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Brief Report

Intranasal hydromorphone for treatment of acute pain in children: A pilot study

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ABSTRACT

Objectives: We aimed to describe the analgesic efficacy, duration of analgesia, and adverse event profile associated with intranasal hydromorphone in children with acute pain presenting to an emergency department.
Methods: Prospective dose titration pilot study of otherwise healthy children 4 to 17-years-old with moderate to severe pain who required a parenteral opioid. All patients received an initial intranasal hydromorophone dose of 0.03 mg/kg. The need for additional analgesia was assessed at 15 and 30 min; an additional 0.015 mg/kg was given at each assessment, if required. Need for rescue analgesic, pain intensity and adverse events were assessed until 6 h after hydromorphone administration or until patients were discharged, underwent a procedure to treat their painful condition, or received a rescue analgesic.
Results: We enrolled 35 children. Fifteen, 11, and 9 children required a total dose of 0.03, 0.045, and 0.06 mg/kg, respectively. Patients in each dose group experienced an absolute decrease in pain score of ≥3/10 and percent reduction >40% within 5–15 min of completing dose-titration administration of hydromorphone. Duration of analgesia (i.e. time until rescue analgesic administered) >1 h was observed in 85.7% of patients. Patients not requiring rescue analgesics had mild or no pain until discharged or their painful conditions were treated. Three (8.6%) patients required a rescue analgesic <1 h after hydromorphone administration. There were no major adverse events.
Conclusions: Intranasal hydromorphone led to rapid, clinically significant and frequently sustained decreases in pain intensity in children. No major adverse events were observed in this preliminary sample.
Clinical Trials Registration Number: NCT02437669

1. Introduction

The intranasal (IN) route is an effective, rapid, and needle-free way of administering analgesics. Fentanyl and ketamine can be administered by the IN route and decrease pain by clinically significant amounts in children with acute pain. However, the duration of analgesia of these medications when administered intranasally has not been well described beyond 1 h [1-4].

Hydromorphone is a semisynthetic opioid that has a molecular weight, lipophilicity, and solubility favorable for nasal transmucosal delivery. [5,6] Bioavailability of hydromorphone after IN administration is approximately 50–60%, with rapid absorption within 5 min of administration [7,8]. IN hydromorphone doses of 2–10 mg have been studied in adults, with doses of ≥4 mg producing clinically significant decreases in pain intensity; onset of analgesia as soon as 5 min after administration; observed durations of analgesia up to 3 h; and no dose-related changes in adverse event profile [9].

IN hydromorphone administration in children has not been previously described, but may be a promising analgesic based on the results of prior studies in adults [7-9]. Before IN hydromorphone can be implemented or compared to other IN analgesics in children, its analgesic efficacy, dosing profile, and adverse event profile must be evaluated.

Our primary aim was to describe the analgesic efficacy of IN hydromorphone in children with moderate to severe pain presenting to the emergency department (ED). Our secondary aims were to describe the associated duration of analgesia and adverse events.

2. Methods

2.1. Study design, setting and population

We conducted a prospective dose titration pilot study in an urban pediatric ED with 55,000 annual visits. We enrolled a convenience sample of children 4 to 17-years-old with moderate to severe pain (pain score ≥ 4/10) who required a parenteral opioid analgesic as per their treating physician. We excluded patients for any of the following: allergy or known contraindication to opioids; receipt of any opioid or benzodiazepine within 6 h; presence of intranasal obstruction that could not be

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readily cleared; unable to complete self-report measures of pain or questionnaires (e.g. developmental delay); known liver or kidney problems; critical illness; chronic disease associated with pain (e.g. sickle cell disease); medical condition necessitating multiple painful procedures (e.g. malignancy); or could not speak English or Spanish. The institutional review board approved this study with written informed consent.

2.2. Measurements

Pain assessments were conducted in all children using the Faces Pain Scale – Revised (FPS-R) and in children 6 to 17-years-old using the Verbal Numerical Rating Scale (VNRS). The FPS-R and VNRS are self-report measures of pain with strong validity and reliability in children 4 to 17 and 6 to 17-years-old, respectively [10,11].

