PROTOCOL TITLE:

Oral Ketorolac as an Adjuvant Agent for Postoperative Pain Control following Arthroscopic Meniscus Surgery

PRINCIPAL INVESTIGATOR:

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OTHER DEPARTMENTS INVOLVED IN THIS STUDY (IF APPLICABLE):

☒ N/A

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Objectives

1. We aim to examine the use of IV and oral ketorolac as an adjunctive agent to the standard of care pain protocol for postoperative pain control following arthroscopic meniscus surgery.

2. We hypothesize that the use of IV and oral ketorolac in addition to the standard of care pain protocol will reduce postoperative opioid consumption following arthroscopic meniscus surgery.

Background

The utilization of arthroscopic surgery to treat meniscus injuries has continued to increase in recent years, partly due to a younger, more active population, and improved technology and technique. However, pain management in the post-operative period is critical to the ability to perform this procedure as an outpatient surgery. Traditionally, oral narcotic agents have been the preferred analgesic postoperatively in orthopaedic surgery. However, these agents are associated with several side effects, including nausea/vomiting, constipation, and somnolence. In addition, opioid agents have a significant potential for abuse in comparison to non-narcotic analgesics. In light of the rising opioid epidemic and nationwide initiatives to limit narcotic usage, surgeons must explore alternate pain modalities in the acute postoperative period. Ketorolac is an NSAID with analgesic and anti-inflammatory properties.1 Multiple prior studies have examined the beneficial effect of oral and IV ketorolac as an analgesic in the postoperative period,1-3 including ACL reconstruction surgery.4-6 However, the beneficial effects of this agent following arthroscopic meniscus surgery have not been extensively studied.

Inclusion and Exclusion Criteria

At University Hospitals, patients in the practices of the orthopaedic investigators meeting the below inclusion and exclusion criteria will be eligible for enrollment in this investigation. Patients will be evaluated for potential inclusion in the office setting during pre-operative discussion. Patients will be evaluated for exclusion criteria before enrollment. The patient's past medical history will be evaluated for contraindications to ketorolac and the other exclusion criteria. A patient's medical record and the pre-operative history form will be reviewed to ensure the patient does not meet any of the exclusion criteria. The patient will also be questioned prior to enrollment about having any of the conditions in the exclusion criteria using the questions on the patient enrollment form created for this study (see "Other Documents" in Sparta submission).

	Inclusion Criteria
1.	*Patients between the ages of 18 and 89 years old, male or female*
2.	*Patients undergoing primary arthroscopic meniscus surgery*
3.	
4.	

	Exclusion Criteria
1.	*Patients below the age of 18 or above the age of 89*
2.	*Illiterate or non-English speaking patients*
3.	*Patients with contraindications to Ketorolac*
4.	*History of alcohol of drug abuse*
5.	*Chronic use of analgesic or psychotropic drugs*

6.	*Known peptic ulcer disease or bleeding diathesis*
7.	*Renal dysfunction*
8.	*Breastfeeding women*

Number of Research Participants

We are seeking to enroll 43 patients in this single-center study.

Recruitment Methods

Patients will only be approached about study enrollment in the outpatient clinics of the orthoapedic investigators after they have agreed to undergo arthroscopic meniscus surgery as part of the standard of care for their meniscus pathology.

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The source of patients will be from the practices of the Drs. Karns, Voos, Goodfellow, and Salata.

Patients will be evaluated for potential inclusion in the research study based on meeting the above inclusion/exclusion criteria. Patient must be between the ages of 18 to 89, and presenting with meniscus pathology amendable to arthroscopic surgery. Patients with a history of prior surgery to the knee will be excluded as no revision procedure will be included in the investigation.

The orthopaedic investigators included in this investigation receives dozens of consults every week for orthopaedic injuries to the knee and pain secondary to meniscus pathology that require operative intervention. As such, the investigators will have access to more than the required number of research participants required to appropriately power this investigation.

