Sufentanil sublingual tablet 30 mcg for moderate-to-severe acute pain in the emergency department

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ABSTRACT

Background: Pharmacological properties of the sufentanil sublingual tablet 30 mcg (SST 30 mcg) could offer potential analgesic advantages in settings requiring noninvasive, acute pain management. The feasibility of using SST 30 mcg for moderate-to-severe pain management in the emergency department (ED) was evaluated.

Methods: This open-label, multicenter feasibility study included patients aged ≥18 years who presented to the ED with moderate-to-severe pain (≥4 on the numeric rating scale of pain intensity (NRS); opioid-tolerant patients were excluded. Patients received a single SST 30-mcg dose (single-dose cohort) or, upon request, ≤3 additional doses ≥60 min apart (multiple-dose cohort) and were evaluated over 1 or 2 h. Effectiveness was assessed by patient-reported pain scores (11-point NRS; 5-point pain relief scale). Safety and tolerability were also assessed.

Results: Overall, 76 patients enrolled into the single-dose (n = 40) and multiple-dose (n = 36) cohorts. In the first hour (combined cohorts), mean pain intensity was significantly lower 15-min post-dosing (P < 0.001; clinically meaningful within 30-minutes post-dosing) and continued to decrease during the first hour (P < 0.001 for each 15-minute interval). Mean pain intensity (multiple-dose cohort) decreased from 7.6 at baseline to 4.5 at 1 h and to 4.6 at 2 h (P < 0.001 for both); mean pain relief increased from baseline to 1.9 at 1 h (P < 0.001) and to 2.0 at 2 h (P < 0.001). Most (79%) patients had no adverse events (AEs), and there were no severe AEs.

Conclusions: SST 30 mcg was feasible for managing moderate-to-severe acute pain in an ED setting.

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1. Introduction

Pain is the most common reason people visit the emergency department (ED). Studies indicate however, that ED physicians often do not provide adequate analgesia to their patients as a result of time constraints, gender and age bias, opioidophobia, and insufficient formal training in acute pain management [1]. Often, these patients are suffering from moderate-to-severe pain, have long delays before obtaining pain relief, and are discharged in a significant degree of pain. In a study of >800 patients treated in 20 EDs with a baseline pain score of 8 out of 10, patients incurred a median delay of 90 min to receive an analgesic, with only 60% of patients receiving any analgesic at all; overall, three-quarters of patients were discharged with moderate-to-severe pain [2]. A recent study showed that difficult intravenous (IV) placement requiring advanced techniques, such as ultrasound guidance, further increased the time to successful IV placement by 118–135 min [3]. Demonstrating the benefit of early pain management, a study of over 2000 ED patients demonstrated that more rapid administration of analgesics was associated with shorter lengths of stay [4].

A commonly used treatment for moderate-to-severe pain is IV opioids, but IV drug administration requires significant ED resources (bed, nurse, equipment, etc.) which may be limited during busy periods, thereby presenting a significant barrier in terms of time delay to pain treatment in the ED [5]. While oral opioids require fewer resources to administer, the time to onset and titratability of oral opioids limit their use in severe pain [6]. Novel classes of analgesics have recently been introduced, but many patients still suffer from acute pain in situations where immediate IV access may be unavailable [7].

The sufentanil sublingual tablet (SST) 30 mcg (SST 30 mcg), dispensed using a single-dose applicator, is being studied in clinical trials for the treatment of moderate-to-severe acute pain in short-term use settings, such as the ED and ambulatory surgery centers. SST 30 mcg, developed to take advantage of the unique pharmacokinetic and pharmacodynamic properties of sufentanil following sublingual administration
(avoids first-pass metabolism, short time of onset as reflected by a plasma:brain equilibrium half-life of 6.2 min, and no active metabolites), could offer potential analgesic advantages in settings requiring noninvasive, acute pain management [8–12].

Several clinical safety and efficacy trials of SST (15 mcg and 30 mcg doses) have demonstrated favorable tolerability in post-operative patients [13–16]. However, because SST 30 mcg has the potential to treat pain in other acute settings where safety has not been studied, the purpose of this open-label study was to determine the feasibility of using SST 30 mcg in patients in the ED, as they represent a relatively unique patient population.

