Official title: How Many Opiates Should we Prescribe for Pain in Patients Undergoing Knee Arthroscopies and ACL Reconstructions?
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PROTOCOL TITLE:
How many opiates should we prescribe for pain in patients undergoing knee arthroscopies and ACL reconstructions?

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1.0 Objectives

- The purpose of the study is to determine if opiates are required to achieve adequate analgesia after knee arthroscopy and ACL reconstruction in outpatient surgery.
- We hypothesize that patients are frequently prescribed more opiates than are needed after surgery, resulting in excess medications that are at risk for misuse, diversion and contribution to the opioid epidemic.

2.0 Background

Perioperative pain management is an important aspect of quality patient care. Opioid pain medications are increasingly being used for pain control, with the United States writing over 250 million prescriptions for painkillers per year[1]. Increased usage has led to unintended negative consequences for individuals and society. It is estimated that 46 people die each day from an overdose of prescription painkillers, and individual use can lead to the development of tolerance and worse treatment outcomes [1, 2]. Further issues arise when opioids are misused, it is estimated that nontherapeutic use has increased three fold in recent years[3]. In the United States alone in 2006 the estimated total cost of opioid prescription misuse was $53.4 billion, of which $42 billion was attributed to lost productivity, $8.2 billion to criminal justice cost and the remainder drug abuse treatment and medical complications[4]. The federal government has recognized this epidemic and raised a call for clinicians to more responsibly prescribe opiate pain medications[5].

Opiate use has increased in recent years, from 2000-2010 the use of opiates in office based visits nearly doubled from 11.3% to 19.6% whereas there was no change in the prescribing of non-opioid pharmacotherapies. Further, when specifically looking at new musculoskeletal pain visits, one half resulted in pharmacologic treatment, with the prescribing of non-opioid pharmacotherapies decreasing from 38% to 29% from 2000 to 2010, respectively[6]. The clinical use of opioids for post-operative pain control has also been linked to the opioid epidemic and risk of future abuse[7]. Legitimate opioid use before high school graduation is independently associated with a 33% increased risk of future misuse after high school[8].

It has been estimated that orthopedic surgeons prescribe 7.7% of all opioids in the United States[9].Special attention needs to be paid to the amount of opioid pain medications orthopedic surgeons prescribe to patients after ambulatory surgery, there is considerable variability among surgeon and procedure in regards to the amount of opioids to prescribe with many patients left with excess unused medication[10].An analysis of 250 patients undergoing outpatient upper extremity surgery found that on average patients consumed 10 opioid pills, with 19 pills left over and a total of 4,639 pills going unused in the cohort[10]. Leftover prescription opioids are at risk for diversion to family and friends for nonmedical use[11]. Further studies are needed to quantify the amount of opioids to prescribe

for specific orthopedic procedures to limit excess narcotic use, misuse, diversion and contribution to the opioid epidemic.

3.0 Inclusion and Exclusion Criteria

- **Inclusion Criteria:**
  - All patients presenting to Northwestern Memorial Hospital (NMH) or to a Northwestern orthopaedic surgery faculty member's clinic undergoing knee arthroscopy with meniscus repair and/or debridement
  - 18 years old or greater
  - Ability to read and speak English
- **Exclusion Criteria:**
  - Revision surgery
  - Oncologic surgery
  - Arthroscopic knee surgery that involves procedures other than ACL or the meniscus (i.e PCL, LCL, MPFL)
  - Patients currently taking narcotics, chronic pain management patients, history of substance abuse
  - Adults unable to consent
  - Individuals who are not yet adults (infants, children, teenagers)
  - Pregnant women
  - Prisoners
  - Patients currently taking narcotics, chronic pain management patients, history of substance abuse

4.0 Study-Wide Number of Subjects

N/A

5.0 Study-Wide Recruitment Methods

N/A

6.0 Multi-Site Research

NA

7.0 Study Timelines

This study will be observational in nature. Patient will fill out a preoperative questionnaire related to specific risk factors for opiate use/abuse. Following their operation a phone call will be placed at 24 hours, 48 hours, and between 7-14 days after surgery and asked how many opiate pain medications they took, how many are left over and when the date they stopped taking them. If they are still taking pain medications at that point 1 follow-up call will be placed at 21 days again asking the same questions. Maximum total length of the study will be 21 days post-surgery.

8.0 Study Endpoints

This study is observational in nature. The study will end once we have collected data for 60 patients for each arm in order to sufficiently power the subsequent analysis as a level 1 prospective study.

