sedated and the treating provider administered supplementary oxygen as a precaution; however there was no respiratory depression or oxygen desaturation. One subject in each of the three groups vomited prior to discharge, with post-discharge vomiting in one subject in the oral group, one in the buccal group and two in the intranasal group. Parents described post-discharge nightmares in one child in the oral group and one child in the intranasal group.

Limitations

Some outcomes were both subjective (video review of adequate sedation, physician rating of sedation) and non-blinded (nurse rating of sedation) and should be interpreted with caution due to their potential for bias. Despite randomization, our results may have been impacted by the higher median age of the children in the buccal midazolam group, although it is unclear which direction the age differential would be most likely to favor for each outcome measure. We used two different nurses to score videotapes and it is possible that their interpretative thresholds may have differed. Finally, the delay from time of adequate sedation to procedure start in all groups may have impacted the results of this study.

Discussion

Physicians are still searching for a non-invasive route of drug administration for common minor procedures in young children who require sedation and anxiolysis. Oral midazolam is unreliable, due to first-pass hepatic metabolism and a reported efficacy of 60–76%.[4,5] The intranasal route now appears more reliable as a result of more effective drug delivery by atomizer. [16–20]

In this study comparing oral, aerosolized buccal, and aerosolized intranasal midazolam, we did not find one route to be definitively superior to the others. Although our primary analysis demonstrated significantly less distress with the buccal route, the magnitude of this effect was modest (median difference 2 CHEOPS score points), this effect may have been exaggerated by lower baseline scores in this group, and no secondary outcomes corroborated superiority of the buccal route. Instead, aerosolized intranasal midazolam appeared superior based upon multiple secondary outcomes: time of sedation onset, parent wanting this type of sedation in the future, and percent of patients with adequate sedation at some point prior to the procedure. Subjects in the intranasal midazolam group, however, did experience more irritation and discomfort from drug administration than the oral and buccal midazolam treatment groups.

An early placebo-controlled trial of intranasal midazolam as a preanesthetic sedation found that it was effective as an anxiolytic and sedative in doses of 0.2 mg/kg and 0.3 mg/kg.[21] Subsequently, Yealy et al retrospectively compared efficacy of different doses of intranasal midazolam, administered by dripping the medication into the nares. They observed the greatest effect at doses of 0.3 mg/kg to 0.5 mg/kg with treatment failure least likely at 0.4 mg/kg to 0.5 mg/kg. Only 27% of patients at a dose under 0.3 mg/kg were adequately

sedated. The biggest drawback noted for dripped intranasal midazolam was the transient burning discomfort with administration.[22]

Administration by intranasal drops and aerosolized intranasal midazolam were compared in a retrospective review of 64 sedations prior to dental procedures in children. Both methods of administration provided effective sedation, though aerosolized administration was better tolerated. In addition, use of an aerosolized spray led to less aversive behavior than drops during administration.[23]

In a prospective study of adults requiring sedation for MRI, intranasal midazolam was found to be more effective than oral administration in decreasing anxiety.[24] In a randomized double-blind study of children requiring premedication prior to anesthesia, intranasal midazolam (0.3mg/kg) was compared to oral midazolam (0.5mg/kg), rectal midazolam (0.5 mg/kg) and sublingual midazolam. All 4 methods were found to be equally effective, with an 83%–93% success rate. It is unclear whether the midazolam was dripped or aerosolized. Although the intranasal route provided the earliest time to sedation, significant nasal irritation was noted.[25] A recent study shows that prior administration of aerosolized lidocaine mitigates the irritation of intranasal midazolam.[26]

Our study results are consistent with a recent retrospective review of aerosolized intranasal midazolam sedation for minor procedures in children in the ED.[11] The authors reviewed 205 patients, 89% requiring laceration repair. They found that aerosolized intranasal midazolam was effective in almost 95% of the patients and that just over 5% required additional sedation (generally ketamine) for the procedure to be completed. There were no adverse events from the midazolam. This study did not discuss nasal irritation from intranasal midazolam administration.

Having a variety of options permits greater flexibility in individualizing each patient's sedation. For children who have nasal congestion, which could impede drug delivery, or a laceration around or near the nares, the buccal or oral routes might be preferable. For other children, intranasal midazolam may be the preferred method. Despite the irritation of administration, aerosolized intranasal midazolam is a quick and effective method of sedating children for laceration repair. Aerosolized midazolam (whether buccal or intranasal) is an effective alternative sedation option for laceration repair in children.