2. Methods

This single-arm, multicenter, open-label feasibility trial was conducted at 3 hospitals in the United States (Hennepin County Medical Center, Minneapolis; Memorial Hermann–Memorial City Medical Center, Houston; and Ben Taub General Hospital, Houston). The study was registered with clinicaltrials.gov (NCT02447848) in May 2015. The protocol was approved by the institutional Review Board for each study site, and written informed consent was obtained from all patients. The study was conducted under the international Conference on Harmonisation, Harmonised Tripartite Guideline for Good Clinical Practice (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; http://www.ich.org/home.html) and the Guidelines of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013; http://www.wma.net/en/30publications/10policies/b3/).

2.1. Primary inclusion and exclusion criteria

Male and nonpregnant female patients aged ≥ 18 years who presented to the ED with moderate-to-severe pain due to obvious trauma or injury on physical examination, who were classified as American Society of Anesthesiologists (ASA) physical class I–III [17,18], and were willing and capable of understanding and cooperating with the requirements of the study were eligible for inclusion. Patients were excluded if they were opioid tolerant (> 15 mg oral morphine sulfate–equivalent daily); used illicit drugs of abuse, abused prescription medication or alcohol, or were dependent on supplemental oxygen; had an allergy or hypersensitivity to opioids; or had a medical condition—in the opinion of the investigator—that could adversely affect the patient’s participation or safety, study conduct, or interfere with pain assessments (including chronic pain or active infection). Prior to dosing, patients were additionally excluded if they were not awake, not breathing spontaneously; were unable to answer questions and follow commands; or had a respiratory rate < 8 or > 24 breaths per minute.

2.2. Study treatment and rescue medication

Eligible patients reporting a moderate-to-severe pain intensity score of ≥ 4 (0–10 numeric rating scale, where 0 represents no pain and 10 represents the worst possible pain) received their SST 30 mcg dose sublingually by a healthcare professional (HCP) [19,20]. The initial patients entering the study (the first 40 patients) received a single dose only (single-dose cohort), with subsequent patients (36 patients) being able to receive additional doses if needed for pain (multiple-dose cohort).

Patients in both cohorts could receive, only upon request by the patient, rescue opioid medication (oral oxycodone elixir; Oxyfast 5 mg/5 mL at 0.1 mg/kg or IV morphine [0.05 mg/kg] if they had an IV catheter in place) ≥ 10 min after dosing with SST 30 mcg. All patients could receive rescue medication starting 10 min after their first SST 30 mcg dose. Patients in the single-dose cohort were restricted to a single SST 30 mcg dose and remained in the study for up to 2 h to accommodate safety assessments; after 1 h, since study drug was no longer available, patients in the single-dose cohort could receive other analgesics if required. Patients in the multiple-dose cohort could receive, upon request, up to 3 additional SST 30 mcg doses ≥ 60 min apart, up to 5 h. Since study drug was available hourly, only the pre-specified rescue opioid medication per the patient’s request could be utilized to treat inadequate analgesia in this cohort.

2.3. Effectiveness and safety assessments included in the analysis

Effectiveness was assessed by patient reports of pain intensity on the 11-point numeric rating scale (0 = no pain; 10 = worst possible pain) and a 5-point pain relief scale (0 = no relief; 1 = a little relief; 2 = moderate relief; 3 = a lot of relief; 4 = complete relief). In addition, all HCPs who administered SST 30 mcg to ≥ 3 patients answered a Study Drug Administration Questionnaire (Supplementary Fig. S1) at the end of the study.

Patient-reported pain intensity was initially recorded by HCPs at baseline prior to dosing. Pain intensity and pain relief scores were then obtained at 15-minute intervals for the first 45 min, followed by every hour (from 1 to 5 h) following the first dose of SST 30 mcg. Effectiveness endpoints included the time-weighted summed pain intensity difference [21–25] from baseline over the first hour of treatment, and individual pain intensity and pain relief scores at designated timepoints, compared with baseline. Overall satisfaction with SST 30 mcg as a method of pain control (indicated as “poor”, “fair”, “good”, or “excellent”) was evaluated at the time of study discontinuation for the multiple-dose cohort via patient and HCP global assessments (PGA and HPGA, respectively) [26–28].

Other effectiveness endpoints included the proportion of patients who required rescue medication while receiving SST 30 mcg (i.e., in the first hour for the single-dose cohort and throughout the study for the multiple-dose cohort); the proportion of patients terminated from the study due to inadequate analgesia; and the total number of doses of study and rescue medication used.

