Study Title: Efficacy and Cost-effectiveness of Intra-Articular Ketorolac Injection for Knee Osteoarthritis: A Randomized, Controlled, Double-Blinded Study

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Study Protocol

1. Title of the Study

Efficacy and Cost-effectiveness of Intra-Articular Ketorolac Injection for Knee Osteoarthritis: A Randomized, Controlled, Double-Blinded Study

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2. Background

Osteoarthritis (OA) of the knee is a common debilitating disorder with tremendous socioeconomic impact.[1,2] The estimated financial burden of OA, including healthcare expenses and loss of productivity, is in excess of $140 billion annually.[2,3] Nonoperative management emphasizing rehabilitation, weight loss, and nonsteroidal anti-inflammatory drugs (NSAIDs) is currently the first line treatment for symptomatic OA of the knee.[4] Other interventions, such as intra-articular injections with either corticosteroids or viscosupplements, remain controversial with mixed results in the literature.[5-8]

There is limited information about NSAIDs injection for the treatment of knee OA. Given that OA involves inflammatory processes leading to cartilage degradation and pain,[9] NSAIDs injection represents a promising modality allowing for higher local tissue concentration and potentially providing potent anti-inflammatory and analgesic effects. In the US, ketorolac is the only NSAID available in injectable form. The advantages of ketorolac injection are multifold: 1) it is a relatively inexpensive medication; 2) there is strong evidence to support NSAIDs use, administered orally or topically, in the treatment of knee OA;[10] 3) injection may be associated with less risk of systemic side effects[11] especially in patients who cannot tolerate oral NSAIDs; 4) ketorolac can potentially avoid the complications associated with corticosteroids, such as joint infection, cartilage breakdown, and loss of cartilage elasticity[9,12,13]; and 5) ketorolac eliminates the risk of acute inflammatory reactions or need for serial clinic visits associated with viscosupplementation, which is ranked as the second highest OA-related healthcare expenditure.[14]

To date, there is a single published study on ketorolac vs. corticosteroid injection for knee OA, which showed similar pain relief but cost savings of 143% when using ketorolac.[15] However, that study had only 35 patients with no power analysis. In addition, patients with no to minimal joint space narrowing or those with concomitant use of the study medications orally were not excluded. Most importantly, the corticosteroid used in that study has been voluntarily discontinued in the US market.

3. Hypothesis, aims and objectives:

- *Hypothesis:* Ketorolac injection is a cost-effective adjunct in the nonoperative treatment of knee osteoarthritis (OA) compared to steroids and viscosupplementation.
- *Aims/objectives*: The objective of this randomized, controlled, double-blinded, prospective study is to assess the efficacy and cost-effectiveness of knee injection with ketorolac in the nonsurgical

management of symptomatic OA compared to injections with corticosteroids and viscosupplements.

4. Study Design & Procedures:

Study Design: A prospective, randomized, controlled, double-blind trial.

- *Screening Procedures and who will perform them:*
  Patients will be screened for eligibility when they present to the office for evaluation of knee pain. Screening will consist of a review of patients' medical history, physical exam, and X-rays which are routinely performed with or without being considered for a research study. If during the visit, a patient is interested in knee injections for symptomatic relief as part of conservative management, the patient will be informed of the possibility of participating in the research study and asked if there is interest in learning more. If the patient is interested, the investigators will make a note to the chart and let the patient know that the Study Coordinator (SC) will come by to present the details of the study, and inform the SC of the patient's interest. The SC will approach the patient at the end of the visit to provide an overview of the study and ask for verbal permission to review the patients chart to confirm eligibility. If found eligible, the SC will then proceed with a full consent process. Alternatively. if the patient prefers, a separate visit may be scheduled to conduct the consent process. Only study members will be allowed to obtain consent for study participation.

- *Randomization:*
  Patients will be allocated to one of three groups using a web-based randomization by the SC: ketolorac, methylprednisolone, or hyaluronic acid. Group assignments will be concealed in opaque sealed envelopes with a numerical code of consecutive numbers reflecting patient enrollment. Envelopes will be stored in a secure, locked desk in the UConn orthopaedic research office and only to be opened once a patient has been determined to be eligible for study inclusion and provided informed consent.

  Once informed consent is obtained, a licensed provider who is not part of the data collection (to maintain blindness) will prepare and inject the study drug. The patient will receive one of three options: 2cc of ketorolac tromethamine (15mg/cc) in 5cc of 0.5% ropivacaine hydrochloride without epinephrine, 2 cc of methylprednisolone acetate (40mg/cc) in 5cc of 0.5% ropivacaine hydrochloride without epinephrine, or Hylan G-F 20 (Synvisc-One) injection. In the US, methylprednisolone actetate is the most commonly used intra-articular steroid.[17]

- *Intervention: Each patient will receive one of the following interventions:*
  1) 2cc of ketorolac *tromethamine* (15mg/cc) in 5cc of 0.5% *ropivacaine hydrochloride* without epinephrine; OR
  2) 2 cc of methylprednisolone acetate (40mg/cc) in 5cc of 0.5% *ropivacaine hydrochloride* without epinephrine; OR
  3) Hylan G-F 20 (*Synvisc*-One) or available hyaluronic acid.

- *Blinding*:
  Both the patient and the investigators will be blinded to the treatment used until after final follow-up. Patients will not be told which drug they received. The investigators will be blinded too because the injections will be performed by a licensed provider who is not part of the data collection. Only the study coordinator will know which drug was administered and will compile the data until the study is completed.

