Pilot study, blinded randomized control trial, single center study to compare Acetaminophen & Codeine versus Ibuprofen/Acetaminophen for pain control and patient satisfaction after ambulatory hand surgery

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Contents

List of Abbreviations

AE: Adverse event

OTC: Over the counter

T3: Tylenol-3

VAS: Visual Analogue Scale

Study Summary

Title	**Blinded Randomized Control Trial** **Optimizing Post-Operative Pain Control in Ambulatory Hand Surgery: Acetaminophen & Codeine versus Ibuprofen/Acetaminophen**
Short Title	**Acetaminophen & Codeine versus Ibuprofen/Acetaminophen in Ambulatory Hand Surgery**
IRB Number	823043
Protocol Number	Penn-Hand 1.0
Phase	Pilot Study
Methodology	Double blinded randomized control trial
Study Duration	12 months
Study Center(s)	University of Pennsylvania Hospital System
Objectives	Primary: To establish, through a randomized control trial, whether post-operative Acetaminophen and Ibuprofen (non-opioid regimen) would provide equivalent post-operative analgesia to ambulatory hand surgery patients compared to Acetaminophen and Codeine (opioid regimen). Primary Outcome variable: VAS pain score Secondary: To establish whether the opioid versus non-opioid post-operative pain regimen influences patient satisfaction. Secondary outcome variables: Quality of Recovery (QoR) scores; Rate of side effects; Rate of medication discontinuation
Number of Subjects	Sixty-three patients enrolled for each group (non-opioid and opioid). Approximately 145 patients will be required to achieve complete data for 63 patients in each group (assuming 15% lost to follow-up & failure to comply with study protocol).

Main Inclusion and Exclusion Criteria	Inclusion criteria: Patients > 18 years old, undergoing ambulatory hand surgery for carpal tunnel and trigger finger, under local anesthesia +/- sedation. Exclusion criteria: ASA> 3; coagulopathy; renal disease, liver disease, history of recent gastro-intestinal bleeding, peptic ulcer disease, congestive heart failure, previous stroke, pregnancy. Patients with a diagnosis of chronic pain currently taking opioid pain medication or with a history of drug abuse. Patients with a self-described allergy to ASA, acetaminophen, NSAIDS and codeine. All patients receiving a brachial plexus block for anesthesia and/or analgesia will be excluded.
Investigational Product (drug, biologic, device, etc.) **For Device include the planned use** **For Drug, food, cosmetic, etc. include the dose, route of administration and dose regiment**	This is a non-superiority trial to compare two over the counter drug medications (OTCs) on post-operative pain control in ambulatory hand surgery: Group 1: Acetaminophen 650 mg; Ibuprofen 400 mg Group 2: Acetaminophen and codeine (acetaminophen 300mg, codeine 30 mg) Route: oral tablets Frequency: Every 6 hours as needed for pain (4 times daily) All of the medications are administered according to their drug monographs.
Duration of administration	Thirty tablets of analgesic medication will be provided to the patient
Reference therapy	In this non-superiority randomized trial, the medications (acetaminophen, ibuprofen and acetaminophen/codeine) and the doses in this randomized control trial are currently prescribed by physicians at the University of Pennsylvania Health Services Orthopedics Department as standard of care and will be used according to drug monographs and FDA regulations.
Statistical Methodology	All analyses comparing the treatment groups will be conducted on an intention-to-treat basis for patients that will have taken at least one dose. Statistical significance set a priori at $P<0.05$.
Safety Evaluations	Potential psychological and physical risks to the study participants are minimal as we are not altering standard of care. Acetaminophen, ibuprofen and codeine have well described pharmacokinetics and minimal side effect profile in appropriately selected patients (refer to inclusion/exclusion criteria)[16]. If the patient experiences self-described pain that is poorly controlled or an adverse event, their physician or treatment team will evaluate the patient as deemed appropriated and prescribe alternative medications if necessary. Contact information will be provided to all study participants to ask questions at any time during the study.

Data and Safety Monitoring Plan	Data will be collected using the Research Electronic Database Capture (RedCap), a de-identified database.

BACKGROUND AND STUDY RATIONALE

This study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations.

