CLINICAL INVESTIGATIONS

Use of Intranasal Fentanyl for the Relief of Pediatric Orthopedic Trauma Pain
Mary Saunders, MD, Kathleen Adelgais, MD, MPH, and Douglas Nelson, MD

Abstract

Objectives: The objective was to evaluate the use of a single 2 µg/kg dose of intranasal fentanyl as analgesia for painful orthopedic injuries in children presenting to a pediatric emergency department (ED).

Methods: This was a prospective, nonblinded interventional trial, in a convenience sample of patients 3 to 18 years of age seen in a tertiary care pediatric ED. All had clinically suspected fractures and were treated between July and November 2006. Eligible patients had moderate to severe pain based on initial pain scores using the Wong Baker Faces Scale (WBS) for patients aged 3–8 years or the Visual Analog Scale (VAS) for patients aged 9–18 years. All enrolled patients received fentanyl via intranasal atomization. Pain scores were obtained at baseline and at 10, 20, and 30 minutes after intranasal fentanyl administration. Satisfaction scores were obtained using a 100-mm VAS. Vital signs and adverse events were recorded.

Results: Eighty-one patients were enrolled, 28 in the VAS group and 53 in the WBS group. The mean patient age was 8 years. Fracture locations included forearm, 38 (47%); supracondylar, 16 (20%); clavicle, 7 (9%); tibia/fibula, 5 (6%); and other, 15 (18%). In the WBS group, the median pain scores decreased from five faces (interquartile range [IQR] = 4–6) at baseline to three faces (IQR = 2–5) at 10 minutes, two faces (IQR = 1–4) at 20 minutes, and two faces (IQR = 1–3) at 30 minutes. The mean pain score in the VAS group at baseline was 70 mm (95% confidence interval [CI] = 63 to 77 mm). In this group, the pain scores decreased by a mean of 21 mm (95% CI = 14 to 28 mm) at 10 minutes, 25 mm (95% CI = 15 to 34 mm) at 20 minutes, and 27 mm (95% CI = 16 to 37 mm) at 30 minutes. Mean satisfaction scores were 79 mm for providers, 74 mm for parents, and 62 mm for patients. No adverse events were recorded.

Conclusions: Intranasal fentanyl at a dose of 2 µg/kg provides effective analgesia for pediatric ED patients with painful orthopedic trauma within 10 minutes of administration.

ACADEMIC EMERGENCY MEDICINE 2010; 17:1155–1161 © 2010 by the Society for Academic Emergency Medicine

Pain is a common complaint for patients presenting to a pediatric emergency department (ED). However, pain in children is often undertreated. In particular, analgesia for patients with orthopedic trauma can be a major issue, although it is often not addressed.1 Inadequate pain control for pediatric patients may result in negative long-term effects.2 As recognition of this problem grows, several guidelines have been developed to address pain assessment and management for children treated in the ED.2,3 Patient satisfaction in the ED has also been demonstrated to increase with adequate treatment of pain.4 Analgesia for orthopedic trauma pain is often provided through the administration of opioid medications. When given via an intravenous (IV) route, opioids have a rapid onset of action and may be titrated to effect. However, placement of an IV line uses staffing and material resources and produces additional pain and anxiety in the pediatric patient. Administration of opiates through an intramuscular injection also causes pain and anxiety for many patients. Another alternative, oral pain medications, may be withheld to protect the patient’s NPO status.2 In addition, the delayed onset of oral medications and intramuscular injections makes these routes suboptimal for timely pain control.