2.3. Study protocol

Baseline pain intensity was assessed within 15 min before IN hydromorphone administration. All children received an initial IN hydromorphone dose (2 mg/mL) of 0.03 mg/kg (maximum dose 4 mg) administered using an LMA® MAD Nasal™ in a standardized fashion. Immediately after administration, the patient reported how much pain they experienced due to IN administration.

Following administration of the initial IN hydromorphone dose, we conducted pain assessments at 5, 15, 30, 45, and 60 min, and then every 30 min thereafter until a maximum of 6 h or until the patient 1) was discharged from the ED (including admission to inpatient service); 2) underwent a procedure to treat their painful condition (e.g. fracture reduction); or 3) received a rescue analgesic (defined as non-IN hydromorphone parenteral analgesic) per the treating physician. During the 15- and 30-min pain assessments, we determined whether each patient required additional IN hydromorphone as part of the dose titration method, in which incremental doses were given to find the total cumulative dose (0.03, 0.045, or 0.06 mg/kg) required to achieve adequate analgesia (i.e. not requiring any more analgesics). First, patients were asked if their pain was "much less, a little less, the same, or worse" compared to before they received hydromorphone. If patients replied "the same" or "worse", they were given an additional 0.015 mg/kg dose of IN hydromorphone (maximum dose 2 mg). If they replied "much less" or "a little less", they were then asked, "Do you want more medicine to make your pain less"? Patients who answered in the affirmative were given an additional 0.015 mg/kg dose. Patients who responded in the affirmative at both the 15- and 30-min pain assessments received a total of 0.06 mg/kg (maximum possible total dose 8 mg). The last (or only) dose administered is referred to as the terminal dose.

The need for rescue analgesic was assessed (and administered, if indicated) at each pain assessment starting from 45 min until 6 h after administration of the initial IN hydromorphone dose by asking the patient if they wanted additional analgesics to make their pain less. The observed duration of analgesia was defined as the time from administration of the initial dose until a rescue analgesic was administered. Requirement of a rescue analgesic is a more patient-centered outcome than using a pain score threshold to indicate inadequate analgesia. For patients who did not require a rescue analgesic but were discharged from the ED or underwent a procedure to treat their painful condition before 6 h, the time from administration of the initial dose until discharge or procedure was designated as their observed duration of analgesia.

We assessed patients for major and minor adverse events every hour after IN hydromorphone administration. Major adverse events assessed included oxygen desaturation (<92%); respiratory depression; hypotension; bradycardia; need for supplemental oxygen, bag-mask ventilation, or non-invasive (e.g. jaw thrust) or invasive (e.g. intubation) airway support; and naloxone administration. Minor adverse events assessed included sleepiness, drowsiness, or tiredness; bad taste in mouth; lightheadedness or dizziness; dry mouth; rhinitis; nausea; confusion; itchiness; vomiting; warm sensation (warm, hot, flushed, or sweaty); and "other" (which patient would specify).

2.4. Outcomes and analyses

Descriptive statistics were used to summarize patient characteristics, self-reported pain scores, changes in pain scores, observed

Table 1
Patient characteristics.