Introduction

1.1 Background and Relevant Literature

Prescription drug overdose has become a serious public health issue and with exploding associated health care costs[7] [8]. This opioid epidemic is not an isolated problem as underlined by a 2013 report by Trust for America's Health in which Philadelphia was ranked as 14th nationwide for drug overdose related deaths.

Ninety-nine percent of carpal tunnel surgery and other hand soft tissue releases such as trigger finger, are performed in the ambulatory setting [9,10]. Post-operative pain prescriptions vary widely across hand surgeons in North America. In one study, Canadian hand surgeons prescribed opioids to 5% of their ambulatory hand surgery patients whereas physicians in the United States prescribed opioids for 66% of their patients for similar surgeries[11]. Studies have investigated the role of post-operative non-steroidal anti-inflammatory (NSAIDS) in post-operative pain control for outpatient general surgery[2,3]. Given that there is no gold standard regimen for post-operative pain control after ambulatory hand surgery and considering the current opioid epidemic in the United States, it would be of utmost importance to establish whether a non-opioid pain regimen would provide equivalent post-operative analgesia to hand surgery patients. Our long term goal is to decrease opioid drug diversion while maintaining adequate pain relief and patient satisfaction.

Patient satisfaction has become an increasingly important metric in healthcare quality and importantly in healthcare payment policies[12]. In fact the Centers for Medicare & Medicaid Services (CMS) incorporated patient satisfaction in part of their value based incentive payments since 2012[13]. Quality of Recovery has been linked to patient satisfaction after anesthesia and surgery[6]. Determining if the post-operative pain regimen has an influence on the Quality of Recovery Score is of prime importance in the consumer model of health care.

2 Study Objectives

The purpose of our study is to conduct a randomized control trial to determine whether a non-opioid based pain regimen is equivalent to an opioid analgesic to control post-operative pain after ambulatory hand surgery (**Aim 1**). At the UPHS Orthopedics Department, approximately 600 cases of carpal tunnel and trigger finger releases are performed yearly. These patients commonly receive a Tylenol 3 script (acetaminophen 300mg, codeine 30 mg). If the script is placed electronically, the system automatically reverts it to the generic equivalent. If the patient self-describes a previous adverse events to Tylenol 3 (T3), the script is commonly substituted for oxycodone-acetaminophen (5mg-325mg). Drug diversion and the opioid epidemic in the United States is a public health concern and surgeons have the obligation to responsibly prescribe opioids for post-operative analgesia. Our ambulatory hand surgery patient population represents a unique opportunity for hand surgeons at UPHS to optimize post-operative pain prescription habits and study its impact on patient satisfaction. Our long term goal is to optimize post-operative prescription practices at our institution and in hand surgery nationwide, while maintaining patient satisfaction **(Aim 2)** and ultimately decrease drug diversion potential.

2.1 Primary Objective:

To establish, through a randomized control trial, whether post-operative Acetaminophen and Ibuprofen (non-opioid regimen) would provide equivalent post-operative analgesia to ambulatory hand surgery patients compared to Acetaminophen and Codeine (opioid regimen).

Rationale: In the setting of ambulatory hand surgery, many of the opioid pain scripts are not utilized. In a telephone survey of patients undergoing ambulatory hand surgery, 52% of patients reported taking their prescribed analgesics for 2 days or less[1]. Ninety-nine percent of these patients received a 30-tablet script for narcotics, leaving the left-over narcotics available for diversion. Studies have investigated the role of post-operative non-steroidal anti-inflammatory (NSAIDS) in post-operative pain control for outpatient surgery[2,3,4], though never as a randomized control trial in hand surgery.

Hypothesis: A non-opioid post-operative regimen of ibuprofen and acetaminophen is equally effective with less side effects as Acetaminophen and codeine for pain relief in the context of ambulatory hand surgery.

Primary Outcome Variable: Visual Analogue Scale Pain Score

2.2 Secondary Objectives:

To establish whether the opioid versus non-opioid post-operative pain regimen influences patient satisfaction through Quality of Recovery (QoR) scores in ambulatory hand surgery.

