
ORIGINAL ARTICLE

Sufentanil Sublingual Tablet System vs. Intravenous Patient-Controlled Analgesia with Morphine for Postoperative Pain Control: A Randomized, Active-Comparator Trial

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■ Abstract

Background: Problems with intravenous patient-controlled analgesia (IV PCA) are well known, including invasive route of delivery and pump programming errors. The primary objective of this study was to evaluate patient satisfaction with a novel sublingual sufentanil PCA system (sufentanil

sublingual tablet system 15 mcg with a 20-minute lockout interval; SSTS) to IV PCA morphine sulfate 1 mg with a 6-minute lockout interval (IV PCA MS) for the management of acute postoperative pain.

Methods: This was a randomized, open-label, 48-hour non-inferiority study with optional extension to 72 hours at 26 U.S. sites enrolling patients scheduled for elective major open abdominal or orthopedic (hip or knee replacement) surgery. The primary outcome measure was the proportion of patients who responded "good" or "excellent" (collectively "success") at the 48-hour timepoint on the Patient Global Assessment of method of pain control (PGA48).

Results: A total of 357 patients received study drug and 78.5% vs. 65.6% of patients achieved PGA48 "success" for SSTS vs. IV PCA MS, respectively, demonstrating non-inferiority ($P < 0.001$ using the one-side Z-test against the non-inferiority margin) as well as statistical superiority for treatment effect ($P = 0.007$). Patients using SSTS reported more rapid onset of analgesia and patient and nurse ease of care and satisfaction scores were higher than IV PCA MS. Adverse events were similar between the 2 groups; however, SSTS had fewer patients experiencing oxygen desaturations below 95% compared to IV PCA MS ($P = 0.028$).

Conclusions: Sufentanil sublingual tablet system is a promising new analgesic technology that may address some of the concerns with IV PCA. ■

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INTRODUCTION

Intravenous patient-controlled analgesia (IV PCA) has been utilized for over 40 years to allow hospitalized patients to self-titrate opioids to relieve moderate-to-severe acute pain. While the patient-controlled aspect of this approach achieves higher patient satisfaction than nurse-administered analgesics, many issues continue to plague IV PCA.^{1,2} The invasive IV route of administration creates risks of infection and analgesic gaps due to catheter infiltration or IV tubing obstructions, while risk of prescribing and programming errors create significant morbidity and mortality.³⁻⁵ The use of morphine, an opioid with slow central nervous system (CNS) equilibration, as the IV PCA opioid of choice has further complicated this approach to acute inpatient pain management. The CNS effector site peak concentration of morphine and its active metabolite, morphine-6-glucuronide (M6G) occurs hours following the IV PCA dosing event and can result in delayed adverse events, such as respiratory depression.⁶ A sufentanil sublingual tablet system (SSTS) (Zalviso™; AcelRx Pharmaceuticals, Redwood City, CA, U.S.A.) is being developed to overcome these shortcomings of IV PCA while still maintaining patient-controlled delivery. Sufentanil lacks active metabolites, possesses a high therapeutic index in preclinical models (26,000 compared to 70 for morphine),⁷ and has a rapid equilibration half-life between plasma and CNS ($t_{1/2k_{e0}} = 6$ minutes compared to 2.8 hours for morphine).^{8,9} Due to its highly lipophilic nature, sufentanil can be rapidly absorbed following sublingual administration in the form of a small bioadhesive tablet (3 mm diameter; 0.75 mm thick), which allows for a non-invasive route of administration. The hand-held SSTS device is stored bedside and is preprogrammed with a 20-minute lockout interval and uses a radio-frequency identification (RFID) thumb tag and security tether attached to the bottom of the controller (Figure 1). Upon set-up of the system, the nurse inserts a small cartridge containing 40 sufentanil tablets (approximately a 2-day supply) into the dispenser tip which is then locked into the controller base and the system is tethered to the bedside or other secure location (wheelchair, gurney, etc.). Phase 2 dose-finding studies in patients following major surgery demonstrated that sufentanil 15 mcg per tablet was the optimal dosage



Figure 1. Sufentanil sublingual tablet system with radio-frequency identification (RFID) patient thumb tag and security tether attached to the bottom of the controller.

strength resulting in high patient satisfaction and a similar adverse event profile to lower dosage strengths.¹⁰

The purpose of this Phase 3 open-label, active comparator study was to compare efficacy and safety of SSTS (15 mcg dose with a 20-minute lockout) to IV PCA morphine sulfate (IV PCA MS) 1 mg dose with a 6-minute lockout for 48 hours following major surgery, with an optional extension to 72 hours. The study's primary objective was to demonstrate non-inferiority to IV PCA MS as measured by the 48-hour patient global assessment of method of pain control (PGA48). This endpoint was selected as it incorporates both an assessment of analgesic efficacy over a typical duration of postoperative PCA use as well as the method in which it was delivered, both critical elements for evaluating PCA modalities.

