Research Article

ISSN 2639-846X

Anesthesia & Pain Research

Intraoperative Sublingual Sufentanil for Acute Pain in the Ambulatory Surgery Center: A Randomized Controlled Trial

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Received: 15 Jun 2025; **Accepted:** 19 Jul 2025; **Published:** 27 Jul 2025

Citation: Aaron A Berg, James M Flaherty, Jonah M Pearson, et al. Intraoperative Sublingual Sufentanil for Acute Pain in the Ambulatory Surgery Center: A Randomized Controlled Trial. Anesth Pain Res. 2025; 9(3): 1-5.

ABSTRACT

Background: *Sublingual sufentanil (SST) is used in the treatment of acute moderate to severe pain. Effects from its use for post operative ambulatory surgery has been shown, but those full benefits may not have been captured due to discharge. The aim of this study was to determine if its postoperative analgesic effects when given prior to emergence from anesthesia would show those benefits.*

Methods: *This was a prospective randomized controlled trial conducted at a single ambulatory surgery center. Patients aged 18-80 undergoing orthopedic surgery under general anesthesia were enrolled and randomized to receive either 30 mcg of SST or nothing 30 minutes prior to emergence. The primary outcome was the initial pain score, assessed via a standard 11-point numerical rating scale (NRS), on arrival to the post-anesthesia care unit (PACU).*

Results: *Fifty patients were included in the final analysis. The pain score on arrival to PACU was not significantly different between groups (SST: 4/10 [IQR 0,6]; control: 4/10 [IQR 3,5]; p = 0.378). However, patients in the sublingual sufentanil group used less opioid while in PACU, were more likely to be opioid free, and had improved overall benefit of analgesia scores (OBAS) compared to the control group.*

Conclusion: *While SST did not improve initial pain scores in PACU, its use may improve PACU opioid requirements and patient satisfaction with analgesia.*

Keywords

Ambulatory Surgery, Sublingual Sufentanil Tablet, Postoperative Analgesia, Acute Pain, Postoperative Pain.

Glossary of Terms

AE: Adverse event, ASC: Ambulatory Surgery Center, IV: Intravenous, IQR: Interquartile range, MME: Milligram morphine equivalent, NRS: Numeric rating scale, OBAS: Overall Benefit of Analgesic Survey, PACU: Post-anesthesia care unit, PONV: Postoperative nausea and vomiting, SST: Sublingual sufentanil tablet.

Introduction

Postoperative pain is a common problem encountered after ambulatory surgery, especially orthopedic surgery [1]. Despite widespread application of multimodal analgesic techniques, opioids continue to be a mainstay for controlling perioperative pain. Intraoperative dosing of opioids is typically restricted to intravenous formulations, which share a common single dose pharmacokinetic profile with an early peak in plasma concentration followed by a precipitous decline. This profile can contribute to prolonged recovery times either through relative overdosing, causing opioid related adverse effects, or relative underdosing with resultant inadequate pain control.

In 2018, the FDA approved the sufentanil sublingual tablet (SST) for treatment of moderate to severe pain in medically supervised settings. As a new formulation of an established opioid analgesic, SST provides rapid onset to analgesic threshold in 30 mins, peak effect in 1 hour, without falling below the analgesic threshold for 3 hours minimizing the peak-and-trough phenomenon typical of IV opioids [2]. Preliminary clinical studies in the surgical and emergency room populations have focused on comparisons of SST with intravenous opioid Patient-Controlled Analgesia (PCA) or as a rescue measure when other opioid-based modalities have failed [3-5]. However, it has yet to be determined what role preemptive intraoperative dosing of SST could play in management of acute post-operative pain.

The primary aim of this study was to determine if a 30 mcg SST given 30 minutes prior to emergence from anesthesia was efficacious in reducing initial post anesthesia care unit (PACU) pain scores, compared to no intervention. Secondary outcomes were time to PACU discharge readiness, PACU opioid consumption, pain score upon discharge from PACU, reduction in pain from initial score to discharge, PONV requiring treatment, adverse events thought related to study intervention, and OBAS scores.

Materials and Methods

This single center, prospective, randomized outcomes study was approved by the University of Minnesota institutional review board on June 5th, 2020, and written informed consent was obtained from all participants (Principal Investigator: Aaron Berg; IRB STUDY00009050; clinicaltrials.gov identifier NCT04387136). This trial adheres to the applicable CONSORT guidelines.