Rational: Quality of Recovery score is a validated health measure based on the answers of a 9-item questionnaire administered to patients after anesthesia[5]. The Quality of Recovery score has been shown to correlate with patient satisfaction post-operatively[6].

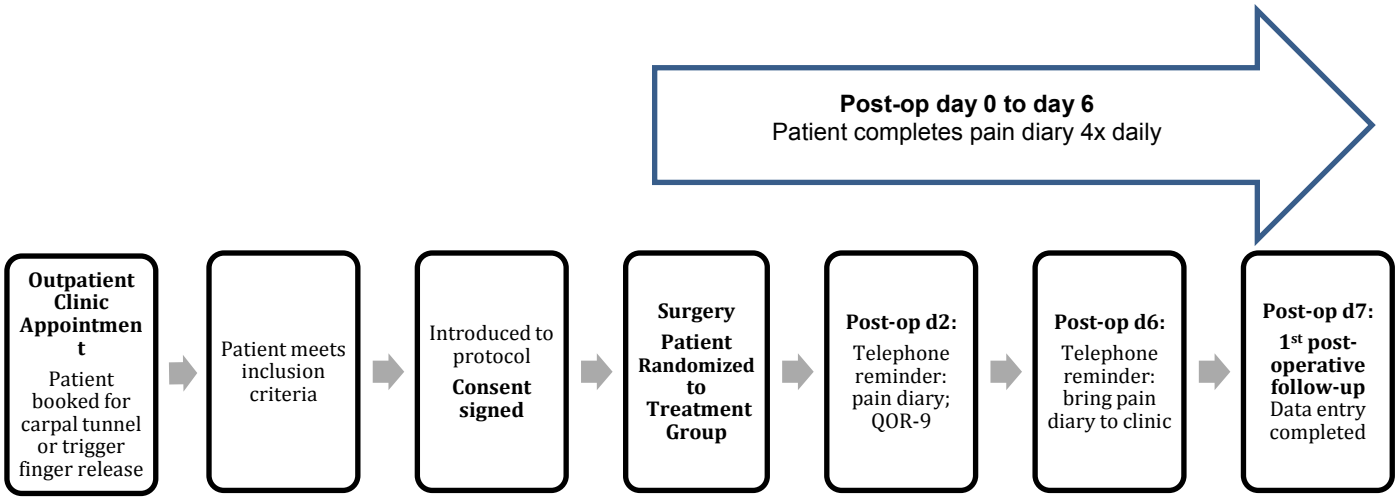
Hypothesis: A non-opioid post-operative regimen will have equivalent Quality of Recovery scores to an opioid post-operative pain regimen.

Secondary Outcome Variables: Adverse events, duration of medication intake, reason for medication discontinuation, patient satisfaction as determined by the Quality of Recovery-9 (QoR-9).

3 Investigational Plan

3.1 General Design

Small scale, pilot, blinded randomized non-superiority control trial



3.1.1 Screening Phase

Patients will be screened through the clinical practices of Penn Orthopaedics. Scheduled clinic encounters are documented in EPIC. Chief complaint or reason for visit is typically captured which will be the primary source of identifying possible patients. Once it is determined either through EPIC or in the course of the clinical encounter that a patient is presenting with carpal tunnel syndrome or trigger fingers they will be evaluated for eligibility by for this study by the study team.

3.1.2 Study Intervention Phase

Patients who meet the inclusion criteria will be randomized into one of two post-operative analgesia treatment groups: an opioid treatment group versus anti-inflammatory and acetaminophen (400mg/650mg) treatment group. Patients in one group will receive either 650 mg of acetaminophen and 400 mg of ibuprofen per dose. Patients in group two will receive 300mg of acetaminophen and 30 mg of codeine (T3 equivalent) per dose. The active medications will be encapsulated into identical capsules containing half of the full dose (2 capsules = 1 dose). The capsules will then be dispensed in identical bottles. The first dose will be administered in the post-anesthesia care unit (PACU). The visual analogue scale (VAS) is simple and commonly used in the clinical setting to measure pain severity[14,15]. The patients will complete a post-operative pain diary. **The entries will consist of a VAS, time of medication intake and side effects (nausea, vomiting, constipation, dizziness, other). Date and reasons for medication discontinuation (pain free versus adverse effect) will also be recorded. The first entry will be recorded pre-operatively to ensure comprehension of the VAS as well as to obtain baseline pain score. The second entry will be in the recovery room.** The patients will complete four entries daily which corresponds to allowed intake of pain medication over a period of 5 days. Patient will return the diary on the first post-operative visit (ranging from 6 to 8 days post-operatively). All patients will be called on post-operative day 2 in order to complete the Quality of Recovery Questionnaire. The 9-item questionnaire will be administered via a telephone interview by a clinical assistant who is blinded to the treatment arm.

