

PROTOCOL TITLE: Sublingual sufentanil vs Intravenous fentanyl for acute pain in the Ambulatory Surgery Center - STUDY00007956

VERSION DATE: 3 12/20/2019

INSTRUCTIONS:

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| Protocol Title | Sublingual sufentanil vs Intravenous fentanyl for acute pain in the ambulatory surgery center. |
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PROTOCOL COVER PAGE

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REVISION HISTORY

| Revision # | Version Date | Summary of Changes | Consent Change? |
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| 2 | 12/5/2019 | Modifications for approval | Yes |
| 3 | 12/20/2019 | Protocol timing adjustment | No |
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ABBREVIATIONS/DEFINITIONS

- SST: Sublingual Sufentanil Tablet
- PACU: Post Anesthesia Care Unit
- IV: Intravenous
- ASC: Ambulatory Surgery Center
- SIS: Six Item Screener
- PONV: Postoperative Nausea and Vomiting

1.0 Objectives

- 1.1* Purpose: The purpose of this study is to determine if a single dose of sublingual sufentanil is as or more efficacious than a single dose of IV fentanyl in a post anesthesia care setting.

2.0 Background

- 2.1* Significance of Research Question/Purpose: This study will help to determine the appropriate place for use of sublingual sufentanil in an ambulatory practice.
- 2.2* Preliminary Data: Existing Literature: Previous studies have demonstrated the superiority of SST to placebo when used for abdominal surgery. Additional open label studies have demonstrated that SST has no change in mental status when given in an emergency room setting and has a safe adverse event profile when used in various inpatient surgical procedures. No studies have compared SST 30 mcg to an active comparator such as IV fentanyl.

3.0 Study Endpoints/Events/Outcomes

- 3.1* Primary Endpoint/Event/Outcome: Time of readiness to discharge after arrival in PACU
- 3.2* Secondary Endpoint(s)/Event(s)/Outcome(s): opioid use after intervention until discharge, adverse events, patient satisfaction, PONV, supplemental oxygen, and OBAS score

4.0 Study Intervention(s)/Investigational Agent(s)

- 4.1* Description: Upon arrival in the ASC PACU patients who have a pain score of 4 or greater will receive one of two interventions. They will be randomly assigned to receive either 50 mcg of IV fentanyl or 30 mcg of sublingual sufentanil. Fentanyl is a potent IV opioid whereas sufentanil is a potent sublingual opioid.
- 4.2* Drug/Device Handling: Both sublingual sufentanil and IV fentanyl will be stored in the PACU pyxis like other controlled substances.
- 4.3* Biosafety: n/a
- 4.4* Stem Cells: n/a

5.0 Procedures Involved

- 5.1* Study Design: This is a level I randomized prospective outcomes study comparing two groups of patients. Upon arrival in the ASC PACU if the patient has a pain score of 4 or greater they will then be randomized to one of two groups. Group 1 will receive 50 mcg of IV fentanyl and group 2 will receive 30 mcg of sublingual sufentanil.

- 5.2 Study Procedures: Patients will be approached on the day of surgery about participating in the trial. This will be done as soon as they arrive at the ASC to allow adequate time for them to review the study procedures and consent form. All questions will be answered and patients will be ensured that they have adequate time to review and understand all study procedures. Patients undergoing surgical procedures with general anesthesia will be eligible to participate. Once consented a baseline six-item screener score will be obtained. Patients will only be enrolled once they reach the PACU and if their pain score is 4/10 or greater via the Numerical Rating Scale. Then they will be randomized and enrolled in the study. If they never have a pain score of 4 or greater they will not be enrolled.

All patients will have received preoperative acetaminophen 975 mg, gabapentin 300 mg and a standardized opioid sparing total IV anesthetic with propofol. No opioids will be used on induction and patients will only receive intraoperative opioids if their HR or BP is increased by 20% above baseline. 2 different PONV prophylaxis (ondansetron and dexamethasone) will be given and Ketamine will not be used in this study.

