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Methylprednisolone Taper to Treat Delayed Post-Operative Recovery After Total Knee Arthroplasty: a Double-Blind Randomized Controlled Trial

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Methylprednisolone Taper Research Protocol

I. Title:

Methylprednisolone Taper to Treat Delayed Post-Operative Recovery After Total Knee Arthroplasty: a Double-Blind Randomized Controlled Trial

II. Authors:

Matthew T. Weintraub, BS, Anne DeBenedetti, BA, Craig J. Della Valle, MD, Denis Nam, MD, MSc, Tad L. Gerlinger, MD, and Vasili Karas, MD

III. Purpose:

To evaluate the efficacy of a methylprednisolone taper on patients with decreased range of motion (ROM) or delayed recovery in the acute postoperative period following total knee arthroplasty (TKA).

IV. Hypothesis:

Patients with decreased ROM or delayed recovery six weeks to three months post-TKA will improve ROM and patient-reported outcomes at two weeks post-treatment initiation of methylprednisolone taper, as compared to similar patients who receive a placebo taper.

V. Background:

Total knee arthroplasty (TKA) is one of the most performed and efficacious orthopaedic procedures, with an estimated 7 million people living with a total knee prosthesis in 2010.[1] The number of annual TKAs is predicted to increase by 85% by 2030 and 143% by 2050, equating to 1.26 million[2] and 1.5 million[3] procedures per year, respectively. In recent studies, knee prostheses have demonstrated their efficacy in 10-, 20-, and 25-year survival rates of 96.1%, 89.7%[4], and 82.3%[5], respectively. Similarly, comparing functional and patient-reported outcomes before and after surgery have confirmed the high success rate achieved with this procedure.[6-10] However, recovery following total knee arthroplasty (TKA) in the acute postoperative period is variable. Most clinical improvements are achieved within the first three months postoperatively but can continue up to one year.[11] There is currently a paucity of data evaluating the efficacy of oral corticosteroids in the six-week to three-month postoperative period in slowly recovering patients.

Few treatments have been studied for patients who fail to achieve early range of motion or pain reduction milestones in the perioperative period. Periarticular and systemic corticosteroids improve pain and function in the immediate postoperative period, without an increase in adverse events.[12-16] Additional doses of corticosteroids administered at 24 and 48 hours postoperatively have demonstrated greater improvements in pain and ROM compared to perioperative administration, with no difference in complication rates.[17-20] However, few studies have evaluated the use of oral corticosteroids within a multimodal pain management regimen. Gardiner et al. evaluated low-dose steroids 10 days immediately following lumbar laminectomy and/or discectomy, in addition to a standard opioid regimen, and reported decreased subjective pain scores.[21] Gottshalk et al. reported decreased patient reported pain from postoperative days 4-7 in early published results of a randomized controlled trial investigating administration of a methylprednisolone taper immediately following distal radius repair.[22] Importantly, the current

literature demonstrates low- and short-dose corticosteroids are safe.[23] Intraoperative corticosteroids have been shown to improve pain and function in the acute postoperative period, and additional doses in the immediate postoperative period can potentiate and prolong this beneficiary effect, without increasing adverse events. Therefore, a methylprednisolone taper six weeks post-TKA may benefit patients experiencing decreased ROM or delayed recovery, including residual pain.

Following TKA, care is taken to control pain, swelling, and stiffness, all of which may contribute to delayed recovery. For instance, more than 20% of TKA patients develop postoperative stiffness,[24] known as arthrofibrosis, accounting for an estimated 28% of 90-day hospital readmissions.[25] In treating patients with delayed recovery, corticosteroids are of particular interest because of its potent anti-inflammatory effect, evidenced by its ability to decrease postoperative levels of IL-6 and CRP.[15] Corticosteroids block prostaglandin synthesis, which is responsible for sensitizing nociceptive pain receptors, and reduce vascular permeability, which causes edema following surgery.[26, 27] Therefore, by reducing pain and edema, corticosteroids may allow for more effective physical therapy sessions and more rapid improvement in ROM and recovery following TKA.

To the best of our knowledge, this is the first study to investigate the utility of a methylprednisolone taper six weeks to three months postoperatively following TKA. The authors present a double-blinded, randomized-controlled trial evaluating the role of a methylprednisolone taper on patients with decreased ROM or delayed recovery in the acute postoperative period.