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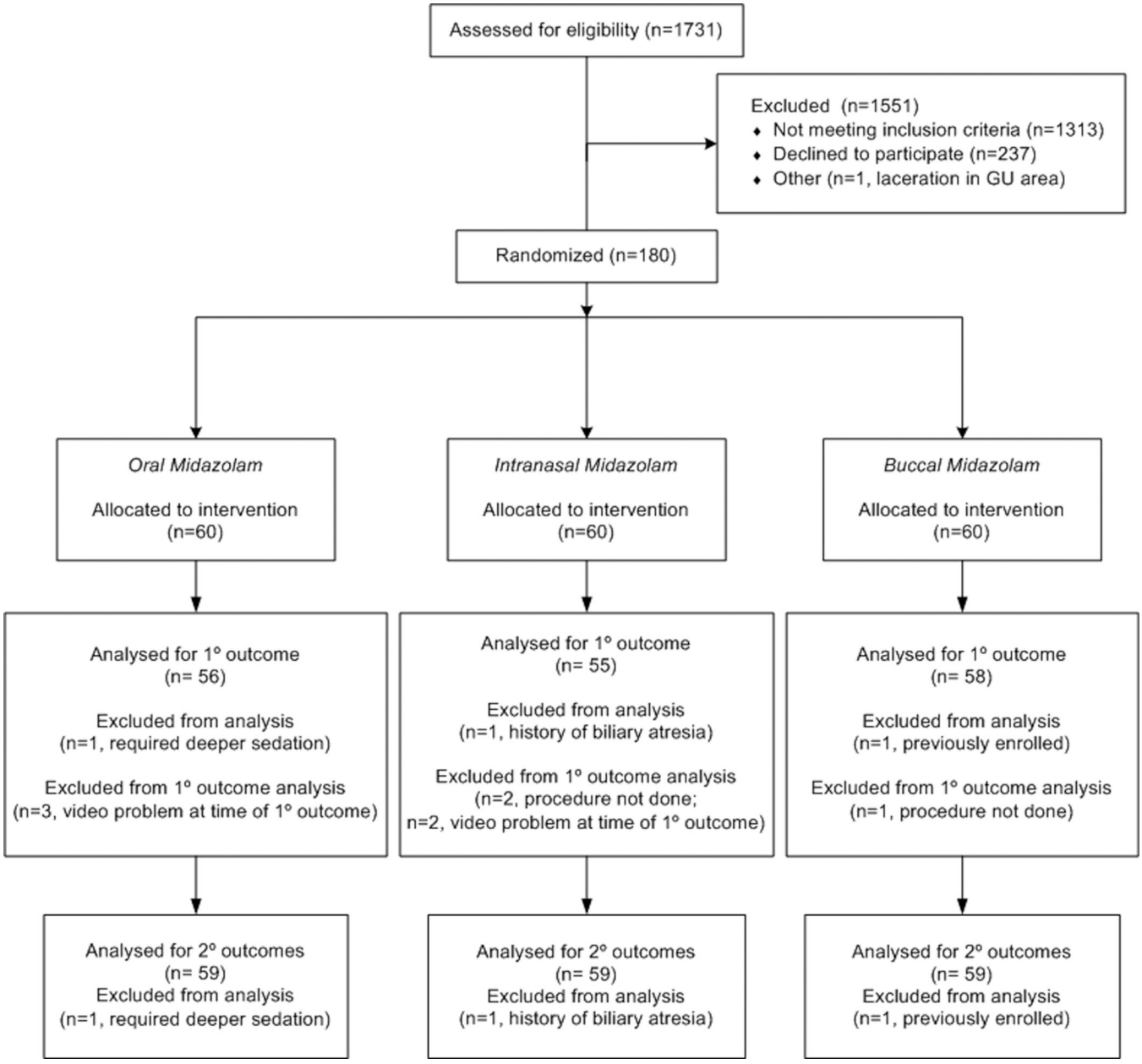