Setting

The research will be conducted at University Hospitals-Cleveland Medical Center, UH Ahuja Medical Center, UH Richmond Medical Center, UH Mentor Health Center, UH Westlake Health Center, and UH Suburban Health Center. Recruitment will occur in the office setting of the orthopaedic investigators in outpatient clinics. The primary research location for University Hospitals will be at UH Cleveland Medical Center (11100 Euclid Ave., Cleveland, OH, 44106), UH Ahuja Medical Center (3999 Richmond Road., Beachwood, OH, 44122), UH Mentor Health Center (9000 Mentor Ave, Mentor, OH 44060), UH Richmond Medial Center (27100 Chardon Rd, Richmond Heights, OH 44143), or UH Westlake Health Center (960 Clague Road., Westlake, Ohio 44145).

Consent Process

Consent will take place in the office setting prior to surgery at one of respective locations listed above. Prior to discussion of the investigation, the patient and family will be asked if they require time to discuss with others their desire to participate in the study. No coercion will be encountered by the patients to serve as a research subject, as patients will be fully able to refuse. Patient may be free to refuse participation at any point in the study. At University Hospitals, and all participating institutions, only IRB-approved study personnel will all be a part of obtaining consent in the clinic setting. All will be up to date on their CITI training. The authors anticipate 10 minutes to discuss the study and patient

involvement, with 5 minutes to answer questions regarding study participation, resulting in a total of 15 minutes. Patients will be informed that the decision to enroll in the study is entirely dependent on their willingness to participate and that no changes in their medical care will be experienced based on their decision to participate or not. An unsigned consent will signify that the patient is not interested in enrollment in the study investigation. Again, it will be emphasized to the patients that no changes during surgery or in medical management during the post-operative time will be experienced based on the patient's decision. Investigators obtaining consent will ensure adequate understanding by asking patients if they have any questions or concerns and if they understand the investigation being performed. All patients who enroll in the study will sign their consent form in the presence of a UH IRB-approved study team member.

Sharing of Results with Research Participants

☒ Results will **not** be shared with research participants

☒ Results will **not** be shared with research participants' doctors

Study Design

This is a prospective randomized clinical study that involves studying ketorolac as an adjuvant pain medication for arthroscopic meniscus surgery patients. All patients enrolled in this study will receive the standard pain control protocol before, during, and after surgery. This includes 1), IV Dexamethasone and IV Odansetron during surgery, and 2) analgesics (as directed by the anesthesiologist) in the PACU. Both groups will also receive the standard of care discharge pain medications for arthroscopic meniscus surgery: oxycodone-acetaminophen 5-325 (1-2 tablets PO q4-6h PRN for moderate to severe pain #28 tabs).

Patients will be randomized into one of two groups. Group 1 will receive standard of care pain protocol, including a prescription for oxycodone-acetaminophen 5-325 on discharge. Group 2 will also receive the standard of care pain protocol before, during, and after surgery but will also receive an intraoperative dose of IV ketorolac at the completion of the procedure and oral ketorolac on discharge (10mg PO q6 x3 days). Patients in this group will also be given omeprazole (20 mg PO, once per day x3 days). Patients will record their pain levels, oxycodone-acetaminophen 5-325 consumption, and pain medication side effects in a diary three times per day for the first five days after surgery. The patient will return the completed diary to their surgeon at the first post-operative appointment. Participation in this study will not require any additional visits to the surgeon's office or hospital outside of the standard pre- and post-operative appointments.

Study Procedures

1. All patients scheduled to undergo elective arthroscopic meniscus surgery identified in the office of one of the orthopaedic investigations will undergo the process of obtaining consent prior to surgery. The consent form will be reviewed in depth with an IRB approved-member of the research team, all questions answered, and written consent obtained by the patient after all questions have been answered and the patient demonstrates a full understanding of the investigation and their role in the study. The patient's home medications will be reviewed, and any potential drug-drug interactions will be discussed with the patient.

2. As part of the standard of care, patients undergoing elective arthroscopic meniscus surgery will undergo pre-operative testing to ensure patients are optimized for surgery from a medical perspective. During the pre-operative testing period, the standard blood draw taken as part of the standard of care, utilizing no more of the patient's time or blood than generally performed if the patient were not enrolled in the investigation. Before surgery patients will fill out the following patient reported outcome metrics: Visual Analogue Score (VAS), Knee Injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee (IKDC) evaluation, and the Lysholm knee score. It is expected that it will take the subject about 5-10 minutes to complete these questionnaires.