Intranasal dosing of opiates can produce rapid treatment of pain without the pain, risk, or delay of alternative administration options. Recognition of this rapid
opiate analgesic effect has resulted in numerous studies evaluating the treatment of acute pain via fentanyl or diamorphine administration across the nasal mucosa.1–10

A study by Borland et al.9 evaluated this method of analgesia in a multidose design in which the intranasal fentanyl was titrated to effect in children over 7 years of age. To the best of our knowledge, to date no study has evaluated the analgesic efficacy of a single dose of intranasal fentanyl for pediatric orthopedic injuries. There have been no prior investigations evaluating parental, patient, and provider satisfaction with the use of intranasal medication for acute fracture pain. Our study used an atomizer to administer intranasal fentanyl to children aged 3 to 18 years, whose pain was evaluated with age-appropriate, validated pain scales.

Our objective was to measure the analgesic effect and time of onset of analgesia, as well as provider, parental, and patient satisfaction, when a single intranasal dose of fentanyl is administered to pediatric patients with painful orthopedic trauma in a pediatric ED.

METHODS

Study Design

This was a prospective interventional trial. The study received approval from the institutional review board. The administration of fentanyl across the nasal mucosa is not approved in the pediatric population, so an investigational new drug (IND) number was obtained from the Food and Drug Administration prior to study initiation. Enrollment was limited to times when a research assistant (RA) was available. Parental consent was obtained in all cases and patient assent was obtained from patients 7 years and older. The study period was from July to November 2006.

Study Setting and Population

The study was conducted in an urban, tertiary care, Level I pediatric trauma center, with an annual ED census of 44,000 patients. A convenience sample of children ages 3–18 years presenting to the ED with a clinically suspected fracture identified by the triage nurse was approached for consent. Inclusion criterion was moderate to severe pain, defined as 3 or greater on an unmarked 100-mm Visual Analog Scale (VAS) for patients 9–18 years. Patients were excluded if they had received narcotic pain medications prior to their ED presentation; suffered multiple trauma; were hemodynamically unstable; had a severe upper respiratory infection; or had an allergy to fentanyl, sufentanil, or other opiate medications.

Study Protocol

Triage nurses notified the RA if a patient presented with a clinically suspected fracture. The RA then obtained a pain score from the patient to determine eligibility for enrollment. We chose to use the WBS and the VAS as these scales have been validated and are widely used to assess pain in the pediatric population.11–13

All patients received a 2 μg/kg dose of fentanyl, administered intranasally. This dose was chosen based on prior studies8–10 and pharmacokinetic data showing that the bioavailability of intranasal fentanyl is 71% of the IV dose.14 The maximum dose administered was 100 μg due to volume constraints. This dose would allow for 1 mL to be administered in each nostril, as the standard IV formulation (50 μg/ml) of fentanyl was used.

Every patient was weighed in triage. Each patient was placed on a cardiorespiratory monitor with continuous pulse oximetry. Vital signs (heart rate, respiratory rate, blood pressure, and pulse oximetry) were recorded at baseline. A baseline pain score was obtained from the patient. The nurse then administered half of the dose into one of the patient’s nares with the mucosal atomizer device (MAD, Wolfe Tory Medical, Salt Lake City, UT).15 The second half of the dose was then administered in the contralateral nare using the same MAD. This device allows for an exact dose of fentanyl to be administered in a fine mist, resulting in an even distribution of the drug onto the nasal mucosa, with minimal oral ingestion. Younger children had the medication administered while sitting in the lap of a parent, with their heads reclined and necks hyperextended. Older children received the medication while lying in a semirecumbent position on the gurney.

The patient’s nurse or the RA obtained a pain score from the patient and vital signs in 10-minute intervals after the intranasal fentanyl was administered. Patients were blinded to their prior scores. If the patient’s pain score did not significantly decrease 20 minutes after intranasal fentanyl administration, the health care provider was notified and asked to evaluate the patient. Rescue analgesia was given at the provider’s discretion. After the last pain score was obtained (30 minutes post–intranasal fentanyl), there was no further interaction with the RA. Definitive treatment of the injury, such as splinting, reduction, and additional pain medication, was directed by the medical provider. Timing of radiographs was not controlled for during the study period.

