Can We Eliminate Opioids After Anterior Cruciate Ligament Reconstruction?
A Prospective, Randomized Controlled Trial

Study Protocol:

This study was designed as a prospective RCT in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement.25 The hypothesis was formulated before collection of data. The study was reviewed and approved by our institutional review board (IRB No. 12315) and was registered at ClinicalTrials.gov (NCT03818932).

Between February 2019 and January 2020, a total of 90 patients undergoing primary ACLR by 2 fellowship-trained sports surgeons at a single academic center were screened for study eligibility (V.M., K.R.O.). Ultimately, 62 patients with a torn ACL consented to participate. The inclusion criteria consisted of patients aged >14 years and patients undergoing primary ACLR. Patients were excluded if they had a history of opioid abuse documented in the medical record, recent or current pregnancy, contraindication to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, renal impairment, peptic ulcer disease, gastrointestinal bleeding), intolerance or allergy to any of the component medications, or history of same-joint surgery for any reason in the previous year or if they were under- going revision surgery. All concomitant meniscal and cartilage procedures were recorded.

Randomization and Masking

Patients who consented to participate were randomly assigned preoperatively to either an opioid or a multimodal nonopioid pain regimen with a 1:1 allocation ratio using adaptive randomization computer software (Adaptive Randomization; MD Anderson Cancer Center). Patients declined to participate for a number of reasons including reluctance to participate in a research study and inability or lack of interest in maintaining compliance with study protocol. At 1 week before surgical intervention, surgeons were notified by secure email of the patient's group designation.

Interventions

Patients underwent an arthroscopically assisted ACLR using bone-patellar tendon-bone autograft or hamstring autograft via anatomic femoral and tibial tunnels. The patients individually determined their graft choice after an informed discussion on potential options with their surgeon. Within 2 hours preoperatively, both groups received 1-time doses of 400 mg of celecoxib orally, 975 mg of acetaminophen orally, 300 mg of gabapentin orally, 8 mg of dexamethasone intravenously, and 50 mg of tramadol orally. All ACLRs were performed with the patient under preoperative blocks at the discretion of the anesthesiologist (4 femoral nerve blocks, 58 adductor canal nerve blocks).

Intraoperatively, a local infiltration cocktail was injected evenly in 2-mL increments along the incision and the subcutaneous tissues before wound closure using a 20-mL syringe with a 1-inch, 22-gauge needle. The local infiltration cock- tail consisted of the following: 150 mg (30 mL) of 0.50% ropivacaine, 30 mg (1 mL) of ketorolac, and 1 mg (1 mL) of epinephrine.22

Patients in the multimodal nonopioid group received a novel nonopioid multimodal analgesic protocol previously described.19 Acetaminophen and NSAIDs (ketorolac and meloxicam) were used to target the pain cascade and post- operative inflammation, respectively. Gabapentin was used to address neuropathic pain and diazepam to control muscle cramps and spasm. Medication dosage and frequency are described in Table 1. It must be noted that patients in the multimodal nonopioid group received 1 dose of 50 mg (5 morphine milligram equivalents [MME]) of tramadol before surgery.

Patients enlisted in the opioid group were prescribed 40 pills, each containing 5 mg of hydrocodone and 325 mg of acetaminophen, and were instructed to take 1 or 2 pills orally every 4 to 6 hours as needed for moderate to severe postoperative pain. This was the standard of care at the authors' institution, and patients in the opioid arm received no other pain medications.

Patients were discharged home on the day of surgery per their group designation pain protocol. All patients were encouraged to contact the on-call physician if pain was unbearable or they were experiencing any complications. Patients in both groups were given instructional pamphlets on the effects of opioids, ways to effectively manage pain postoperatively, and pain treatment goals after surgery.

Outcomes

Data collection was performed by observers who were blinded to group randomization. Patients were instructed to complete the PROMIS PI-SF questionnaire preoperatively. After surgery, a mobile messaging-based software (Mosio; Mosio Inc) was used to collect patient data. Surveys were sent to patients 3 times a day for 10 days postoperatively. A 10-day follow-up was selected to evaluate pain control in the acute postoperative period when patients are typically most susceptible to surgical pain.

Patients were asked to report their current pain level 3 times per day using a VAS score (range, 0-10, where 10 = maximum). Patients were asked to report medical side effects each evening, as well as how many opioid pills were taken in the last 24 hours (if applicable). Opioid consumption was con- verted to MME. At the first postoperative visit (7-10 days), patients completed the PROMIS PI-SF questionnaires. The following variables were obtained from medical records: demographic characteristics, smoking status, anxiety/depression status, workers' compensation status, history of opioid abuse, and preoperative opioid consumption.

Statistical Plan:

The primary outcome of this study was an average daily pain difference of 1.3 points on the VAS score, as a previous study has demonstrated that this difference represents the minimal clinically important difference for the VAS pain score.8 Prestudy power analysis, using a power of 80% (b level = .80, a level = .05), revealed that a minimum of 25 patients per group (n = 50) would be necessary to properly evaluate the primary hypothesis. A sample size of 90 patients (45 per group) was selected to account for patients with incomplete data collection (eg, lost to follow-up). Secondary outcomes included patient-reported outcomes, demographic

differences, complications, and patient satisfaction. There was no crossover of patients between study arms.

Continuous data were summarized using mean and standard deviation for normally distributed variables and median with interquartile range for nonnormally distributed variables; categorical data were reported as counts with percentages. For continuous variables, univariate 2- group comparisons were performed using independent 2- sample t tests when the variable was normally distributed and Wilcoxon rank sum tests when the variable was non- normally distributed. For categorical variables, univariable 2-group comparisons were performed using the chi- square test when expected cell counts were ?5 and the Fisher exact test when expected cell counts were \5. The Pearson coefficient (r) was used to establish correlation between outcome measures. Correlation strength was defined as very high (r = 0.90-1.00), high (r = 0.70-0.89), moderate (r = 0.50-0.69), and low (r = 0.30-0.49).20 Repeated-measures analyses were performed using mixed models and included the effects of time and group and the interaction between time and group. Models were then adjusted using specified variables selected a priori in an attempt to adjust for possible confounders. Predicted means resulting from the adjusted models were plotted for the outcome variables. If needed, significant interaction effects were analyzed using post hoc comparisons using a Tukey-Kramer P value correction. Predicted means resulting from the adjusted models were plotted for the outcome variables. Statistical significance was set at P \ .05 for group comparisons and main effect testing and P \ .10 for interaction testing. All analyses were per- formed using SAS Version 9.4 (SAS Institute Inc).

Results

A total of 62 patients were included. One week following surgery, patients reported a mean VAS level of 3.2 ± 2.3 and required on average 2.6 ± 3.6 breakthrough oxycodone pills (8.6 ± 12.0 morphine equivalents). Forty-five percent of patients did not require any breakthrough prescription opioids and reported satisfaction with pain management. Patients who required opioids were more likely to have a history of anxiety/depression (44.2% vs 23.8%, P = .012) and reported greater pain scores as compared with nonusers (3.94 ± 2.5 vs 2.41 ± 1.75, P = .016). The most common side effect of the pain protocol was feeling drowsy (23.5%). All patients were satisfied with their pain management postoperatively.