		Total dose received		
	All patients n = 35	0.03 mg/kg n = 15	0.045 mg/kg (0.03 + 0.015 mg/kg)[a] n = 11	0.06 mg/kg (0.03 + 0.015 + 0.015 mg/kg)[b] n = 9
Age, median (IQR)	11 (8, 14)	10 (7, 14)	14 (12, 14)	11 (7.5, 13.5)
Age group, n (%)				
4–7 years old	6 (17.1)	4 (26.7)	0	2 (22.2)
8–12 years old	16 (45.7)	7 (46.6)	5 (45.5)	4 (44.5)
13–17 years old	13 (37.2)	4 (26.7)	6 (54.5)	3 (33.3)
Sex, n (%)				
Female	13 (37.1)	4 (26.7)	5 (45.5)	4 (44.5)
Male	22 (62.9)	11 (73.3)	6 (54.5)	5 (55.5)
Race/ethnicity, n (%)				
Hispanic	26 (74.3)	11 (73.3)	9 (81.8)	6 (66.7)
White	5 (14.3)	4 (26.7)	1 (9.1)	0
Black	3 (8.5)	0	0	3 (33.3)
More than one	1 (2.9)	0	1 (9.1)	0
Primary language, n (%)				
English	33 (94.3)	14 (93.3)	11 (100)	8 (88.9)
Spanish	2 (5.7)	1 (6.7)	0	1 (11.1)
Painful condition, n (%)				
Fracture[c]	17 (48.5)	6 (40)	6 (54.5)	5 (55.6)
Abdominal pain	10 (28.5)	5 (33.3)	2 (18.2)	3 (33.3)
Soft tissue injury	3 (8.6)	1 (6.7)	1 (9.1)	1 (11.1)
Abscess	1 (2.9)	1 (6.7)	0	0
Laceration	1 (2.9)	0	1 (9.1)	0
Other[d]	3 (8.6)	2 (13.3)	1 (9.1)	0

[a] 0.045 mg/kg dose consists of first 0.03 mg/kg dose, and then 0.015 mg/kg dose given at 15 min after first dose.
[b] 0.06 mg/kg dose consists of first 0.03 mg/kg dose, 0.015 mg/kg dose given at 15 min after first dose, and second 0.015 mg/kg dose given at 30 min after first dose.
[c] All fractures required either closed or open reduction.
[d] Other = Testicular pain, mastoiditis, cellulitis.

durations of analgesia, and adverse events. Sample size was based on similar pilot studies, including those aimed to assess changes in pain intensity in patients receiving IN analgesics. [2,12]

3. Results

3.1. Characteristics of study subjects

We enrolled 35 children. Table 1 shows the characteristics of the patients analyzed. We enrolled children of every year of age except for 9-year-olds. Most patients presented with fractures. The baseline pain score was similar between the groups receiving three different doses of IN hydromorphone (Table 2). A larger proportion of patients who received only 0.03 mg/kg were male.

3.2. Main results

Table 2 shows the outcomes associated with IN hydromorphone. More than half the patients (57.1%) required at least 0.045 mg/kg. We documented pain scores measured from time after administration of the initial 0.03 mg/kg dose of IN hydromorphone. In addition, we reported pain scores measured from time after administration of the terminal dose, which better represents the time to decreases in pain score associated with the total dose administered. All three doses of IN hydromorphone (0.03, 0.045, and 0.06 mg/kg) decreased the mean pain score reported by patients to ≤3/10 in 5–15 min after the terminal dose was administered. Patients achieved an absolute decrease in pain score of approximately 3/10 and a percent reduction of >40% in 5–15 min after the terminal dose was administered (Table 2). Patients achieved an absolute decrease in pain score of approximately 4–5/10 and a percent reduction of 50–70% at 1 h after the terminal dose was administered (Table 2). Similar pain scores and changes in pain score were observed when children 6 to 17-years-old were assessed using the VNRS (Supplemental Table 1).

Fig. 1 shows the observed durations of analgesia for each patient. Duration of analgesia >1 h was observed in 85.7% of patients receiving IN hydromorphone. Of the 5 patients who did not experience analgesia beyond 1 h, 3 (8.6%) failed to achieve that threshold because they required a rescue analgesic while the other two underwent a procedure within 1 h that treated their painful condition.

There were no major adverse events. The most common minor adverse events were feeling sleepy, drowsy or tired (31.4%); bad taste in mouth (22.9%); or feeling lightheaded or dizzy (22.9%) (Table 2). There was a similar adverse event profile across all three doses. There

Table 2
Outcomes associated with intranasal (IN) hydromorphone.