Patients who had assented to the study (age 7 and older), parents, nurses, and providers were asked to rate their satisfaction with the efficacy of the intranasal fentanyl with a 100-mm VAS. The satisfaction scale was given to patients and parents after the last pain score was obtained. Patients were also asked by the RA to report any nasal symptoms (e.g., pain, rhinorrhea, epistaxis) before intranasal fentanyl administration and after the last pain score. Adverse events including vomiting, hypotension, and hypoxia were recorded.

Measures

The primary outcome to measure analgesic effect was analysis of the change in pain scores from baseline at 10, 20, and 30 minutes after medication administration. Time of onset and duration of analgesia reported by the patient were also studied. Pain scores were measured using age-based scoring systems. For children aged 3–8 years, the WBS was used, which has been previously validated in this age group.16 This is a categorical scale where each face represents a stepwise increase in
intensity of pain that the child is experiencing. For patients aged 9–18 years, a VAS was used where children point to a place along a 100-mm line that represents the intensity of their pain, 0 mm representing “no pain” and 100 mm representing the “worst possible pain.” This scale has also been previously validated in this age group.\textsuperscript{17} A significant decrease in pain scores was defined as a decrease of one face on the WBS or 13 mm on the VAS, which has been determined to be clinically significant in previous studies in children.\textsuperscript{11–13} Secondary outcomes included patient, parent, and provider satisfaction with the intranasal fentanyl. This measure was obtained using a 100-mm unmarked VAS with “did not help at all” at the left and “helped a lot” at the right end.

**Data Analysis**

Normality of pre- and postanalgesia data was assessed using histograms. Data were analyzed using medians with interquartile range (IQR) for WBS data (a ranked scale) and means with 95% CI for VAS data (a continuous scale). Differences in median pre- and postanalgesia pain scores obtained using the WBS were assessed using the Friedman’s test. Differences in pre- and postanalgesia pain scores obtained using the VAS were assessed with a mixed between- and within-subjects analysis of variance, which allowed for testing of repeated measures. The study sample size was calculated to detect a decrease of 13 mm in the VAS. For a power of 0.8, an alpha of 0.05, and a standard deviation (SD) of 17, a sample size of 27 patients was required. Conversely, the study sample size for the WBS group to detect a decrease of one face was found to be 46 patients, with a power of 0.8, an alpha of 0.05, and an SD of 1.7. Data were analyzed using SPSS 14.0 statistical software (SPSS, Inc., Chicago, IL).

**RESULTS**

During the enrollment period when an RA was available, 168 patients were identified who had clinically suspected fractures. Sixty-five patients were ineligible based on our exclusion criteria, leaving a total of 103 patients who were identified as eligible (Figure 1). Of the 20 “other” ineligible patients, four patients had multisystem trauma, one had an allergy to codeine, and the exclusion criterion was not documented for the remaining 15 patients. Of the eligible patients, 19 declined, and three patients were excluded from data analysis; one of the patients was found to be too young, and two patients had incomplete data. Fifty-three patients (65%) were in the WBS group and 28 (35%) were in the VAS group. The mean age of our patients was 8 years (SD ± 3.7), with a range of 3–17 years (Figure 2), and 61% were male. Forearm fractures accounted for 47% of our sample; 68% of these underwent reduction. The remaining patients had supracondylar (20%), clavicle (9%), tibia or fibula (6%), or other fractures. Injuries in the “other” category included sprains, contusions, dislocations, and other fractures.

For children less than 8 years of age, the WBS pain scores assessed at each time point during the study are
shown in Figure 3. The median score at baseline was five faces. At each subsequent time interval, the median pain scores decreased. These decreases were found to be statistically significant with $p < 0.05$ at each time interval. Ten minutes after intranasal fentanyl administration, 39 of 50 patients (78%) had a clinically significant decrease in their pain scores for the entire study period. The overall number of patients with a clinically significant decrease in their pain scores decreased at each time interval, as shown in Table 1.