METHODS

This was a multicenter, randomized, open-label, active-controlled, parallel design study with patients randomized to SSMS or IV PCA MS. The study was registered on ClinicalTrials.gov on February 24, 2012 (NCT01539538). After centralized Institutional Review Board (IRB) approval of the study by Copernicus IRB (Research Triangle Park, NC, USA) or by the clinical sites local IRB, patients 18 years and older, who had provided written informed consent and were scheduled within 30 days to undergo elective major

open abdominal (including laparoscopic-assisted open abdominal procedures) or orthopedic (total knee or hip replacement) surgery, were allowed to enroll. Patients undergoing fully laparoscopic abdominal surgeries were excluded, however, surgeries utilizing a laparoscopic-assisted approach, such as partial colectomy, could enroll. Following surgery, qualifying patients were randomized 1:1 to SSTS (15 mcg/dose with a 20-minute lockout) or IV PCA MS (1 mg/dose with a 6-minute lockout) across all study sites. The dose for IV PCA MS was selected to reflect the standard 1 mg morphine on-demand dosing practiced at many hospitals as well as to allow an equivalent opioid dose within the same time period (dosing over 20 minutes allows 15 mcg sublingual sufentanil = 3 mg IV morphine based on 300 to 400 potency factor and 60% bioavailability of sublingual sufentanil). A stratified randomization was applied in this study, with age (< 65 years and \geq 65 years) and type of surgery (total knee replacement and other surgeries) as stratification factors. Key screening exclusion criteria included opioid tolerance (patients could not be taking more than 15 mg oral morphine equivalent per day), documented sleep apnea, or patients requiring supplemental outpatient oxygen therapy. Key exclusion criteria perioperatively were evidence of respiratory difficulties or intractable vomiting in the recovery room, use of perioperative regional anesthetic techniques and local anesthetic wound infiltration in the operating room, or premedication with long-acting opioids. The use of any drug that may affect postoperative pain levels, such as gabapentanoids, steroids, or anti-inflammatory drugs were not allowed intra- or postoperatively. Therefore, patients with a chronic pain condition necessitating treatment with these agents were excluded from the study.

As a criteria for continued eligibility in the study, at some point during the patient's stay in the recovery room they had to report a pain score < 5 on an 11-point numerical rating scale (NRS), where 0 = no pain, and 10 = worst possible pain. This was required in order to avoid enrolling patients with uncontrolled pain after surgery. However, in order to determine the analgesic benefit of the study drug and to avoid dosing patients with only mild pain intensities, the patient's pain score after leaving the recovery room needed to increase to > 4 just prior to self-administering the first dose of study drug, which initiated the study treatment period. Patients self-administered study drug as needed for pain relief for the full 48-hour study period, with an option to continue for up to 72 hours, if needed.

No analgesic medication other than study drug was allowed during the study period with the exception of supplemental opioid medication (2 mg IV MS bolus) if necessary in the first 30 minutes of the study to keep a patient comfortable at study initiation or only for pain due to ambulation or with the initiation of passive range-of-motion therapy at any other time in the study. No more than 2 mg IV MS could be administered per hour. If at any time the patient felt that his or her analgesia was not sufficient to remain in the study, the patient was allowed to drop-out of the study due to inadequate analgesia and receive any opioid or adjuvant analgesic as deemed appropriate by the clinical investigator.

Patients with oxygen saturation levels that could not be maintained at 95% or greater with or without the use of supplemental oxygen, respiratory rate < 8 breaths per minute, or excessive sedation were not allowed access to study drug or supplemental opioid medication until these vital signs had improved. If each adverse event did not rapidly improve under supervision with arousal and vital sign checks, the patient was to be removed from the study.

The primary efficacy variable was the patient global assessment of the method of pain control (using a 4-point categorical scale where 1 = poor, 2 = fair, 3 = good, and 4 = excellent) at the 48-hour time point (PGA48) with "success" defined as the proportion of patients who responded "good" or "excellent". The prespecified criteria for non-inferiority was that the lower limit of the 95% confidence interval (CI) of the difference in success rates (SSTS minus IV PCA MS) could not be less than a -15%.

Secondary endpoints included PGA at 24 and 72 hours, as well as healthcare professional global assessment of method of pain control (HPGA) at these time points. Pain responses were assessed using patient reports of pain intensity on an 11-point NRS; and pain relief using a 5-point categorical scale (0 = no relief, 1 = a little relief, 2 = moderate relief, 3 = a lot of relief, 4 = complete relief). Pain responses were measured prior to first dose and at 15, 30 and 45 minutes, 1, 2, 4, 6, 8, 10 and 12 hours after study initiation, then every 4 hours through the remainder of the study period. A pain intensity and pain relief score was also obtained prior to each administration of supplemental opioid medication.