		Total dose received		
	All patients n = 35	0.03 mg/kg n = 15	0.045 mg/kg (0.03 + 0.015 mg/kg)[b] n = 11	0.06 mg/kg (0.03 + 0.015 + 0.015 mg/kg)[c] n = 9
Baseline pain score, mean (95% CI)	7 (6.3, 7.7)	7.3 (6.2, 8.4)	6.7 (5.2, 8.2)	6.9 (5, 8.8)
Pain score at time after initial dose of IN hydromorphone, mean (95% CI)[a]				
5 min	5.1 (4.2, 6)	4.3 (3, 5.6)	5.6 (4.1, 7.1)	5.8 (3.6, 8)
15 min	4 (3.1, 4.9)	2.7 (1.6, 3.8)	4.4 (2.9, 5.9)	5.6 (3.3, 7.9)
30 min	2.9 (2, 3.8)	1.9 (0.8, 3)	3.1 (1.8, 4.4)	4.2 (1.7, 6.7)
45 min	2.5 (1.6, 3.4)	1.4 (0.5, 2.3)	3.1 (1.6, 4.6)	3.3 (0.8, 5.8)
1 h	2.1 (1.4, 2.8)	1.7 (0.4, 3)	1.8 (0.5, 3.1)	3 (1.5, 4.5)
1.5 h	2.3 (1.4, 3.2)	1.9 (0.5, 3.3)	2.9 (0.9, 4.9)	2 (0.5, 3.5)
2 h	2.3 (1.3, 3.3)	2.4 (0.5, 4.3)	2 (0.3, 3.8)	2.4 (0.4, 4.4)
2.5 h	2.4 (1.5, 3.3)	2.4 (0.7, 4.1)	2.3 (0.7, 3.9)	2.4 (0.7, 4.1)
3 h	1.8 (1, 2.6)	1.2 (0, 2.5)	1.5 (0.2, 2.8)	3 (1, 5)
3.5 h	1.2 (0.6, 1.8)	0.4 (0, 0.9)	1.3 (0.5, 2.1)	2 (0, 4.2)
4 h	1.7 (0.9, 2.5)	0.5 (0, 1.1)	2 (0.1, 3.9)	2.5 (0.6, 4.4)
4.5 h	1.4 (0.9, 1.9)	1 (0.2, 1.8)	1.5 (0.2, 2.8)	2 (N/A)[d]
5 h	1.7 (1, 2.4)	2 (0.5, 3.6)	1.3 (0, 2.8)	2 (N/A)[d]
5.5 h	1 (0.4, 1.6)	0	1.3 (0, 2.8)	2 (N/A)[d]
6 h	1.2 (0.9, 1.5)	1 (0.2, 1.8)	1(0.3, 1.7)	2 (N/A)[d]
Decrease in pain score at time after terminal dose of IN hydromorphone, mean (95% CI)				
5 min	N/A	3.1 (1.9, 4.2)	N/A	N/A
15 min	4 (3.2, 4.7)	4.6 (6.1, 6.7)	3.6 (2.6, 4.6)	3.6 (1.9, 5.2)
30 min	4.4 (3.6, 5.1)	5.4 (3.9, 6.9)	3.6 (2.8, 4.4)	3.5 (2, 5)
1 h[e]	4.7 (3.7, 5.7)	5.4 (3.6, 7.2)	3.8 (2.4, 5.2)	4.4 (1.2, 7.6)
Pain associated with intranasal administration of hydromorphone, mean (95% CI)	0.4 (0.2, 0.8)	0.3 (0, 0.7)	0.4 (0, 0.9)	0.3 (0, 0.8)
Major adverse events, n (%)[f]	0	0	0	0
Minor adverse events, n (%)				
Sleepy, drowsy or tired	11 (31.4)	4 (26.7)	6 (54.5)	1 (11.1)
Bad taste in mouth	8 (22.9)	3 (20)	4 (36.4)	1 (11.1)
Lightheaded, dizzy	8 (22.9)	3 (20)	3 (27.3)	2 (22.2)
Dry mouth	5 (14.3)	2 (13.3)	3 (27.3)	0
Rhinitis	3 (8.6)	1 (6.7)	2 (18.2)	0
Nausea	2 (5.7)	0	2 (18.2)	0
Confused	1 (2.9)	0	0	1 (11.1)
Itchiness	1 (2.9)	1 (6.7)	0	0
Vomiting	0	0	0	0
Warm sensation (warm, hot, flushed or sweaty)	0	0	0	0
Other	0	0	0	0