The mean (±SD) dose of fentanyl administered overall was 1.9 (±0.2) μg/kg. In the VAS group, the mean (±SD) fentanyl dose was 1.8 (±0.2) μg/kg. However, 12 of 28 patients (42.8%) weighed more than 50 kg. The mean (±SD) age for these patients was 13.8 (±1.9) years. The mean (±SD) dose of fentanyl administered in this group was 1.6 (±0.2) μg/kg, with a range of doses between 1.2 and 1.96 μg/kg. This lower dosage per kilogram in larger patients was due to volume constraints, as 2 mL was the maximum intranasal volume tolerated.

Nineteen of 81 patients (23%) were considered for rescue analgesia, as they did not achieve a significant decrease in pain at 20 minutes: nine in the VAS group and 10 in the WBS group. Of these patients, seven of 10 (70%) in the WBS group had a significant decrease in their pain scores at the 30-minute interval, and this was also true in one of the nine (11%) of the VAS patients. Ultimately, seven of 81 patients (9%) received rescue analgesia: three from the WBS group and four from the VAS group. None of these patients had a clinically significant decrease in their pain scores. Among these patients, the proportion of injury types did not differ significantly compared to those patients who did not receive rescue analgesia. All of these patients did have fractures that required reduction.

Of the remaining 12 patients who did not receive rescue analgesia, six required an IV line for conscious sedation for reduction of their fractures. It is not documented why these patients did not receive rescue pain medication. For the six patients who did not receive rescue analgesia and did not require conscious sedation, three were in the WBS group and three were in the VAS group. The injuries for the patients in the WBS group were a wrist sprain, a radius buckle fracture, and a supracondylar fracture. The injuries in the VAS group patients were a clavicle fracture, a fibular fracture, and a hip sprain.
The mean provider satisfaction score was 79 mm (95% CI = 74 to 83 mm), while parents’ mean satisfaction score was 74 mm (95% CI = 69 to 79 mm), and patients had a mean satisfaction score of 62 mm (95% CI = 53 to 70 mm). Only patients who had given assent were asked to give a satisfaction score (15 patients in the WBS group and 28 in the VAS group).

No patients had vomiting, hypoxia, or hypotension. No patients had rhinorrhea, epistaxis, or nasal complaints after medication administration. Our study, however, was not powered to detect adverse events.

**DISCUSSION**

Our findings demonstrated that a single 2 μg/kg dose of fentanyl administered intranasally to pediatric patients with orthopedic trauma provided rapid analgesia that was sustained for 30 minutes for the majority of patients.

Intranasal medications have been used in multiple patient care settings including preinduction of anesthesia,18–20 conscious sedation,21 during delivery of anesthesia,22 postoperative pain control7,8,23,24 and acute pain management in the ED.5,6,9,10 For selected small-molecular-weight medications, transmucosal delivery can result in rapid medication absorption with serum and CSF levels approaching those comparable to IV administration.

This is made possible by the large surface area (180 cm² in an adult) of the nasal mucosa, thinness of its outer layers, and excellent blood supply. This route of administration also bypasses the first-pass metabolism of medications by the liver.14,25

The administration of intranasal fentanyl provides adequate analgesia and obviates the need for IV placement for the treatment of pain in some ED patients. Analgesia via intranasal medication administration may be achieved more rapidly than that provided by the IV route, since the latter requires more materials, time, and personnel. Placement of IV lines also produces pain in pediatric patients.25 Intranasal fentanyl also provides initial analgesia in patients in whom IV access is difficult to obtain or for children who are anxious about IV placement. This method of analgesia may also have practical applications in the prehospital setting or clinic setting when IV access is unobtainable.