- Data collection:

Patients will be asked to complete VAS, WOMAC, Oxford Knee questionnaire and Koos, Jr. Knee Survey prior to knee injection. Follow-up length is 6 months.

- *Sample Size and Justification:*
  A sample size calculation was performed to determine the adequate number of patients needed per group. A difference of 2 points in pain on a visual analog scale (VAS) was selected as the threshold for a meaningful between group difference. A standard deviation of 2.0 points was assumed based on previous research comparing steroid to viscosupplementation for osteoarthritis of the knee. A sample size of 20 patients per group will provide 80% power (β of 0.20) to detect a 2-point difference at an α level of 0.05 among the 3 treatment groups in an omnibus one-way ANOVA. To account for post hoc comparisons, a second calculation was carried our using a Bonferroni correction. A sample size of 25 patients per group will provide 81% power (β of 0.20) to detect a 2-point difference between each group in post hoc testing. To verify the sample size calculation, a Monte Carlo program was used to simulate 1,000 ANOVAs using these estimates with a sample size of 25 per group. This analysis resulted in greater than 90% power for the omnibus one-way ANOVA and greater than 80% for post hoc testing of between group means.

  Explain on what basis it is reasonable to assume that sample size will be obtained:
  Knee OA is a very common musculoskeletal condition, accounting for a significant proportion of patients presenting to orthopaedic providers.

  Subject Characteristics and Justifications:
  - Age: 18 years or older
  - Ethnicity: No restrictions.
  - Gender: No restrictions.
  - Vulnerable Populations: None will be included.

  Inclusion Criteria:
  Patients over the age of 18 who present with 1) symptomatic knee OA and radiographic evidence of joint space narrowing and 2) are interested in knee injections for pain relief.

  Exclusion Criteria:
  - Patients interested in bilateral knee injections,
  - Prior injections into the same knee within the past 3 months,
  - Pregnant and/or lactating women,
  - Inflammatory joint disease including rheumatoid or psoriatic arthritis,
  - Concurrent use of anti-rheumatic drugs.
  - Allergy or hypersensitivity to the study medications,
  - Patients on an active pain management contract,
  - Inability to make own decisions regarding the informed consent,
  - Inability to read and/or understand English,
  - Patients who are unable to return for follow-up or be reached by phone
  - Patients with insurance that requires pre-certification for any of the study drugs.

  Describe length of subject's participation in the study including number of visits, frequency of visits and length of visits:
  Patients will be in the study for 6 months. This time period will encompass their initial visit at which point they will be enrolled in the study and receive the injection as well their follow up visits. Patients will be asked to return at 3 and 6 months for evaluation and data collection. These visits are considered routine practice at our institution. Patients may also be contacted via telephone or email for follow-up if necessary. Participation will be voluntary with no financial compensation.

Methods of Data Collection and Types of Data to be Collected:
Data will consist of demographic information (age, gender, body mass index, comorbidities, etc.), as well as previous treatment modalities. The primary outcome is a visual analogue scale (VAS) for pain. Secondary measures will include the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), length of pain relief, patient satisfaction, non-routine visits due to inadequate pain relief or complications, and cost of intervention.

Methods of Data Analysis:
Results for continuous variables will be described using means, standard deviations, medians, and/or interquartile ranges. Categorical variables will be described using counts and percentages. Numerical variables will be compared between groups using Wilcoxon's rank-sum test or Welch's two sample t-test. Categorical variables will be compared between groups using Pearson's chi-squared test or Fisher's exact test. All analyses will be done using R software (R version 3.2.3 (2015-12-10), Vienna, Austria) assuming a 5% level of significance.

5. Timetable*:*
Expected start date: 1/1/18
General Time Table: 1 year
Expected Completion Date: 7/31/20

6. Budget/Resources:
We will be applying for Orthopaedic Research and Education Foundation Grant during the IRB review.

7. Dissemination:
We plan to disseminate the results of our research in the form of peer reviewed publication and presentation at specialty meetings.

APPENDIX A
INVESTIGATOR INITIATED PROTOCOL TEMPLATE

Additional Details Pertaining to Study Design for Clinical Trials

1. For a clinical trial (e.g. a Phase I, II or III study), the use of the intervention must be fully described e.g., the treatment regimen for use of drugs, placebo, medical device etc. Also include plans for receipt of test article, storage, dispensing and reconciliation.

   Intervention: Each patient will receive one of the following interventions:
   4) 2cc of ketorolac *tromethamine* (15mg/cc) in 5cc of 0.5% *ropivacaine hydrochloride* without epinephrine; OR
   5) 2 cc of methylprednisolone acetate (40mg/cc) in 5cc of 0.5% *ropivacaine hydrochloride* without epinephrine; OR
   6) Hylan G-F 20 (*Synvisc*-One) or available hyaluronic acid.

   Drug storage: Pyxis machine.

2. Provide a description of known adverse events due to the intervention and the plan to deal with such adverse events (e.g. does reduction, removal of device, removal from trial.):

   The drug doses to be administered follow the standard of care (see pharmacy approval letter). Perhaps the main potential adverse event is infection. Patients will be counseled on signs of infection as part of the standard risks/benefits routinely performed with knee injection with instructions to call the clinic or report to the emergency room should any issues arise following the injection.

3. Describe circumstances that may lead to a subject being removed from the trial by the PI, e.g. due to failure to follow study procedures, and the process for doing so:

   Meeting any of the exclusion criteria during study participation or failure/refusal to complete follow-up questionnaires.

4. Describe any stopping rules for the study:

   None. All study drugs are routinely used for symptomatic knee OA.

5. Additional Comments by PI.

   None.

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