A Randomized Controlled Trial Comparing Intranasal Fentanyl to Intravenous Morphine for Managing Acute Pain in Children in the Emergency Department

Meredith Borland, MBBS, FACEM
Ian Jacobs, PhD, FRCNA
Barbara King, MBBS, FRACP
Debra O'Brien, MBBS, FACEM

From the Princess Margaret Hospital for Children, Subiaco (Borland, King); School of Paediatrics and Child Health, University of Western Australia, Perth (King); Discipline of Emergency Medicine, University of Western Australia, Perth (Jacobs); and the Emergency Department, Sir Charles Gairdner Hospital, Nedlands (O'Brien) WA, Australia.

Study objective: We compare the efficacy of intranasal fentanyl versus intravenous morphine in a pediatric population presenting to an emergency department (ED) with acute long-bone fractures.

Methods: We conducted a prospective, randomized, double-blind, placebo-controlled, clinical trial in a tertiary pediatric ED between September 2001 and January 2005. A convenience sample of children aged 7 to 15 years with clinically deformed closed long-bone fractures was included to receive either active intravenous morphine (10 mg/mL) and intranasal placebo or active intranasal concentrated fentanyl (150 μg/mL) and intravenous placebo. Exclusion criteria were narcotic analgesia within 4 hours of arrival, significant head injury, allergy to opiates, nasal blockage, or inability to perform pain scoring. Pain scores were rated by using a 100-mm visual analog scale at 0, 5, 10, 20, and 30 minutes. Routine clinical observations and adverse events were recorded.

Results: Sixty-seven children were enrolled (mean age 10.9 years [SD 2.4]). Fractures were radius or ulna 53 (79.1%), humerus 9 (13.4%), tibia or fibula 4 (6.0%), and femur 1 (1.5%). Thirty-four children received intravenous (IV) morphine and 33 received intranasal fentanyl. Statistically significant differences in visual analog scale scores were not observed between the 2 treatment arms either preanalgesia or at 5, 10, 20, or 30 minutes postanalgesia (P=.333). At 10 minutes, the difference in mean visual analog scale between the morphine and fentanyl groups was −5 mm (95% confidence interval −16 to 7 mm). Reductions in combined pain scores occurred at 5 minutes (20 mm; P=.000), 10 minutes (4 mm; P=.012), and 20 minutes (8 mm; P=.000) postanalgesia. The mean total INF dose was 1.7 μg/kg, and the mean total IV morphine dose was 0.11 mg/kg. There were no serious adverse events.

Conclusion: Intranasal fentanyl delivered as 150 μg/mL at a dose of 1.7 μg/kg was shown to be an effective analgesic in children aged 7 to 15 years presenting to an ED with an acute fracture when compared to intravenous morphine at 0.1 mg/kg. [Ann Emerg Med. 2007;49:335-340.]

INTRODUCTION

Background

In the pediatric emergency department (ED), rapid, effective, and painless delivery of analgesia is desired.[1,2] As a consequence, it is routine in many facilities to give intravenous (IV) morphine to children presenting to the ED in moderate to severe pain.[3,4] However, the insertion of an IV cannula can, at times, require special skills, is time and staff dependent, and is painful and anxiety provoking for some children. Alternative methods of providing safe and effective analgesia include the intranasal route for the administration of opiates such as fentanyl and diamorphine.[5-9] A study in a tertiary pediatric ED illustrated the safety and efficacy of intranasal fentanyl in a pediatric population.[8] Two other ED studies have compared an intranasal opiate with intramuscular morphine as their criterion standard.[5,6]

Importance

There has not been a study comparing an intranasal opiate with a drug with a similar onset of action. Intramuscular morphine would be expected to take up to 30 minutes to

Figure 1. Mucosal Atomiser Device.

achieve adequate analgesia, whereas intranasal formulations take 5 to 10 minutes. In addition, if it were possible to provide adequate analgesia without IV access, then the administration of analgesia would be hastened, which would equate to greater patient comfort and satisfaction.