3.1.3 Follow Up Phase

Patients will return to hand clinic per their usual post-operative visit schedule. Their first visit generally ranges from 6 to 8 days after their surgery. At this visit the patient will return the diary and remaining medication. This will conclude the patient's participation in the study.

3.1.4 Allocation to Interventional Group

Stratified block randomization using tables of random numbers, stratified according to hand surgery type (carpal tunnel, trigger finger) will be used to ensure equivalent numbers of patients in each treatment group for each of the 2 procedures. Patients will be randomized in blocks of 4. Randomization will be performed by the Investigational Drug Service (IDS) using computer-generated tables. The treatment allocation will be concealed from the study investigators, physicians, nurses, patients, and statistician. Allocation assignments will be held securely in the IDS until all primary analyses are performed; this code will be broken for subgroup and post hoc analyses. Patients who meet the inclusion criteria will be randomized into one of two post-operative analgesia treatment groups: an opioid treatment group versus anti-inflammatory and acetaminophen (400mg/650mg) treatment group. Patients in one group will receive either 650 mg of acetaminophen and 400 mg of ibuprofen per dose. Patients in group two will receive 300mg of acetaminophen and 30 mg of codeine (T3 equivalent) per dose. The active medications will be encapsulated into identical capsules containing half of the full dose (2 capsules = 1 dose). The capsules will then be dispensed in identical bottles. In this manner, both patients and investigators are blinded.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

Ten millimeter Pain Visual Analogue Scale.

We chose a threshold of 5 mm difference in VAS score to ensure that even a smaller efficacy difference could be identified statistically.

3.2.2 Secondary Study Endpoints

Adverse events, duration of medication intake, reason for medication discontinuation, patient satisfaction as determined by the Quality of Recovery-9 (QoR-9).

4 Study Population and Duration of Participation

4.1 Inclusion Criteria

Patients > 18 years old, undergoing ambulatory hand surgery for carpal tunnel and trigger finger, under local anesthesia with or without sedation.

4.2 Exclusion Criteria

ASA> 3; coagulopathy; renal disease, liver disease, history of recent gastro-intestinal bleeding, pregnancy. Patients with a diagnosis of chronic pain currently taking opioid pain medication or with a history of drug abuse. Patients with a self-described allergy to ASA, acetaminophen, NSAIDS and codeine. Finally all patients receiving a brachial plexus block for anesthesia and/or analgesia will be excluded.

4.3 Subject Recruitment

Subjects will be recruited from the investigators clinical practices. If the patient meet the inclusion criteria, they will be approach by the physicians. Should they show interest in the study, a member of the clinical research team will review the study, consent and answer any additional questions regarding the protocol.

4.4 Duration of Study Participation

Enrollment Timeline: With an average of 10 operations for trigger finger or carpal tunnel per week, we estimate that with a voluntary participation rate of 50%, the enrollment of patients should be complete within 8 months.

Subject Participation: Individual subjects will participate in the study from the day of their surgery to their first post-operative visit (generally 6 to 8 days after their surgery).

4.5 Total Number of Subjects and Sites

Site: Penn Presbytarian Medical Center

Sample size: 63 per group. Assuming a 15% lost to follow-up and failure to comply with study protocol, 145 patients will be required to achieve complete data for 63 patients in each group.