To assess the ease of use of the 2 patient-controlled analgesia systems, validated patient and nurse ease-of-care (EOC) questionnaires were completed and results tabulated.^{11,12} The patient EOC questionnaire has 23 questions; 21 of which are scored on a scale of 0 to 5 (where 0 = not at all and 5 = a very great deal) and

summarized into 6 subscale scores (confidence with device, comfort with device, movement, dosing confidence, pain control, and knowledge/understanding) and a total EOC score. The other 2 questions (satisfaction with level of pain control and satisfaction with method of administration of pain medication) are scored on a 6-point scale (extremely dissatisfied to extremely satisfied) and combined into an overall satisfaction score. The nurse EOC questionnaire has 22 questions, 20 of which are scored on a scale of 0 to 5 (where 0 = not at all and 5 = a very great deal) and summarized into 2 subscale scores (time-consuming and bothersome) and a total EOC score. Two other questions (satisfaction with level of pain control and satisfaction with device) were scored on a 6-point scale (extremely dissatisfied to extremely satisfied) and combined into a total satisfaction score.

Safety assessments included spontaneously reported adverse events, vital signs (blood pressure, heart rate, and respiratory rate), continuous oxygen saturation monitoring, sedation levels measured using the Richmond Agitation Sedation Scale (RASS)^{13,14} and the use of concomitant medications. Blood samples were collected at 24 and 48 hours after the first dose of study drug or at the time of early termination for analysis of either sufentanil concentrations for patients in SSTS group, or MS, morphine-3-glucuronide (M3G), and M6G concentrations for patients in the IV PCA MS group.

Statistical Methodology

The intent-to-treat (ITT) population included randomized patients who received study drug. The primary efficacy analysis was the construction of the 95% CI of the difference in PGA48 success rates between the 2 treatment groups. If the lower boundary of the CI of the difference in the success rate was not less than -15%, SSTS treatment would be considered non-inferior to IV PCA MS. A 2-sample, one-sided Z test on proportions of the primary efficacy variable against the lower equivalence margin (-15%) was performed at the $\alpha = 0.025$ significance level. A 2-sided superiority test was also performed on this primary efficacy variable as a key secondary analysis.

Assuming a success rate of 75% for both treatment groups, a sample size of 352 patients (176 per treatment group) was sufficient to provide 90% power to demonstrate therapeutic non-inferiority of SSTS vs. the IV PCA MS treatment. This sample size calculation was based on a one-sided test with $\alpha = 0.025$ and a non-inferiority margin of 15%.

A parallel lines analysis of covariance (ANCOVA) model was used for the analysis of continuous secondary efficacy endpoints derived from the pain assessment data. This ANCOVA model included treatment, center, and surgery type (knee, hip, and abdominal) factors, and baseline pain intensity as a covariate. The least squares (LS) mean of each treatment and its 95% CI were constructed.

For the analysis of ordinal categorical data, a Cochran-Mantel-Haenszel test of general association stratified by age group and surgery type (knee, hip, and abdominal) with modified ridit scores was used for the comparison between 2 treatment groups. The survival analysis method was used to analyze the time to event data. Kaplan-Meier product limit estimators of cumulative rates of patients who reached the event (ie, termination due to inadequate analgesia) at follow-up time point were calculated. A log-rank test was used to compare 2 treatment groups.

RESULTS

Patient Disposition

Twenty-six U.S. sites participated in the study. The first patient was enrolled in April 2012 and the last patient completed in November 2012. Figure 2 presents the patient disposition flow diagram of the study. Three hundred fifty-seven patients (SSTS [$n = 177$] and IV PCA MS [$n = 180$]) were treated and 282 patients (79.0%) completed the 48-hour study period. The most common reasons for study discontinuation prior to 48 hours were adverse events with 31 patients (8.7%) and lack of efficacy with 29 patients (8.1%). There were no notable differences between treatment groups for the proportion of patients who completed the study or who discontinued due to an adverse event or lack of efficacy.

Table 1 presents a summary of the demographic and baseline characteristics of the study population. Over half of all patients were at least 65 years old. There were no age or body mass index (BMI) limits on patient enrollment, resulting in an age range of 19 to 88 years of age and a BMI range of 16 to 54. There were no statistically significant differences between treatment groups for any demographic or baseline characteristic.