Safety was monitored via periodic measurement of vital signs (i.e., respiratory rate, radial pulse rate, and blood pressure) and continuous monitoring of oxygen saturation (SpO2) via pulse oximetry monitors (but was only recorded at the time points when respiratory rates were measured and recorded), per direct observation, as well as assessment and recording of spontaneously reported adverse events (AEs; including cognitive impairment–associated AEs), and assessment of the use of concomitant medications. The study site investigators assessed and described AE severity and relatedness (not related or possibly/probably related) to the study drug (Supplementary Text).

Heart rate was measured over 30 s and respiratory rate was measured over 1 min. Respiratory rate and other vital signs could be checked at additional times on an ad-hoc basis per clinical judgment. SpO2 was measured continuously by pulse oximetry and recorded at predose and every 15 min following drug dosing for the first hour and every 30 min thereafter.

A 6-item screener (SIS) [29] was used to detect cognitive impairment and generate a SIS score (0–6). In general, SIS scores of 5 and 6 are considered non-impaired and a score < 5 is considered as cognitive impairment. Assessment of cognitive impairment (e.g., confusion, somnolence, memory impairment, and reaction time) before and 1 h after dosing with SST 30 mcg was requested by the United States Department of Defense (study sponsor), due to the concern of impaired cognitive skills with other field-based analgesics used in the military, such as ketamine [30].

2.4. Statistical analysis

A sample size of approximately 120 patients was planned for this analysis based on clinical judgment. All enrolled patients who had both baseline and follow-up data were included in the analysis. Effectiveness data from the intent-to-treat (ITT) population, defined as all...
patients who received ≥ 1 dose of SST 30 mcg, were summarized by descriptive statistics. All enrolled patients who received at least 1 dose of SST 30 mcg were included in the analyses and summaries of safety data. Effectiveness data from the entire patient population were combined for the first study hour (i.e., after the first dose); effectiveness data at hour 2 were reported only for the multiple-dosing cohort, as the single-dose cohort no longer had access to SST 30 mcg after the first hour. Given the nature of ED studies, a limited number of patients had available pain data after 2 h (< 10% of patients remained in the study), therefore, pain variables by evaluation time point were analyzed only up through the 2-hour study period. Subgroup analyses for age (≥ 65 years and ≥ 65 years), sex (male and female), race (Caucasian and non-Caucasian), and body mass index (BMI) (< 30 kg/m² and ≥ 30 kg/m²) were performed for the effectiveness endpoint (time-weighted summed pain intensity difference from baseline over the first hour of treatment for all enrolled patients). For baseline pain intensity, the least squares (LS) mean and standard error of the mean (SEM) were estimated from the analysis of variance model that included each subgroup factor, and for the time-weighted summed pain intensity difference from baseline over the first hour of treatment, the LS mean and SEM were estimated from the analysis of covariance model that included each subgroup factor and baseline pain intensity as a covariate. Pain intensity scores were derived from data from the Study Drug Administration Questionnaire.

Patients who had baseline vital signs, including blood pressure, heart rate, respiratory rate, and SpO₂, and at least 1 follow-up data point were included in these analyses of vital signs. Vitals signs taken at baseline and follow-up time points, and AEs occurring after patients received the first dose were summarized. A paired t-test was used for the test of mean change from baseline to follow-up time points within the group. Other safety data, such as termination data and concomitant medications used during the study were tabulated. Analyses of all effectiveness and safety data were performed at a significance level of α = 0.05.

Missing pain intensity or pain relief data were first imputed on a patient-by-patient basis by linear interpolation method between 2 observed pain scale values. Missing pain data at follow-up time points post-termination up to the end of the study period were imputed on a patient-by-patient basis. If rescue analgesics were used, pain scores just prior to dosing with rescue medications were imputed for a 1-hour time interval. The worst observation carried forward method was used to impute any remaining missing data points after termination up to the end of the study period. The worst pain intensity difference from baseline was the smaller number between “0” and the last pain intensity difference from baseline obtained prior to termination. The worst pain relief was “0”. For patients who enrolled in the single-dose cohort, the missing pain intensity and pain relief data after the 2-hour evaluation time point was not imputed.