Goal of This Investigation

Our objective was to illustrate the comparative effectiveness of intranasal fentanyl to IV morphine in the pediatric ED. The primary endpoint was to demonstrate equivalence in pain control.

MATERIALS AND METHODS
Study Design and Setting

This study was a double-blind, placebo-controlled, randomized trial within a tertiary pediatric ED with an annual census of 42,000 attendances. Enrollments were made from September 2001 to January 2005.

Selection of Participants

A convenience sample of children aged 7 to 15 years, presenting with clinically deformed closed long-bone fractures, was identified at triage and invited to join the study. Verbal consent was obtained from both the accompanying parent and the child, when appropriate. Written consent was not obtained to minimize "time to analgesia" in the setting of acute extreme pain. These ethical issues were discussed with the institution's ethics committee and approval was obtained. These findings were consistent with published guidelines for ethical research.[10]

Patients were excluded if they had received narcotic analgesic within 4 hours of arrival in ED; had sustained a head injury resulting in impaired judgment; were known to be allergic to opiate analgesics; had a blocked or traumatized nose, preventing nasal administration; or were unable to perform pain scoring for any reason.

Interventions

After enrollment, every patient was weighed on the same sitting scale, irrespective of injury sustained, and had routine observations (pulse rate, respiratory rate, blood pressure, and oxygen saturations) taken. The patient was then shown a 100-mm unmarked visual analog scale with "no pain" at the left end and "worst pain" on the right end and invited to mark the level of pain. Patients were not excluded if their pain score fell below a certain number. Appropriate splintage and icing were applied.

An IV cannula was then inserted into a peripheral vein in every patient. During the study design, commercially available concentrated fentanyl solutions were not available; therefore, a concentrated fentanyl (150 μg/mL) was manufactured in our hospital pharmacy from fentanyl powder sourced from the drug manufacturer (AstraZeneca Pty Ltd, Balcatta, WA, Australia). Study packs contained either the concentrated fentanyl solution or normal saline solution in identical containers plus a 1-mL ampoule of morphine (10 mg/mL) or normal saline solution also in identical containers. The nasal atomizer (MAD device; Wolfe Tory Medical, Salt Lake City, UT) and syringes for drawing up the medication was also included (Figure 1). The IV medication was diluted to 10 mL with normal saline solution before administration. The study packs were randomly allocated in the pharmacy and supplied to the department in blocks of 10, and the next available pack was taken on enrollment of the patient.

Drug doses were based on weight intervals of 10 kg (Table 1). The initial fentanyl dose was calculated to be approximately 1.4 μg/kg (equivalent to 1 μg/kg IV, with 71% bioavailability).[10] Additional doses of 15 μg were available for administration to a
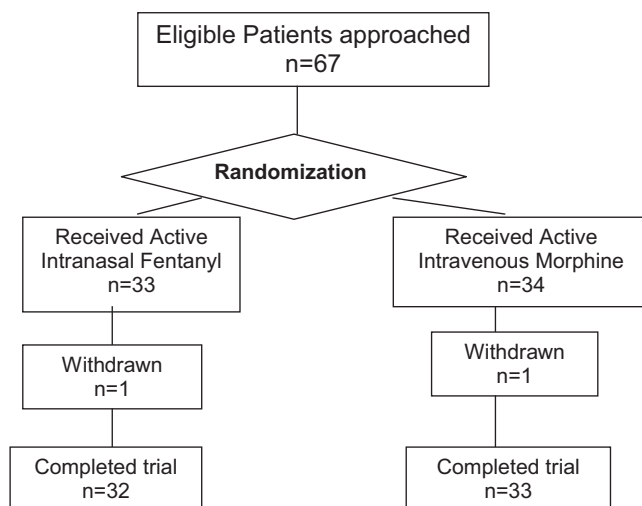
Table 1. Study drug dosage schedule.

| Weight (kg) | Dosage Schedule for Intranasal Fentanyl | | Dosage Schedule for IV Morphine | |
	Initial Dose (μg)	Max No. Additional Doses (15 μg)	Initial Dose (mg)	Max No. Additional Doses (1.0 mg)
21–30	30	2	2.0	2
31–40	45	3	3.0	3
41–50	60	4	4.0	4

