A Pilot Study Assessing the Effects of Sublingual Sufentanil 30 µg on Postoperative Recovery from Ambulatory Surgery

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Interventions	Sufentanil 30 µg versus 50 µg IV fentanyl

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Study Summary

Title	A Pilot Study Assessing the Effects of Sublingual Sufentanil 30 μg on Postoperative Recovery from Ambulatory Surgery
Methodology	Randomized trial
Study Duration	6 months
Single vs. Multicenter Design	Single center
Objectives	A pilot study to evaluate the effect of incorporating sublingual sufentanil into our perioperative opioid regimen for ambulatory orthopedic surgery. The results will help us estimate treatment effect and determine sample size for a subsequent full-scale clinical trial. Primary Endpoint: total amount of fentanyl consumed during PACU admission. Secondary Endpoints: 1) phase I recovery time; and, 2) time to fitness for discharge. Exploratory Endpoints 1) intraoperative hemodynamics; 2) intraoperative opioid use; 3) intraoperative sevoflurane use; 4) postoperative pain; 5) postoperative sedation and cognitive recovery 6) time to first request for analgesia; and, 7) incidence of nausea and vomiting between the end of anesthesia and hospital discharge.
Number of Subjects	Total randomized sample: 75 plus ≤6 pilot patients.
Main Inclusion and Exclusion Criteria	Inclusion Criteria: patients aged ≥ 18; having elective outpatient knee arthroscopy surgery without ligamentous repair. Exclusion Criteria: opioid tolerance and medical contraindication.
Treatment Groups	- Intervention group: 30 μg tablet of sublingual sufentanil preoperatively and fentanyl placebo at induction of anesthesia. - Control group: placebo sublingual sufentanil preoperatively and 50 μg fentanyl at induction of anesthesia
Data and Safety Monitoring	Responsibility for monitoring data quality and ongoing safety of subjects will be that of AcelRx, the PI, and study coordination staff.

Background and Rationale:

Opioid medications are indicated and frequently used in the treatment of acute moderate-to-severe pain. Delivering timely, safe, and efficient analgesia in fast-paced care environments, such as the emergency room or ambulatory surgery center, can present challenges where intravenous opioid formulations, though fast-acting, carry disadvantages non-conducive to patient safety and care efficiency. For example, intravenous delivery require insertion of an IV catheter and connection to tubing and delivery apparatus. IV's, in addition to the discomfort and minor risks associated with any invasive procedure, also create a means by which one of the most common medication dosing errors is created [1-3]. Human factors concerning technical delivery of drug exist for understandable reasons – the similar appearance of many IV liquids, the potential for misreading labels, the need for calculations, the accuracy required for drawing medication into syringes or programming pumps, etc. – but the pharmacy of IV opioids tends to make their use in the acute ambulatory setting challenging for reasons intrinsic to the medication.

Compounding the chances for error is the pharmacokinetic profile of commonly administered IV analgesics, such as fentanyl. Their rapid plasma fluctuations, corresponding to onset and offset, make them difficult to titrate acutely for analgesia and often require frequent re-dosing. Additionally, the delayed plasma response of their active metabolites not only contribute to the phenomenon of dose stacking, but also account for side effects that can be both dangerous and unpleasant to the patient. Nausea/vomiting, itching, ileus, etc., all negatively impact patient experience as well significantly delay their discharge from facility and increase the cost of care.

A benefit of IV delivery in higher acuity out-patient settings is rapid onset and relief of pain as compared to oral formulations. But many of the traditional advantages of intravenous drug and fluid administration do not apply. The ability to continue infusions for several days; the ability to administer large volumes of fluids and blood products; the ability to administer several other IV medications; etc. – these are some of the typical gains that help offset the drawbacks of IV addressed previously. But none of these apply to the care of patients undergoing common outpatient surgical procedures or ER visits that don't require admission but still entail a significant amount of pain. For these care units, historically, one could argue that the selection of IV opioids is less about the full utilization of a line that offsets its risks and drawbacks, but rather, is a reluctant choice made despite them without an equally effective alternative analgesic that can be administered differently.