3. Results

3.1. Baseline demographics and patient disposition

The first patient enrolled October 5, 2015 and the final patient completed the study June 17, 2016. Despite the inherent difficulty in recruiting patients in the ED with acute injury or trauma to take part in a study of an experimental analgesic, 78 patients in total were ultimately recruited and screened, and 76 eligible patients were enrolled and included in the ITT population and effectiveness and safety analyses (Fig. 1). The initial 40 patients received a single dose of SST 30 mcg; an additional 36 patients enrolled and were eligible to receive multiple SST 30-mcg doses. Eleven of 76 total patients terminated prior to the end of the 2-hour study period due to either early hospital discharge (n = 4), lack of effectiveness (n = 4), exiting hospital before notifying investigators (n = 1), or no longer wanting to take part in the study, despite an improvement in pain relief (n = 1); 1 patient did not cite a reason for withdrawal. Overall, 86% (65/76) of patients from the combined cohort completed 2 h in the study.

The mean age was 42 years (12% were aged ≥ 65 years), 61% were male, mean BMI was 30.6, and the majority (61%) of patients were ASA Class I (Table 1). The most common types of trauma presented in the ED were fractures (33%), sprains/strains (30%), and contusions/soft tissue hematomas (17%). Mean baseline pain intensity was 8.1 (on a scale from 1 to 10).

3.2. Study drug dosing

All patients received at least 1 dose of SST 30 mcg. Of the 36 patients in the multiple-dose cohort, 19% (n = 7) received 2 additional doses and 6% (n = 2) received 3 additional doses of SST 30 mcg (mean [SD] number of doses: 1.3 [0.6]).

3.3. Effectiveness

3.3.1. Effectiveness within the first hour of study dosing (combined cohorts)

For the combined cohort over the first hour (n = 76), the mean pain intensity significantly decreased from baseline within 15 min following initiation of SST 30 mcg (P < 0.001), and the difference from baseline continued to decrease during the first hour of the study period (Fig. 2A). At 60 min, pain intensity decreased by 2.9 (from 8.08 at baseline to 5.20 at 60 min), a drop of 36%. Within the first hour of study drug dosing, increases (P < 0.001 at each timepoint) in pain relief (1.7, on a scale from 0 to 4) were also reported (Fig. 2B).

To evaluate the overall drop in pain intensity in both cohorts between different demographic subgroups, the time-weighted summed pain intensity difference from baseline over 1 h was analyzed by age group (< 65 vs ≥ 65 years), sex (male vs female), race (Caucasian vs non-Caucasian), and BMI (< 30 vs ≥ 30 kg/m²). No significant differences within each subgroup were observed (Table 2).

3.3.2. Effectiveness within the first 2 h of study dosing (multiple-dose cohort)

Although study drug was available every hour, the majority (75%; 27/36) of patients in the multiple-dose cohort required only 1 dose of SST 30 mcg. Mean pain intensity was 7.6 at baseline and decreased to 4.5 at 60 min and remained relatively stable (4.6) at 2 h (P = 0.001 compared to baseline at each timepoint (Fig. 3A). Mean pain relief increased from baseline to 1.9 at 60 min and 2.0 at 2 h (P < 0.001 at each timepoint) (Fig. 3B).

3.3.3. Termination due to inadequate analgesia

Prior to the end of the 2-hour study period, early termination due to inadequate analgesia occurred for 4 of 76 patients (5.3%). There were an additional 2 patients in the multiple-dose cohort who remained in the study after 2 h but terminated the study before the 5-hour study period due to inadequate analgesia.

3.3.4. Rescue medication

Overall, rates of rescue opioid usage were low. Only 3 (7.5%) patients in the single-dose cohort utilized rescue medication within the first hour. For the multiple-dose cohort (which had access to study drug for the full 5-hour study period), 3 (8.3%) patients required rescue medication throughout the study period.