Figure 1.
Enrollment flow diagram

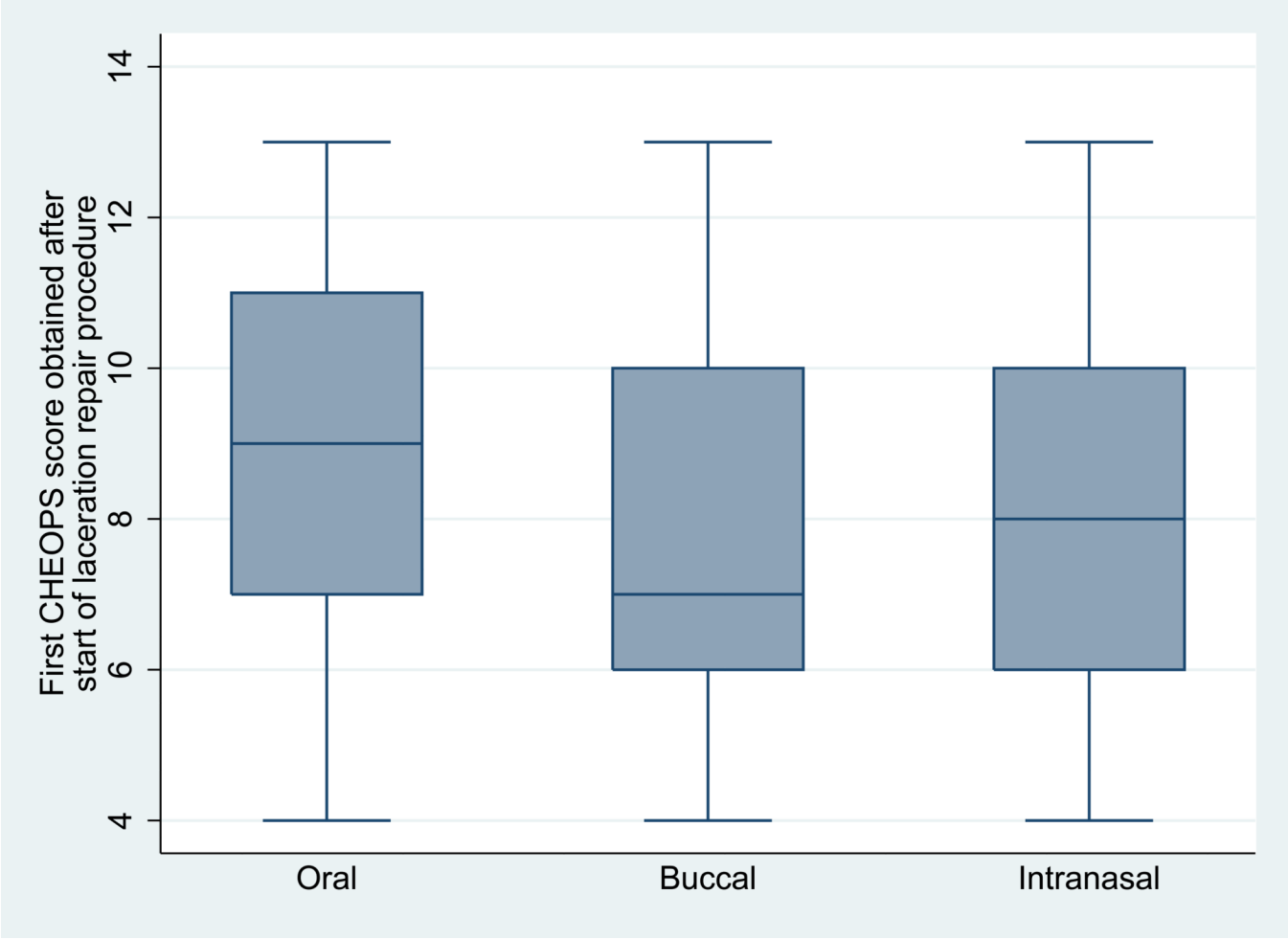

Figure 2.
Distress score (CHEOPS) at start of procedure for midazolam treatment groups

