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Original Contribution

Safety and effectiveness of intranasal midazolam and fentanyl used in combination in the pediatric emergency department☆,☆☆

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ABSTRACT

Objective: To examine the safety and effectiveness of intranasal midazolam and fentanyl used in combination for laceration repair in the pediatric emergency department.

Methods: We performed a retrospective chart review of a random sample of 546 children less than 18 years of age who received both intranasal midazolam and fentanyl for laceration repair in the pediatric emergency department at a large, urban children's hospital. Records were reviewed from April 1, 2012 to June 31, 2015. The primary outcome measures were adverse events and failed laceration repair.

Results: Of the 546 subjects analyzed, 5.1% had multiple lacerations. Facial lacerations were the most common site representing 70.3%, followed by lacerations to the hand (9.9%) and leg (7.0%). The median length of lacerations was 1.5 cm [1.0–2.5]. The median dose of fentanyl was 2.0 μg/kg [1.9–2.0] and midazolam was 0.2 mg/kg [0.19–0.20].

There were no serious adverse events reported. The rate of minor side effects was 0.7% (95% CI 0.2% to 1.9%); 0.5% (95% CI 0.1% to 1.6%) experienced anxiety and 0.2% (95% CI 0.0% to 1.0%) vomited. No patients developed hypotension or hypoxia. Of the 546 patients, 2.4% (95% CI 1.3% to 4.0%) experienced a treatment failure. 2.0% (95% CI 1.3% to 4.0%) required IV sedation and 0.4% (95% CI 0.0% to 1.3%) were repaired in the operating room.

Conclusions: Our results suggest that the combination of INM and INF may be a safe and effective strategy for procedural sedation in young children undergoing simple laceration repair.

1. Introduction

1.1. Background

Pain and anxiety are common among pediatric patients presenting to the emergency department with injuries and acute illnesses. Painful procedures, such as laceration repair, can be especially distressful to young children. Inadequately relieving the discomfort and anxiety associated with a procedure can lead to lasting emotional trauma [1-5]. Numerous routes of administration for both analgesia and anxiolysis have been utilized with varying degrees of success [6]. Parenteral medications require intramuscular administration or placement of a peripheral IV, which can be painful and anxiety provoking, and may consume both time and resources. Oral medications have a slower onset of action and are dependent on the cooperation of the patient and their ability to tolerate oral intake. Pre-procedural sedation with intranasal medication has been used to mitigate anxiety and emotional trauma related to minimally invasive procedures. These medications have a rapid onset of action, limited resource utilization, and are generally well tolerated [8,15]. Intra-nasal midazolam (INM) is a sedative that has been shown to be both safe and efficacious for pre-procedural sedation in the Pediatric Emergency Department (PED) [9-12]. Similarly, several studies have shown intranasal fentanyl (INF) to be safe and effective for managing acute pain in the pediatric emergency department, especially with regard to orthopedic injuries [13-16]. In April of 2009, intranasal medications were introduced in our Pediatric Emergency Department (PED) as part of the Comfort Zone initiative, aimed at recognizing and reducing pain and anxiety in children [17]. Since that time, it has become common practice to utilize INM and INF in combination for minor procedures, such as laceration repair, in the PED.

1.2. Importance

To our knowledge, there is no data in the pediatric literature assessing the utility of INM and INF in combination for pediatric

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☆☆ We appreciate your time and look forward to receiving feedback on this manuscript. Please don't hesitate to contact me for any clarification.

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procedural sedation. If this combination is proven to be safe and effective, it would expand the armamentarium for managing pain and anxiety associated with minor procedures in the PED.

1.3. Goals of this investigation

The goal of this study was to evaluate and report the safety and effectiveness of intranasal midazolam and fentanyl used in combination for laceration repair in the PED through a retrospective chart review.

2. Materials and methods study design, setting and selection of participants

The study site was the emergency department of an urban, tertiary pediatric hospital with an annual volume of approximately 80,000 visits.

We conducted a retrospective chart review of children less than 18 years of age who received both intranasal midazolam and fentanyl for laceration repair in the PED. All authors reviewed records from April 1, 2012 (the time when reliable electronic pharmacy record of intranasal medication delivery first became available) to June 31, 2015. The authors were not blinded to the study purpose at the time of data abstraction. We determined our sample size using an anticipated complication rate of 1% and a 95% confidence width of 2.0% (±1.0%), yielding a total sample of 546. A random sample of 546 subjects meeting inclusion and exclusion criteria during the study period was analyzed. Randomization was achieved through the use computerized random number generation.