3. Patients will be re-identified in the preoperative holding area. Both Group 1 and Group 2 will receive the standard of care pain protocol for arthroscopic meniscus surgery, which consists of: 1) IV Dexamethasone and IV Odansetron during surgery, and 2) analgesics (as directed by the anesthesiologist) in the PACU. Both groups will also receive the standard of care discharge pain medications for arthroscopic meniscus surgery: oxycodone-acetaminophen 5-325 (1-2 tablets PO q4-6h PRN for moderate to severe pain #28 tabs). Group 1 will receive only the standard of care pain protocol on the day of their surgery and discharge pain medications. Group 2 will receive the standard of care pain protocol on the day of surgery and an intraoperative dose of IV ketorolac at the completion of surgery (dosing individualized by patient age and weight). The operating surgeon will be responsible for directing the anesthesiologist to administer the IV Ketorolac. Group 2 will also receive the standard of care discharge pain medications and scheduled oral ketorolac (10mg PO q6 x3 days). In addition, all Group 2 patients will receive a prescription for omeprazole (20 mg PO, once per day x3 days) to take for 3 days after surgery to decrease their risk of developing stomach ulcers. Patients in Group 1 will not receive a prescription for omeprazole. A 1:1 randomization ratio will be used (an equal number of patients will be placed in each group). Patients will then undergo standard arthroscopic meniscus surgery with one of the surgical investigators. Prior to discharge, all patients will be provided a handout on safely using opioids.

4. Following discharge from the ambulatory surgery center, patients in Group 1 and Group 2 will be asked to document their VAS pain scores at 6 hour intervals (morning, afternoon, and evening) for five days in a journal administered to them at the time of study enrollment. They will also be asked to record the number of oxycodone-acetaminophen 5-325 pills they take during this time interval in their journal. At the end of each day, patients will be asked to document the following adverse effects: nausea, vomiting, somnolence, dizziness, headache, pain, pruritis, other in their journal. All patients in Group 2 will be instructed to take ketorolac every 6 hours for pain every day for the first 3 days after surgery. Thus, patients in Group 2 will not be required to record the number of ketorolac pills they take each day. To ensure safety, all patients assigned to Group 2 will receive a form outlining the common and serious side effects of Ketorolac and specific instructions for when they should call their doctor or go to the emergency room. All patients who receive meniscus surgery at UH are instructed to call their surgeon's office if they feel their pain is not controlled at home after surgery.

5. Patients in Group 1 and Group 2 will receive a phone call from a member of the study team on Day 2 after surgery to see if they have any questions and to ensure they are filling out their journal. Patients in Group 2 will also be asked if they are experiencing any of the side effects from ketorolac. Patients in Group 2 will be given an educational handout on the side effects of ketorolac when they are discharged from the hospital.

6. Patients will follow up in clinic on a routine basis based on the recommendations of the surgeon, typically at 1-2 weeks, 6 weeks, 3 months, 6 months and 1 year following surgery. During these follow up appointments, patients will be screened per standard of care for range of motion to the operative knee, pain levels, strength and questioned regarding functionality of the operative knee. In the setting of a complication (wound breakdown, infection), patient information will be recorded and communicated using university password protected email to communicate with the primary investigator. At the first two follow-up clinic appointment after surgery, patients will fill out the following patient reported outcome metrics: VAS, KOOS, IKDC, and Lysholm questionnaires. The first appointment is about 1-2 weeks after surgery and the second appointment is about 6-8 weeks after surgery. Filling out these questionnaires should only take 5-10 minutes to complete at each clinic visit.

7. After 1 month from their surgery date, patients will receive a phone call from a member of the study team to ask how many refills they have received for their prescription for oxycodone-acetaminophen 5-325. After the second follow-up appointment, the subjects participation in the research will be complete.

