Multimodal Nonopioid Pain Protocol Provides Better or Equivalent Pain Control Compared to Opioid Analgesia Following Arthroscopic Rotator Cuff Surgery: A Prospective Randomized Controlled Trial

Study Protocol:

This study was a prospective observer-blinded randomized controlled trial with 2-week follow-up and was developed in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement. This investigation received institutional re- view board approval at our institution (IRB no. 12316) and was registered at ClinicalTrials.gov (NCT03818919). A hypothesis was formulated prior to trial initiation. Between August 2019 and December 2020, 70 consecutive patients who presented to two fellowship-trained sports surgeons and were scheduled to undergo a primary arthroscopic rotator cuff repair were screened for inclusion. Inclusion criteria required patients to be between the ages of 18 and 75 and scheduled for a primary arthroscopic RCR. Exclusion criteria included being non-English speaking, history of ipsilateral surgery in the previous year, undergoing revision surgery, use of blood thinner medication, his- tory of peptic ulcer disease, history of substance abuse, and intolerance or allergies to study medication.

Following the surgical consult, patients consented to participate in the study. Using an adaptive randomization software (MD Anderson Cancer Center, Houston, TX) with a 1:1 allocation, patients were randomized into the opioid or nonopioid cohort. A secure computer database was used to store all deidentified patient data. One week prior to the date of surgery, the project coordinator used a secure e-mail to inform the surgical staff of the patient's group designation. Because of the fact that all outcomes would be self-reported by the patient, it was not necessary for the treating physician to be blinded. The research coordinator was not involved in patient care and performed patient enrollment and data collection.

Intervention

All patients indeterminate of treatment group received the following medication preoperatively: celecoxib 400 mg, acetaminophen 975 mg, tramadol 50 mg, gabapentin 300 mg, and 8 mg dexamethasone intravenously. Arthroscopic RCR was performed under preoperative block. Intraoperatively, all patients received a local infiltration of 30 mg (1 mL) ketorolac, 1 mg (1 mL) epinephrine, and 150 mg (30 mL) of .5% ropivacaine. Using a 20-mL syringe and 22-gauge needle, local infiltrate was administered in 2-mL increments in the subcutaneous tissue around the portal sites.

Patients who randomized into the control group were prescribed 40 pills of 5 mg oxycodone. Patients were instructed to take 1-2 pills every 4-6 hours as needed (PRN) and told not to supplement their analgesia with ibuprofen or acetaminophen.

Patients in the nonopioid group received a multi- modal nonopioid analgesic regimen previously described in the literature. The protocol was developed to target various postoperative pain generators. Gabapentin was used to target neuropathic pain. Methocarbamol was selected

because of its excellent control of muscle spasms and cramps. Acetaminophen and NSAIDs (ketorolac and meloxicam) were used to target the pain cascade and the inflammatory process.

Prior to discharge patients were instructed to call the on-call physician regarding uncontrolled pain or adverse drug events postoperatively. Patients were provided an educational pamphlet describing the effects of narcotics, providing ways to manage pain, and treatment goals after surgery. All patients were discharged home the same day of surgery.

Outcomes

The data collection was performed by blinded observers. Preoperatively, patients completed the Patient- Reported Outcomes Measurement and Information System Pain Interference Short Form (PROMIS PI-SF) questionnaire. Postoperatively, a mobile messaging- based outcomes collection software (Mosio, Inc, Seattle, WA) was used to collect patient-reported outcomes. Patients' responses were submitted as numerical response via text message. This process allowed for the timely collection of data. Surveys were distributed to patients 3 times daily for 10 postoperative days.

Patient-reported pain scores were collected using a 11-point visual analog scale 3 times a day; in the morning (9 AM), afternoon (1 PM), and evening (7 PM). Questions regarding adverse drug effects and the number of opioids consumed in the last 24-hour period (if applicable) were distributed each evening. Responses regarding the amount of opioid consumption daily was converted to morphine milligram equivalents (MME). During the first postoperative clinic visit (Postoperative days 7-10), patients completed the PROMIS-PI SF questionnaires.

Information regarding the patients' demographic data (age, body mass index [BMI], race), anxiety/depression status, workers compensation, and previous opioid use was extracted from the electronic medical record.

Statistical Plan:

A power analysis was performed prior to the initiation of this investigation. Following a primary arthroscopic rotator cuff repair, previous literature has indicated that the minimal clinically significant difference (MCID) in VAS pain scores is 2.4 mm on a 10-mm scale. Additionally, a previous case series demonstrated that the standard of deviation among VAS pain scores in patients following an arthroscopic rotator cuff repair was 2.3 mm on a 10-point scale. With a power of 80% (b level 1⁄4 .80, a level 1⁄4 .05), effect size of 2.4 mm, and standard deviation of 2.3 mm; the minimum number of patients was 16 per cohort (n 1⁄4 32) to evaluate the primary outcome.

Continuous variables are reported as means and standard deviations, while frequency counts and per- centages are displayed for categorical variables. Com- parisons between the two pain control groups (traditional and nonopioid) are performed using chi- square tests, while Fisher's exact test is used when expected cell counts are <5. For continuous variables, two-group comparisons are performed using independent 2-sample t-tests if the variable is normally distributed and using Wilcoxon rank sum tests if the variable is non-normally distributed.

Pearson correlation coefficients and their corresponding P values are provided to show the correlation between select variables for the traditional pain control group, the nonopioid pain control group, and all patients.

Repeated-measures analyses of variance were performed using mixed models and included the effects of time, pain control group, and the interaction between time and pain control group as applicable. If needed, significant interaction effects were analyzed with post hoc comparisons using a Tukey-Kramer P value correction. Predicted means of the outcome variables resulting from the models were plotted. Statistical significance is set at $P < .05$ for group comparisons and main effect testing. Significance is set at $P < .10$ for interaction testing. All analyses are performed using SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results:

Thirty patients declined to participate or were excluded, and 40 patients were included in the final analysis. A total of 23 patients were in the traditional group, and 17 patients were in the nonopioid group. Control patients on opioid pain management reported a significantly higher VAS pain score on postoperative day 1 (opioid: 5.7 ± 2, nonopioid: 3.7 ± 2.2; P = .011) and postoperative day 4 (opioid: 4.4 ± 2.7, nonopioid: 2.4 ± 2.2; P = .023). No significant difference was seen on any other postoperative day. When mixed measured models were used to control for confounding factors, the nonopioid group demonstrated significantly lower VAS and PROMIS-PI scores ($P < .01$) at every time point. Patients in the traditional analgesia group reported significantly more days with constipation (P = .003) and days with upset stomach (P = .020) than those in the nonopioid group.