Sublingual sufentanil, an under-the-tongue opioid formulation, offers a unique solution that addresses many context-specific pain treatment problems. Importantly, the sublingual form is absorbed directly into veins that drain the tongue, not by oral digestion, and thus approximates intravenous delivery without requiring intravenous access. However, sublingual administration differs from a pure intravenous delivery in a crucial way. In stark contrast to IV, sublingual sufentanil creates a depot in sublingual fat that is released slowly which blunts peak serum concentration, lessening the chance for respiratory depression (figure below).

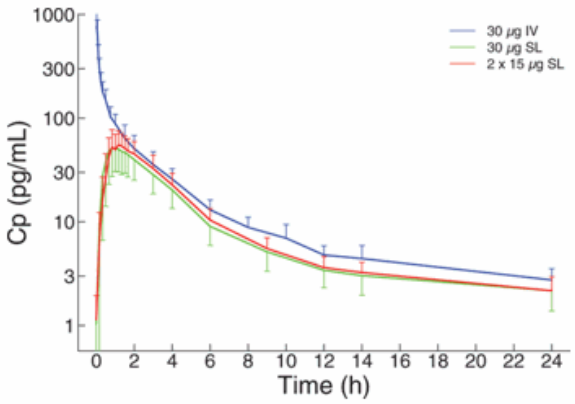

Figure Legend:
Plasma concentration profile (mean, SD of venous concentrations) for 30 µg of sufentanil administered to 39 subjects in study SAP101. Colors indicate dose and route of administration. Cp = plasma concentration; IV = intravenous; SL = sublingual.

Slow release from sublingual fat depots prolongs the drug's effect, typically providing effective analgesia lasting up to 3 hours – a sufficient window within which to treat pain in the ER or for ambulatory surgery. Sufentanil has no active metabolites that "stack" its effects or contribute to side effects. Available literature remains sparse, making it well worth examining the potential benefits of sublingual sufentanil on post-operative recovery, especially the extent to which sublingual sufentanil might provide safe and effective analgesia for minor ambulatory surgery.

Objectives:

Objective: A pilot study to evaluate the effect of incorporating sublingual sufentanil into our perioperative opioid regimen for ambulatory orthopedic surgery. The results will help us estimate treatment effect and determine sample size for a subsequent full-scale clinical trial.

Primary Endpoint: total amount of fentanyl consumed during PACU admission.

Secondary Endpoints: 1) phase I recovery time; and, 2) time to fitness for discharge.

Exploratory Endpoints: 1) intraoperative hemodynamics 2) intraoperative opioid use; 3) intraoperative sevoflurane use 4) postoperative pain; 5) time to first request for analgesia;

and, 6) incidence of nausea and vomiting between end of anesthesia and hospital discharge.

Safety Monitoring: all adverse events will be recorded as detailed below.

Methods

A pilot for a randomized, controlled trial.

Subject selection

Study coordinators at Fairview Hospital will call patients scheduled for knee arthroscopy at least 1 day prior to the day of surgery to notify them of eligibility with the use of an IRB approved phone script (to be submitted in a supplemental document not contained in the protocol). Interested patients will be met in the facility on the day of surgery to provide private consultation, wherein the purpose, objectives, risks, and benefits of the investigation will be thoroughly addressed. Signed copies of the consent form will be stored on-site in a secure location.

Team consensus from the PI, anesthesiologist, and the patient's surgeon regarding research enrollment will be obtained. Each team member must agree as to the suitability for research and safety of the intervention as it pertains to each case. Communication will be documented in the electronic medical record system.

Inclusion Criteria:

- Adults aged ≥ 18 years;
- Scheduled for elective knee arthroscopy without anticipated ligamentous repair;
- Planned general anesthesia without a regional block or wound infiltration with local anesthesia;
- Planned day-of-surgery discharge.