Study Timeline

Patients are evaluated in the orthopaedic investigators' outpatient clinics for meniscus pathology. If a patient's condition is amenable to arthroscopic surgery and they elect to undergo the procedure they will be approached for participation in this study. This evaluation and discussion of the surgical procedure should take 10-15 minutes. The time for enrolling a patient should take 10 minutes with 5 minutes for patients' questions. Therefore, an outpatient visit for a patient enrolling this study would take 25-30 minutes. This will be the only visit before surgery. After the surgery, patients will complete their pain diaries at home each day, which should take about 5 minutes each day to fill in. They will bring these completed diaries to their first post-op visit.

Data to be Collected for your study (AFTER consent and HIPAA Authorization have been obtained)

Name, dates, telephone number, MRN,
Pre-operative diagnosis

- *Mechanism of injury/disease, if relevant*
- *Narcotic pain medication and side effects in patient journal (number of opioid pills consumed at six hour intervals for five days postoperative)*
- *Pre- and post-operative scores for the following*
- *Patient-Reported Outcomes Measurement Information System (PROMIS)*
    - *Visual Analog (VAS)*
    - *Knee injury and osteoarthritis outcome (KOOS)*
    - *International Knee Documentation Committee (IKDC)*
    - *Lysholm*

Data Analysis Plan

Statistically significant differences in patient demographics and comorbidities between Group 1 and Group 2 will be determined initially with univariate analysis. Students t-test will be utilized to compare the differences in mean VAS scores and narcotics utilization between the two groups at each time point. Linear regression models will be utilized to identify trends over time. Descriptive analyses (e.g., percentages) will be used to report qualitative data as appropriate.

*The minimal clinically important difference in VAS scores is 13 in patients with rotator cuff disease.4 A prior study by White et al.1 comparing oxycodone-acetaminophen versus oral ketorolac for analgesia following arthroscopic tubal ligation, the common standard deviation in VAS scores was 11 points. Only one published study, by Honig et al.,7 has reported pain levels after administering IV or oral ketorolac to patients undergoing meniscus surgery, with a common standard deviation in VAS scores of 13.3. Using this data, our power analysis showed that, with an alpha of 0.05 and 90% power, we would need 34 patients, or 17 per group, to achieve adequate power. However, to account for a 20% dropout rate we will recruit for 43 patients. Power analysis was performed using G*Power 3.1.9.2.*

The primary endpoint of this study is VAS pain scores and number of narcotic medications consumed. Secondary scores include, KOOS, IKDC, Lysholm, and PROMIS scores.

Drugs or Devices

Ketorolac is an FDA-approved drug for pain relief. Omeprazole is an FDA-approved drug for the prevention and treatment of gastroesophageal reflux disease (GERD).

Patients randomized to Group 2 will be provided IV and oral ketorolac during the study, as well as oral omeprazole. The IV ketorolac will be provided by the anesthesia team in the operating room at the conclusion of the study. The study investigators will provide patients with a prescription for the oral ketorolac and oral omeprazole, which they may fill at a pharmacy of their choice.

Confidentiality

Data collected from subjects participating in the study will be immediately protected as each subject will be assigned a number based on their enrollment and the institution in which they were enrolled that will in no way correspond to any pertinent data relating to the subject's protected health information. Following the results of lab studies and follow up appointments, all data will be entered electronically into RedCap software. Electronic copies of any documentation will be stored in the UH Secure Network drive or UH Encrypted Drive (Iron Key) while any physical documentation be placed within the locked file cabinets located within the institution's investigators office. Data will be accessed by only approved study personnel. Data will be assessed for completeness, accuracy and per strict adherence to the approved protocol by the orthopaedic resident (LS) and during bi-monthly meetings with the investigative team who will be responsible for data protection using files on only protected hospital computers. In addition, monitoring of the data by the entire investigative team will be conducted frequently during these bi-monthly meeting in which the standards and rules of the protocol will be reviewed to ensure that all regulations set forth in the confidentiality agreement are met and complete. Following the complete data transfer electronically, all documentation will be properly disposed of to ensure complete participant protection of information. Following the conclusion of the study, all documentation will be disposed of while maintaining patient confidentiality for 3 years following study closure per UH policy.

