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INTRANASAL SUFENTANIL VERSUS INTRAVENOUS MORPHINE FOR ACUTE PAIN IN THE EMERGENCY DEPARTMENT: A RANDOMIZED PILOT TRIAL

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☐ **Abstract—Background: Patients in the United States frequently seek medical attention in the emergency department (ED) to address their pain. The intranasal (i.n.) route provides a safe, effective, and painless alternative method of drug administration. Sufentanil is an inexpensive synthetic opioid with a high therapeutic index and rapid onset of action, making it an attractive agent for management of acute pain in the ED. Objective: The objective of our study was to evaluate the safety and efficacy of i.n. sufentanil as the primary analgesic for acute pain in the ED. Methods: This was a single-center, prospective, randomized, double-blind, double-dummy, controlled trial that evaluated the use of i.n. sufentanil 0.7 μg/kg via mucosal atomizer device vs. intravenous morphine 0.1 mg/kg in adult patients who presented to the ED with acute pain. The primary outcome was patient's pain score at 10 min after administration of intervention. Secondary outcomes were adverse events, the need for rescue analgesia, and patient satisfaction after treatment. Results: Thirty patients were enrolled in each group. There was no significant difference in pain scores at 10 min after administration of intervention (sufentanil: 2.0, interquartile range = 2.0–3.3 vs. morphine: 3.0, interquartile range = 2.0–5.3, $p = 0.198$). No serious adverse events were reported. Rescue analgesia was not requested in either group. No significant difference in median satisfaction scores was found. Conclusion: The use of i.n. sufentanil at 0.7 μg/kg/dose resulted in rapid and safe analgesia with comparable efficacy to i.v. morphine for up to 30 min in patients who presented with acute pain in the ED.**

☐ **Keywords—acute pain; intranasal; sufentanil analgesia**

INTRODUCTION

Acute pain is a common presentation for emergency department (ED) visits in the United States. Each year, EDs provide medical attention to more than 136 million patients for pain-related visits (1,2). Common types of pain include: abdominal (8%), headache (3.1%), back (2.8%), and generalized (2.2%) (1). Patient satisfaction is increasingly being used as a measure of performance in the ED (2). Given that the effectiveness of treatment is determined largely by patient self-reporting, the provision of timely, safe, and effective analgesia continues to be a topic of interest in emergency medicine (2,3).

Traditional routes of analgesic administration include oral, intravenous (i.v.), or intramuscular (i.m.) (3). The use of oral analgesics is often not desired due to extensive first-pass metabolism and slow onset of action (4).

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Administration via the i.v. route requires i.v. access, and in EDs where supply or staff shortages are common, delivery of analgesia could be delayed (3). Although i.m. injections do not require i.v. access, it often induces additional pain at the site of injection (3). Intramuscular injections may also be difficult in patients who are obese, and often result in unpredictable drug absorption (3,5). The intranasal (i.n.) route provides a safe, effective, and painless alternative for the timely administration of analgesics (3,5–9). The rich capillary network of the respiratory mucosa allows for drugs to be absorbed rapidly while bypassing the first pass effect (4,8,9).

Sufentanil is an inexpensive synthetic opioid that has a high therapeutic index, rapid onset of action, and short half-life after i.n. administration (4,7,9). These properties make it an attractive agent for the management of acute pain in the ED. The use of i.n. sufentanil has already been evaluated in the management of procedural and postoperative pain and cancer-associated breakthrough pain (5,6,10,11). Despite these data, the use of i.n. sufentanil in the ED is not a common practice. Literature that describes its use in the ED is limited and has been focused on the management of traumatic pain (12–14).

MATERIALS AND METHODS

This was a single-center, prospective, randomized, double-blind, double-dummy, controlled trial comparing the use of i.n. sufentanil to i.v. morphine for moderate to severe acute pain in the ED.