Exclusion Criteria:

- Opioid tolerance defined by ≥15 mg of oral morphine daily or equianalgesic dose of another opioid within 30 days of surgery;
- Known hypersensitivity to sufentanil or components of DSUVIA;
- Patients with an allergy or hypersensitivity to opioids.
- Pregnancy or actively breastfeeding;
- Patients who are currently taking monoamine oxidase inhibitors (MAOIs) or have taken MAOIs within 14 days of the first dose of study drug;
- Patients with a medical condition that, in the Investigator's opinion, could adversely impact the patient's participation or safety, conduct of the study, or interfere with the pain assessments, including chronic pain or active infection.

Protocol

Preoperative Assessment:

- Baseline Blessed Orientation-Memory-Concentration (BOMC).

- Pain Catastrophizing Scale
- PEG 3 Item Scale

Preoperative Medication:

Participating patients will be given 2 mg of midazolam to alleviate pre-procedure anxiety unless the drug is considered contra-indicated by the attending anesthesiologist. Patients will be given 1 g oral acetaminophen with a sip of water about 30 minutes before induction of anesthesia.

Randomization:

75 patients will undergo 1:2 randomization without stratification to either placebo or sufentanil (25 placebo patients and 50 sufentanil patients). The randomization list will be prepared by trial statisticians and administered by the research pharmacy. Allocation will be concealed until just before induction of anesthesia by a web-based system. Patients will be randomized to:

> **Intervention:** Sufentanil 30 μg tablet sublingually prior to induction of anesthesia and placebo fentanyl at induction.
>
> **Control:** Placebo sublingual sufentanil prior to induction of anesthesia and 50 μg IV fentanyl at induction.

Timing of Administration for Sufentanil/Placebo:

As the method of airway management requires different analgesic thresholds, administration of sufentanil will be staggered accordingly:

In the event that the airway will be secured via laryngeal mask, the sufentanil tablet/placebo will be administered approximately 15 minutes prior to induction.

In the event that the airway will instead be secured via endotracheal tube, the sufentanil tablet/placebo will be administered approximately 30 minutes prior to induction just following the dose of oral acetaminophen.

Standardized Anesthetic Regimen:

General anesthesia will be induced with IV propofol, dose per judgment of the attending anesthesiologist. The airway will be secured with a laryngeal mask airway or endotracheal tube. Anesthesia will be maintained with sevoflurane, titrated to a Bispectral Index (BIS) of 40-60. 4 mg of IV ondansetron will be given intravenously before emergence from anesthesia.

No NSAIDs or other opioids will be given during surgery unless clinically indicated. Post-operatively, patients will follow the standard of care (SOC) protocol for recovery analgesia that includes PRN acetaminophen and IV fentanyl injections. Patients will be given 500 mg acetaminophen for reported pain scores in the range of 1-3. For pain in the range of 4-10, 25 μg IV fentanyl can be given at 5-minute intervals. No long-acting opioids will be given.

Treatment Blinding:

The research pharmacist will be the designated unblinded member of the team responsible for preparation of treatment and corresponding placebo. Blinded study coordinators will receive from pharmacy: 1) a sublingual applicator loaded with either active sufentanil or matching

placebo; and, 2) an IV syringe containing either fentanyl or fentanyl placebo. These will be delivered to perioperative personnel for use as described above.

Post-Operative Recovery Assessments:

- Pain Score: every 15 minutes for the first hour after PACU admission and then 30 minute intervals until PACU discharge.
- Richmond Agitation Sedation Score (RASS) completed at intervals above until patient is non-sedated. Afterwards, BOMC is conducted in place of RASS.
- Blessed Orientation-Memory-Concentration (BOMC) test, at intervals above or until baseline is achieved.
- Postoperative Nausea and Vomiting (PONV) Intensity Scale prior to discharge.

Post Discharge

Patients will be called at post-operative day 7 (POD7) to assess for interim adverse events.