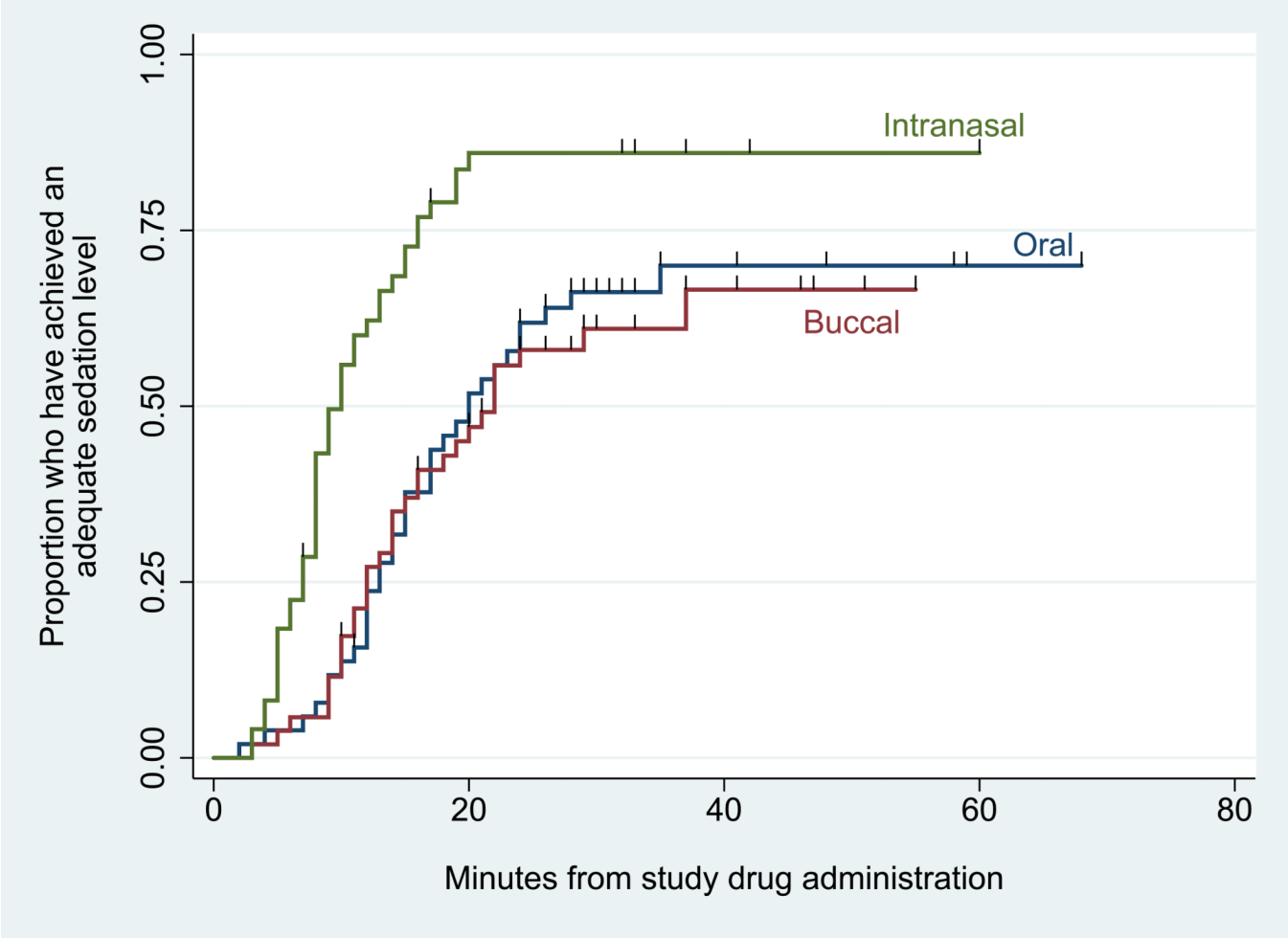

Figure 3.
Kaplan-Meier curve showing time to adequate sedation

Table 1

Patient and care provider characteristics

Characteristic	Study Group		
	Oral Midazolam	Buccal Midazolam	Intranasal Midazolam
N‡	59	59	59
Age, median (range)	2.7 (1.2, 6.7)	3.8 (1.1, 6.1)	2.9 (1.2, 7.0)
Gender, # (%) male	33 (56%)	40 (68%)	40 (68%)
Weight-for-age Z score, mean (SD)	0.2 (1.0)	0.5 (1.0)	0.6 (1.0)
Laceration size	2 missing		1 missing
<2 cm	39 (68%)	37 (63%)	37 (64%)
2–4 cm	18 (32%)	20 (34%)	19 (33%)
>4 cm	0 (0%)	2 (3%)	2 (3%)
Laceration location			
face	45 (76%)	37 (63%)	45 (76%)
scalp	4 (7%)	5 (8%)	1 (2%)
hand	5 (8%)	4 (7%)	9 (15%)
other location	5 (8%)	12 (20%)	3 (5%)
multiple sites*	0 (0%)	1 (2%)	1 (2%)
Other injury**	1 (2%)	1 (2%)	1 (2%)
Prior history of laceration†	4 (7%)	10 (17%)	5 (8%)
Prior history of sedation†	4 (7%)	8 (14%)	7 (12%)
Medications (ED)	2 missing	2 missing	3 missing
topical	10 (18%)	10 (18%)	12 (21%)
injectable	11 (19%)	8 (14%)	6 (11%)
both	36 (63%)	37 (65%)	38 (68%)
none	0 (0%)	2 (4%)	0 (0%)
Type of care provider	1 missing		1 missing
resident	37 (64%)	41 (69%	45 (78%)
attending	9 (16%)	9 (15%)	8 (14%)
fellow	7 (12%)	4 (7%)	2 (3%)
ARNP	5 (9%)	5 (8%)	3 (5%)
Care provider's experience	3 missing	6 missing	3 missing
1 year	20 (36%)	25 (47%)	29 (52%)
2 years	9 (16%)	11 (21%)	12 (21%)
3 years	9 (16%)	6 (11%)	6 (11%)
>=4 years	18 (32%)	11 (21%)	9 (16%)

‡These are the Ns used in each analysis, except where missing observations are otherwise noted in the table.