The study was conducted in a community teaching hospital with a Level II trauma ED where more than 77,000 patients are treated annually. Prior to patient enrollment, the study was registered at ClinicalTrials.gov (NCT03224039). The hospital's Institutional Review Board approved the study protocol. Written and signed informed consent was obtained in accordance with institutional policy. The study was performed and reported according to the CONSORT statement (15).

The objective of the study was to evaluate the safety and efficacy of i.n. sufentanil as the primary analgesic for acute pain in the ED. We hypothesized that i.n. sufentanil would provide safe and effective pain relief compared with i.v. morphine. The primary outcome used to test our hypothesis was patients' reported pain score at 10 min after initial administration of study intervention. To evaluate the primary outcome, we used the numeric rating scale (NRS) to measure the patient's perceived level of pain from 0 (no pain) to 10 (worst pain). The NRS system is a validated and effective tool used frequently for the assessment of pain (16). The secondary outcomes of interest were: incidence of adverse events, mean consumption of rescue analgesia, and patient satisfaction regarding pain management received at the ED based on a 10-point Likert scale.

Study Protocol

The inclusion criteria for study eligibility were: age 18 years or older, English speaking and able to communicate severity of pain, willing to provide informed consent, and presentation to the ED with the chief complaint of acute pain with moderate to severe intensity ($\geq$4/10 on the NRS). Acute pain was defined as pain with an onset of $\leq$ 15 days. Exclusion criteria were: hemodynamic instability (respiratory rate < 12 or > 20 breaths/min, heart rate < 60 or > 110 beats/min, blood pressure < 90/50 mm Hg or >180/100 mm Hg, oxygen saturation <94%), altered mental status, weight over 140 kg, currently pregnant or breastfeeding, allergy to morphine or sufentanil, use of analgesia within 4 h of presentation to the ED, inability to effectively communicate pain, nasal obstruction or congestion, chest pain, acute hepatic or renal impairment, history of chronic liver or renal disease (including history of transplant), chronic alcohol abuse, seizure disorder, or thyroid disorder. Patients suspected of having or presenting with a traumatic head injury with or without loss of consciousness, myocardial ischemia, a headache or migraine, or increased intracranial/intraocular pressure were also excluded.

Prior to commencement of the study, the pharmacy investigator (BS) was responsible for the generation and maintenance of study numbers (randomly generated via computer-generated block randomization with block sizes of four). The study numbers were sealed individually in opaque and sequentially numbered envelopes that were securely stored in the ED Office of Research. Each study number corresponded to either 1) i.n. sufentanil 0.7 μg/kg administered via a mucosal atomizer device (MAD) and normal saline 1 mL i.v. push (i.v.p.) or 2) morphine 0.1 mg/kg i.v.p. and normal saline i.n. administered via a MAD. Each group received a one-time dose of the intervention during the study period. To maintain blinding of study investigators and nurses assigned to the patient, the volume of normal saline administered i.n. in the morphine group was equivalent to the volume of i.n. sufentanil in the sufentanil group. To further ensure blinding of the study interventions, the name of the intervention for either group was titled "study intervention." The study interventions were prepared and dispensed by the pharmacist stationed in the ED pharmacy satellite based on the intervention allocation key. Patients were recruited and enrolled 7 days per week, during three 4-h blocks (8 AM to 12 PM, 12 PM to 4 PM, and 4 PM to 8 PM) over a 17-month period from January 2017 to June 2018. During each block, two trained Research Associates (RAs) identified and screened patients for potential

study-eligibility from the ED's electronic medical record system. All RAs received didactic training by study investigator (BS, SD), in which the study protocol, process for patient enrollment, data recording, transcribing, and maintenance per Institutional Review Board and Health Insurance Portability and Accountability Act policies were reviewed.