[a] Pain scores in patients who had an observed duration of analgesia at each time. Patients who did not have a documented pain score at a time were not included in the mean pain score for that time. Times shown are after initial 0.03 mg/kg dose of IN hydromorphone.
[b] 0.045 mg/kg dose consists of first 0.03 mg/kg dose, and then 0.015 mg/kg dose given at 15 min after first dose.
[c] 0.06 mg/kg dose consists of first 0.03 mg/kg dose, 0.015 mg/kg dose given at 15 min after first dose, and second 0.015 mg/kg dose given at 30 min after first dose.
[d] Only one patient in the 0.06 mg/kg group had pain assessments after 4.5 h.
[e] Decrease in pain score 1h15min after administration of terminal dose for 0.045 mg/kg group.
[f] Oxygen desaturation (<92%); respiratory depression; hypotension; bradycardia; need for supplemental oxygen, bag-mask ventilation, or non-invasive (e.g. jaw thrust) or invasive (e.g. intubation) airway support; and naloxone administration.

did not appear to be any nasal pain associated with the administration of IN hydromorphone (Table 2).

4. Discussion

We present the first report of IN hydromorphone administration in children. In children 4 to 17-years-old with acute pain, IN hydromorphone appears to rapidly decrease pain intensity by a clinically significant amount, with a duration of analgesia >1 h for many patients. More than half the patients required at least 0.045 mg/kg of IN hydromorphone to treat their pain. There was a similar adverse event profile across all three doses.

Our findings show that all three doses of IN hydromorphone produce clinically significant outcomes in children. Patients experienced decreases in pain score greater than the previously identified minimum clinically significant difference (i.e. 2/10 absolute decrease, 25% percent reduction) in 5–15 min, and greater than the ideal clinically significant difference (i.e. 3/10 absolute decrease, 60% percent reduction) in 45–60 min, after the terminal dose was administered [13]. In addition, patients not requiring rescue analgesics sustained pain scores associated with mild or no pain (i.e. 0–4/10) for as long as 3–6 h. [14] Therefore, IN hydromorphone appears to be a reasonable analgesic for children who require rapid relief of moderate to severe pain, including those anticipating a potentially aggravating procedure (e.g. long-bone fracture prior to obtaining x-rays). Compared to shorter-acting IN analgesics such as fentanyl, the longer duration of analgesia may be beneficial in the unpredictable ED setting where there may be unanticipated delays in obtaining IV access or administering longer-acting analgesics; inability to obtain IV access; or delays in providing definitive treatment in patients with moderate to severe pain who may not routinely require IV access (e.g. abscess requiring incision and drainage).

To evaluate the dose of IN hydromorphone required by children, we chose a dose titration method to facilitate an individualized, patient-centered approach based on adequacy of analgesia achieved. This method was chosen in anticipation of differences in how individuals may perceive pain or respond to an analgesic, and allowed us to evaluate the analgesic efficacy of a lowest possible dose while minimizing the chance of inadequately treating pain in each patient. Our findings showed that the degree of analgesia and observed duration of analgesia achieved appeared similar between the three doses. Prior investigators, however, showed that escalating doses of IN hydromorphone (ranging from 2 to 10 mg) in adults were associated with a greater degree of pain relief and fewer patients requiring rescue analgesics. Although escalating doses were associated with increased incidence of nausea in this prior study, there were no other dose-related changes in minor or major adverse events [9]. Our cohort was too small to comment on major adverse events, and the frequency of minor adverse events appeared to be similar between the three groups.

There are clear limitations to comparing our findings to those of IN fentanyl and ketamine described in other studies. However, in a cohort of children with isolated limb injuries presenting to an ED, investigators demonstrated a median decrease in visual analog scale rating after IN fentanyl and ketamine administration of 30 mm (out of 100 mm) at 15 min, and 50 mm at 60 min [1]. Although these investigators used a different self-report measure of pain and studied a more homogenous cohort, the decreases in pain intensity associated with IN fentanyl and ketamine appeared comparable to those we observed with IN hydromorphone. Future study comparing these three IN analgesics would be reasonable to evaluate for differences in clinically important outcomes.