Figure 2. Flow chart.

maximum total intranasal dose. When receiving the intranasal medication, each child received an IV injection of morphine or placebo. The initial morphine dose was approximately 0.1 mg/kg. Additional IV doses were 1.0 mg. Every child received 1 active drug (either intranasal or IV) and 1 placebo drug by the opposite route. Requirements for additional analgesia were determined by the treating nurse or physician, who was blinded to the visual analog scale assessment. When required, additional doses were given of both the IV and intranasal drugs to ensure an active agent was given. Additional doses could be given every 5 minutes until pain was relieved, patient refused further analgesia, or maximum doses had been given according to the dosing schedule. If pain relief was inadequate after 30 minutes, then analgesia in the form of titrated IV morphine was offered in the traditional way. The child could withdraw at any time during the trial period and be offered rescue morphine. The decision to withdraw could be made by the patient, parent, or treating physician.

During the study period, routine observations were undertaken in accordance with our institution's nursing protocols for the administration of narcotics. These observations included blood pressure, pulse rate, respiratory rate, and oxygen saturations every 5 minutes. At the end of the 30 minutes, the trial period finished and ongoing treatment was at the discretion of the attending ED medical staff. Most fracture manipulations at that time were undertaken in the operating theatre, and hence if the child's pain relief was adequate, there would be no further need for IV medication within the ED.

Methods of Measurement

The primary outcome measure was pain scores using a 100-mm unmarked visual analog scale. When adverse effects occurred, these were documented by the attending physician or nurse. In particular, they were asked to document sedation, respiratory or cardiovascular signs, nausea, vomiting, and discomfort related to the nasal spray. The patient provided a pain score with the visual analog scale at 0, 5, 10, 20, and 30 minutes after the administration of analgesia. They also completed a second assessment to compare their current pain with the previous rating verbally as "much better," "little better," "the same," "little worse," or "much worse." The child was blinded to previous scores.

Primary Data Analysis

The study hypothesis was to test equivalence of the 2 analgesic agents. Means, medians, and 95% confidence interval (CI) were calculated for all continuous data with proportions, and 95% CI was determined for all categorical variables. Between the 2 treatment arms, differences in age and weight were assessed using the independent sample t test with the Mann-Whitney U test used to assess differences in number of additional doses given. Differences in pre- and postanalgesia pain scores were assessed with a mixed between- and within-subjects analysis of variance, which allowed for simultaneous testing of repeated measures during the study intervals (visual analog scale scores), in addition to assessment of differences between the 2 treatment arms. The potential for interaction effects was also assessed in the model. Normality of the data was assessed visually with a histogram of visual analog scale scores. Analysis was conducted using the Statistical Package for Social Sciences (SPSS version 14.0).

If a power of 0.90, α of 0.05, baseline pain score of 80 mm $\pm$ 18 mm, and a change in pain score of 13 mm were clinically significant,[11,12] then 32 subjects would be required in each treatment arm. Analysis was undertaken on an intention-to-treat basis. The study was approved by the hospital's ethics committee, with the specific provision for obtaining verbal consent.

RESULTS

We enrolled 67 children between September 2001 and January 2005 (Figure 2). Baseline characteristics were similar between groups (Table 2).

The visual analog scale scores during the 5 periods at which pain was assessed and between intranasal fentanyl and IV morphine are illustrated in Figure 3. Overall, no statistically significant differences in visual analog scale scores between the 2 treatment arms either preanalgesia or at 5, 10, 20, or 30 minutes

Table 2. Characteristics of study patients.