Primary Efficacy Endpoint

Overall, 78.5% and 65.6% achieved "success" on the PGA48 for the SSTS and IV PCA MS groups respectively,

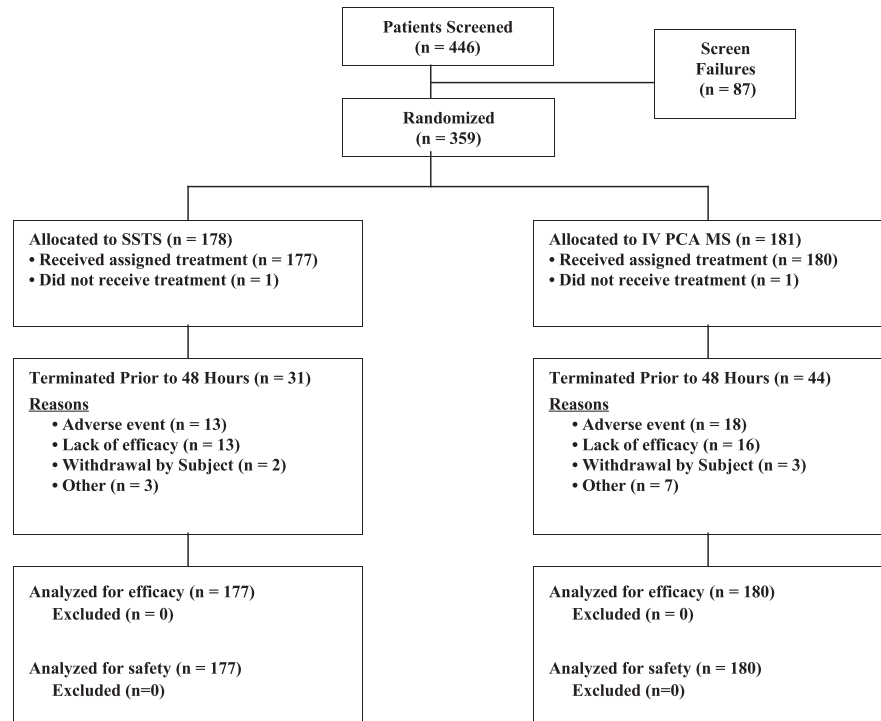


Figure 2. Patient disposition flow diagram.

Table 1. Demographics and Baseline Characteristics: ITT Population

Characteristic	SSTS n (%) (n = 177)	IV PCA MS n (%) (n = 180)	Total n (%) (n = 357)
Age (years)			
< 65	85 (48.0)	85 (47.2)	170 (47.6)
≥ 65	92 (52.0)	95 (52.8)	187 (52.4)
Mean (SD)	63.8 (12.1)	64.0 (12.6)	63.9 (12.4)
Sex			
Male	54 (30.5)	72 (40.0)	126 (35.3)
Female	123 (69.5)	108 (60.0)	231 (64.7)
Race			
White	160 (90.4)	162 (90.0)	322 (90.2)
Black or African American	17 (9.6)	17 (9.4)	34 (9.5)
Other	0	1 (0.6)	1 (0.3)
Ethnicity			
Hispanic or Latino	1 (0.6)	1 (0.6)	2 (0.6)
Not Hispanic or Latino	176 (99.4)	178 (99.4)	354 (99.4)
Weight (kg)			
Mean (SD)	84.3 (22.0)	87.1 (22.3)	85.7 (22.2)
Body mass index (kg/m ²)			
< 30	105 (59.3)	99 (55.0)	204 (57.1)
≥ 30	72 (40.7)	81 (45.0)	153 (42.9)
Mean (SD)	29.5 (6.3)	30.3 (6.6)	29.9 (6.4)
Type of surgery			
Knee arthroplasty	56 (31.6)	60 (33.3)	116 (32.5)
Hip arthroplasty	84 (47.5)	78 (43.3)	162 (45.4)
Open abdominal	37 (20.9)	42 (23.3)	79 (22.1)

ITT, intent-to-treat; IV PCA MS, Intravenous patient-controlled analgesia morphine sulfate; SSTS, sufentanil sublingual tablet system.

demonstrating both non-inferiority based on the 95% CI ($P < 0.001$ using the one-side Z-test against the -15% non-inferiority margin) as well as statistical superiority in favor of the SSTS group ($P = 0.007$).

Secondary Efficacy Endpoints

Success on the PGA was also statistically superior at 24 and 72 hour assessments for the SSTS ($P \leq 0.024$ for both timepoints). Healthcare professionals also reported success on the HPGA at 24, 48 and 72 hour assessments in favor of SSTS ($P \leq 0.012$ for all timepoints). The SSTS group had faster onset of pain reduction based on significantly greater pain intensity differences to baseline (PID) at 1, 2, and 4 hours ($P < 0.01$; Figure 3). Similar results were seen for pain relief at 1, 2, and 4 hours ($P < 0.01$). Overall, the time-weighted summed PID (SPID) and the total pain relief (TOTPAR) scores were either in favor of SSTS or equivalent between the 2 groups (Table 2).

