A Multimodal Analgesia Protocol Adapted for Ambulatory Surgery

Protocol Summary

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Background and Introduction

Opioids are associated with addiction and accidental overdose, yet they continue to be the most commonly prescribed analgesics after ambulatory surgery. In 2017, there were 456 deaths from opioid overdose in Utah. Prescription opioids accounted for 70% of those deaths (wonder.cdc.gov).

Multimodal analgesia is a promising alternative to opioids. It is based on the theory that combining more than one non-opioid analgesic can provide pain relief equal to or exceeding that of opioids alone.

The three drug classes that have demonstrated analgesic effects capable of reducing opioid requirements are GABA agents (pregabalin, gabapentin), NSAIDS (ibuprofen,celecoxib), and acetaminophen. Although many studies have been performed using these drugs in isolation, surprisingly little information exists about their combined effect on opioid requirements.

The combination of three non-opioid analgesics may provide effective analgesia while reducing or eliminating opioid related side effects such as respiratory depression, nausea, constipation, and itching.

Implementation of multi-modal analgesia in an ambulatory setting is challenging for a number of reasons.

First, patient compliance with multiple medications and complex dosing schedules is poor.

Second, widespread misinformation exists about concurrent dosing of acetaminophen and NSAIDS (non-steroidal anti-imflammatory drugs). For example, many patients and health care providers believe that acetaminophen and NSAIDS cannot be taken simultaneously. As a result, the additive analgesic effect of combining these drugs is not achieved.

Finally, some medications used for multimodal analgesia cannot be procured in the ambulatory setting. For example, pregabalin (trade name Lryica) has been used successfully to treat acute pain and reduce opioid requirements after surgery. However, because its mechanism of action is similar to that of gabapentin (an older and less expensive drug), insurers are reluctant to approve its use over the expensive alternative.

Although gabapentin is a useful analgesic for chronic pain, its delayed onset of activity and unpredictable blood levels after oral administration make it impractical to use in the setting of acute pain. In fact, optimal dosing of gabapentin may require several days or weeks to establish.By contrast, pregabalin has a rapid onset of action with consistent and predictable plasma levels after oral administration.

For this trial, patients in the control group would receive traditional postoperative pain medication consisting of a combination of oxycodone and acetaminophen (trade name Percocet) as needed at 4-6 hour intervals.

Patients in the study group would receive the following:

- Three non-opioid pain medications (acetaminophen,celecoxib, and pregabalin) would be taken concurrently at six hour intervals for a period of 7 days.

-These three non-opioid medications (acetaminophen, celecoxib, and pregabalin) would be provided in a "blister pack". All scheduled pain medication for a given 6 hour interval would be contained in a single compartment to simplify compliance for the patient. Study patients would also have access to oxycodone as a "rescue medication".

The principles of postoperative pain management addressed in this protocol are supported by existing literature.

1. Patient compliance with complex medication dosing protocols may be improved using calander and time based "blister packs".[1]

2. Pain control using combined acetaminophen and NSAID is superior to that either drug in isolation.[2]

3. Pregabalin can reduce opioid requirements and opioid related nausea when treating acute pain.[3]

Purpose and Objectives

The primary objective of this trial is to determine whether the combination of three non-opioid analgesics (multimodal analgesia) can significantly reduce or eliminate the need for opioids after ambulatory surgery.

A secondary objective would be to present credible data for insurance providers about the opioid sparing effect of these medications. This data may encourage insurance providers to support payment for short term use of certain analgesics that currently require prior authorization.

Study Population

Age of Participants: 18-65

Sample Size:

At Utah:	300
All Centers:	300

Inclusion Criteria:

All patients between the ages of 18 and 65 having one of three elective procedures as an outpatient. These procedures are associated with moderate to severe postoperative pain.

1. anterior cruciate ligament reconstruction (knee)
2. ankle ligament reconstruction (foot/ankle)
3. ligament reconstruction with tendon interposition (hand)

Patients should have operative risk category of ASA 1 or 2 (American Society of Anesthesiolgists).

