Manipulation Under Anesthesia (MUA) to Treat Postoperative Stiffness after Total Knee Arthroplasty: A Multicenter Randomized Clinical Trial

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INTRODUCTION

Stiffness after total knee arthroplasty (TKA) occurs when patients have difficulty flexing and extending their knee for routine activities of daily living. Patients require 67 degrees of knee flexion during the swing phase of gait, 83 degrees to ascend stairs, 90 degrees to descend stairs and 93 degrees to rise from a standard chair.[1] When less than 90 degrees of motion is reached after TKA, the quality of life for patients is substantially decreased since simple activities like walking can become difficult.[2 3]

Despite advancements in surgical technique, implant design and pain management, arthrofibrosis (i.e., malignant stiffness) remains one of the top five reasons for revision TKA. At the upcoming 2016 American Academy of Orthopaedic Surgeons annual meeting, Matthew P. Abdel, M.D., and colleagues will present their data indicating a contemporary arthrofibrosis rate of 5.8 percent after primary TKA at Mayo Clinic. In addition, 2.8 percent of patients require a manipulation under anesthesia (MUA). While there are alternatives to MUA, physical therapy shows only modest gains and surgery is reserved for patients that fail non-operative management. With MUA, mean flexion improved 35 degrees. However, 5 percent of patients failed to maintain at least 90 degrees of flexion after the MUA at our institution. More concerning, these results were similar to the previous decade, where the rate of arthrofibrosis was 5.4 percent, with 2.9 percent requiring MUA. The only identifiable risk factor for MUA was previous knee operation. Lastly, a manipulation under anesthesia significantly increased the risk for revision. As one can see, the incidence of arthrofibrosis following primary TKA has remained unchanged over the past two decades. With the exponential increase in primary TKAs, arthrofibrosis is a large burden to the patient, surgeon and entire U.S. health care system ($8.75 billion annually).

Preliminary clinical and translational research has indicated that an inflammatory disorder of the musculoskeletal system may be responsible for post-operative stiffness in some patients.[4-8] Although evidence remains limited to animal models, the inflammatory cascade plays a central role in the formation, and recurrence, of arthrofibrosis, particularly at the time of insult (i.e. time of index arthroplasty and/or MUA).[7,9,10] This is essential as some insurance companies have stopped covering this procedure. The purpose of this study was to determine the efficacy of manipulation under anesthesia (MUA), with and without perioperative oral celecoxib and intravenous (IV) corticosteroid.

PATIENTS AND METHODS

Study Design

This study is a prospective, multicenter, randomized clinical trial (RCT) designed to evaluate the use of anti-inflammatory medications for the management of arthrofibrosis following primary TKA. Patients will be randomly assigned to either the control or experimental group. Both groups will receive a manipulation under anesthesia (MUA) if flexion is < 90 degrees at 4 –12 weeks postoperatively. Manipulation under anesthesia is the international standard of care for early arthrofibrosis. The control group will not receive any IV corticosteroids or PO non-steroidal anti-inflammatory medications (NSAIDs). The experimental group will receive a single dose of IV corticosteroids (8 mg IV dexamethasone immediately prior to MUA) and 2 weeks of PO celecoxib at a dose of 200 mg daily. Many surgeons, including several at the Mayo Clinic, consider the use of IV corticosteroids and PO celecoxib the standard of care with a MUA.

Patients

Patients will be recruited from sixteen high-volume, academic, tertiary-care referral centers (Table 1). All enrolling centers have been vetted, as only surgeons that are members of the prestigious closed Knee Society (representing the top 100 knee surgeons in the world) are participating. Patients approached for enrollment will have received a primary unilateral TKA for a diagnosis of osteoarthritis. All primary TKA constructs will have constraint that is less than that of varus-valgus constraint (VVC). All VVC and hinged TKAs will be excluded. Only MUAs scheduled between 4 –12weeks postoperatively will be included.

Institutional Review Board (IRB) approval will be obtained from all respective institutions prior to initiation of the study. The Mayo Clinic will serve as the coordinating site. Patients will be excluded from the study if any of the following exist: (1) intolerance to NSAIDs, (2) renal dysfunction, (3) age < 18 or > 90 years, (4) primary diagnosis of rheumatoid arthritis and (5) patients with GFR <60 as the cut off for CKD (stage 3 CKD). Use of non-steroidal anti-inflammatory medications during the first two weeks after manipulation under anesthesia will exclude patients from participation in this study. However, celecoxib (a non-steroidal anti-inflamatory medication) will be provided for those patients randomized to the experimental group, once daily for fourteen days following the manipulation under anesthesia. Aspirin, used routinely for DVT prophylaxis post-operatively, did not restrict patients from participation in this study. Patients who are on NSAIDs prior to MUA, is ok to enroll. Patient demographics were noted, including age at index arthroplasty, sex, body mass index (BMI), ASA score, and Charlson Index.

