A Randomized Clinical Trial Comparing Oral, Aerosolized Intranasal, and Aerosolized Buccal Midazolam

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Study objective: We determine whether aerosolized intranasal or buccal midazolam reduces the distress of pediatric laceration repair compared with oral midazolam.

Methods: Children aged 0.5 to 7 years and needing nonparenteral 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 with the oral route group ($P=.04$; difference −2; 95% confidence interval −4 to 0) and a corresponding nonsignificant trend for the intranasal route ($P=.08$; difference −1; 95% confidence interval −3 to 1). Secondary outcomes (177 subjects) favored the intranasal group, including a greater proportion of patients 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 administration. Adverse events were similar between groups.

Conclusion: When comparing the administration of midazolam by 3 routes to facilitate pediatric laceration repair, we observed slightly less distress in the aerosolized buccal group. The intranasal route demonstrated a greater proportion of patients 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 administration. Aerosolized buccal or intranasal midazolam represents an effective and useful alternative to oral midazolam for sedation for laceration repair. [Ann Emerg Med. 2011;58:323-329.]

Please see page 324 for the Editor's Capsule Summary of this article.

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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 most commonly used sedative agents in the emergency department (ED) for minor procedures[2,3] and is effective approximately 60% to 76% of the time.[4,5] Intranasal midazolam dripped into the nares has not been well tolerated because of 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]

Goals of This Investigation

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

MATERIALS AND METHODS

Study 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 received oral midazolam, whereas parenteral agents such as ketamine are reserved

Editor's Capsule Summary

What is already known on this topic

Emergency physicians sometimes administer oral midazolam when pediatric procedures are minor enough not to warrant parenteral sedation.

What question this study addressed

For laceration repair in children, is midazolam more effective if administered by buccal or intranasal aerosol compared with simple oral administration?

What this study adds to our knowledge

This 169-child randomized controlled trial demonstrated slightly less initial patient distress with the buccal route, whereas several secondary outcomes slightly favored the intranasal route instead.

How this is relevant to clinical practice

This study demonstrates that pediatric sedation with buccal or nasal midazolam aerosol is effective but not clearly superior to the oral route. Even in the best of these groups, one fourth of children were inadequately sedated.

for patients with very large or complex lacerations or inadequate sedation with oral midazolam. This study was approved by our institutional review board with informed consent.

Selection of Participants

Between November 2006 and December 2009, ED clinical research associates enrolled children aged 6 months to younger than 7 years and requiring laceration repair who had nothing by mouth for solids and liquids for at least 2 hours, had English-speaking parents, and for whom the parents and emergency 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 examination result; 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 affect benzodiazepine metabolism); or previous enrollment.

Interventions

We randomized children into 3 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 and Processing

Children were videorecorded before 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, pulse 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 2 weeks of ED discharge, a research staff member contacted parents by telephone and asked about delayed complications and their satisfaction with the sedation.

Videorecordings were scored by one of 2 trained nurse evaluators, who were blinded to treatment group and the purpose of the study. At 5-minute intervals, they recorded the child's distress by using the modified Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)[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 evaluators recorded their subjective assessment of the time at which the child appeared to be adequately sedated.

Primary Data Analysis

Our primary outcome was the first CHEOPS score after the laceration repair procedure began, comparing each of the 2 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 2 comparisons such that an adjusted $P<.05$ 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 $\alpha=.05$. To achieve these design characteristics, 180 subjects (60 per treatment group) were required.

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