Demographics	Both Groups, n=67	Morphine Group, n=34	Fentanyl Group, n=33
Mean age, y (range)	10.9 (6–15)	10.7 (6–15)	11.1 (7–15)
Mean weight, kg (range)	43.7 (19–88)	41.9 (19–80)	45.7 (26–88)
Diagnosis (%)			
Fractured humerus	9 (13.4)	5 (14.7)	4 (12.1)
Fractured radius or ulna	53 (79.1)	27 (79.4)	26 (78.8)
Fractured femur	1 (1.5)	0	1 (3.0)
Fractured tibia/fibula	4 (6.0)	2 (5.9)	2 (6.1)
Median initial dose/kg		0.08 mg	1.2 μg
Median no. of additional doses (range)		1.0 (0–5)	1.0 (0–6)
Mean total dose/kg		0.11 mg	1.7 μg

postanalgesia were observed (P=.333). Because there were no statistically significant differences between the 2 treatment arms, visual analog scale scores were combined to form an overall visual analog scale score for each time point. There were statistically significant reductions in the combined visual analog scale score at 5 minutes postanalgesia of 20 mm (P=.000), at 10 minutes of 4 mm (P=.012), and at 20 minutes of 8 mm (P=.000). There were no further significant reductions in visual analog scale score beyond 20 minutes (P=.753).

Three children reported a bad taste in the mouth after the nasal spray; all had received active fentanyl, but this did not affect their receiving further doses if required. One child had a momentary flush at the IV site after the IV morphine. One child vomited at 20 minutes after receiving active fentanyl but had been vomiting before any analgesia administration. There were no significant alterations in the routine observations undertaken for all patients. There were no other adverse events.

Two children required rescue morphine; 1 child was withdrawn when IV access failed and intramuscular analgesia was administered; 1 child received 1 dose of intranasal fentanyl and withdrew at 5 minutes. One child (having active morphine) had 5 additional doses (protocol maximum=4), receiving a total of 0.2 mg/kg of morphine. Another child (having active fentanyl) was given 6 additional doses within the study time (protocol maximum=4), which equated to a total of 2 μg/kg of fentanyl. Twenty children weighed more than 50 kg; 9 received IV morphine and 11, intranasal fentanyl.

LIMITATIONS

We used the visual analog scale as our pain measurement tool because it has been validated in recent studies.[11] In the clinical setting, it is a somewhat cumbersome tool, requiring a 100-mm diagram and the child to mark his or her pain level. Children older than 6 years were included to avoid difficulty with understanding a pain measurement tool in the acute setting without previous education.[13,14] The verbal 0-to-10 scale (numeric rating scale) has been less validated in the pediatric population[15] but possibly would be a more convenient tool for use in this clinical setting.

We used a convenience sample for enrollments that was dependent on suitable patients being identified at triage. The chief investigator (M.B.) worked during discontinuous periods between 2002 and 2003, resulting in a reduction in enrollments of these suitable patients. No record was kept of potential patients who were not enrolled, so no conclusion can be drawn about reasons for nonenrollments.

For reasons of simplicity, the dosage regimen was calculated for 3 weight intervals. The inclusion of 21 children outside of the weight intervals (1 less than 20 kg and 20 greater than 50 kg) may have actually increased the study population posttreatment mean pain scores (and potentially undertreated these children's pain) because the majority of these children received smaller per-kilogram doses of both IV morphine and INF.

DISCUSSION

Intranasal drug administration has been studied widely in postoperative patients[16-18] and burn patients.[19-21] To our knowledge, this study is the first to compare directly intranasal fentanyl with IV morphine in a pediatric population. We were able to demonstrate equivalence in pain scores at all intervals during the study. The combined visual analog scale score showed significant reduction at all intervals postanalgesia except at 30 minutes, which reflects reduction in pain for both treatment arms throughout the study.