Our study had a number of limitations. We enrolled a convenience sample and may not have been able to detect less common major adverse events due to the small sample size. We did not assess for sedation-related adverse events in patients who subsequently received procedural sedation. We could not definitively determine the duration of analgesia associated with IN hydromorphone for most patients because we did not want to interfere with the clinical management being provided (e.g. ED discharge, treatment of painful condition). Our findings may not be generalizable to patients with illnesses associated with chronic pain or those <4-years-old.

5. Conclusions

Intranasal hydromorphone produces rapid and clinically significant decreases in pain intensity in children using doses of 0.03, 0.045 and 0.06 mg/kg. The duration of analgesia appears to be at least 1 h in most patients, up to as long as 6 h. The adverse events observed in this study were all minor, but a larger sample size is needed to better

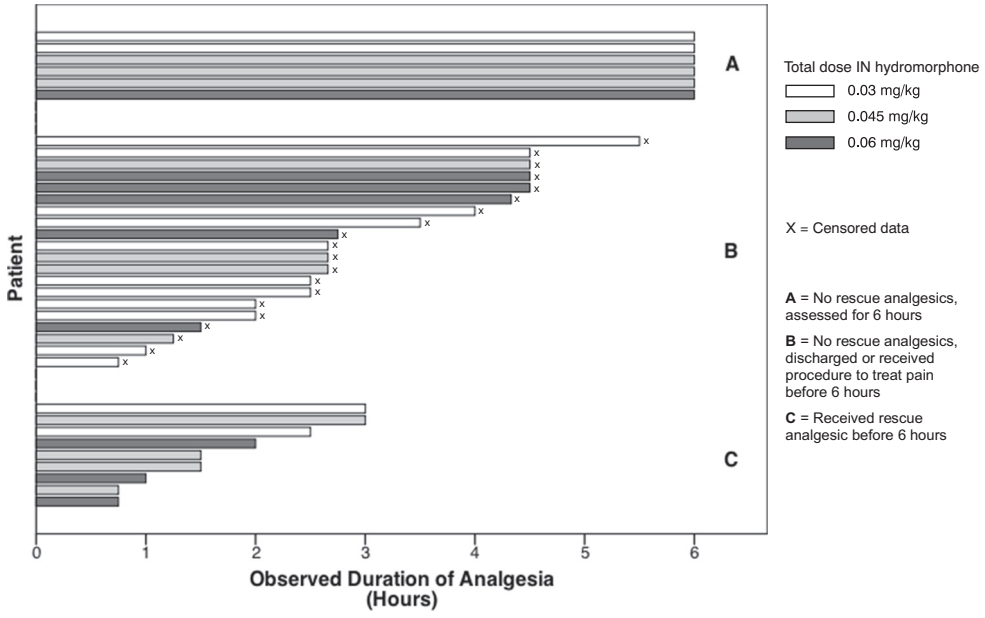

Fig. 1. Observed duration of analgesia associated with intranasal (IN) hydromorphone. Observed duration of analgesia defined as time without requiring a rescue analgesic, starting from time of initial IN hydromorphone dose administration (Time 0), up to 6 h or up to time until patient discharged or received procedure to treat their pain (before 6 h) without requiring a rescue analgesic (i.e. censored data). Each bar represents the duration of analgesia observed for a single patient.

delineate major adverse events. Future trials comparing IN hydromorphone, fentanyl and ketamine may be warranted so that the most efficacious IN analgesic for children can be identified.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2019.03.013.

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Conflict of interest

The authors have no relevant conflict of interests to declare.

Author contributions

DT and **PD** conceptualized and designed the study. **DT** supervised the conduct of the study and data collection, conducted the statistical analyses for the study, and drafted the manuscript. **DT**, **SP**, **KD**, **AW** and **SG** undertook enrollment of participating patients. All authors contributed substantially to its revision. **DT** takes responsibility for the paper as a whole.

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