4.6 Vulnerable Populations: none

5 Study Intervention

Group 1: Acetaminophen 650 mg; Ibuprofen 400 mg

Group 2: Acetaminophen 300mg, Codeine 30 mg

5.1 Description

Acetaminophen

Please refer to full monograph: Acetaminophen Entire Monograph - Epocrates Online. https://online.epocrates.com/u/10a307/acetaminophen. 2015. Accessed 6/28/2015

Ibuprofen

Please refer to full monograph: Ibuprofen Entire Monograph - Epocrates Online. https://online.epocrates.com/u/10a234/ibuprofen. 2015. Accessed 6/28/2015

Acetaminophen and Codeine Phosphate Tablets: combined analgesic effect of a centrally acting analgesic, codeine, with a peripherally acting analgesic, acetaminophen.

Please refer to the following FDA reference:

Food and Drug Administration. http://www.accessdata.fda.gov/spl/data/f1762dc1-b238-47bb-b5ab-33c0156724c5/f1762dc1-b238-47bb-b5ab-33c0156724c5.xml. 5/2011. Accessed 6/28/2015.

5.2 Intervention Regimen

Dose: Acetaminophen 650 mg; Ibuprofen 400 mg; Codeine 30 mg
Route: blinded opaque oral capsules
Frequency: 1st dose given in PACU on day of surgery; every 6 hours as needed for pain (4 times daily)
Duration: Total of 30 capsules will be distributed to the subjects

5.3 Receipt

For each subject, IDS would prepare 30 blinded capsules (containing either APAP 300/Codeine 30, or APAP 325/IBU 200 per capsule) and dispense from IDS main location (Ground Maloney, HUP) the day before surgery or the IDS satellite (1 Mutch, Penn Presbytarian Medical Center) on day before or the morning of surgery.

The IDS will purchase APAP 300mg/Codeine 30mg tablets, APAP 325mg tablets and Ibuprofen 200mg tablets commercially. IDS will purchase pharmaceutical-grade opaque gelatin capsules and NF (National Formulary) grade inert fillers (microcrystalline cellulose NF) from FDA-registered facilities. All encapsulation takes place using 316-grade surgical stainless steel equipment.

5.4 Storage

All medication will be stored in the Investigational Drug Service, which maintains high level security and is inaccessible to non-IDS personnel, including other members of the study team. Medication is maintained at USP controlled room temperature (20-25 Celsius) in tightly-sealed containers which comply with USP<671> and the Poison Prevention Packaging Act.

5.5 Preparation and Packaging

Encapsulation will take place in a controlled environment following cGCP and USP<795> guidelines, with all activities performed by trained research technicians and research pharmacists.

Medication will be packaged in standard USP<671>-compliant prescription packaging by IDS personnel, pursuant to an individual signed or electronically-transmitted legal prescription for each study participant. Medication will be dispensed in a sealed, labeled package on the day of surgery and transferred to a member of the study team who will provide the medication to the participant prior to discharge from the surgery center.

5.6 Blinding

The Investigational Drug Service will prepare medication for both treatment conditions, which is indistinguishable to the study team or to study participants. IDS staff will assign subjects sequentially to treatment arms following the secure randomization tables (maintained in the IDS) as prescriptions are received and medication dispensed.

The IDS maintains an emergency unmasking website through Penn Medicine Academic Computing Services, through which the PI can, in an emergency situation, obtain access to the treatment assignment for one individual participant. The website is secured both through PennKey authentication and because only an IDS pharmacist can grant individual user access to an individual trial. The website maintains an audit trail of all unmasking activity and categorizes requests for later follow-up.

5.7 Administration and Accountability

The IDS accounts for all study medications, including bulk purchased medications as well as blinded capsules, through an electronic accountability record system in compliance with 21CFR11. The record system is accessible only to IDS personnel and the Director of IDS has ultimate control over all user accounts. The system uses electronic, time/date-stamped signatures for every transaction, as well as maintains patient profiles which span all research participation longitudinally as well as across all schools and researchers who use IDS services, in compliance with Pennsylvania Code.

5.3 Subject Compliance Monitoring

Patients enrolled in the study are asked to complete a post-operative pain diary (please refer to attached).
In this diary, they are asked to record side effects and the number of doses taken within a 24 hour period.
The patients will be asked to return the remaining tablets. This number of remaining tablets should match their diary entries.

5.3.1 Return or Destruction of Investigational Product

The patients will be asked to return the remaining number of tablets on their first post-operative visit.