3.3.5. Patient and HCP global assessments of methods of pain control

Of the patients who completed the PGA in the multiple-dose cohort (n = 33), the majority responded that SST 30 mcg provided “excellent” (n = 9, 27.3%) or “good” (n = 15, 51.5%) control of their pain (Table 3). Similarly, 27 of 36 HCPs responded “excellent” (n = 12, 33.3%) or “good” (n = 15, 41.7%) on the HPGA at the time of discontinuation from the study.
3.3.6. HCP assessment of single-dose applicator for SST 30 mcg administration

The majority of HCPs who administered SST 30 mcg to ≥ 3 patients indicated that SST 30 mcg was “somewhat easy” or “easy” to administer when patients were dosed in an upright (100%; 7/7) or reclined (83.4%, 5/6) position, and in limited-lighting situations (85.7%; 6/7). Most HCPs considered the single-dose applicator to be “somewhat intuitive” or “intuitive” (85.7%, 6/7), and that, when dispensed, the SST 30-mcg tablet was “somewhat detectable” or “detectable” (85.7%; 6/7).

3.4. Safety

3.4.1. Cognitive impairment (SIS cognitive test)

Of the 75 patients who had SIS scores recorded both pre- and post-dosing, 73 (97%) had either the same or improved SIS scoring 1 h after dosing. The remaining 2 patients demonstrated a single-point drop in SIS scoring at the 1-hour time point compared with baseline. Of these 2 patients, one was a 47-year-old male (BMI: 26 kg/m²) who presented with a closed mandible fracture and other facial trauma (ie, abrasions, lacerations, and swelling to his left eye and cheek). The other patient was a 26-year-old female (BMI: 27 kg/m²) who presented with partial thickness second-degree burns on her left thigh (approximately 10 cm in diameter). Both patients had a baseline pain score of 8 (on a scale from 1 to 10).

3.4.2. Adverse events

Adverse events were analyzed for both cohorts together. Overall, 79% (60/76) of patients did not incur an AE (Table 4). The most frequently (in ≥2% of patients) reported AEs were nausea (9%), somnolence (5%), vomiting (4%), and oxygen desaturation (3%). Eleven (15%) patients had ≥1 AE considered possibly or probably related to SST 30 mcg. The most frequently reported AEs related to SST 30 mcg were nausea (7%) and vomiting (4%). Two patients experienced transient room air oxygen desaturations below 95% (88% and 94%) that immediately improved with nasal cannula oxygen; both events were considered related to SST 30 mcg.

All AEs were mild, with the exception of 1 event each of angina pectoris (considered possibly treatment-related by the investigator) and nausea (unrelated to treatment) that were considered moderate in severity; there were no severe AEs. The only serious AE (angina pectoris, moderate in severity) occurred in a woman aged 65 years with a medical history that was significant for coronary artery disease. No patient discontinued the study due to an AE. There were no clinically meaningful changes in mean vital signs and no patient required use of naloxone.

4. Discussion

Results from this open-label feasibility study suggest that SST 30 mcg has potential as a noninvasive (e.g., not requiring intravenous access) treatment for moderate-to-severe acute pain in patients in an ED setting. A single dose resulted in an approximate 3-point decrease in pain intensity within 60 min (36% reduction from baseline). Significant reductions in pain intensity from baseline were observed as early as 15 min after the start of SST 30-mcg dosing. Clinically meaningful analgesia—as defined by a ≥1.3-point reduction on the numeric rating scale for acute pain in the ED [31]—occurred on average in <20 min in the combined cohort. Pain intensity continued to decline through 1 h post-dose, and for patients allowed to receive additional doses of study drug after the 1-hour time point, the reduction was maintained through 2 h. Similarly, significant improvements in pain relief were observed within 15 min, continued until 1 h, and were maintained through 2 h after the initial dose. Although the majority (75%) of patients in the multiple-dose cohort only required 1 dose of study drug (ie., did not re-dose), some of those patients were not available for re-dosing at the 1-hour time point (ie., 2 patients were discharged; 1 patient left the hospital early without notifying the investigator). For the multiple-dose cohort, there was a significant decrease in pain intensity from 7.6 at baseline to 4.5 at 1 h, and this pain control was maintained at 2 h. Similarly, there were significant increases in pain relief at 1 and 2 h.
compared with baseline. Although pain intensity remained relatively high (4.6) in the multiple-dose cohort at 2 h, SST 30 mcg was considered effective in managing pain since the majority of patients in this cohort did not request a second dose of SST 30 mcg, and the majority of patients (78.8%) and nurses (75.0%) noted satisfaction ratings of “good or excellent” on the PGA and HPGA, respectively.