Measurements

1) Total consumption of fentanyl: the cumulative μg dose of fentanyl received between arrival to and discharge from PACU per patient's Medication Administration Report.

2) Phase I recovery time: per anesthesia record, the time documented for end-of-case will be taken as the time that the patient entered phase I recovery. Recovery will be considered complete at the time an order is placed for progression to phase II, limiting the extent to which PACU traffic and bed availability can affect the assessment. Determination of phase I discharge readiness is made at regular intervals according to criteria detailed in Cleveland Clinic's Routine Postoperative Patient Care Protocol.

3) Time to Fitness for PACU Discharge: will be determined per facility protocol-scheduled assessments using the CCF Phase II Discharge Scoring tool. The time that the minimum acceptable score of 14 is achieved will be recorded.

3) Postoperative Pain Score: measured as 0-10 Verbal Response Scores conducted at rest.

4) Intraoperative Hemodynamics: the incidence of induction hypotension as measured by the area under a MAP of 65 mmHg during the initial 15 minutes of anesthesia.

5) Intraoperative IV Opioid Use: amount of clinically indicated opioid outside of standardized anesthetic regimen, in oral morphine equivalents (OME).

6) Intraoperative Sevoflurane Use

7) Postoperative Pain Score: measured as 0-10 Verbal Response Scores conducted at rest.

8) Postoperative Sedation and Cognitive Recovery: there is no validated scoring tool which assesses cognitive recovery after anesthesia in ambulatory surgery. Still, there may be value in trying to elucidate an approximation in this trial given anecdotal evidence that sufentanil reduces the use of intraoperative anesthetic gas and promotes faster recovery to arousal/cognitive baseline. To measure this, first RASS will be utilized by a member of the staff to capture early recovery while patients are less able (or unable) to answer questions. When a patient is no longer

sedated according to RASS and able to "spontaneously pay attention", the BOMC test will be administered to measure improvements in executive cognitive functions thereafter.

9) Time to first request for analgesia: defined as the time from official case end until the first recorded Verbal Response Pain Score of greater than 4 (necessitating intervention).

10) Incidence of post-operative nausea/vomiting: the number of cases identified as clinically significant PONV using the PONV Intensity Scale.

Opioid-related adverse events will be recorded, including nausea and vomiting and respiratory depression requiring treatment (naloxone, airway support, etc.). Adverse event reporting will proceed in accordance with Cleveland Clinic IRB-60 Policy.

Data analysis

Randomized groups will be compared for baseline balance using standard descriptive statistics and the standardized difference (difference in means or proportions divided by the pooled standard deviation).

Firstly, we will describe and plot the distribution of the primary outcome, which is the total amount of fentanyl consumed during PACU. If the distribution is approximately normal, we will calculate the standard deviation directly; if it is log-normal, we will estimate the geometric mean and the coefficient of variance. Then we will assess the effect of treatment using t-test or linear regression after log transformation as appropriate.

To assess the treatment effect on Phase I recovery time and time to fitness for discharge, we will use t-test or Wilcoxon test, depending on the distribution of the outcome variables. The difference in mean or median will be reported with 95% confidence interval.

Exploratory outcomes will be summarized by treatment group. The pain level will be summarized by time and the difference across all times will be summarized as difference in mean with 95% confidence interval; the difference in time to first request for analgesia will be summarized as median difference with 95% confidence interval; difference in nausea and vomiting will be summarized as relative risk with 95% confidence interval.

The overall alpha will be 0.05 for both primary and secondary outcomes. Thus the significance level is 0.05 for the primary outcome and 0.025 (i.e. 0.05/2, Bonferroni correction) for all secondary outcomes.

Sample size and power consideration

As this is a pilot study, we aim to estimate the standard deviation of various outcomes, but not to achieve statistical significance. Pilot trial recommendations are usually for 30 to 70 patients [5]. We thus propose to enroll 75 patients, excluding up to 6 pilot patients.

References:

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