Any unused medication at the end of a subject's course of treatment, is returned to the IDS, where research technicians count and log the returned quantities under the subject's profile in the accountability system. Electronic, blinded patient-return reports can be generated for the study team to assist in calculating patient compliance with the regimen.

6 Study Procedures

6.1 Screening

The screening visit will take place during the patient's clinical encounter to schedule an operation for trigger finger or carpal tunnel.

- Informed Consent
- Medical Record Review to determine eligibility
- Physical Exam (Height and Weight)

6.2 Study Intervention Phase

6.2.1 Visit 1 (operative day)

Patients will be randomized to either study group the day of their surgery. They will receive the first dose of the study medication while they are in the recovery room. Subjects will complete the pain diary 4 times every day following surgery (3 times the day of surgery).

6.2.2 Follow Up

Telephone: Patients will be contacted by telephone on their 2nd post-operative day to administer the QoRs-9. Patients will also be telephoned on the day prior to their first post-operative visit as a reminder to bring the diary and remainder of the medication.
Clinic Visit: Patients will return to clinic for their first post-operative visit (generally 6 to 8 days after their surgery).

6.2.3 End of Study Visit

The study will conclude at the time of the patient's first post-operative encounter with their treating hand surgeon (usually between 6 to 8 post-operative days). After conclusion of the study, the patient's will continue on their regular post-operative schedule as deemed necessary by the treating hand surgeon.

Patients will be unblinded after final data analysis.

6.3 Unscheduled Visits

All patients will be able to contact their treating physician during the course of the study, and/or schedule an early visit if deemed necessary. Data collection will proceed as initially described unless the patient requires unblinding.

6.4 Subject Withdrawal/Early Termination Visits

If the patient experiences self-described pain that is poorly controlled or an adverse event, their physician or treatment team will evaluate the patient as deemed appropriated and prescribe alternative medications if necessary. Subjects who withdraw early will continue to follow with their treating hand surgeons as per standard of care. We will follow intention to treat in our statistical analysis. Hence if a patient requires unblinding, the last available measurement for each individual at the time point prior to withdrawal from the study will be retained in the analysis.

6.4.1 Data Collection and Follow-up for Withdrawn Subjects

Data collection will stop for withdrawn subjects. If patients fail to follow-up, they will be contacted by telephone. If they were compliant with the diary completion, we will ask the patient to mail the diary or to bring the diary at their next scheduled appointment. We will follow ITT in our statistical analysis, thereby the last available measurement for each individual at the time point prior to withdrawal from the study will be retained in the analysis.

6.5 Medical Record Review

- Date of birth
- Height
- Weight
- Past medical history with particular focus on:
    - coagulopathy
    - renal disease
    - liver disease
    - thromboembolic disease (stroke)

- history of recent gastro-intestinal bleeding or peptic ulcer disease
- pregnancy
- chronic pain currently taking opioid pain medication or with a history of drug abuse
- self-described allergy to ASA, acetaminophen, NSAIDS and codeine

6.6 Physical Examination

- Height
- Weight

6.7 Vital Signs: N/A

6.8 Laboratory Evaluations

Standard pre-operative work-up as indicated for the patient's past medical history and surgical risk factors.

6.9 Pregnancy Testing

A urine pregnancy test will done the day of the surgery for all women of child-bearing age per usual pre-operative work-up. Patients with a positive urine pregnancy test will be excluded from the study.

6.10 Other Evaluations, Measures

Visual Analogue Scale, diary and QoR-9 (please refer to attached)

7 Statistical Plan

All analyses comparing the treatment groups were conducted on an intention-to-treat basis. Two-tailed tests were used at all times, and statistical significance was set a priori at $P<0.05$.

7.1 Primary Endpoint

The primary end point of this study is pain intensity, measured with a 100-mm VAS (with 0 mm being no pain and 100 mm being maximum pain), and analyzed as daily mean scores. In patients that will have forgotten to complete the VAS scores 4 times daily, the missing values will be completed with the last recorded score.

7.2 Secondary Endpoints

Adverse events, duration of medication intake, reason for medication discontinuation, patient satisfaction as determined by the Quality of Recovery-9 (QoR-9).