All but 2 patients in the study had either no change in cognition or an increase in cognitive skills, as indicated by no change or an increase from baseline to 1 h in SIS scores, with both patients (aged ≤65 years) having only a 1-point drop from baseline. In early studies, IV morphine has been shown to impair recall and reaction time [32,33], and in more recent studies, patients with acute dosing of opioids had an increased risk of developing delirium [34,35], shown to be especially prevalent in the elderly population [36,37]. In the current study, no patient aged ≥65 years had a decrease in cognitive skills. Further, concern of possible cognitive effects in older and elderly patients have been associated with poorer quality pain care, with patients being prescribed lower doses of opioid analgesics or longer delays in treatment compared with younger patients [38-41]. However, conflicting data from studies of elderly postoperative patients following hip fracture has shown that among the opioids morphine, hydromorphone, fentanyl, oxycodone, and meperidine, only meperidine was associated with cognitive dysfunction [42,43]. Ketamine, a N-methyl-D-aspartate antagonist gaining widespread use in emergency medicine and in battlefield medicine for its rapid-acting analgesic and sedation properties [44], is limited by its psychomimetic effects (e.g., cognitive dysfunction, hallucinations, nightmares, and excessive sedation) at higher (>2 mg/kg) doses [45,46].

Most (79%) patients in this study did not experience an AE, and the types of AEs reported were generally as expected in this type of patient population in an ED setting [47,48]. One serious AE (angina pectoris) was reported in a patient aged ≥65 years who had a history of coronary artery disease, and 2 patients experienced transient room air oxygen desaturations below 95%, which was considered related to SST 30 mcg. Rates of AEs in this study were generally similar or lower with SST 30 mcg compared with AE rates in other recent studies of IV opioids in a similar setting [47-49]. In a prospective study of 150 patients treated with IV morphine in the ED, 22.6% of patients experienced nausea and 4.4% experienced vomiting [49]. In a retrospective analysis of >30,000 ED patients treated with opioids, the IV route of opioid administration was associated with an 8.5% rate of reported nausea/vomiting, as well as a 7.5% rate of oxygen saturation levels falling below 92% [47]. AEs were also reported in a randomized clinical trial where 224 patients in an ED were treated with either IV hydromorphone or an IV opioid, as determined by the treating physician [48]. Patients treated with IV hydromorphone experienced high rates of nausea (17.2%), pruritus (6.5%), and vomiting (4.7%). In a retrospective analysis of >30,000 ED patients treated with opioids, the IV route of opioid administration was associated with an 8.5% rate of reported nausea/vomiting, as well as a 7.5% rate of oxygen saturation levels falling below 92% [47]. AEs were also reported in a randomized clinical trial where 224 patients in an ED were treated with either IV hydromorphone or an IV opioid, as determined by the treating physician [48]. Patients treated with IV hydromorphone experienced high rates of nausea (17.2%), pruritus (6.5%), and vomiting (4.7%).

Current reports on the use of IV opioids (i.e., morphine and hydromorphone) in the ED indicate that they may be inadequate in treating severe acute pain [50]. Analgesic onset—the time it takes the drug to reach the central nervous system—occurs more rapidly with sufentanil than with hydromorphone or morphine, which is reflected by the $t_{1/2}k_{on}$ (6.2 [10], 46 [51], and 168 [9] minutes, respectively).
between plasma and the central nervous system. Slow onset of analgesia can lead to early drug redosing which may ultimately cause a CNS overdose due to “dose stacking”, with potential risk for incurring AEs [52-56]. AEs, including respiratory depression, may also be exacerbated by active metabolites, present following treatment with morphine (i.e., morphine-3-glucuronide and morphine-6-glucuronide) and hydromorphone (i.e., hydromorphone-3-glucuronide and hydromorphone-6-glucuronide), but not sufentanil [12], particularly in patients with renal impairment [52,53,57-59].