*The site combinations for the two patients with lacerations at multiple sites were: face/scalp and face/hand.

** The other injuries noted at the time of the ED visit were: crush injury to fingers associated with the laceration (1 patient), scrape on nose (1 patient), secondary laceration on forehead (1 patient). The buccal and intranasal groups each had one patient with missing data for this item.

† The oral group had one patient with missing data for these two items.

Table 2

Summary statistics and effect size estimates for secondary outcomes

Outcome Measure	Study Group		
	Oral Midazolam	Buccal Midazolam	Intranasal Midazolam
	median (range) [N]	median (range) ***Difference from Oral (95% CI)*** [N]	median (range) ***Difference from Oral (95% CI)*** [N]
Change in CHEOPS score from baseline to beginning of procedure	+2 (−2, +7) [56]	+1 (−6, +6) ***−1 (−2, 0)*** [56]	+2 (−3, +7) ***0 (−1, +1)*** [51]
Time from study drug administration to start of procedure (minutes)	34 (11, 68) [58]	32 (10, 59) ***−2 (−7, +4)*** [58]	28 (5, 60) ***−6 (−12, +1)*** [55]
Duration of procedure (minutes)	12 (1, 40) [58]	10 (1, 39) ***−2 (−5, +1)*** [58]	12 (1, 40) ***0 (−4, +4)*** [54]
Physician rating of sedation	6.7 (0, 10) [57]	7.1 (0, 10) ***+0.4 (−2.1, +2.9)*** [58]	8.1 (1, 10) ***+1.4 (−0.5, +3.2)*** [52]
Nurse rating of sedation	6.8 (0, 10) [43]	7.6 (0, 10) ***+0.8 (−1.0, +2.6)*** [44]	7.7 (1, 10) ***+0.9 (−0.4, +2.2)*** [44]
Categorical Outcomes	Number of patients (%)	Number of patients (%) ***Difference from Oral (95% CI)***	Number of patients (%) ***Difference from Oral (95% CI)***
Patient Activity Score at first time point after start of repair procedure is in optimal range**	32 / 57 (56.1%)	34 / 58 (58.6%) ***+2.5% (−15.6%, +20.6%)***	41 / 55 (74.5%) ***+18.4% (+1.1%, +35.7%)***
Parent satisfied/very satisfied with sedation:	42 / 55 (76.3%)	41 / 56 (73.2%) ***−3.1% (−19.3%,+ 13.0%)***	49 / 55 (89.1%) ***+12.7% (−1.2%, +26.7%)***
Parent would choose same sedation again, % yes	35 / 55 (63.6%)	38 / 56 (67.9%) ***+4.2% (−13.4%, +21.9%)***	47 / 55 (85.5%) ***+21.8% (+6.1%, +37.6%)***
Subjects who where deemed adequately sedated at some time point prior to the start of the procedure	34 / 51 (66.7%)	31 / 52 (59.6%) ***−7.1% (−25.6%, +11.5%)***	44 / 52 (84.6%) ***+17.9% (+1.7%, +34.2%)***

** An Activity Score of 3 to 4 is considered in the optimal range for laceration repair in the ED.

Table 3

Tolerability of Study Drug Administration

Variable	Study Group		
	Oral Midazolam	Buccal Midazolam	Intranasal Midazolam
N	58	59	57
Medication Acceptance			
Took easily	38 (66%)	32 (54%)	26 (46%)
Mildly resistant	14 (24%)	20 (34%)	27 (47%)
Very resistant	6 (10%)	7 (12%)	4 (7%)
Irritation – any	9 (16%)	10 (17%)	23 (40%)
cough†	3 (5%)	7 (12%)	14 (24%)
gag†	7 (12%)	9 (15%)	14 (24%)
sore throat†	0 (0%)	1 (2%)	1 (2%)

† Irritation symptoms are not mutually exclusive. Many subjects experienced more than one type of irritation symptom.