At the study institution the IV formulations for Midazolam (5 mg/ml) and Fentanyl (50 μg/ml) are administered intranasally via a mucosal atomizer device. A 1-ml syringe is used with the atomizer attached to the end. A maximum of 1-ml per nostril is administered with a rapid push. INF is usually given first at our institution because of the brief burning sensation associated with INV. The standard practice at our institution is to monitor patients on pulse oximetry during procedural sedation with INF and INM. Additionally, it is standard practice for all patients with simple lacerations to have a topical anesthetic gel (lidocaine/epinephrine/tetracaine) applied unless contraindicated. Additional lidocaine is occasionally used at the discretion of emergency department physician. We have child life personnel to provide distraction techniques when available. We do not use papoose boards at our institution, however, emergency department technicians often help with holding young children during laceration repair.

This study was approved by the local institutional review board.

2.1. Data collection and processing

Data was abstracted from electronic and scanned paper medical records. Two abstractors conducted chart reviews independently using a standardized data collection form. Patient demographics recorded included age, weight, ethnicity, gender, and insurance status. Variables of interest for the analysis included number of and total length of laceration(s), location of laceration(s), wound treatment, closure type, use of local or regional anesthesia, procedure time, intranasal medications used, use of oral medications, use of parenteral medications, patient disposition, and PED length of stay. Adverse events of interest included use of positive pressure ventilation, need for intubation, aspiration, hypotension, death, and need for rescue medications. Other minor side effects were also recorded, including nausea, vomiting, rash, dizziness, and ataxia. We defined treatment failure as a need for IV procedural sedation (typically with ketamine) or a need for repair in the operating room under anesthesia. Subjects with injuries in addition to a laceration(s) had their chart reviewed by two of the authors to determine eligibility for inclusion. If the additional injury(s) were judged to be significant enough to potentially lead to an endpoint failure (for example needing the operating room for a more significant injury), those subjects were excluded. If there was disagreement, a third author reviewed the chart.

2.2. Outcome measures

The primary outcome measures for this study were adverse events and failed laceration repair, defined by those needing IV sedation and those requiring operative repair.

2.3. Primary data analysis

This was a descriptive study. Demographic and clinical characteristics of the cohort are presented as percentages or medians with interquartile range as appropriate. Complications rates are reported as percentages with 95% confidence intervals. Intranasal sedation failure rates are similarly reported as percentages with 95% confidence intervals.

3. Results characteristics of study subjects

During the study period 1885 children received combination INM and INF for laceration repair in the PED. A random sample of 546 subjects was analyzed. Demographic variables are summarized in Table 1. 68.9% were male, and the median age was 4.1 years. Of the subjects analyzed, 5.1% had multiple lacerations. Facial lacerations were the most common site representing 70.3%, followed by lacerations to the hand (9.9%) and leg (7.0%). The median length of lacerations was 1.5 cm [1.0–2.5]. The median dose of fentanyl was 2.0 μg/kg [1.9–2.0] and midazolam was 0.2 mg/kg [0.19–0.20] (Table 2). Standard dosing in the study institution was 2 μg/kg for fentanyl (max 100 μg) and 0.2 mg/kg for midazolam (max 10 mg).

There were no serious adverse events reported. The rate of minor side effects was 0.7% (95% CI 0.2% to 1.9%); 0.5% (95% CI 0.1% to 1.6%) experienced anxiety and 0.2% (95% CI 0.0% to 1.0%) vomited. No patients developed hypotension or hypoxia. Of the 546 patients, 2.4% (95% CI 1.3% to 4.0%) experienced a treatment failure. 2.0% (95% CI 1.3% to 4.0%) required IV sedation and 0.4% (95% CI 0.0% to 1.3%) were repaired in the operating room (Table 3).

4. Limitations

This study was conducted at a single center and is limited to patients who presented to our PED. The findings may not be generalizable to other emergency departments. In addition, the retrospective design of our study limits information to what has been recorded in the medical record. Identification of the safety endpoints required that they were indicated in the physician or nursing record. Given the rarity of serious adverse events such as hypoxia and hypotension, this study may not be adequately powered to assess safety. A large, multi-center, randomized

Table 1
Demographic variables.

Variable	Percent (n = 546)
	68.9
Insurance	
Private	40.8
Public	51.1
None	8.1
Ethnicity	
Caucasian	42.3
Hispanic	44.9
African American	8.8
Asian	2.0
Other	2.0

Table 2
Clinical variables.