The results from the patient and nurse EOC questionnaires are presented in Table 3. For both questionnaires, overall EOC scores and overall satisfaction scores were statistically significantly higher (better) for SSTS. Similarly for all 6 patient EOC validated subscales, SSTS was rated higher than IV PCA MS. For the 2 satisfaction subscale scores, SSTS was numerically better than IV PCA MS for satisfaction with level of pain control and statistically better for satisfaction with drug administration.

On the nurse EOC questionnaire (Table 3), healthcare professionals rated SSTS higher (better) on satisfaction with the device and satisfaction with pain

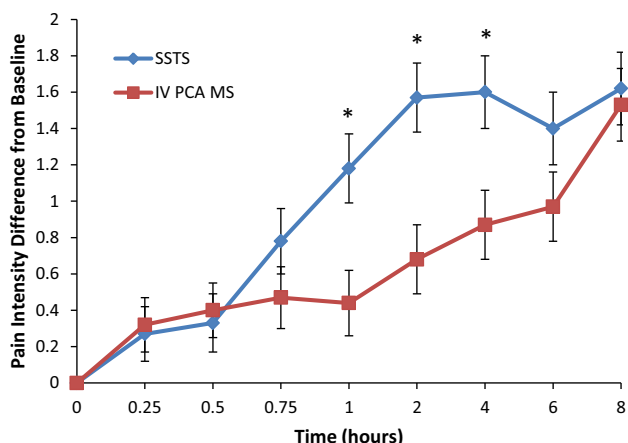


Figure 3. The pain intensity difference to baseline (PID) over the first 8 hours; * $P < 0.01$.

Table 2. Summed Pain Intensity Difference (SPID) and Total Pain Relief (TOTPAR) Scores over 24, 48, and 72 Hours

Summed Score (LS Mean [SEM])	SSTS (n = 177)	IV PCA MS (n = 177)*	P-value
SPID24	34.38 (3.88)	30.72 (3.75)	0.422
SPID48	77.94 (8.40)	72.33 (8.10)	0.569
SPID72	133.62 (13.45)	122.51 (12.98)	0.482
TOTPAR24	47.95 (1.63)	43.82 (1.57)	0.031
TOTPAR48	99.89 (3.52)	91.94 (3.39)	0.055
TOTPAR72	156.85 (5.88)	141.23 (5.67)	0.024

*Three patients in the intravenous patient-controlled analgesia morphine sulfate (IV PCA MS) treatment group were dosed prior to obtaining baseline pain scores and therefore were excluded from these analyses. LS, least squares; SEM, standard error of the mean; STSS, sufentanil sublingual tablet system.

control delivered to the patient. For the nurse EOC subscales of “time-consuming” and “bothersome”, in which case lower scores were superior, healthcare professionals rated SSTS numerically less time-consuming and significantly less bothersome.

Thirteen patients (7.3%) in the SSTS group and 16 patients (8.9%) in the IV PCA MS group discontinued due to inadequate analgesia and Figure 4 shows the Kaplan–Meier cumulative event rate graph. Although not statistically significant, patients have earlier terminations due to inadequate analgesia with IV PCA MS, most notably in the first 6 hours. Throughout the study, the mean inter-dosing interval for SSTS and IV PCA MS were 81 minutes and 47 minutes, respectively. While patients in the SSTS group used more supplemental IV morphine than patients in the IV PCA MS group (mean of 2.6 mg vs. 1.0 mg, respectively; $P < 0.001$), the difference of 1.6 mg IV MS over 48 hours is not clinically meaningful.