All adult patients aged 18-80 undergoing general anesthesia for orthopedic surgery at our ambulatory surgery center between 10/14/2020 to 2/4/2021 were screened for participation. Exclusion criteria included history of chronic pain, daily opioid use for greater than 3 weeks prior to enrollment, and prone positioning during surgery. Patients were additionally excluded if they received a regional anesthetic block, expected to eliminate postoperative pain (ie supraclavicular block for forearm surgery). Following informed consent, patients were randomized sequentially to either receive SST 30 mcg (SST group) or no intervention (control group) within 30 minutes of emergence from general anesthesia. Randomization assignment was kept in a sealed envelope, opened by the intraoperative certified registered nurse anesthetist (CRNA) at the beginning of surgical closure. No additional analgesic interventions were allowed after opening the envelope. The anesthesiologist, patient and nursing were all blinded to the intervention and the CRNA was during the case, only to be unblinded for the administration of the medication and PACU transport.

Preoperatively, all patients received a single dose of acetaminophen 975 mg and gabapentin 300 mg, unless contraindicated. General anesthesia was conducted with a standardized opioid-sparing total intravenous anesthesia with propofol. Opioids were not permitted for induction and 25-50 mcgs of IV fentanyl every 3 mins up to 200 mcgs, was only allowed intraoperatively for an increase in heart rate or blood pressure of 20% above baseline. No other opioids were given intraoperatively. Intravenous ketorolac was allowed but decided upon prior to opening the randomization envelope.

After arrival in PACU, initial pain scores were recorded using a standard 11-point numeric rating scale (NRS). Standardized supplemental opioids were administered in PACU for all patients who reported a pain score of 4 or greater. Intravenous fentanyl was titrated in 25-50 mcg doses up to a total of 100 mcg. If pain scores remained above 7/10, IV hydromorphone 0.3 mg was administered every ten minutes as needed up to 1 mg. Once patients were able to tolerate oral medications, pain scores ≥ 4 were managed with 5 mg oral oxycodone (or 2 mg of oral hydromorphone if allergic to oxycodone) every 10 mins. All opioid medications were converted to milligram morphine equivalents (MME) using www.globalrph.com for overall opioid comparison [6]. Upon meeting discharge criteria, a PACU nurse or research assistant administered the Overall Benefit of Analgesic Score (OBAS), a 7 question survey about pain intensity and opioid related side effects [7]. A final pain score was recorded prior to discharge.

Statistical Analysis

The power analysis was based on a previous prospective randomized controlled trial at this same surgery center which showed average initial pain scores of 6.63 (SD= 2.13) for patients undergoing orthopedic surgery. Assuming a two sample t test with $\alpha = 0.05$, the sample size needed to detect a decrease in pain score of two or more with 90% statistical power was calculated to be 25 per group.

Categorical variables are summarized with frequency (percent). Continuous variables are summarized with median (25th percentile, 75th percentile) after evaluation for normality based on the Shapiro-Wilk test and graphical summaries indicated most were not normally distributed. Unadjusted comparisons between the two randomized groups were based on the nonparametric Mann-Whitney U-test and Fisher's exact test for continuous and categorical measures, respectively. P-values for secondary outcomes were not adjusted for multiple comparisons. All analyses and power calculations were completed using R v3.6.3 (Vienna, Austria).

Results

Fifty patients completed the study per-protocol, 25 per group. One patient was excluded due to a protocol violation, one due to case cancellation, and one who endorsed chronic pain after signing consent. There were no significant differences in baseline characteristics between the two groups, nor was there a significant difference in the duration of surgery (Table 1). There was no difference in intraoperative opioid use between the two groups (p=0.628).

Table 1: Demographics.

	Control [Median (IQR) or N (%)] N=25	Sublingual Sufentanil Median (IQR) or N (%) N=25	p-value
Male	9 (36.0%)	13 (52.0%)	0.393
Age (years)	39.0 (27.0, 49.0)	33.0 (26.0, 52.0)	0.719
Preoperative Block	7 (28%)	7 (28%)	1.000
BMI (kg/m^2)	27.5 (25.7, 34.5)	29.1 (27.3, 32.2)	0.628
Surgical Duration (minutes)	39.0 (25.0, 57.0)	42.0 (27.0, 63.0)	0.676
ASA I	11 (44.0%)	11 (44.0%)	1.000
ASA II	12 (48.0%)	11 (44.0%)	
ASA III	2 (8.0%)	3 (12.0%)	

Abbreviations: BMI: body mass index ASA: American Society of Anesthesiologists IQR: interquartile range N: number.