Once a potential patient was identified, the RAs notified the emergency physician (attending or resident) of potential patient eligibility. After a physical examination by the ED attending, the RAs approached the patient regarding interest in participating in the study. Once the patient expressed interest, the RAs used a customized screening form to further determine the patient's eligibility for inclusion. If eligible, the RAs, along with a study investigator (IJ, ZH, AA, TW, AL, SD, MW), acquired informed consent and the patient was enrolled. Participants were sequentially assigned a study number (from 1–60) by the RAs. A medication order for the research intervention was then placed in the electronic medical record by the emergency physician assigned to the patient. Within the electronic order, the physician recorded the study number under a query field for additional comments. The medication order was then verified and prepared by the pharmacist stationed in the ED pharmacy satellite. To ensure proper blinding, the RAs provided the pharmacist with the sealed opaque envelope containing the study number and delivered the study intervention to the nurse assigned to the patient. At no point did the pharmacist who procured the study intervention observe or interact with the patient. Only the primary investigator (BS), statistician (JR), and the pharmacist procuring the intervention had knowledge of the study arm in which the participant was assigned. The ED providers, participant, RAs, and study investigators (IJ, ZH, AA, TW, AL, SD, MW) were blinded. Once the study intervention was administered by the nurse, the RAs or study investigator (IJ, ZH, AA, TW, AL, SD, MW) collected pain scores, vital signs, adverse events, and any use of rescue analgesia at designated intervals (5 [*t*5], 10 [*t*10], 20 [*t*20], and 30 [*t*30]) minutes after administration of study intervention. Rescue analgesia, in the form of morphine 0.1 mg/kg i.v.p., max 10 mg, was offered at *t*10, *t*20, and *t*30, if the patient reported an NRS ≥ 4. Data collection ended at *t*30 or upon patient discharge, whichever occurred first.

Statistical Analysis

Based on previous research by Bijur et al. and Holdgate et al. that evaluated the use of verbally administered pain scores to record acute pain, we assumed a primary outcome consisting of a minimal clinically meaningful difference of 1.5 between the two groups at the 10-minute pain assessment (*t*10) (15,16). Assuming a standard deviation of 3.0, a power analysis determined that an independent *t*-test with a sample size of 60 (30 in each group) provided at least 80% power to detect a difference of at least 1.5 at *t*10 (as well as all other designated intervals), with an alpha = .05. The sample size was increased from the original estimate of 40 to provide a smaller margin of error. IBM SPSS Statistics version 23 (IBM, Armonk, NY) was used for statistical analyses. After assessing the normality of the data via Shapiro-Wilk tests, Mann-Whitney *U* tests were used to determine differences in pain scores at each time interval, patient demographics, and patient satisfaction scores. The Fisher's exact test was used to determine the difference in occurrence of adverse events between the two groups.

RESULTS

The CONSORT diagram for study enrollment is displayed in Figure 1. Sixty patients (30 sufentanil, 30 morphine) were enrolled in the study. A summary of patient demographics is presented in Table 1. No significant differences in the patients' baseline characteristics were detected. The median age of patients enrolled in the morphine and sufentanil groups was 47 years (interquartile range [IQR] 33.8–63.3) and 43 (IQR 32–53.8), respectively. The most commonly reported types of pain in both groups were abdominal (morphine: 18/30 [60%], sufentanil: 16/30 [53.3%]) and back (morphine: 5/30 [16.7%], sufentanil: 5/30 [16.7%]). A summary of the pain scores recorded at each interval is presented in Table 2. No significant difference in pain scores was detected at triage and at *t*0 (time immediately prior to administration of study medication). At *t*10, no significant difference in median NRS was detected between patients who received sufentanil (2.0, IQR 2.0–3.3) vs. morphine (3.0, IQR 2.0–5.3, $p = 0.198$). No significant differences in pain scores were found at other time intervals.