Table 3. Ease-of-Care (EOC) Questionnaire Results

Score	SSTS	IV PCA MS	P-value
Patient EOC subscale results: Mean (SD)			
Confidence with device	4.69 (0.55)	4.51 (0.81)	0.015
Comfort with device	4.47 (0.65)	4.33 (0.68)	0.041
Ease of movement	4.73 (0.65)	3.88 (1.35)	< 0.001
Dosing confidence	4.74 (0.71)	4.47 (0.94)	0.003
Pain control	3.58 (1.28)	3.16 (1.39)	0.004
Knowledge/understanding	4.47 (0.91)	4.05 (1.12)	< 0.001
Patient ease-of-care total: Mean (SD)	4.45 (0.51)	4.07 (0.66)	< 0.001
Satisfaction scores			
Level of pain control; n (%)			
Extremely dissatisfied	5 (2.9)	8 (4.5)	0.065
Very dissatisfied	7 (4.0)	7 (3.9)	
Dissatisfied	10 (5.7)	17 (9.6)	
Satisfied	25 (14.3)	39 (21.9)	
Very satisfied	48 (27.4)	53 (29.8)	
Extremely satisfied	80 (45.7)	54 (30.3)	
Drug administration; n (%)			
Extremely dissatisfied	1 (0.6)	1 (0.6)	0.037
Very dissatisfied	3 (1.7)	1 (0.6)	
Dissatisfied	1 (0.6)	7 (3.9)	
Satisfied	25 (14.3)	41 (23.0)	
Very satisfied	48 (27.4)	52 (29.2)	
Extremely satisfied	97 (55.4)	76 (42.7)	
Overall patient satisfaction: Mean (SD)	4.15 (0.99)	3.84 (1.01)	0.004
Nurse EOC subscale results: Mean (SD)			
Time-consuming	0.92 (0.67)	1.24 (0.85)	0.076
Bothersome	0.54 (0.55)	1.09 (0.91)	0.006
Nurse ease-of-care total: Mean (SD)	4.27 (0.58)	3.82 (0.84)	0.017
Satisfaction scores			
Pain control; n (%)			
Extremely dissatisfied	0 (0.0)	0 (0.0)	< 0.001
Very dissatisfied	0 (0.0)	0 (0.0)	
Dissatisfied	0 (0.0)	3 (7.0)	
Satisfied	9 (20.5)	25 (58.1)	
Very satisfied	25 (56.8)	14 (32.6)	
Extremely satisfied	10 (22.7)	1 (2.3)	
Device satisfaction; n (%)			
Extremely dissatisfied	0 (0.0)	0 (0.0)	0.013
Very dissatisfied	0 (0.0)	0 (0.0)	
Dissatisfied	2 (4.5)	1 (2.3)	
Satisfied	13 (29.5)	25 (58.1)	
Very satisfied	20 (45.5)	16 (37.2)	
Extremely satisfied	9 (20.5)	1 (2.3)	
Overall nurse satisfaction: Mean (SD)	3.92 (0.65)	3.35 (0.57)	< 0.001

IV PCA MS, Intravenous patient-controlled analgesia morphine sulfate; SSTS, sufentanil sublingual tablet system.

Safety Results

The majority of patients (88.8%) had at least one adverse event. Adverse events were similar between

groups and most were mild or moderate in severity and typical for postoperative patients utilizing opioid analgesics. Three patients and 5 patients in the SSTS group and IV PCA MS group, respectively, experienced a treatment-emergent serious adverse event (SAE). One patient in the IV PCA MS group died (18 days after discontinuation of study drug) due to sepsis that was unrelated to study drug. Table 4 shows the most common adverse events reported as possibly or probably related to study drug by the principle investigators at each site. There were no significant differences for any adverse event between treatment groups.

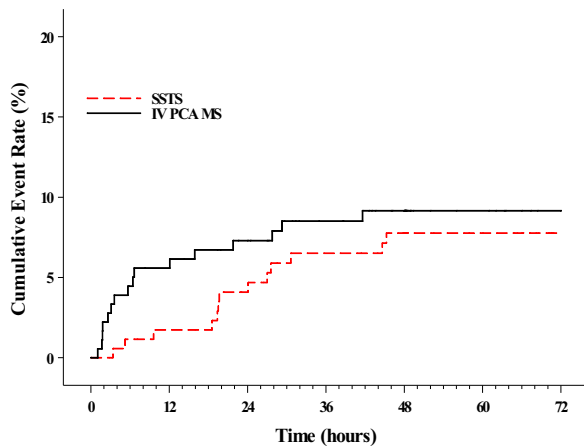
Maintaining oxygen saturation levels at or above 95% using supplemental oxygen was mandated by the

study protocol; therefore, patients were closely monitored by study personnel and oxygen saturation was measured continuously. The vast majority of desaturation events were in the 90 to 94% range. While spontaneously reported adverse events of oxygen desaturation were not different between the 2 treatment groups, based on recorded pulse oximetry data, there was a statistically lower percent of patients who experienced oxygen desaturation episodes < 95% in the SSTS group vs. IV PCA MS ($P = 0.028$) and numerically fewer patients with oxygen saturation less 94% or less than 93% (Figure 5).

Pharmacokinetic Results

Mean (SD) plasma sufentanil concentrations were 98 (62) pg/mL at 24 hours and 101 (79) pg/mL at 48 hours. Mean (SD) plasma MS, M3G, and M6G concentrations were 28 (123) ng/mL, 181 (177) ng/mL, and 29 (27) ng/mL at 24 hours and 22 (99) ng/mL, 141 (133) ng/mL, and 23 (20) ng/mL at 48 hours.