Our results suggest that intranasal fentanyl is more efficacious in younger children. We postulate that this group benefited from receiving a full 2 μg/kg dose of the intranasal fentanyl. The overwhelming majority of patients in this group achieved a clinically significant decrease in pain by 30 minutes. Clinically, this age group may benefit most from this method of analgesia, as they are the patients in whom IV access can be most difficult to obtain, and for whom practitioners are historically most hesitant to prescribe analgesia.1,26

The decrease in pain scores for the patients in the VAS group was not as considerable in comparison to the WBS group. In this group, the proportion of injury types did not differ between the patients who had a clinically significant decrease in their pain and those who did not. The satisfaction scores among patients were also lower than those of the providers and parents. This may be a result of the discomfort associated with the administration of a medication intranasally.

We believe that the higher satisfaction scores of providers and parents reflect the ease of administration and efficacy of this mode of analgesia. Approximately 40% of the patients in the VAS group weighed more than 50 kg. Due to volume constraints, these patients did not receive the entire 2 μg/kg dose of fentanyl. Further studies using a more concentrated solution of fentanyl in this age group could address this issue. We do note that the majority of patients, regardless of age and size, who required rescue analgesia did receive a full dose of 2 μg/kg of fentanyl. We could speculate that the older group may have experienced more anxiety about their injuries, and this anxiety may have contributed to pain perception. Anxiety has a known association with chronic pain; however, its role in acute pain among children is not well understood.27 Kain et al.28 demonstrated that children who were assessed and found to be anxious prior to elective outpatient tonsillectomy and adenoidectomy experienced more pain postoperatively than nonanxious children, both in the hospital and over the first 3 days at home. As we did not have a comparison group, our study was not designed to control for possible confounders, such as anxiety or pain with administration of intranasal medication.

Similar to previous studies, our patients did not have any significant adverse events.7,8 The adverse effect profile for the intranasal administration of fentanyl is superior to that of oral transmucosal administration of fentanyl. Prior studies with oral transmucosal fentanyl demonstrated vomiting, pruritis, and hypoxia.29,30 Schutzman et al.29 reported a 5% to 7% incidence of facial pruritis and a 3% to 4% vomiting rate in children receiving low-dose (10–15 μg/kg) or high-dose (15–20 μg/kg) oral transmucosal fentanyl for laceration repair. Klein et al.30 reported an 11% rate of oxygen desaturation when oral transmucosal fentanyl was combined with oral midazolam for sedation during laceration repair.

**LIMITATIONS**

The study was conducted using a convenience sample. RAs worked during discontinuous periods during the enrollment period. As the study was designed to assess the efficacy of a single, larger dose of intranasal fentanyl in comparison to doses used in prior studies, we did not randomize our patients to receive other types of analgesia. We did not have a placebo group because we felt it was unethical to withhold analgesia from children with painful injuries.

We were unable to administer a full 2 μg/kg dose of fentanyl to some patients. The standard concentration of fentanyl (50 μg/ml) was used in this study, and as a result, we restricted our maximum dose to 100 μg due to volume constraints. Larger volumes of the medication may have allowed some to run through the nasal cavity into the oropharynx and be absorbed through the less effective oral route. Pharmacokinetic studies would be needed to evaluate the effect this would have on overall bioavailability.

Given the constraints of a busy ED, we did not standardize the timing of radiographs relative to medication...
administration, nor did we control for this in the analysis. This may have increased pain scores if manipulation of the fracture for the radiograph caused the child additional pain. This study was too small to make any statements regarding adverse events. Further studies with larger sample sizes are needed to determine the safety of intranasal fentanyl.

CONCLUSIONS

Intranasal fentanyl at a dose of 2 µg/kg provided rapid and sustained analgesia in a majority of pediatric patients with pain due to orthopedic trauma. This mode of analgesia was given high satisfaction marks from providers and parents and was particularly efficacious in younger patients. Our findings support the use of a 2 µg/kg dose of intranasally administered fentanyl as an initial analgesic in pediatric patients with painful orthopedic injuries.

References