9.0 Procedures Involved

This study will be a pilot randomized control trial to establish non-inferiority in opiate prescribing patterns.

Eligible patients will be identified in clinic by the treating attending physician. Patients will subsequently be approached by research personnel at that time. In the event that a patient determines that they wish to pursue surgery and this is discussed by phone without an additional clinic visit they will be approached on the day of surgery by our research staff.

All patients will fill out a preoperative questionnaire asking them the questions below related to specific risk factors for opiate use/abuse.

- Age
- Sex
- BMI
- Do you actively smoke cigarettes?
- If no, have you ever consistently smoked cigarettes (daily for > 1 month)?
- What is your employment status?
- Is this injury part of a workers' compensation claim?
- Are you actively participating in organized sporting activities? If so, at what level (i.e. professional, college, recreational)?
- Are you currently using narcotic pain medications?
- Do you have a personal history of substance abuse (ex. prescription or illicit drugs, alcohol)?
- Do you have a family history of substance abuse (ex. prescription or illicit drugs, alcohol)?
- What is the highest level of education you attained?
- What is your average yearly household income?

Additionally, the patients undergoing knee arthroscopy will be randomized into two groups prior to surgery by the research staff. The surgeons' physician assistants will be responsible for prescribing the appropriate medications.

- **Group 1:** Will have all of their post-operative prescriptions sent down to the pharmacy on the day of surgery to be collected.
- **Group 2:** Will have all prescriptions sent to pharmacy with the exception of an opiate prescription. Instead, they will be handed a

physical paper prescription. They will be instructed to only fill the prescription if absolutely needed.

The patients undergoing ACL reconstruction surgery will be randomized into two groups prior to surgery by the research staff. The surgeons' physician assistants will be responsible for prescribing the appropriate medications.

- **Group 1:** Will be prescribed 60 opiate tablets in addition to other routine post-operative pain medication regimens.
- **Group 2:** Will be prescribed 30 opiate tablets in addition to other routine post-operative pain medication regimens.

In order to limit potential variability in sample size, block randomization will be utilized with the following parameters: 18 blocks with 5 patients in each block. The blocks will be as follows (Block #/#/#):

Block (1/7/13)
22112

Block (2/8/14)
11221

Block (3/9/15)
21121

Block (4/10/16)
21122

Block (5/11/17)
21211

Block (6/12/18)
22121

A computer program will randomly select a block number. Once a block is selected patients will be enrolled in the order listed in the block. For example, if block 6 is selected initially Patient 1 will be enrolled in Group 2, Patient 2 will be enrolled in group 2, Patient 3 will be enrolled in group 1, etc. After every 5th patient is randomized to a group a new block will be randomly selected.

The surgeons' physician assistants will be responsible for prescribing the appropriate medications. To clarify, we do not electronically prescribe C2 medications as a routine part of practice and do not intend to as part of the study.

All patients will be provided the same counseling regardless of the amount of narcotics they are prescribed. In the event that a patient requires additional narcotics on top of the original prescription the treating surgeon will need to be notified in order to accurately assess the amount already consumed and appropriately prescribe additional medications.

Please note that there is considerable variability in opiate prescribing between practitioners. Patient's that undergo ACL reconstruction typically are prescribed between 30-60 Norco depending on the practitioner. Our randomization falls within the variability of the current standard for which there is no evidence based literature. Additionally, we are attempting to discern if 30 opiate tablets would be sufficient for patients undergoing ACL reconstruction. We suspect that the majority of patients prescribed 60 tablets do not take greater than 50% of what they are prescribed. We are interested in determining the number of opiates left over after ACL reconstruction and if the amount prescribed affects the total amount consumed.

Following their operation, all patients will have Pain -Numeric Pain Rating Scale (NPRS) assessed at 2 hours post-surgery by the authorized co-investigators or research staff while the patient is recovering in the post-anesthesia care unit (PACU).

Additionally, a phone call will be placed at 24 hours, 48 hours and between 7-14 days after surgery and asked a Numeric Pain Rating Score (NPRS), how many opiate pain medications they took, how many are left over and when the date they stopped taking them.

NPRS scores can be performed verbally. The following statement will be provided to patients:

The 11-point numeric scale ranges from '0' representing one pain extreme (e.g. “no pain”) to '10' representing the other pain extreme (e.g. “pain as bad as you can imagine” or “worst pain imaginable”), please rate your pain on a scale of 0-10.