There were no significant differences in plasma sufentanil or MS concentrations measured at 24 or 48 hours between patients with renal impairment (glomerular filtration rate estimate based upon creatinine) and those with normal renal function. However, patients with renal impairment had significantly increased morphine metabolites M3G and M6G at 24 and 48 hours (Table 5). There were no significant differences for plasma sufentanil, M3G, or M6G when comparing those patients with mild to moderate hepatic impairment (as assessed by aspartate and alanine aminotransferases and total bilirubin) and those with normal hepatic function, however, there was a significant



SSTS: N=	177	169	160	152	141	55	31
IV PCA MS: N=	180	167	160	144	131	36	28

Figure 4. Kaplan–Meier cumulative event rates for time to termination from the study due to inadequate analgesia (log-rank test $P = 0.551$)

Table 4. Possibly or Probably Related Adverse Events (> 2% in either treatment group)

Adverse Event	SSTS n (%) (n = 177)	IV PCA MS n (%) (n = 180)	Total n (%) (n = 357)
Nausea	76 (42.9)	72 (40.0)	148 (41.5)
Vomiting	23 (13.0)	20 (11.1)	43 (12.0)
Constipation	20 (11.3)	15 (8.3)	35 (9.8)
Oxygen saturation decreased	17 (9.6)	17 (9.4)	34 (9.5)
Headache	14 (7.9)	12 (6.7)	26 (7.3)
Hypotension	11 (6.2)	20 (11.1)	31 (8.7)
Dizziness	10 (5.6)	6 (3.3)	16 (4.5)
Pruritus	7 (4.0)	14 (7.8)	21 (5.9)
Dyspepsia	6 (3.4)	2 (1.1)	8 (2.2)
Confusional state	4 (2.3)	3 (1.7)	7 (2.0)
Othostatic hypotension	4 (2.3)	2 (1.1)	6 (1.7)
Urinary retention	2 (1.1)	5 (2.8)	7 (2.0)

IV PCA MS, Intravenous patient-controlled analgesia morphine sulfate; SSTS, sufentanil sublingual tablet system.

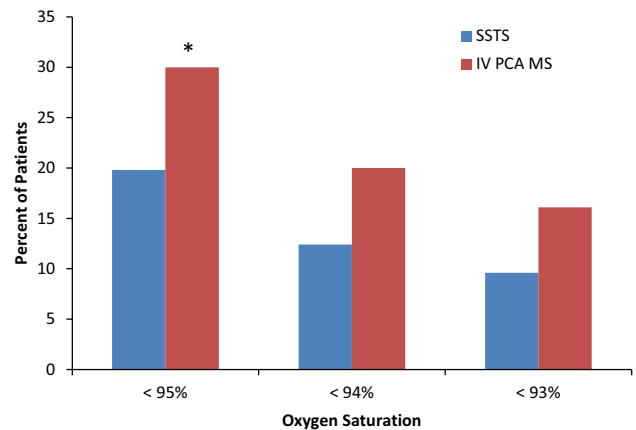


Figure 5. Percent of patients with oxygen desaturation events; $*P = 0.028$.

Table 5. Morphine Metabolite Plasma Concentrations based on Renal Function

Renal Function*	Plasma Concentration (mean (SD); ng/mL)				P-value†
	Normal	Mild	Moderate	Severe	
24 hours					
M3G	165 (118)	271 (165)	250 (264)	896 (1137)	< 0.001
M6G	26 (19)	43 (26)	43 (47)	130 (162)	< 0.001
48 hours					
M3G	126 (93)	259 (177)	291 (405)	460 (620)	< 0.001
M6G	20 (14)	42 (28)	49 (68)	59 (79)	< 0.001

*Renal impairment was defined as a creatinine value above the normal range and a calculated glomerular filtration rate of > 60 (mild), 30 to 60 (moderate), and < 30 (severe).

†The P-value for the overall comparison among groups is based on the F-test of Type III group factor from the ANOVA model including only the group factor for numeric data. M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide.

increase with increased hepatic impairment in plasma MS at 24 hours, but not 48 hours.

DISCUSSION

The major finding of this open-label, active-comparator study was that SSTS was rated a success by significantly more patients with respect to patient global assessment of method of pain control at all timepoints tested (24, 48, and 72 hours) compared to IV PCA MS. Key secondary endpoints supportive of this finding were faster onset of analgesia and higher patient and nurse satisfaction scores as measured by validated ease-of-care questionnaires. Rapid onset of analgesia, even with sublingual administration of sufentanil tablets, should not be surprising given the high lipophilicity and the rapid $t_{1/2k_{e0}}$ equilibration half-life of 6 minutes for sufentanil.⁸ As shown in Figure 3, patients utilizing IV PCA MS on average required approximately 5-fold longer (7 hours vs. 1.3 hours) to obtain a mean PID of 1.3, which has been demonstrated as the clinically meaningful pain intensity difference for acute pain conditions.¹⁵ Over time, the time-weighted summed pain intensity difference scores were similar between the 2 treatment groups; however, the total pain relief scores remained higher in the SSTS group.