Once in PACU, if their pain score is 4 or greater on a Numerical rating scale they will be randomized into one of the two groups. One group will receive 50 mcg of IV fentanyl and the other will receive 30 mcg of sublingual sufentanil. They will be eligible to receive additional rescue opioids 10 minutes after their first dose. Rescue opioids will be 25 mcg of IV fentanyl given up to every 3 minutes for max dose of 100 mcg (max dose will count only rescue IV fentanyl, but not the initial randomization of IV fentanyl 50 mcg) if pain score remains at 4 or greater out of 10 during this time. If pain scores are 3 or less, no opioids will be given. After 100 mcg of rescue fentanyl if pain score remains above 4 out of 10 they will receive 5 mg of oral oxycodone or 2 mg of oral hydromorphone if allergic to oxycodone. Another six-item screener test will occur 30 minutes after administration of sublingual sufentanil or initial IV fentanyl.

Time until readiness to discharge (minutes), rescue opioid use (mcgs), Overall benefit of analgesia score, PONV (defined as needed to treat or not), need for supplemental oxygen (at 30 mins into recovery) and patient satisfaction will be recorded. Six-item screener scores, Baseline demographics such as surgical procedure, intraoperative opioids, surgical procedure length, BMI, weight, age, and sex will be recorded.

- 5.3 Study Duration: Once ready to discharge from PACU the patient recording will stop and they will finish participation by answering questions for the OBAS survey. It should take 4 weeks to enroll all patients and another 2 months for full data analysis.

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5.4 Individually Identifiable Health Information: This study does involve PHI and please see attached combined HIPAA and consent form.

5.5 Use of radiation: n/a

5.6 Use of Center for Magnetic Resonance Research: n/a

6.0 Data and Specimen Banking

6.1 Storage and Access: All study data will be stored on excel spreadsheets in University affiliated Box and REDCap. Only the PI and members of the research team will have access to the data.

6.2 Data: The data from this study will be collected both from Epic and directly from the patient. The data collected includes: demographic data, age, weight, ASA class, duration of surgery, length of stay in recovery room both phase 1 and 2, amount of opioids given intraoperatively and post-operatively, non-opioid pain medication, pain score (0-10) at arrival in PACU, satisfaction with treatment, PONV, need for supplemental oxygen, OBAS score at time to ready to discharge, baseline and 30 minutes post administration six item screener score and any adverse events.

7.0 Sharing of Results with Participants

7.1 Study results will not be shared with participants. Deidentified study data may be shared with the peer-reviewed journal.

8.0 Study Population

8.1 Inclusion Criteria: Adult patients aged 18-80 undergoing outpatient ambulatory surgery under general anesthesia and who have a pain score of 4 or greater in the PACU.

8.2 Exclusion Criteria: Patients under the age of 18, non-english speaking patients, cancer surgeries, patients who have allergy or intolerance to the study drugs or derivatives, and patients on chronic opioids (defined as daily opioids for 3 months or longer)

8.3 Screening: Patients will be screened by looking at the surgical schedule. They will be contacted by the research team ahead of time and have the study introduced when they check in on the day of surgery. They will have adequate time to evaluate the study and read through the consent and ask questions.

9.0 Vulnerable Populations

9.1 Vulnerable Populations:

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| Population / Group | |
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|--|-----------------------------|
| Children | Excluded from Participation |
| Pregnant women/fetuses/neonates | Excluded from Participation |
| Prisoners | Excluded from Participation |
| Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders | Excluded from Participation |
| Non-English speakers | Excluded from Participation |
| Those unable to read (illiterate) | Excluded from Participation |
| Employees of the researcher | Excluded from Participation |
| Students of the researcher | Excluded from Participation |
| Undervalued or disenfranchised social group | Excluded from Participation |
| Active members of the military (service members), DoD personnel (including civilian employees) | Excluded from Participation |
| Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc. | Excluded from Participation |
| Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare. | Excluded from Participation |
| Individual or group with a serious health condition for which there are no satisfactory standard treatments. | Excluded from Participation |

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| Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior). | Excluded from Participation |
| Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research. | Excluded from Participation |

9.2 Additional Safeguards:

- n/a

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented: 200

11.0 Local Recruitment Methods

11.1 Recruitment Process: Patients will be recruited from the group of adult patients undergoing surgery under general anesthesia at the University of Minnesota Ambulatory Surgery Center. On the day of surgery as soon as they are checked in, patients will be informed of a research opportunity by a member of the clinical care staff, including the check-in staff, nursing staff, or member of the anesthesiology team, and asked if they are interested in talking with a member of the research team. A research team member will then explain the study and present the consent form. All patients will have sufficient time to review the consent and ask questions and go over the potential risks of the study with the research team as they arrive several hours prior to the procedure. If they decide to participate they will be consented and given a copy of the consent form for their records.