If they are still taking pain medications at that point, an additional follow-up call will be placed at 21 days (+1-3 days) after surgery asking the same questions. We will allow 4 total phone calls (24 hours, 48 hours, 7-14 days, and 21 (+ 1 to 3) days post-surgery. If patients continue to take narcotics 21 days after surgery they will be listed as >3 weeks of narcotic use)

Refill requests will also be recorded.

Maximum total length of the study will be 21 days post-surgery.

<table>
<tr><th colspan="2">Knee Arthroscopy</th></tr>
<tr><td colspan="2">All Patients: Preoperative Questionnaire</td></tr>
<tr><th colspan="2">Randomization – Two Groups</th></tr>
<tr><td>Group 1, n=60</td><td>Group 2, n=60</td></tr>
<tr><td>• Post-Operative Medication Regimen:
o <u>All scripts sent to pharmacy</u>
- Aspirin 325mg BID x7 days (14 tabs)
- Naproxen 500mg BID x7 days (14 tabs)
- Tylenol 1000mg BID x7 days (14 tabs)
- Oxycodone 20mg q6 PRN (20 tabs)</td><td>• Post-Operative Medication Regimen:
o <u>All scripts EXCEPT Oxycodone sent to pharmacy</u>
- Aspirin 325mg BID x7 days (14 tabs)
- Naproxen 500mg BID x7 days (14 tabs)
- Tylenol 1000mg BID x7 days (14 tabs)
- Oxycodone 20mg q6 PRN 20 tab prescription</td></tr>
<tr><th colspan="2">Postoperative Follow-Up</th></tr>
<tr><td colspan="2">2 hours – NPRS Pain Scores
24 hours – NPRS Pain Scores, Opiate Count, Side Effects, Still Taking?, Refill Requests
48 hours – NPRS Pain Scores, Opiate Count, Side Effects, Still Taking?, Refill Requests
7 -14 days – NPRS Pain Scores, Opiate Count, Side Effects, Still Taking?, Refill Requests</td></tr>
</table>

<table>
<tr><th colspan="2">ACL Reconstruction</th></tr>
<tr><td colspan="2">All Patients: Preoperative Questionnaire</td></tr>
<tr><th colspan="2">Randomization – Two Groups</th></tr>
<tr><td>Group 1, n=60</td><td>Group 2, n=60</td></tr>
<tr><td>• Post-Operative Medication Regimen:
o <u>All scripts sent to pharmacy</u>
- Aspirin 325mg BID x7 days (14 tabs)</td><td>• Post-Operative Medication Regimen:
o <u>All scripts sent to pharmacy</u>
- Aspirin 325mg BID x7 days (14 tabs)</td></tr>
</table>

- Naproxen 500mg BID x7 days (14 tabs) - Norco 10-325, 1-2 tabs q6 PRN (60 tabs)	- Naproxen 500mg BID x7 days (14 tabs) - Norco 10-325, 1-2 tabs q6 PRN (30 tabs)
Postoperative Follow-Up – All Patients	
2 hours – NPRS Pain Scores 24 hours – NPRS Pain Scores, Opiate Count, Side Effects, Still Taking?, Refill Requests 48 hours – NPRS Pain Scores, Opiate Count, Side Effects, Still Taking?, Refill Requests 7 -14 days – NPRS Pain Scores, Opiate Count, Side Effects, Still Taking?, Refill Requests	

The following data will also be retrieved from each study subject's EMR through the NMEDW:

- Intra-operative reports
- Results of clinical examinations
- Medical history (i.e. comorbid conditions, historical/current medications, surgical history)
- Perioperative data (pain scores before and after surgery, drugs given, anesthesia blocks)

10.0 Data and Specimen Banking

Identifiable data will be collected and transcribed into NU SharePoint in Excel format. All survey data will be collected through REDCap. Access to both these databased will only be available to members of Dr. Tjong's research team. Identifying information will be kept separately. Subjects' privacy interest will be maintained as they will only interact with or provide sensitive information to members of Dr. Tjong's research team after they have confirmed interest in enrolling in the study.

Research data will be stored electronically, password-protected, and encrypted on NU SharePoint and REDCap. Only members of the research team will have access to the data. Recorded data will be retained for a period of 5 years following completion of the study per NU policy on data retention for Human Subjects research. All data will thereafter be permanently deleted.

11.0 Data and Specimen Management

The above data will be collected for each patient. Mean opiate use and left over opiates will be reported. Demographic data will be recorded, linear regression will be performed to determine risk for prolonged opiate use.

