Optimal Volume of Administration of Intranasal Midazolam in Children: A Randomized Clinical Trial

Daniel S. Tsze, MD, MPH*; Maria Ieni, MD; Daniel B. Fenster, MD, MS; John Babineau, MD; Joshua Kriger, MS; Bruce Levin, PhD; Peter S. Dayan, MD, MSc

*Corresponding Author. E-mail: dst2141@columbia.edu.

Study objective: The optimal intranasal volume of administration for achieving timely and effective sedation in children is unclear. We aimed to compare clinical outcomes relevant to procedural sedation associated with using escalating volumes of administration to administer intranasal midazolam.

Methods: We conducted a randomized, single-blinded, 3-arm, superiority clinical trial. Children aged 1 to 7 years and undergoing laceration repair requiring 0.5 mg/kg intranasal midazolam (5 mg/mL) were block-randomized to receive midazolam using 1 of 3 volumes of administration: 0.2, 0.5, or 1 mL. Procedures were videotaped, with outcome assessors blinded to volume of administration. Primary outcome was time to onset of minimal sedation (ie, score of 1 on the University of Michigan Sedation Scale). Secondary outcomes included procedural distress, time to procedure start, deepest level of sedation achieved, adverse events, and clinician and caregiver satisfaction.

Results: Ninety-nine children were enrolled; 96 were analyzed for the primary outcome and secondary outcomes, except for the outcome of procedural distress, for which only 90 were analyzed. Time to onset of minimal sedation for each escalating volume of administration was 4.7 minutes (95% confidence interval [CI] 3.8 to 5.4 minutes), 4.3 minutes (95% CI 3.9 to 4.9 minutes), and 5.2 minutes (95% CI 4.6 to 7.0 minutes), respectively. There were no differences in secondary outcomes except for clinician satisfaction with ease of administration: fewer clinicians were satisfied when using a volume of administration of 0.2 mL.

Conclusion: There was a slightly shorter time to onset of minimal sedation when a volume of administration of 0.5 mL was used compared with 1 mL, but all 3 volumes of administration produced comparable clinical outcomes. Fewer clinicians were satisfied with ease of administration with a volume of administration of 0.2 mL. [Ann Emerg Med. 2017;69:600-609.]

Please see page 601 for the Editor's Capsule Summary of this article.

0196-0644/$-see front matter

http://dx.doi.org/10.1016/j.annemergmed.2016.08.450

INTRODUCTION

Background

The intranasal route is an effective means of administering sedatives to children who require procedural sedation.[1-3] Intranasal administration delivers the sedative to the highly vascularized nasal mucosa and the olfactory tissue that is in direct contact with the central nervous system (termed the "nose-brain pathway"), thereby bypassing first-pass metabolism.[1,4] Although there are commercial products designed specifically for intranasal drug delivery, it is common practice in emergency departments (EDs) to use parenteral formulations of sedatives for intranasal administration.[1-3,5-7] However, commonly available concentrations of these sedatives often necessitate large total volumes to deliver the required weight-based dose in children. In the clinical setting, this total volume is often divided into smaller aliquots, or volumes of administration, that are administered repeatedly by alternating between both nostrils until the total volume is delivered.

Importance

Although the volume of administration is a fundamental aspect of intranasal administration, it is unclear what volume is optimal for achieving timely and effective sedation when intranasal sedatives, such as midazolam, are administered to children. Intranasal medications are typically administered with a mucosal atomization device, with a commonly recommended optimal volume of administration of approximately 0.3 mL and

Editor's Capsule Summary

What is already known on this topic

The intranasal route is an effective way to provide sedative medication to children.

What question this study addressed

What is the optimal volume to administer aliquots of intranasal midazolam?

What this study adds to our knowledge

In this 3-arm randomized controlled trial in 96 children receiving 0.2-, 0.5-, or 1-mL aliquots, time to onset and adequacy of sedation were clinically similar among groups. Clinicians least preferred the 0.2-mL volume because administration was more challenging.

How this is relevant to clinical practice

This study suggests that each volume may have pros and cons and that optimal volume may vary among patients and clinicians.

a maximum of 1 mL.[1,8] This is in contrast to other recommendations stating that a volume of administration should not exceed 0.15 or 0.2 mL because of concerns that any volume in excess of these limits will become runoff, drain out of the nose and not be absorbed, or will be swallowed and subject to first-pass metabolism.[4,9-15]

Goals of This Investigation

The aim of this study was to determine the optimal volume of administration of intranasal midazolam in children by comparing clinical outcomes relevant to procedural sedation associated with escalating volumes of administration (0.2, 0.5, and 1 mL) during laceration repair in an ED. Our primary outcome was time to onset of minimal sedation. Our secondary outcomes included procedural distress, time to procedure start, deepest level of sedation achieved, adverse events, and clinician and caregiver satisfaction. We hypothesized that using a volume of administration of 0.2 mL would be associated with a shorter time to onset of minimal sedation compared with using a volume of administration of either 0.5 or 1 mL because we expected that a volume of administration of 0.2 mL would have the least amount of runoff compared with larger volumes.[4,9-15]

MATERIALS AND METHODS

Study Design

We conducted a randomized, outcome assessor-blinded, 3-arm parallel group (1:1:1), superiority clinical trial in a single urban pediatric ED with an annual census of approximately 55,000 children per year. Our institutional review board approved this study, and written informed consent was obtained from each participant's legal guardian.

Selection of Participants

Between November 2013 and September 2015, we enrolled a convenience sample of children aged 1 to 7 years who presented to the ED with a simple laceration (defined as length <5 cm and not requiring wound revision) and whose attending physician determined that intranasal midazolam was indicated to facilitate the repair. Patients were enrolled when a research coordinator or study physician was available (9 AM to 10 PM on weekdays; variable on overnights and weekends). We excluded children for any of the following: a history of developmental delay, underlying neurologic abnormality, or autism; illness associated with chronic pain; known allergy to midazolam or any other benzodiazepine; weight less than 10 kg; eyelid lacerations (ie, repair would necessitate closed eyes); nasal obstruction that could not be easily cleared; did not speak English or Spanish; or was a foster child or ward of the state.

Interventions

We used an online randomization program, which maintained allocation concealment, to randomize children in blocks of 3 to receive the total dose of midazolam, using 1 of 3 volumes of administration: 0.2, 0.5, and 1 mL. These volumes were selected according to previous recommendations regarding optimal volume of administration, clinical feasibility, and current clinical practice.[1,4,8-15] Clinicians applied lidocaine-epinephrine-tetracaine gel to all lacerations in a standardized fashion, unless contraindicated. Lidocaine injection for local anesthesia was administered at the discretion of the clinician performing the laceration repair (ie, the "proceduralist"). All children received an integrative (nonpharmacologic) intervention, such as a child life specialist, or a developmentally appropriate form of active or passive distraction.

All children received midazolam at 0.5 mg/kg (concentration 5 mg/mL), with a maximum total dose of 10 mg (maximum volume of 2 mL). The medication was administered in aliquots based on the assigned volume of administration by an attending pediatric emergency physician using an LMA MAD Nasal (Teleflex, Morrisville, NC) device attached to a 1-mL syringe with 0.01-mL scale markings.[8] Before every administration, the attending