Risks to Research Participants

The risks to patient are minimal. All patients scheduled for elective arthroscopic meniscus surgery undergo pre-operative testing to ensure they are medically optimized for surgery. Patients with contraindications to Ketorolac will not be enrolled in the study:

- *Previous allergic reaction to Ketorolac*
- *History of any of the following: peptic ulcer disease, gastrointestinal bleeding, or perforation of the stomach or bowel*
- *Having experienced an asthma, urticarial, or a allergic-type reactions after taking aspirin or other NSAIDs*
- *History of kidney disease or kidney failure*
- *History of a brain bleed*
- *History of a bleeding disorder*
- *Currently taking the medication probenecid*
- *Currently taking the medication pentoxifylline*

The investigators will ensure no patient with contraindications to Ketorolac are enrolled via the following: 1) the patient's past medical history in their electronic medical record and pre-operative history form will be evaluated for contraindications to ketorolac, and 2) the patient will be questioned prior to enrollment about having any of the conditions that are contraindications to Ketorolac using the patient enrollment form created for this study (see "Other Documents" in Sparta submission).
Common non-serious side effects of Ketorolac:

- *Nausea, stomach pain, indigestion, diarrhea*
- *Dizziness, drowsiness*
- *Headache*
- *Swelling*

Serious side effects of Ketorolac:

- *Gastrointestinal problems: ulcers, bleeding, or peforation*
- *Hemorrhage*
- *Impaired renal function*
- *Impaired liver function*
- *Allergic or anaphylactoid reaction*
- *Anemia*
- *Ketorolac, like other NSAIDs, may cause serious cardiovascular side effects, such as myocardial infarction or stroke, which may result in hospitalization and even death*

All patients that receive ketorolac will be monitored in the PACU for side effects to Ketorolac after receiving an IV dose at the end of their surgery, and will be given an informative handout on ketorolac and its side effects (see "Other Documents" in Sparta submission). This handout also has instructions for when patients should call their surgeon's office or seek immediate medical assistance. In addition, all patients enrolled in this study will receive a phone call on Day 2 after surgery to ensure they are filling out their pain diary. Patients who received ketorolac will also be questioned about having any side effects of ketorolac.

Also, enrollment in the investigation does increase the risk for breach of confidentiality during subject enrollment in study.

Provisions to Protect the Privacy Interests of Research Participants

Privacy of the study subjects will be protected throughout all phases of the research study. Consent will be obtained by only a member of the investigative team and patients will be given the opportunity to discuss participation with an investigator out of the room, allowing the patient to remain alone or with

family. During the study period, all subject data will be protected through careful handling of patient information by assigning each subject a research number. After completion and collection of all study documents, all documentation will then be securely transported back to the appropriate investigators office securely locked away after being entered electronically after the identifiable information is converted to a study number which will not contain any protected health information. All patient information will be stored confidentially on protected hospitals computers and files using RedCap software to ensure added protection. Following conclusion of the study, all hard documentation will be stored within the locked file cabinet in the investigators office after being transferred onto electronic files protected by RedCap. All documentation will be disposed of at the end of the study to ensure confidentiality is maintained. In addition, participants and their information will not be discussed in any public areas or with any medical or non-medical personnel not directly involved with and approved as an active investigative member of the research study.

Potential Benefit to Research Participants

There is no guaranteed direct benefit from participating in the study. All subjects undergoing surgery will benefit from the known effects of arthroscopic meniscus surgery following surgery whether or not they are enrolled in the study. Possible benefit of the research is patients could experience increased pain relief, compared to standard pain control protocols, after surgery from receiving intra-operative IV and PO Ketorolac. This will make their post-op period more comfortable.

Withdrawal of Research Participants

Patients can withdraw at any point during the study period. Patients will be withdrawn if they fail to appropriately follow up in the post-operative period. If a patient withdraws from the study before their surgery, they will proceed with their arthroscopic meniscus surgery and clinical follow-up, and no further data will be collected on them. If a patient withdraws during the post-operative period, then no more follow-up data will be collected past their withdrawal date.