Study is observational with reporting of means as the main outcome measure, no power analysis is necessary.

Each member of Dr. Tjong's research team has been CITI-certified for human subjects' research. Only members of Dr. Tjong's research team will have access to study data, which will be encrypted on a secure server with separations of identifiers and subject data.

Research data will be stored electronically, password-protected, and encrypted on a Northwestern Medicine secure server. Only members of the research team will have access to the data. Recorded data will be deleted at study completion and transcripts stored in a locked file drawer at Northwestern Memorial Hospital for future studies.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

N/A

13.0 Withdrawal of Subjects*

N/A

14.0 Risks to Subjects*

No identifiable physical risks to the patient are foreseen. Some of the preoperative questionnaire questions may be upsetting to patients. Specifically questions about personal or family history of substance abuse.

There are no procedures included in this study that have risks that are currently unknown. Our planned opiate prescription amounts fall within the normal variability of current practice at Northwestern.

There are no risks to others who are not subjects of the study.

15.0 Potential Benefits to Subjects

N/A

16.0 Vulnerable Populations

N/A

17.0 Community-Based Participatory Research

N/A

18.0 Sharing of Results with Subjects

N/A

19.0 Setting

Northwestern Memorial Hospital (NMH) or to a Northwestern orthopedic surgery faculty member's clinic.

20.0 Resources Available

Our Northwestern faculty are board certified orthopedic surgeons and foremost experts in their respective fields. The study is observational in nature.

Drs. Tjong, Terry, and Gryzlo combined perform approximately 250 knee arthroscopy procedures per year. We anticipate at least 80% will enroll in the study and data will be able to be collected within 3-6 months. There are no anticipated medical risks to this study, should any psychological issues arise patients will be referred to Northwestern faculty in the psychiatry department. All persons involved in the research will be CITI certified, they will be briefed on the protocol, their duties and functions to ensure absolute understanding of our study.

21.0 Prior Approvals

N/A

22.0 Recruitment Methods

Eligible patients will be identified in clinic by the treating attending physician. Patients will subsequently be approached by research personnel at that time. In the event that a patient determines that they wish to pursue surgery and this is discussed by phone without an additional clinic visit they will be approached on the day of surgery by our research staff.

Each patient will be provided with a paper copy of the consent form at their pre-operative assessment to review and sign for their participation in the study.

23.0 Local Number of Subjects

N = 120 (for knee arthroscopies); 60 in each arm
N = 120 (for ACL reconstructions); 60 in each arm

24.0 Confidentiality

N/A

25.0 Provisions to Protect the Privacy Interests of Subjects

Confidentiality of patient information will be maintained using a secure, password-protected web portal and database. This database will be de-

identified. Access to this database will only be available to members of Dr. Tjong's research team. Identifying information will be kept separately in a password-protected desktop database or locked-file drawer. Subjects' privacy interest will be maintained as they will only interact with or provide sensitive information to members of Dr. Tjong's research team after they have confirmed interest in enrolling in the study.

Efforts will be made to make subjects feel at ease with the research by explaining risks and benefits of participation in the study. A member of Dr. Tjong's research team will explain the preoperative questionnaire and the post-operative phone call.

Dr. Tjong's team only has permission to access the subjects' medical records for research purposes after they have provided informed consent to enroll in the study.

26.0 Compensation for Research-Related Injury

N/A

27.0 Economic Burden to Subjects

There may be the possibility that there will be a greater expense to subjects who are in ACL-Group 1 as they will be required to pay for two times the number of pain pills. However, for patient's paying cash, the cost for 30 and 60 Norco at the Northwestern Walgreens are $31.49 and $56.99 respectively. This discrepancy will likely be less for those with prescription insurance. Some patients are prescribed 60 Norco as standard of practice so those being prescribed 30 are incurring less of an expense. This could potentially be somewhat of a benefit of the study.

28.0 Consent Process

Each subject enrolled in the study will provide informed consent for participation in the study.

Informed consent will initially take place during initial contact with potential subjects in the orthopedic surgery clinic. Risks, benefits, and alternatives of participation in the study as well as the ability to withdraw participation at any time will be discussed with the eligible subject. Understanding of these aspects of the study as well as whether the potential subject would like to enroll in the study will be confirmed over the phone.

The study will follow "SOP: Informed Consent Process for Research (HRP-090)."

29.0 Process to Document Consent in Writing

This study will be following: “SOP: Written Documentation of Consent (HRP-091).

30.0 Drugs or Devices

N/A