Variable	Percent (n = 546)
Multiple lacerations	5.1
Location	
Face	70.3
Scalp	5.9
Trunk	0.2
Arm	2.4
Leg	7.0
Hand	9.9
Foot	3.1
Other	1.3

Variable	Mean	SD
Age (yrs)	4.7	2.8
Weight (kg)	20.3	10.3
Laceration length (cm)	2.0	1.5
Fentanyl dose (mcg/kg)	1.96	0.23
Midazolam dose (mg/kg)	0.19	0.03

control trial is needed to achieve the number of patents required to more confidently assess safety and efficacy.

5. Discussion

Repair of lacerations in young children in the emergency department setting can be anxiety provoking, both for the patient and the family members. There is limited data on the use of the combination of INM and INF as a means of sedation in young children. There have been multiple studies looking at the efficacy of INM for pre- procedural anxiolysis [7,9-12]. Likewise, there is a body of evidence supporting the use of INF alone for pain management in children [13-16,18]. Through a retrospective chart review, we sought to investigate the safety and effectiveness of the two medications used in combination specifically for procedural sedation in children requiring laceration repair.

INM used for minor procedures in the PED has been shown to be an effective anxiolytic.9 Lane and Schunk studied INM at a mean initial dose of 0.4 mg/kg (range, 0.3–0.8 mg/kg) for minor procedures in the PED [9]. They reviewed 205 patients, most of whom (89%) were undergoing laceration repair. Their failure rate (patients who required an additional sedative) was 5.4% (95% CI, 3.0% to 9.0%). In our study, we defined failure as those patients who required IV sedation or operative repair. The majority of the failures (85%) required intravenous sedation with ketamine to complete the procedure. Most of these patients (9 of 11) had lacerations on their face/scalp. The remaining two patients had partial finger amputations. Yealy and colleagues performed a retrospective chart review of young children requiring laceration repair using doses of INM ranging from 0.2 to 0.5 mg/kg and reported 73% (95% CI, 56% to 85%) of the patients achieved adequate sedation [12]. Despite dosing INM at the lower end of that range in our study, our failure rate was only 2.4%. We hypothesize that our higher success rate was due to the use of INF in combination with INM which provided more effective procedural sedation.

Table 3
Outcome variables.

Outcomes	Percent (95% CI)
Total adverse events	0.7 (0.2–1.9)
Anxiety	0.5 (0.1–1.6)
Vomiting	0.2 (0.0–1.0)
Hypotension	0.0 (0.0–0.7)
Hypoxia	0.0 (0.0–0.7)
Failure rate	2.4 (1.3–4.0)
Required IV sedation	2.0 (1.0–3.6)
Required operating room	0.4 (0.0–1.3)

A 2014 Cochrane review of INF for the management of acute pain in children concluded that it is an effective modality for managing pain, and found no adverse events [18]. Borland and colleagues compared INF to IV morphine for pain control in pediatric patients with long bone fractures in the PED [15]. The authors concluded no difference in the onset of action, ability to achieve analgesia, or the safety profile between the two forms of delivery. They concluded that INF was superior because it was easier to administer, painless, and relieved pain faster by eliminating the need for a peripheral IV. Similarly, other data supports the use of INF in the emergency department for pain control in children with orthopedic injuries [14-16].

INM and INF have both been independently shown to be safe for use in children in the emergency department. INM has a good safety profile at doses of 0.3–0.8 mg/kg. Many studies investigating the safety of INM have reported no serious side effects [9-11]. The most common side effect reported in the literature is nasal discomfort and a bitter taste in the mouth. Given the retrospective nature of our study, we cannot comment on this adverse effect, although we did not identify any such symptoms charted in the medical records of our patients. Minimal to no adverse effects have been reported with the use of INF when used alone for pain control [13-16]. We had a safety profile consistent with the literature using INM and INF in combination. Of the 546 patients reviewed, there was one episode of vomiting and three patients with agitation. According to the medical records, there were no documented serious adverse events such as hypoxia, hypotension, or apnea.

6. Conclusion

To our knowledge, this study is the first to examine the safety and effectiveness of INM and INF used in combination for laceration repair in the PED. Our results suggest that the combination of INM and INF may be a safe and effective strategy for procedural sedation in young children undergoing simple laceration repair. A prospective, multicenter trial is needed to further investigate the safety and efficacy of this approach. Our hope is that these results will add to the body of knowledge for this topic, lead to the improved management of pain and anxiety in pediatric patients, and reduce the need for IV procedural sedation for laceration repair in the PED.

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