7.3 Sample Size and Power Determination

A sample size of 63 in each group has 80 % power to detect a difference in means of 5 mm assuming a common standard deviation of 10 mm by a two-group Student's t test with a 0.05 two-sided significance level. Assuming a 30% lost to follow-up and failure to comply with study protocol, 145 patients will be required to achieve complete data for 63 patients in each group.

7.4 Statistical Methods

7.4.1 Baseline Data

We will use means and standard deviations (SDs), medians and interquartile ranges (IQRs) or frequencies and percentages, as appropriate, to summarize baseline characteristics. We will assessed comparisons between participants who did and did not take analgesia using an unpaired t test for continuous variables and a Pearson $\chi 2$ test for categorical variables. We will use a parametric student t test to assess the primary end point (VAS).

7.5 Subject Population(s) for Analysis

All-treated population: Any subjects randomized into the study that received at least one dose of either Acetaminophen/codeine or acetaminophen/ibuprofen.

8 Safety and Adverse Events

8.1 Definitions

8.1.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

8.2 Recording of Adverse Events

At each contact with the subject (such as the post-op telephone calls and the post-op clinic visit), the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

8.3 Relationship of AE to Study

The principal investigator will determination the relationship of the AE to the study and will be classified as definitely related, probably related, possibly related, unlikely or unrelated.

8.4 Reporting of Adverse Events and Unanticipated Problems

We will report adverse events and/or unanticipated problems in accordance with the Penn IRB policy on Reportable Events.

8.2 Unblinding Procedures

The IDS maintains an emergency unmasking website through Penn Medicine Academic Computing Services, through which the PI can, in an emergency situation, obtain access to the treatment assignment for one individual participant. The website is secured both through PennKey authentication and because only an IDS pharmacist can grant individual user access to an individual trial. The website maintains an audit trail of all unmasking activity and categorizes requests for later follow-up.

8.3 Medical Monitoring

The Principal Investigator will oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above.

9 Study Administration, Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Data Collection and Management

The Department of Orthopaedics has two standard methods to capture electronic data: these are RedCap and secure departmental shared drives on the UPHS servers behind the UPHS firewalls. We also routinely code files by assigning subject study ID numbers.

Data will only be accessed by investigators identified on the IRB. Data will be stored for at least 7 years after the study ends.

9.3 Records Retention

Study records will be stored for at least 7 years after the study ends. The storage of the study records will be in accordance with departmental and institutional policies/requirements.

10 Study Monitoring, Auditing, and Inspecting

10.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

11.1 Risks

Potential psychological and physical risks to the study participants are minimal as we are not altering standard of care. Risks to subject confidentiality are minimized by the use of vigilant de-identification processes, secure data storage, and private facilities as applicable. The patients can choose to opt out of the study at any point in time with no impact on their surgical or medical care.

11.2 Benefits

This randomized control study will enable us to determine if pain after ambulatory hand surgery can be adequately controlled with non-opioid pain medication as effectively as with opioid pain medication. Results of this study will be submitted to a peer reviewed journal such that the results can benefit the medical and general population.

11.3 Risk Benefit Assessment

The risks of participating in the study are outweighed by the potential benefits of participating in the study.

11.4 Informed Consent Process / HIPAA Authorization

Patients will be adults capable of providing informed consent for themselves. Patients will be identified from routine clinical encounters and will be invited to participate in the study by a member of the study team. The patient will be provided the informed consent form (ICF) and the study team member will describe the study. The patient will also be given an opportunity to read the ICF and to ask questions about the study. We will let patients know that they are able to withdraw from the study at any time. Written consent will be obtained from the patient at the time of clinical encounter for surgical scheduling.

12 Study Finances

12.1 Funding Source

This study is financed through a grant from the Presbytarian Hospital Bach Fund in the amount of $11,000

12.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

12.3 Subject Stipends or Payments

There are no subject payments or stipends.

Patients will receive the medication (either Acetaminophen and codeine or Acetaminophen-ibuprofen) free of charge during their participation in the study.

13 Publication Plan

This is a single site study. The investigators of this study will submit the results for publication in a peer-reviewed scientific journal.

14 References

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