No significant difference was observed in the number of patients who reported adverse events ($p = 1.0$) between the two groups. Nausea and vomiting was observed in only one patient who received morphine (3.3%). The patient reported nausea at *t*5 and vomited at *t*20. However, it should be noted that the patient presented to the ED complaining of abdominal pain and nausea prior to enrollment. Ondansetron 4 mg i.v. was administered at *t*5 for symptomatic management. Dizziness was reported by another patient in the morphine group at *t*5, which transiently resolved by *t*20. In the sufentanil group, one patient reported being sleepy at *t*10 whereas another patient experienced a transient decrease in oxygen saturation from 96% to 93% at *t*10 that resolved at *t*20 with no medical management. With regard to both groups, no cases of headache, hypoxia (oxygen saturation < 88%), dysphoria, flushing,

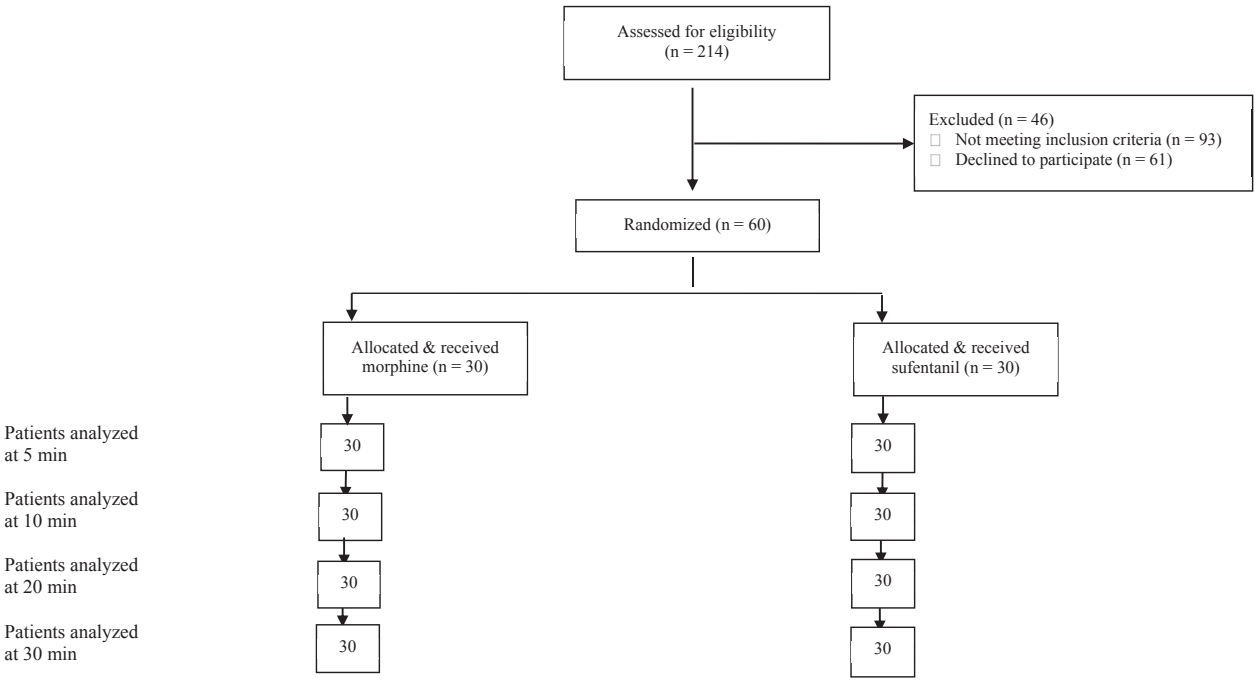

Figure 1. Participant flow diagram.

hypotension, or nasal irritation were reported. All adverse events were non-life-threatening. No rescue analgesia was requested or administered during the study. No significant difference in the patients' median satisfaction scores was observed (morphine group: 8.0, IQR 6.0–10.0 vs. sufentanil: 10, IQR 7.8–10.0, $p = 0.152$).