Theoretically, an IV narcotic would be likely to be superior to an intranasal narcotic at 5 minutes because of the slight delay in absorption of intranasal fentanyl in comparison to IV administration of morphine. However, our results showed no significant difference in IV morphine in comparison to intranasal fentanyl at any period, which correlates with the rapid bioavailability of the intranasal fentanyl. Intranasal fentanyl has been shown to have therapeutic serum levels in 2 minutes, reflecting the good venous outflow of nasal mucosa and the bypassing of the liver, avoiding hepatic first-pass metabolism.[22] In the clinical setting, intranasal fentanyl can be administered promptly into the nasal cavity without the delays inherent in placing an IV. As part of the study protocol, every child had an IV placed before the study drugs were administered; however, in routine practice the intranasal drug can be administered before the IV insertion, resulting in effective earlier analgesia. Having achieved initial improvement in pain and having instituted other measures (eg, splinting and ice), the child may not have any further need for IV access in the ED for opiate analgesia. Alternatively, if longer-acting opiate is required, it will allow time for topical local anesthetic agents to work before IV insertion.

There is the potential for the intranasal fentanyl administration to be part of the triage assessment by nursing staff in an effort to reduce "time to analgesia," which has now become routine practice in our department with a commercially manufactured concentrated fentanyl solution. Other possibilities for this method of analgesia include the out-of-hospital and general practice settings, in which IV insertion may be difficult or unavailable and provision of analgesia can be a challenge.
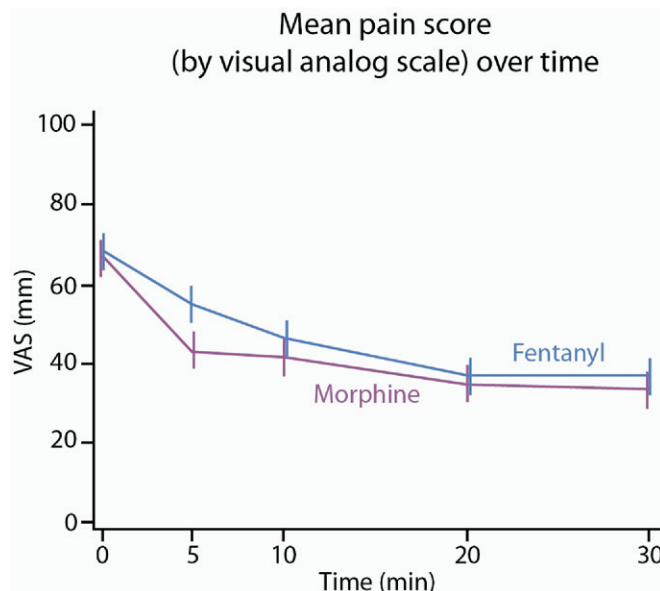
Figure 3. Mean visual analog scale.

	0 min	5 min	10 min	20 min	30 min
Morphine mm	67	42	41	35	33
Fentanyl mm	68	55	46	37	37
Difference mm (95% CI)	−1 (−12 to 9)	−13 (−23 to −3)	−5 (−16 to 7)	−2 (−13 to 10)	−4 (−16 to 8)

Given the equianalgesic effect between the 2 agents, the choice of first analgesia will be determined by tolerability and acceptability. In practice, intranasal administration was simple, with only 3 children expressing a dislike of the intranasal medication, which did not prevent further use of the medication. The concentrated fentanyl solution developed for this study (150 μg/mL) allowed a small volume of fluid to be administered, minimizing difficulties such as sneezing out or swallowing the solution and improving bioavailability.[5,22]

There were no significant adverse effects of either active drug in our study. This adverse effect profile was similar to that of other studies.[5,6,8,16]

In summary, intranasal fentanyl delivered as 150 μg/mL at doses of 1.7 μg/kg has been shown in this randomized, double-blinded, placebo-controlled study to provide analgesia equivalent to that of IV morphine at the dose of 0.1 mg/kg for children aged 7 to 15 years with acute fractures in the ED setting. It has the advantage of being able to be administered quickly before the placing of an IV cannula. There is potential for it to be a nurse-initiated analgesic in the ED or used in the out-of-hospital or general practice settings in children presenting with acutely painful conditions.

Address for correspondence: Meredith Borland, MBBS, FACEM, GPO Box D184, Perth WA 6840, Australia; 61-(0)-8-9340-8222, fax 61-(0)-8-9340-8118; E-mail Meredith.Borland@health.wa.gov.au.

