Evaluating the Efficacy and Safety of Pregabalin in Total Knee Arthroplasty Patients with Central Sensitization

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Protocol:

Following the consent process the participants will be asked to participate in the following:
1. Participants will complete Central Sensitization Inventory (CSI) and the Columbia Suicide Severity Rating (CSSR) as well as any necessary labs. These will be done in person at the time of consent/enrollment. If the participant answers Yes on any of the CSSR questions, they will exit the study. If any participant scores < 40 on the CSI, they will exit the study.

2. If they still qualify for the study, they will complete (1) the Baseline Subject Demographic form, (2) the Pain, Enjoyment of Life and General Activity form (PEG-3), and (3) the Knee Injury and Osteoarthritis Outcomes Score (KOOS). These will be done in person at the pre-op visit.

3. All participants will meet with a physical therapist prior to surgery to assess baseline functional levels using established assessment surveys. The approximate time to complete these assessments is 30 minutes.
The surveys used include: Timed Up and Go (TUG)
Stand-Up, Sit-Down (STS)
Patient-Specific Functional Scale Assessment (PSFS)

3. Participants are randomized at the pre-op visit to standard of care vs study treatment arm using a computer-generated block randomization sequence. The allocation of concealment will be ensured using a sealed envelope technique.

4. If the participant is not randomized to the study medication arm, they will proceed with usual peri-operative management.

5. If the participant is randomized to study medication arm, they will be directed to the UIHC Discharge Pharmacy to retrieve the study drug. Additionally, they will be provided information about the medication, possible side effects and dosing schedule.
Dosing Schedule
Pre-surgery (days 1-7) pregabalin 75mg twice daily
Post-surgery (days 1-7) pregabalin 150mg twice daily, then (days 8-14) pregabalin 75mg twice daily

6. Day of Surgery (DOS): Someone from the research team will meet with all participants in DOSA to (1) answer any questions about continued participation in the study. For those participants in the study medication arm, the research team member will also evaluate if they have (2) completed the study medication schedule, (3) determine if they have noticed any side effects from the medication (including the CSSR scale), and (4) remind the participant of post-surgical medication dosing schedule. If the participant did not tolerate the study medication they will exit the study and continue to receive standard surgical care. If the patient answers Yes to any of the CSSR items, they will be advised to seek out behavioral healthcare. If they answer Yes to questions 4,5, or 6, they will be immediately taken to the ED by study team member for evaluation. They will stop the study medication and exit the study at that time. Proceeding with surgery will be deferred to the primary surgery team. This visit is expected to take less than 15 minutes.

7. All participants undergo a post-operative Physical Therapy assessment, which normally

occurs within a week of surgery per standard of care. At that time, the functional levels as outlined above including TUG, STS, and PSFS will be re-evaluated. The approximate time spent is 30 minutes.

8. All participants will be contacted by the study pharmacist about 7 days after surgery by telephone. The pharmacist will also determine the amount of other pain medications that have been needed for pain relief for all participants. The goal of this assessment is to determine how the participant is faring with the study medication (if randomized to the study medication arm) and other pain medications. The pharmacist will review the study medication dosing schedule with these participants and re-assess with the CSSR scale. If the participant did not tolerate the study medication they will exit the study and continue to receive standard post-surgical care. If the patient answers Yes to any of the CSSR items, they will be advised to seek out behavioral healthcare. If they answer Yes to questions 4,5, or 6, they will be advised to seek immediate medical attention or local EMS will be contacted by the pharmacist. They will stop the study medication and exit the study at that time.

9. Patients will have a 6-week post-operative visit with their surgical team and research study team. At this time, all participants will again complete the Knee Injury and Osteoarthritis Outcomes Score (KOOS), the PEG-3 pain survey, and the Central Sensitization Inventory (CSI) assessments. Also the participant will be asked to report how much opioid medication (if any) they are taking and the physical therapist will repeat the functional tests (TUG, STS, PSFS). The time to complete these evaluations is approximately 60 minutes.

10. This will complete the study participation.

Analysis/Statistical Plan:

Treatment-stratified summary statistics will be calculated for all baseline measures, including demographics and clinical outcomes. Categorical measures will be presented as counts and percentages. Continuous measures will be assessed for normality and presented as either means and standard deviations or medians and interquartile ranges. Assessments of between-group differences will be conducted for all baseline non-subscale measures using Fisher's exact, two-sample t-, or Wilcoxon rank sum tests. Between-group differences for baseline subscale measures (following a 5-point Likert scale) will be assessed using cumulative logistic regression to utilize the ordinality of the measure.
Between-group changes (baseline to week 6) in the primary outcome (KOOS- ADL) and secondary outcomes (KOOS subscale scores (pain, symptoms, sports/recreation, and quality of life subscales, pain scores, differences Timed Up and Go Test (TUG), the Sit-to-Stand Test (STS) and the Patient Specific Functional Scale (PSFS) will be assessed by calculating the within-subject differences. Distributions for each outcome's 6-week change will be examined. Measures with normally distributed differences will follow the two-sample t-test to compare changes between treatment groups, and measures with non-normally distributed differences will follow the Wilcoxon rank sum test. Tests with p-values < 0.05 will be considered statistically significant.
As an exploratory outcome, we will investigate the relationship between 6-week changes in CSI scores and changes in pain and function outcomes. Associations between normally and non-normally distributed measures will be investigated using Pearson's and Spearman's correlations, respectively.

Adverse effects will be calculated for each treatment group and presented counts and percentages.