Patients weighing between 70-100kg will be included to allow standardization of medication dosing

Exclusion Criteria:

Exclusion criteria include:

Allergy to Study Medications

Previous History of chronic opioid or any central nervous system depressant use

Patient Refusal to Participate

Known of Suspected History of Sleep Apnea

Known History of Chronic Pain Syndrome

Weight less than 70kg or greater than 100kg due to standardization of medication doses.

Revision Surgery

Inability to take study medications due to medication incompatibility or co-existing disease

Patients refusing or unable to receive US guided nerve block for postoperative pain

Patients unable to read and comprehend written consent document

Pregnant or lactating women

Design

Prospective Biomedical Intervention or Experiment
Randomized Trial

Study Procedures

Recruitment/Participant Identification Process:

In the orthopedic clinic, patients being scheduled for the following surgeries will be considered:

Ligament Resection with Tendon Interposition (hand)

Ankle Ligament Recontruction (foot/ankle)

Anterior Cruciate Ligament Reconstruction (knee)

Patients without exclusion criteria will be introduced to the pending study protocol. Specifically, they will be told that the study involves postoperative pain management and alternatives to opioid analgesics. Those patients who express a willingness to participate will be given a copy of the written consent form to review before the scheduled date of surgery.

On the day of surgery, patients who agree to participate will have any further questions answered and may choose to enroll in the study.

Informed Consent:

Description of location(s) where consent will be obtained:

University of Utah Orthopedic Center

Description of the consent process(es), including the timing of consent:

Patients will be introduced to the study concept during the orthopedic clinic visit. Those patients who meet study criteria will be given a copy of the study consent to review for at least one week before actually signing the consent on the day of surgery.

Procedures:

After written informed consent, patients will be randomized to receive either multi-modal or conventional postoperative pain medication. Each of the three surgical procedures will have a separate randomization sequence. These three randomization sequences will be generated using Research Randomizer (Lancaster, Pennsylvania).

Surgery, anesthesia, and intra-operative care will be standardized for all patients. Likewise, all patients will receive an US guided peripheral nerve block for pain control after surgery.

All patients in the study will have continuous cell phone access to the senior investigator for questions or concerns about the protocol or for reporting inadequate pain control.

Multimodal Treatment Group

3 Different Non-opioid pain medication taken every 6 hours

Celecoxib 100mg

Acetaminophen 325mg

Pregabalin 50 mg

Plus, for breakthrough pain, oxycodone 5-10 mg will be taken every 4 hours as needed.

Prior to discharge from the PACU, patients in the multi-modal treatment protocol will receive a "blister pack" containing a 7 day supply of multi-modal pain medication. This pill pack will be prepared by the University of Utah Pharmacy.

The pack will consist of 7 rows of pre-filled drug compartments. Each row will have 4 compartments corresponding to the 6 hour dosing intervals for each day.
Each compartment will contain pregabalin 50 mg, celecoxib 100 mg, and acetaminophen 325 mg.

In addition, patients in the multimodal group will be given a 7 day supply of oxycodone to be taken as needed for "breakthrough" pain. The dosing for oxycodone will be 5-10 mg by mouth every 4 hours as needed for pain.

Control Group

Patients in the control group will be given a 7 day supply of oxycodone 5-10 mg/acetaminophen 325 mg (a combination drug commonly known as Percocet) to be taken by mouth every 4 hours as needed for pain.

Patient Assessment

All patients will be asked to rate their average pain on an 11 point scale (0-10) at awakening each morning and evening before bed. At the same intervals, patients will be asked to rate nausea and itching on an 11 point scale (0-10). These notations will be made by each patient in a written log provided for the patient.

During the postoperative period, patients may transition to plain acetaminophen or stop all pain medication at their discretion.