DISCUSSION

The use of i.n. analgesia is an attractive method for managing acute pain in the ED, as it is a convenient and painless mode of drug administration. However, a limitation of this mode of delivery is the relatively small volume of liquid that can be administered into the nares (8,13). Due to limited space and surface area for drug absorption, the ideal volume for i.n. drug administration is 0.5–1 mL (8,13). Sufentanil is a viable agent for i.n. administration given its desirable pharmacokinetic and pharmacodynamics. It is an inexpensive lipophilic agent that has rapid onset of action (within 20 min) and short half-life (15–20 min) (4,8,9,12). Furthermore, it is commercially available in 50-μg/mL vials, a concentration that would result in minimal volume runoff from the nares. Taken together, these features allow sufentanil to be an ideal medication for i.n. administration. Despite these properties, literature describing the use of sufentanil for acute pain management in the ED is limited (12–14).

Stephen et al. conducted a nonrandomized, open-label dose trial to determine safety and efficacy of i.n. sufentanil in patients with moderate to severe pain secondary to distal extremity injury (12). Patients who presented with NRS ≥ 5 received i.n. sufentanil (0.5 μg/kg, max 50 μg/dose) via a MAD. At 30 min after administration of sufentanil, it was reported that the average pain score decreased 4.3 points (from 7.8 to 3.5). Eight patients (53%) reported a final pain score of ≤ 3. Of note, 7 patients (46.6%) reported experiencing mild dysphoria, which was described as feeling "loopy, fuzzy, floaty, woozy." Nausea was reported in 2 patients (13.3%). No information was provided on the

Table 1. Demographics for Patients Enrolled in the Study

Patient Characteristics	Morphine, n (%)	Sufentanil, n (%)
Gender		
Male	10 (33.3)	12 (40)
Female	20 (66.7)	18 (60)
Age (median years ± IQR)	47 (33.8–63.3)	43 (32–53.8)
Weight (median kg ± IQR)	77.9 (70–89.3)	76.05 (67.9–94.1)
Race		
African-American	24 (80)	23 (76.6)
Caucasian	3 (10)	3 (10)
Hispanic	3 (10)	4 (13.3)
Pain etiology		
Abdominal pain	18 (60)	16 (53.3)
Back	5 (16.7)	5 (16.7)
Musculoskeletal	4 (13.3)	3 (10)
Flank	2 (6.7)	4 (13.3)
Fracture	0 (0)	1 (3.3)
Right testicular	1 (3.3)	0 (0)
Endometriosis	0 (0)	1 (3.3)
Baseline NRS (median ± IQR)	9.0 (6.0–10)	10.0 (8.0–10)

IQR = interquartile range; kg = kilogram; NRS = numeric rating scale.

Table 2. Pain Scores Recorded During Designated Intervals

	Pain NRS, Median (IQR)		
Time Interval	Morphine (n = 30)	Sufentanil (n = 30)	*p*-Value
*t*0	9.0 (6.0–0.0)	10.0 (8.0–10.0)	0.224
*t*5	2.0 (0–5.3)	2.0 (1.0–3.0)	0.340
*t*10	3.0 (2.0–5.3)	2.0 (2.0–3.3)	0.198
*t*20	4.0 (2.4–6.0)	3.0 (2.0–6.3)	0.766
*t*30	5.0 (3.0–6.0)	5.0 (2.8–8.3)	0.255

NRS = numeric rating scale; IQR = interquartile range.