We found no significant difference in median pain score on arrival to PACU between the groups (SST: 4/10 [IQR 0,6]; control: 4/10 [IQR 3,5]; p = 0.378) (Table 2). The SST group showed significantly lower PACU MME requirement (SST: 7.5 mg [IQR 0.0, 22.5]; control: 15.0 mg [IQR 7.5, 37.5]; p = 0.018). More patients in the SST group were opioid free during their PACU stay (36% vs 8%; p = 0.037). The SST group also demonstrated a significantly superior median OBAS score compared to the control group (SST: 1.0 [IQR 0.0, 2.0]; control: 3.0 [IQR 1.0, 3.0]; p = 0.006).

Table 2: Recovery Room Data.

	Control [Median (IQR) or N (%)] N=25	Sublingual Sufentanil [Median (IQR) or N (%)] N=25	p-value
Phase 1 to Phase 2 discharge criteria met (minutes)	64 (52.0, 81)	62 (54, 82)	0.969
Initial Pain score in PACU	4.0 (3.0, 5.0)	4.0 (0.0, 6.0)	0.378
Max Pain in PACU	5.0 (4.0, 6.0)	4.0 (2.0, 6.0)	0.132
Pain at discharge	3.0 (2.0, 3.0)	2.0 (0.0, 4.0)	0.213
Initial pain minus pain at discharge	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	0.929
IntraOp MME (MG)	0.0 (0.0, 15.0)	0.0 (0.0, 15.0)	0.628
Rescue MME (mg)	15.0 (7.5, 37.5)	7.5 (0.0, 22.5)	0.018
Opioid Free in PACU	2 (8%)	9 (36%)	0.037
OBAS score*	3.0 (1.0, 3.0)	1.0 (0.0, 2.0)	0.006

Abbreviations: OBAS: overall benefit of analgesia score, PACU: post-anesthesia care unit mg: milligrams MME: milligrams morphine equivalents IQR: interquartile range N: number

* 1 patient in the sublingual sufentanil group was missing the OBAS score.

The maximum pain score during PACU stay, pain score on discharge, change from initial pain score to pain score on discharge, and time from PACU arrival to discharge readiness were not found to be significantly different between the two groups. There were 2 patients in the SST group and 0 in the control group with post-operative nausea and vomiting (p=0.490) and 2 patients in the control group and 1 in the SST group who needed oxygen greater than 30 minutes into their PACU stay (p=1.000).

Discussion

Our prospective, randomized study failed to show a significant difference in pain scores upon arrival to PACU between groups. However, several secondary outcomes favored the SST group. Patients in the SST group used significantly fewer opioids, had higher OBAS scores and were four times more likely to be opioid free in PACU. This opioid reduction is not surprising given that patients in the intervention group received an opioid as the study intervention. However, the improvement in OBAS scores does potentially demonstrate greater analgesic satisfaction despite the lack of difference in NRS pain scores.