Alternatives to Participation

Patients may elect to proceed with arthroscopic meniscus surgery with the standard of care postoperative pain regiment oxycodone-acetaminophen 5-325 (1-2 tabs PO q4-6h PRN moderate to severe pain #28 tabs))

Arthroscopic repair is a well-established treatment option for patients with meniscus pathology. Therefore, if their surgeon has recommended they receive arthroscopic repair, it will be because the surgeon believes it is the best treatment option for their condition, not for research purposes. If a patient elects to withdraw from the Ketorolac arm, they will simply be asked to discontinue use of Ketorolac and continue with the use of oxycodone-acetaminophen 5-325. Since this is the standard of care there is no alternative treatment to list in the consent.

Costs to Research Participants

There are not sufficient funds within our department to cover the cost of ketorolac and omeprazole for patients randomized into Group 2. As such, the patient's insurance company will be responsible for the cost of ketorolac and omeprazole. However, ketorolac is a generic drug that is commonly utilized both within and outside of Orthopaedics. Patients will ultimately be responsible if the insurance company does not pay, and for any associated co-pay. Paying for Ketorolac and Omeprazole will be discussed with the patient in clinic during the consent process.

Research Participant Compensation

There is no compensation for subjects.

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

Data collected from subjects participating in the study will be immediately protected as each subject will be assigned a number that will in no way correspond to any pertinent data relating to the subject's protected health information. Following collection of data from questionnaires and pain journals, the orthopaedic resident will collect all documentation and after being entered electronically behind RedCap software, will be placed within the locked file cabinets located within the primary investigators office. Data will be accessed by only approved study personnel. Data will be assessed for completeness, accuracy and per strict adherence to the approved protocol by the orthopaedic resident and during bi-monthly (once per two months) meetings with the investigative team who will be responsible for data protection using files on only protected hospital computers. In addition, monitoring of the data by the entire investigative team will be conducted frequently during these bi-monthly meeting in which the standards and rules of the protocol will be reviewed to ensure that all regulations set forth in the confidentiality agreement are met and complete. Recorded adverse/safety events will be actively monitored by the Orthopaedic Resident, and reviewed during the bi-monthly meetings. Monitoring Following the complete data transfer electronically, all documentation will be properly disposed of to ensure complete participant protection of information. Following the conclusion of the study, all information and hard copies will remain stored in a locked file cabinet located within the primary investigators office per UH policy.

References

1. White PF, Joshi GP, Carpenter RL, Fragen RJ. A comparison of oral ketorolac and hydrocodone-acetaminophen for analgesia after ambulatory surgery: arthroscopy versus laparoscopic tubal ligation. Anesth Analg. 1997 Jul;85(1):37-43. Epub 1997/07/01.

2. Gebuhr PH, Soelberg M, Strauss W. A multiple-dose, double-blind comparison of intramuscularly and orally administered ketorolac tromethamine and Ketogan in patients with pain following orthopaedic surgery. J Int Med Res. 1994 Jul-Aug;22(4):202-17. Epub 1994/07/01.

3. McQuay HJ, Poppleton P, Carroll D, Summerfield RJ, Bullingham RE, Moore RA. Ketorolac and acetaminophen for orthopedic postoperative pain. Clin Pharmacol Ther. 1986 Jan;39(1):89-93. Epub 1986/01/01.

4. Barber FA, Gladu DE. Comparison of oral ketorolac and hydrocodone for pain relief after anterior cruciate ligament reconstruction. Arthroscopy. 1998 Sep;14(6):605-12. Epub 1998/10/01.

5. Tierney GS, Wright RW, Smith JP, Fischer DA. Anterior cruciate ligament reconstruction as an outpatient procedure. Am J Sports Med. 1995 Nov-Dec;23(6):755-6. Epub 1995/11/01.

6. Brown DW, Curry CM, Ruterbories LM, Avery FL, Anson PS. Evaluation of pain after arthroscopically assisted anterior cruciate ligament reconstruction. Am J Sports Med. 1997 Mar-Apr;25(2):182-6. Epub 1997/03/01.