use of rescue analgesia. Steenblik et al. evaluated the use of i.n. sufentanil in a nonrandomized observational study with 40 patients who presented with acute moderate to severe pain secondary to extremity injury at a ski resort (13). Similar to Stephen et al., patients received one dose of i.n. sufentanil (0.5 μg/kg) administered via a MAD (12). However, there was no maximum dose per administration, and 75% of patients were male. The average dose of sufentanil administered was 37.7 μg, and the mean reduction in pain scores was 4.7 (95% confidence interval [CI] 3.67–5.57), 5.79 (95% CI 4.81–6.77), 5.74 (95% CI 4.72–6.76) at 10, 20, and 30 min, respectively. Dizziness, the most common adverse event, was reported in 3 (7.5%) patients. No episodes of dysphoria or apnea were observed. Dolatabadi et al. conducted a randomized trial to evaluate i.n. sufentanil (0.3 μg/kg) vs. i.m. morphine (0.1 mg/kg) in 88 patients who presented to the ED with pain secondary to trauma in Iran (14). Eighty-eight patients were equally randomized to receive either treatment. No significant differences in pain scores at 15, 30, and 60 min after administration of study interventions were detected. Although the study investigators concluded that i.n. sufentanil has similar effects to i.v. morphine, it should be noted that only the study abstract was published in English. Therefore, the process for randomization of study intervention, methodology used for statistical analysis, and device used to administer i.n. sufentanil all remain unknown to English readers. With these limitations, it is difficult to extrapolate the findings of the study to practice in the United States.

To the best of our knowledge, this is the first study to evaluate the use of i.n. sufentanil against i.v. morphine, which is commonly used for management of acute pain in the ED. However, the use of i.v. morphine requires the placement of i.v. access. The process for obtaining i.v. access could be difficult and cause delays in drug administration, whereas administration via i.n. route provides safe and painless drug administration with quick onset of action. In our prospective, double-blind, randomized trial, we administered sufentanil via a MAD to facilitate ease of drug administration. To prevent run-off of the drug, no more than 1 mL was administered in each nare. If the total volume of the dose was above 1 mL, the volume was divided evenly between each nare. For the purposes of the study, we excluded patients who weighed more than 140 kg, as the required volume of sufentanil would be too much for effective i.n. administration. Although no differences in pain scores between the two groups were identified, our results indicate a shorter time to pain reduction compared with data previously reported by Steenblik et al. (15 min) and Stephen et al. (30 min) (12,13). A potential explanation for this difference is that a higher dose of sufentanil was used in our study. Our dosing of sufentanil 0.7 μg/kg was based on anecdotal observations from our experience that patients who received this dose were provided safe and effective analgesic therapy. Despite the use of a higher sufentanil dose in our study compared with previous ED literature, adverse events were rare and non-life-threatening. In particular, we did not observe hypoxia or dysphoria. Rescue analgesia was not requested or required in either treatment group.

Limitations

This study was conducted at a Level II trauma center with a small sample size. Due to our study's limited patient volume, despite a lack of statistical significance, the patient's sources of pain varied, potentially limiting external validity. As well, it was impossible to determine if i.n. administration reduced time to treatment compared with i.v. administration, as i.v. access was required for every patient to maintain blinding. It is likely that i.n. administration results in faster procurement and administration, but we were unable to confirm this potential benefit in our study. Furthermore, patient recruitment was possible only when the study investigators or RAs were on staff. This likely limited the number of patients we were able to screen and enroll. RA fidelity to study protocol was not measured.

CONCLUSION

The use of i.n. sufentanil at 0.7 μg/kg/dose resulted in rapid and safe analgesia with comparable efficacy to i.v. morphine for up to 30 min in patients who presented with acute pain in the ED.

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ARTICLE SUMMARY

1. Why is this topic important?

This topic is important as it explores the efficacy, safety, and feasibility of intranasal sufentanil for the management of acute pain.

2. What does this study attempt to show?

This study attempts to demonstrate the safety and efficacy of intranasal sufentanil for management of acute pain.

3. What are the key findings?

There were no significant differences in pain scores and incidence of adverse events when intranasal sufentanil, administered at 0.7 μg/kg/dose, is compared with intravenous morphine 0.1 mg/kg/dose for patients who present with acute pain in the emergency department.

4. How is patient care impacted?

The use of intranasal sufentanil may be a viable alternative to standard therapy (e.g., i.v. morphine) for the management of acute pain.