REFERENCES
1. Simpson N, Finlay F. Only one fifth of A&E departments were found to have pain control policy for children [letter]. *BMJ*. 1998; 316:396.
2. Friedland LR, Pancioli AM, Duncan KM. Pediatric emergency department analgesic practice. *Pediatr Emerg Care*. 1997;13: 103-106.

3. Brent A. The management of pain in the emergency department. *Pediatr Clin North Am*. 2000;47:651-679.

4. Kennedy RM, Luhmann JD. The "ouchless emergency department" getting closer: advances in decreasing distress during painful procedures in the emergency department. *Pediatr Clin North Am*. 1999;46:1215-1247.

5. Younge PA, Nicol MF, Kendall JM, et al. A prospective randomised pilot comparison of intranasal fentanyl and intramuscular morphine for analgesia in children presenting to the emergency department with clinical fractures. *Emerg Med (Fremantle)*. 1999;11:90-94.

6. Kendall JM, Reeves BC, Latter VS. Multicentre randomised controlled trial of nasal diamorphine for analgesia in children and teenagers with clinical fractures. *BMJ*. 2001;322:261-265.

7. Manjushree R, Lahiri A, Ghosh BR, et al. Intranasal fentanyl provides adequate postoperative analgesia in pediatric patients. *Can J Anesth*. 2002;49:190-193.

8. Borland ML, Jacobs I, Geelhoed G. Intranasal fentanyl reduces acute pain in children in the emergency department: a safety and efficacy study. *Emerg Med (Fremantle)*. 2002;14:275-280.

9. Striebel HW, Pommerening J, Rieger A. Intranasal fentanyl titration for postoperative pain management in an unselected population. *Anaesthesia*. 1993;48:753-757.

10. NHMRC Guidelines for Ethical Research 1999. Commonwealth of Australia Canberra.

11. Lim CB, Paech MJ, Sunderland VB, et al. Pharmacokinetics of nasal fentanyl. *J Pharm Pract Res*. 2003;33:59-63.

12. Powell CV, Kelly A-M, Williams A. Determining the minimum clinically significant difference in visual analog pain score for children. *Ann Emerg Med*. 2001;37:28-31.

13. Todd KH, Funk KG, Funk JP, et al. Clinical significance of reported changes in pain severity. *Ann Emerg Med*. 1996;27:485-489.

14. Ho K, Spence J, Murphy MF. Review of pain-measurement tools. *Ann Emerg Med*. 1996;27:427-432.

15. Spagrud LJ, Piira T, von Baeyer CL. Children's self-report of pain intensity. *Am J Nurs*. 2003;103:62-64.

16. Holdgate A, Asha S, Craig J, et al. Comparison of a verbal numeric rating scale with the VAS for the measurement of acute pain. *Emerg Med (Fremantle)*. 2003;15:441-446.

17. Paech MJ, Lim CB, Banks SL, et al. A new formulation of nasal fentanyl spray for postoperative analgesia: a pilot study. *Anaesthesia*. 2003;58:740-744.

18. Wong P, Chadwick FD, Karovits J. Intranasal fentanyl for postoperative analgesia after elective caesarean section. *Anaesthesia*. 2003;58:818-819.

19. Galinkin JL, Fazi LM, Cuy RM, et al. Use of intranasal fentanyl in children undergoing myringotomy and tube placement during halothane and sevoflurane anesthesia. *Anesthesiology*. 2000;93:1378-1383.

20. O'Neil G, Paech M, Wood F. Preliminary clinical use of a patient controlled intranasal analgesia (PCINA) device. *Anaesth Intensive Care*. 1997;25:408-412.

21. Finn J, Wright J, Fong J, et al. A randomised crossover trial of patient controlled intranasal fentanyl and oral morphine for procedural wound care in adult patients with burns. *Burns*. 2004;30:262-268.

22. Borland ML, Bergesio R, Pascoe EM, et al. Intranasal fentanyl is an equivalent analgesic to oral morphine in paediatric burns patients for dressing changes: a randomised double blind crossover study. *Burns*. 2005;31:831-837.