At least 1 study (N = 119) has reported that the standard dose of 0.1 mg/kg of IV morphine is not effective in treating acute severe pain in an ED setting [60], and, in a similar study, that higher doses of IV morphine (0.15 mg/kg) did not provide clinically superior pain relief compared with 0.1 mg/kg of IV morphine [61]. Further, patient pain may be prolonged due to time constraints associated with the setup of an IV line [1,5], which is estimated to take an additional 2 or more hours when advanced IV placement techniques are required (overall mean time from triage to IV setup: 64–81 min [traditional IV] vs 199 min [advanced placement]) [3]. In contrast, the current study demonstrates the feasibility of using SST 30 mcg in an ED setting and provides evidence that SST 30 mcg is effective in managing acute pain, and therefore may be considered a reasonable alternative to IV morphine. The unique characteristics of SST 30 mcg (including rapid onset and no IV required) may be advantageous in an ED population, in which patients are, by nature, not prescreened (i.e., without benefit of a complete physical examination and laboratory workup afforded a pre- and post-operative patient) and are matriculating through a rapid-paced environment.

5. Limitations

By virtue of the inherent difficulty in recruiting ED patients with trauma into an experimental analgesic study, this was a relatively small (N = 76) single-arm study; as such, the lack of a comparator group limits our interpretation of effectiveness results. Also, only a single dose of SST 30 mcg was used or required for much of this study, which may further limit the ability to interpret effectiveness and safety data in trauma patients who may otherwise require multiple dosing; however, the safety profile of SST 30 mcg in this study was similar to the safety profile of sublingual sufentanil 15 mcg in 1 active (vs IV patient-controlled analgesia with morphine sulfate) and 2 placebo-controlled phase 3 studies in post-surgical patient populations [13-15]. Further, in a phase 2, dose-finding, placebo-controlled study of sublingual sufentanil for the management of pain following bunionectomy, SST 30 mcg was well tolerated; all but 1 AE were considered mild-to-moderate in severity [16]. Finally, pain intensity data were not collected earlier than 15 min post-dosing (per protocol), limiting the ability to gauge effectiveness earlier than this timepoint.


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Table 3  
Response to the PGA and HPGA at 2 h (multiple-dose cohort)  

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>PGA n = 33</th>
<th>HPGA n = 36</th>
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<tbody>
<tr>
<td>Excellent</td>
<td>9 (27.3)</td>
<td>12 (33)</td>
</tr>
<tr>
<td>Good</td>
<td>17 (51.5)</td>
<td>15 (41.7)</td>
</tr>
<tr>
<td>Fair</td>
<td>3 (9.1)</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>Poor</td>
<td>4 (12.1)</td>
<td>2 (5.6)</td>
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HPGA = healthcare professional global assessment; PGA = patient global assessment.

6. Conclusions

Sufentanil sublingual tablet (30 mcg) was demonstrated to be a potentially feasible option for managing moderate-to-severe acute pain in the ED. Additional research is needed to assess the safety, efficacy, and ease of use relative to other pain treatments in the ED.

Supplementary data to this article can be found online at https://doi.org/10.1016/ajem.2017.10.058.

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Conflict of interest disclosures

JRM is a consultant to AcelRx and has received investigator grants for the conduct of the study. 
ZR has received investigator grants for the conduct of the study and has stock ownership of AcelRx Pharmaceuticals.

PPP is an employee and has stock ownership of AcelRx Pharmaceuticals.

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Table 4  
Summary of AEs and related AEs (combined cohorts)  

<table>
<thead>
<tr>
<th>Summary of AEs, patients, %</th>
<th>N = 76</th>
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<tbody>
<tr>
<td>No AEs</td>
<td>79</td>
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<tr>
<td>≥ 1AE</td>
<td>21</td>
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<tr>
<td>≥ 1 related AE</td>
<td>15</td>
</tr>
<tr>
<td>SAEs</td>
<td>1</td>
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<tr>
<td>Severe AEs</td>
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AEs leading to SST 30 mcg discontinuation 0

Patients with AEs, %  

<table>
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<th>All AEs</th>
<th>Related AEs</th>
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</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>9</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
</tr>
<tr>
<td>Oxygen desaturations</td>
<td>3h</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>1</td>
</tr>
<tr>
<td>Conversion disorder</td>
<td>1</td>
</tr>
<tr>
<td>Feeling hot</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
</tr>
<tr>
<td>Facial hypoesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
</tr>
</tbody>
</table>

AE = adverse event; SAE = serious AE; SST = sufentanil sublingual tablet.

* All events were considered to be mild in severity with the exception of angina pectoris (n = 1; related) and nausea (n = 1, unrelated) that were considered moderate in severity.

* Two patients experienced transient room air oxygen desaturations below 95% (88% and 94%) which immediately improved with nasal cannula oxygen.

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