Patient Follow-up

All patients will be evaluated in the orthopedic surgery clinic one week following surgery. At that time, the blister pack will be collected and unused medication returned.

All PHI will be kept separate from study data. PHI will be stored on an excel file containing a study ID. The study ID will be used in the data files. All study files will be stored on encrypted computers in locked offices on the SOM campus.

Procedures performed for research purposes only:

All patients are given a pregnancy test prior to survey. This information will be used to determine if the patient should be included in the study. This is a standard of care procedu

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Statistical Methods, Data Analysis and Interpretation

Sample Size

ClinCalc.com was used to calculate sample size

Primary outcome measure - Anticipated reduction in 24 hr opioid(oxycodone) consumption

Anticipated 24 hr opioid (oxycodone) use for control group is 30 mg (S.D. 10mg).

The anticipated reduction in opioid use is 20%.

Alpha value was 0.05, Power =80%.

Based on these parameters, sample size needed to detect this difference would be 44 in each group.

We plan to include 50 patients in each group to allow for attrition that may occur

The request to enroll 300 patients is based on the intent to study 3 separate surgical procedures.

This would allow 100 patients for each procedure (50 patients for study group/ 50 patients for control group)

Statistical Analysis

The multimodal and control groups will be compared with respect to opioid use, pain scores and the incidence of opioid related side effects.

The primary outcome measure will be the amount and duration of opioid use in the multimodal and control groups.

Secondary outcome measures will include average pain scores, nausea, itching (scale 0-10).

These scores will be recorded twice daily at awakening and retiring.

Data Analysis

Demographic Data will be compared using an **unpaired "t" test**

Single Measures of opioid consumption will be compared using an **unpaired "t" test**

Repeated measures of secondary outcomes such as pain, nausea, itching willbe compared using a repeated measures analysis of variance (**ANOVA**)

For all comparisons, a "p-value" of <0.05 will be considered significant

Statistical Analysis Plan

The sample size was based on an anticipated reduction in opioid consumption of 20% in the intervention group. With a chosen alpha of .05 and setting power of 80%, the sample size per group was 44 patients (http://ClinCalc.com). To account for possible attrition of patients, the planned study size was 100 patients with a 1:1 balance of intervention and control groups. Demographic and anesthetic agent variables were displayed as mean (±SD) or count (%). Covariate balance between the intervention and control groups after randomization and before intervention was done by standardized mean difference (SMD). The primary outcome measure was pain reported twice daily for 6 days. The planned secondary outcomes were nausea and itching, also reported twice daily for 6 days. A post hoc secondary outcome was daily oxycodone use (number of tablets) for 6 days. The 11-point verbal scale scores and the count of oxycodone tablets were analyzed as ordinal variables. Cumulative patient scores for pain, nausea, itching, and tablet use for the 6 days were compared between groups by Wilcoxon rank-sum test with estimation of the median of the difference between intervention and control samples. The 6 days of measurements represent longitudinal data. To avoid assumptions about the probability distribution of the ordinal outcomes, robust rank-base analysis of variance methods was used to compare intervention and control samples with interaction by postoperative day.[20] Also, pairwise comparison for each 12-hour or 24-hour period was estimated by Wilcoxon nonparametric tests, with a false discovery rate adjustment of the P values using the Benjamini-Yekutieli procedure. Tolerance intervals are estimated from a sample and provide limits that at least a certain proportion of a population falls within a given confidence interval.[29] In addition to comparing the cumulative opioid requirements for patients in the control and intervention groups, analysis was performed to determine the upper tolerance limit to provide sufficient oxycodone tablets without requiring a refill (the opioid requirements) in 90% or 95% of control and intervention patients, respectively. All analyses were performed using the R software language (Version 4.1.0) and the R packages nparLD (Version 2.1) and tolerance (Version 2.0.0). No data were imputed for the control patient who was lost to follow-up. The null hypothesis was rejected for $P < .05$; 95% CIs were obtained. Some statistics were rounded.