11.2 Identification of Potential Participants: Patients will be identified by members of the research team by evaluating the surgical schedule. Patients known to have opted out of research will not be approached. Patients who agree to participate will sign a consent and HIPAA authorization.

11.3 Recruitment Materials: N/a

11.4 Payment: No payment will be provided to patients.

12.0 Withdrawal of Participants

- 12.1* Withdrawal Circumstances: Subjects who have consented and for some reason choose not to participate will be withdrawn and a notation will be made in the study records and these people will be considered screen failures. The surgeon may choose to withdraw the patient from the study prior to surgery for any medical reason or if they suffer a major life-threatening adverse event.
- 12.2* Withdrawal Procedures: If the patient is withdrawn from study prior to the procedure, they will be noted in study records as screen failures. If they undergo the procedure and they decide they no longer want to be a part of the study or withdrawn by the physician, they will be withdrawn and no further data will be collected. This will also be noted in the study documentation.
- 12.3* Termination Procedures: If the study is terminated for any reason, or there are more than 5% major adverse events the data that is already collected will be stored in a secure location only accessible to research personnel on this study. No further data will be collected if the study is terminated. Data will only be used for publication if an adequate amount has been collected for statistical considerations. Patient research participation duration will be on the day of the surgery, therefore if the study is terminated the reason would likely not be relevant to previously enrolled patients and they would correspondingly not be notified of study termination. If however the termination reason is thought to be potentially relevant to previously enrolled patients by the Data and Safety Monitoring Committee, they would be called and notified by a member of the research team.

13.0 Risks to Participants

- 13.1* Foreseeable Risks: This study has the following risks:

- Life threatening respiratory depression
- Addiction, abuse, and misuse
- Adrenal insufficiency
- Severe hypotension
- Gastrointestinal adverse reactions
- PONV
- Seizures

These risks all fall within the standard risks of using opioids. Any intervention being provided as a part of this study falls within the standard of care as both medication options are within the standard treatments for post-operative pain and are currently used as analgesic options at University of MN ASC.

- 13.2* Reproduction Risks: n/a

- 13.3* Risks to Others: n/a

14.0 Potential Benefits to Participants

14.1 Potential Benefits: The potential benefits of participating in this study include reduced pain and shortened recovery room stay.

15.0 Statistical Considerations

15.1 Data Analysis Plan: We plan to collect our data using REDCap and excel which will be maintained in Box. When the study is completed and ready for statistical analysis the data will be shared with our staff statistician.

15.2 Power Analysis: No prior studies have been done. Therefore, a power analysis was done using recovery room time data collected here at the ASC from July to September 2019 for similar general anesthesia cases that we would expect to enroll in this study. These power calculations found that we would need to enroll 33 per group to reach a 0.95 power for an absolute time difference of 30 minutes.

15.3 Statistical Analysis: This study will be analyzed by our staff biostatistician. The statistician will be provided the protocol so they are able to analyze for primary and secondary objectives.

15.4 Data Integrity: All patients will be assigned a unique patient identifier. The data will be sent to the statistician will be deidentified.

16.0 Confidentiality

16.1 Data Security: All paper documents and consent forms will be stored in a locked cabinet in the anesthesia research office in B573 Mayo. All study data will be stored electronically in Box and REDCap. Only the PI and members of the research team will have access to the data.

17.0 Provisions to Monitor the Data to Ensure the Safety of Participants

17.1 Data Integrity Monitoring.

- The PI, co-investigators, and research assistants will all have access to the study data stored in the University's Box storage system. All the research assistants have experience collecting pain scores and other relevant study information. The PI of the study will periodically review the study data to ensure accuracy and completeness of study data.

17.2 Data Safety Monitoring.

The Department of Anesthesiology has established a Data and Safety Monitoring Committee consisting of several staff anesthesiologists which include persons who are board certified as pain specialists. Data will be transmitted in box to persons on the board on a monthly basis for review. If there are patterns of adverse events, the board will meet as needed and provide recommendations.