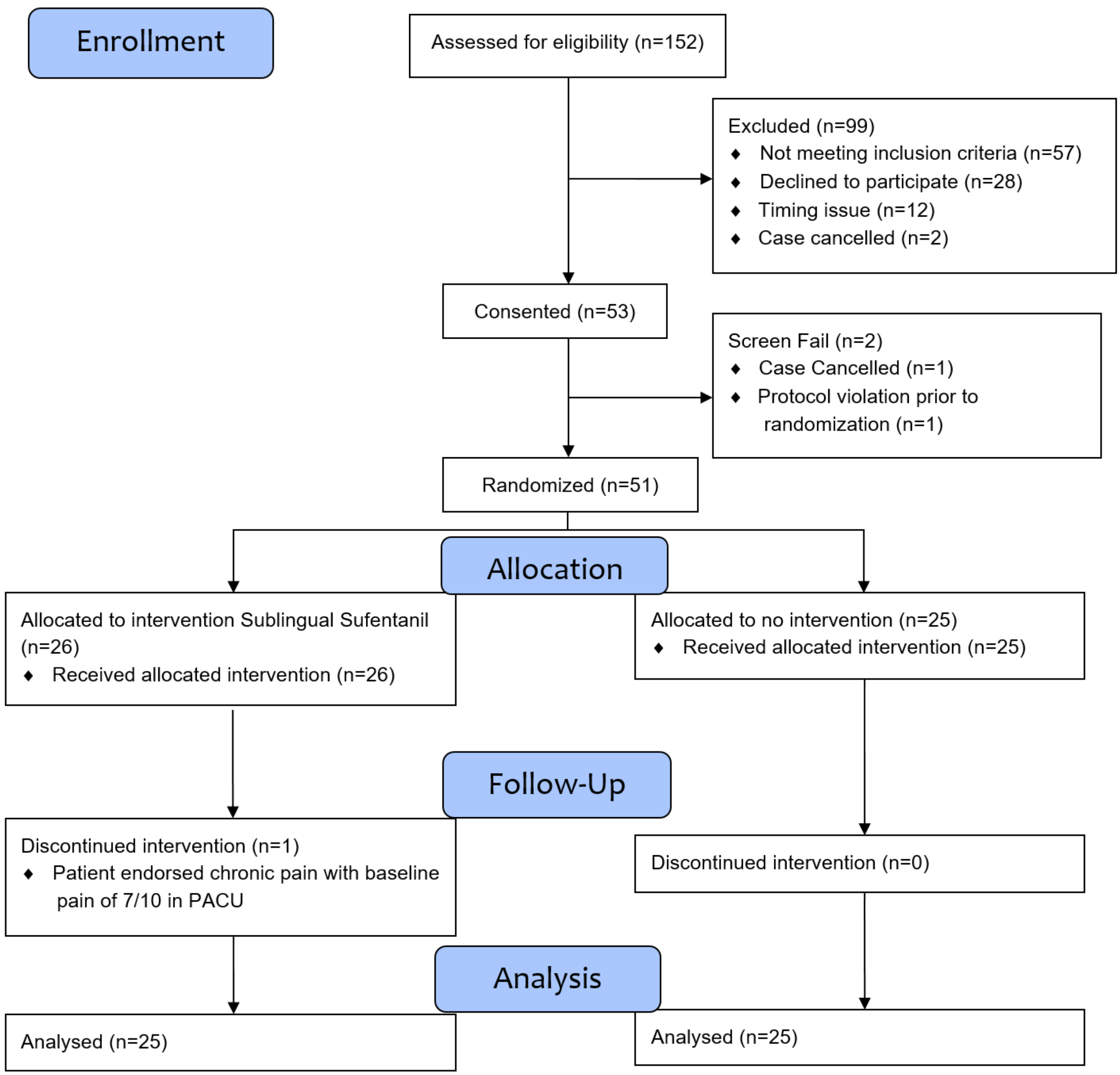
SST has previously been shown to be safe, effective, and well tolerated in a previous systematic review [8]. Recent studies have evaluated the effectiveness of 30 mcg SST in the management of perioperative pain assessing opioid utilization and recovery times. Nearly all the patients in the Cassavaugh et al. study that received SST were dosed just prior to induction or intraoperatively, with 10% receiving a second dose postoperatively [9]. In their wide variety of outpatient and inpatient cases they found that patients in the matched control group received 66% higher mean dosing of opioids intraoperatively and that opioid requirements in the recovery room were 50% less in patients receiving SST. Orthopedic procedures were found to be the group with the largest percent reduction (69%) in PACU opioid use [9]. This opiate reduction is similar to what we saw in our prospective trial (33%) yet was not significant [10]. In the Tvetenstrand and Wolff study, patients were given 30 mcg SST preoperatively and compared to a matched retrospective control group and found a 50% reduction in opioid requirements peri-operatively for the SST group [11]. Both studies found a reduction in phase 1 recovery times for the SST group [9,11]. In contrast to both of those studies, our prospective randomized study found no difference between the two groups in time to readiness to discharge. This may be due to the fact that our combined phase 1 and phase 2 times were similar to their phase 1 times and thus may already be at the optimal PACU duration and thus may not change with any intervention.

There are several limitations to our study. The first is that the sublingual sufentanil was not compared to an active comparator and thus may have magnified the significance of our results. Second, the intraoperative provider was eventually unblinded in order to administer the study medication. However, they made no additional pain interventions after becoming unblinded. Finally, our study data collection was completed at discharge and thus we may not have observed any further analgesic benefit beyond discharge from PACU.

In conclusion, initial NRS pain scores on arrival to PACU were not improved in patients receiving preoperative sublingual sufentanil. However, patients receiving this intervention had reduced opioid consumption and improved OBAS scores.

CONSORT
TRANSPARENT REPORTING of TRIALS

ONSORT 2010 Flow Diagram



Conflict of Interests

JH is a speaker, consultant, and has received research funds from Pacira Bioscience, he is a consultant and owns stock with Insitu Biologics, is a consultant and speaker for Acel RX, a consultant for Worrell, received research funds from Avanos, and a consultant for Johnson and Johnson. AB is a consultant for Pacira Bioscience and AtriCure. None of the other authors have any conflicts of interest.

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