The slow CNS penetration of IV MS not only results in delayed onset of analgesia but also sets up the risk of dose-stacking and delayed adverse events due to a decoupling of the patient's request for analgesia and the resultant peak CNS concentration. While the overall spontaneously reported adverse events were similar between the 2 groups, the more objective measurement of continuous oxygen saturation monitoring demonstrated fewer patients had desaturation events in the

STSS group. Whether this is due to the lower therapeutic index for morphine compared to sufentanil, or due to morphine's delayed effector site penetration, is difficult to determine as the desaturation events occurred throughout the 72-hour study. It is also possible that the active metabolite M6G could be contributing to the increased rate of oxygen desaturation. M6G has an even longer equilibration half-life than morphine ($t_{1/2k_{e0}} = 6.4$ hours),⁹ and as demonstrated in this study, is significantly increased with renal impairment. Some hospitals utilize hydromorphone with IV PCA instead of morphine to achieve a more rapid analgesic effect, however, the CNS equilibration half-life is still fairly long ($t_{1/2k_{e0}} = 46$ minutes).¹⁶

While one theoretical advantage of IV PCA is the programmable nature of the device, this flexibility in dosing allows the risk of programming errors, as well as the risk of inappropriately increasing a patient's dose in response to inadequate analgesia. This can occur when the delayed onset of analgesia observed with morphine is attempted to be overcome by increasing the patient's on-demand dose. The delayed wave of morphine entering the effector site in the CNS is then further compounded by the increase in morphine administered per dose and adverse events can ensue. As a result, many hospitals have pre-printed IV PCA parameters to avoid non-opioid tolerant patients from being exposed to these risks. Therefore, the inherent complexity of the IV PCA programmable pump could be avoidable since, for most patients, the increased functionality is never utilized. The data from this study demonstrate that a fixed dosage strength patient-controlled modality, such as SSTS, allows adequate flexibility among patients given the nature of its "as needed" dosing paradigm. With no age or body-mass index limits, the varied demographics of patients entered in this study who were able to achieve safe and effective analgesia is evidence that the rapid CNS-equilibrating opioid sufentanil can be dosed sublingually using a less complex delivery device and avoid the issue of programming or dosing errors. The small percentage of in-hospital patients who are highly opioid-tolerant, on the other hand, do benefit from the additional option of IV PCA basal infusions and programming of higher bolus doses.

Although evenly distributed between the groups, this study did have a preponderance of white female patients. This is not surprising as it is the most common demographic group among hip and knee replacement patients, which were the majority of surgical patients in

this study (Table 1).^{17,18} The flexible nature of dosing with patient-controlled analgesia systems in general should minimize concern that these results are representative of only a demographic subpopulation.

Patient EOC questionnaire results show SSTS patients gave higher scores for all aspects of the system (eg, comfort with device, ease of movement, confidence with dosing) compared to IV PCA MS patients. The SSTS is hand-held and is stored in a bedside holster within clear view of the patient compared to an IV PCA pump which is often not visible to the patient. The device has lights indicating lock-out status, the dosing button lights up and flashes when it recognizes the RFID thumb tag, and the system emits a positive dosing sound when the device has dispensed a tablet. This greater degree of feedback with the SSTS device compared to IV PCA pumps may underlie the higher patient ratings. Nurses similarly had higher EOC questionnaire ratings. The SSTS is preprogrammed and dispenses a solid dosage form, therefore does not require nurse programming, nursing double-checks, or IV tubing concerns, such as priming, patency, carrier fluid and pump requirements. These factors may have contributed to the less “bothersome” EOC subscale rating that the SSTS received by nurses compared to IV PCA. It cannot be ruled out that a new technology may in general be more appealing to patients and nurses, thereby influencing the EOC scoring to some degree.

Patient-specific RFID technology to minimize “proxy” dosing is an advantage over traditional PCA dosing which can allow family members to dose the patient, resulting in adverse events. Healthcare providers should be observant for diversion of medication; however, this issue in hospitalized patients is very limited compared to the much larger problem of diversion of outpatient-prescribed opioids.

In summary, the SSTS is an investigational patient-controlled system utilizing sublingual sufentanil tablets to treat moderate-to-severe acute pain in the hospital setting. The system has advantages over IV PCA and has been demonstrated to provide rapid analgesia and achieves high patient and nurse satisfaction ratings in clinical use. Although not utilized in this study to avoid confounding analgesic endpoint assessments, a multimodal approach utilized alongside the SSTS would minimize adverse events and optimize postoperative analgesia. Furthermore, compelling pharmacoeconomic advantages should also play an important factor for utilization of SSTS if approved for commercial use in hospitals.

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