All safety data will be collected on a case report form and transferred into an excel spread sheet that will be stored in box.

The data will be reviewed on a regular basis (weekly) by the PI and research staff. If there are consistent complications noted a meeting will be convened by the DSMB for recommendations.

The statistical tests for analyzing the safety data to determine whether harm is occurring.

The statistician uses R or SAS for analysis. Most likely a regression analysis will be performed to see which event is most likely the contributor for the complications. Also, a chi-square analysis can be performed. All is very dependent on data variability.

A fatal or serious adverse event that is attributable to either the delivery or the study medication itself.

18.0 Provisions to Protect the Privacy Interests of Participants

18.1 Protecting Privacy: Patients will be asked if this is a good time to answer questions. All patients will have the right to refuse to answer questions when asked. All data will be deidentified when entered and stored using a unique study identifier.

18.2 Access to Participants: All patients will be required to sign a combined HIPAA and study consent that states their privacy of the data being collected. It also describes that all data is deidentified and stored in a secure database. They will be informed that data is stored and reviewed in box which is HIPAA compliant and that only study personnel have access.

19.0 Compensation for Research-Related Injury

19.1 Compensation for Research-Related Injury: In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment, and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to the patient and/or insurance company.

19.2 Contract Language: N/A.

20.0 Consent Process

20.1 Consent Process (when consent will be obtained):

- Consent Process (when consent will be obtained): Patients will be identified in the pre-operative time period by the research team on the day of surgery. As soon as they enter their pre-operative room, an anesthesiologist will mention the study and ask permission for a research staff member to discuss it further if they are interested. If an anesthesiologist is not available when they are roomed, check-in or

nursing staff will mention the study and ask the patient if a research member can discuss it with them further. If they are interested they will meet a research staff member and be presented with a combined Health and Insurance Portability and Accountability Act (HIPAA) and study consent form. The patient will review the form with a member of the research team. Subjects will be reminded that participation is completely voluntary, and that they may stop participation at any time without question or penalty. The research team will answer any questions that the subjects may have about the study. They will also be notified that we will ensure they have the time to contact their insurance regarding coverage concerns if they wish. If the patient decides to participate, they will be asked to sign the consent and HIPAA form. One copy will be saved for study records, and the subject will be provided with a copy of the forms for their own records.

- 20.2 Waiver or Alteration of Consent Process (when consent will not be obtained): N/A
- 20.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained): N/A
- 20.4 Non-English Speaking Participants: N/A
- 20.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): N/A
- 20.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A
- 20.7 Adults Unable to Consent:
 - Permission: N/A
 - Assent: N/A
 - Dissent: N/A

21.0 Setting

- 21.1 Research Sites: Patients will be consented and post-surgical care will take place at the M Health Fairview ASC.
- 21.2 International Research: N/A

22.0 Multi-Site Research

- N/a

23.0 Resources Available

- 23.1 Resources Available:

Research assistants are available to aid in consent and data acquisition. All research assistants will be familiar with the study protocol and have experience working with similar studies.

We plan to enroll 66 subjects. To accomplish this we will need to screen 200 subjects (assuming nearly 70% of patients will not have moderate to severe pain in PACU) and enroll 75 (assuming roughly around 10% drop out/screen fail) to reach this target population. This center performs approximately 50 qualifying surgical procedures weekly and therefore this should be able to be completed in 4 weeks.

Once we reach 33 patients in each group, enrollment and data collection will be completed at this time. Statistical Analysis will take approximately one month to complete.

All procedures will be performed in the clinical facilities at the M Health Fairview Clinics and Surgery Center. Data storage and analysis will be done using IT equipment which is available at the Research Office B573 Mayo.

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to the patient and/or insurance company.

All study personnel will be adequately trained by the Principle Investigator on the study protocol and study conduct. A log will be maintained to track which personnel are trained. A delegation of authority log will also be maintained to track which personnel are responsible for specific duties.

24.0 References

1. Hutchins JL et al An Open-Label study of sufentanil sublingual tablet 30 mcg in patients with postoperative pain. Pain Med 2017
2. Minkowitz HS et al. Sufentanil sublingual tablet 30 mcg for the management of pain following abdominal surgery: A randomized, placebo-controlled phase-3 study. Pain Pract. 2017;17:848-858.