Randomization

Patients will be randomized into one of 2 groups: (1) MUA only (i.e. control group) or (2) MUA plus 8 mg of IV dexamethasone immediately before MUA, followed by 2 weeks of PO celecoxib (200 mg daily) (experimental group). Assignment of patients into either group will be made prior to the initiation of enrollment for the study. Patients will be randomized using a computer generated (SAS PROC) block randomization schedule to ensure equivalent numbers of patients in each group over the course of the study in case early stopping is required. The randomization schedule will be generated by the Mayo Clinic Department of Epidemiology and Biostatistics with the randomization list provided to the investigators prior to initiation of patient recruitment. Neither the patient nor the treating physician were blinded the randomization group.

Manipulation Under Anesthesia

Patients will undergo MUA per their institutional protocol. As previously noted, these will be completed between 4 and 10 weeks postoperatively for flexion < 90 degrees. Patients will receive sedation per their institutional protocol. Physical therapy (either supervised or unsupervised) will be prescribed 2 -3 times per week for 4 – 6 weeks thereafter.

Outcome Measures

The primary outcome measure will be knee range of motion, including both passive and active flexion and extension 6 weeks after the manipulation and 1 year from the date of the TKA. Secondary outcomes will include comparison of Knee Society Scores (KSS), 12-item Short Form Survey (SF-12v2), Knee Injury and Osteoarthritis Outcome Score (KOOS), and the Promise-29 outcome form (Appendices 1-4). Outcomes will be documented pre-MUA, 6 weeks

after the MUA, and 1 year after the TKA. A standardize evaluation form will be shared amongst all participating sites, and will be used consistently for all patients (Appendix 1-4).

Power Analysis

The mean and standard deviation for sample size calculation were derived from a study by Yercan et al. In that study, the authors found that the mean ROM following MUA was 114° ± 16°.[11] We hypothesized that a 10° difference in total range of motion would constitute a clinically significant difference. With a type I error rate of 5%, 108 total patients (54 per arm) are required to have 90% power to detect this difference. Accounting for a dropout rate of 20%, 65 patients per arm (130 total patients) will be recruited.

Statistical Analysis

All data will be summarized and reported descriptively using appropriate summary statistics, including mean and standard deviation (SD) for continuous variables, and count and percentage for categorical variables. The analysis was focused on the two primary study outcomes: range of motion (total arc of motion as well as angle of terminal knee flexion, measured in degrees), and subjective outcome (KSS, SF-12v2, KOOS, and PROMIS). Outcomes were compared between the two study groups using two-sample t-tests if the data are approximately normally distributed; if the data are not sufficiently normally distributed, non-parametric Wilcoxon rank sum tests was used. Since the subjects were assigned to the study groups in a randomized manner, no significant differences between the subjects in the two groups were expected. However, apparent differences in subject demographics or baseline clinical data were evaluated, and further analysis was undertaken using multivariable modeling to compare the two groups while

adjusting for other important variables. When necessary and appropriate, the analysis was adjusted for enrolling center. Categorical outcomes were analyzed using chi-square tests and logistic regression. Separate analyses were performed for the 6-week and 1-year outcomes. All statistical tests were two-sided and p-values less than 0.05 will be considered significant.

Sources of Funding

This study is partially supported by the Knee Society Branded Multi-Center Randomized Clinical Trial Grant.

TABLES

Table 1. List of participating institutions included

Aria 3B Orthopaedic Specialists
Colorado Joint Replacement
Duke University Medical Center
HipKnee Arkansas Foundation
Hospital for Joint Diseases
Hospital for Special Surgery
Houston Methodist
Joint Implant Surgeons
Mayo Clinic
New York-Presbyterian at Columbia University
OrthoCarolina
Rothman Institute
Rush University Medical Center
Cleveland Clinic
University of Nebraska Medical Center
University of Utah Orthopaedic Center

Table 2. Baseline demographics and clinical characteristics

Demographic and Clinical Characteristics	**MUA (N = X)**	**MUA + AI (N = X)**
Demographic Characteristics Age (year) Sex (female/male) (no. of patients) Weight (kg) Height (cm) BMI (kg/m^2) ASA Status (no. of patients)		
Implant Type		
Range of Motion Total Flexion Contracture Extension Deficit		

252

253

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255

256

257 **Table 3.** Outcome following manipulation under anesthesia for stiffness after total knee

258 arthroplasty

Blood Loss, Drain Output, and Rate of Blood Transfusions	**MUA (N = X)**	**MUA + AI (N = X)**	***p* value**
Six Week ROM Total Pre-Manipulation Flexion Total 6 weeks Post-MUA Flexion < 90 degrees < 80 degrees Total 6 weeks Post-MUA Flexion < 90 degrees < 80 degrees			
Six Week Subjective Outcome KSS SF-12v2 KOOS Promis 29			

Blood Loss, Drain Output, and Rate of Blood Transfusions	MUA (N = X)	MUA + AI (N = X)	*p* value
One Year ROM Total Pre-Manipulation Flexion Total 6 weeks Post-MUA Flexion < 90 degrees < 80 degrees Total 6 weeks Post-MUA Flexion < 90 degrees < 80 degrees			
One Year Subjective Outcome KSS SF-12v2 KOOS Promis 29			

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