VI. Study Design:
Level I: Prospective, double-blinded, randomized controlled trial

VII. Inclusion Criteria:
- Any patient undergoing primary TKA with a diagnosis of osteoarthritis
- ≥ 18 years old
- ROM <90° by 3 weeks postoperatively without improvement to >90° by 6 weeks
- Requiring a 30-pill oxycodone refill
- NSAID allergy
- Thigh circumference discrepancy >2cm between legs from 3 to 6 weeks
- Defense and Veterans Pain Rating Scale (DVPRS) > 5 between 3 and 6 weeks
- Willingness to undergo randomization

VIII. Exclusion Criteria:
- Reported chronic corticosteroid or opiate use
- Suspected or confirmed periprosthetic joint infection
- Revision TKA
- Primary diagnosis other than osteoarthritis, including avascular necrosis, fracture, or post-traumatic arthritis
- American Society of Anesthesiologists (ASA) score ≥ 4
- Reported history of liver or renal disease
- Uncontrolled diabetes

- Immunosuppression
- ≤ 18 years old
- Inability to take oral medications
- Unable to provide consent

IX. Demographics:
Age, sex, height, weight, BMI, ASA score, comorbidities, and smoking status will be collected

X: Primary Outcome Measure:
Change in ROM from pre-treatment to 8 and 12 weeks post-operatively

XI: Secondary Outcome Measures:
1. Patient Reported Outcome Measures:
    a. DVPRS and Knee Society Score (KSS) at pre-treatment, and 1 week, 3 weeks, 6 weeks, 12 weeks post-treatment
    b. Daily Visual Analogue Scale (VAS) pain score on days 1-6 of treatment
    c. Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS Jr), Veterans Rand 12-Item Health Survey (VR-12), Single Assessment Numeric Evaluation (SANE), Forgotten Joint Score, and UCLA activity score preoperatively, 6 weeks, and 3 months
2. Number of manipulations under anesthesia (MUAs)
3. Adverse outcomes including infection, avascular necrosis, and 90-day readmission rates

XII. Patients and Protocols:
Recruitment will include patients of four fellowship-trained orthopaedic surgeons in the Division of Adult Reconstruction at Midwest Orthopedics at Rush. Surgeons will include Dr. Craig Della Valle, Dr. Denis Nam, Dr. Tad Gerlinger, and Dr. Vasili Karas, and enrollment sites will include Midwest Orthopedics at Rush and affiliated outpatient surgical centers. Patient charts will be used to identify qualifying patients at three weeks postoperatively based on inclusion criteria. If these patients continue to meet inclusion criteria at six weeks postoperatively, they will be approached by the attending surgeon and study staff to consent to participation in the study during their regularly scheduled follow-up appointment.

If patients consent to participation in this double-blinded study, they will be randomized to one of two treatment groups. The experimental group will receive a methylprednisolone taper (21 x 4mg capsules) and the control group will receive a placebo taper (21 sugar capsules). In addition to taking assigned capsules, patients will undergo standard postoperative management, including physical therapy. Patients will qualify for MUA if flexion ROM remains <90° at 8 weeks.

Methylprednisolone and placebo capsules will be stored securely in locked cabinets at the Research Coordinator's desk. At the time of consent, a sealed, numbered envelope will be drawn from a box, and will contain the patient's randomization assignment (i.e. a piece of paper indicating experimental or control group). To maintain blinding, these envelopes will be packaged by study staff, but not the attending surgeon. Assigned capsules, stored in prescription pill bottles, will be administered at the conclusion of the follow-up appointment based upon the randomization assignment within the sealed envelopes. Patients will be provided with paper

instructions regarding how take the medication, including six capsules per os (PO) on day one, five capsules on day two, four on day three, three on day four, two on day five, and one on day six. These instructions will contain a chart detailing how many capsules to take, and at what time to take them (Appendix 1). Day one is defined as day of consent. The methylprednisolone and placebo capsules will be provided by Dermasave Labs, Inc. (Pleasant Valley, NY), a registered compounding pharmacy with the state of New York, operated by a New York licensed pharmacist with 36 years of industry experience.

Patients will be enrolled in STREAMD, a text messaging service that texts prompts to patients. Daily text messages will include reminders with the required number of pills to be taken on the corresponding day of the taper. At the time of consent, knee flexion ROM will be recorded by the attending physician and this information will be extracted from the chart. ROM will then be extracted from patient charts weekly for eight weeks using clinic or physical therapy notes as needed. PROMs collected at the time of consent will include DVPRS and KSS. DVPRS and KSS will also be collected at one week, 3 weeks, 6 weeks, and 12 weeks post-treatment. DVPRS will be administered via STREAMD. Patients will respond directly via text message reply indicating a score. VAS pain score will be collected daily on days 1-6 of the taper, via STREAMD. KSS will be completed via the PatientIQ system, which is currently used for all research related forms. For any patient that cannot use these services, surveys will be administered over the phone. All patients, whether enrolled in studies or not, complete KOOS Jr, VR-12, SANE, Forgotten Joint, and UCLA scores preoperatively, and at six weeks and three months postoperatively.

XIII. Sample Size:

Power analysis used mean flexion of 111.4° ± 16.0°, reported by Bettger et al. at 6 weeks post-TKA.[28] Control and treatment groups are assumed to have the same standard deviation. Following precedent, a change in ROM of 10° was defined as clinically important.[29, 30] At an alpha of 0.05, 112 patients (56 per arm) will provide 90% power to detect a 10° change. Assuming a 20% dropout, 136 patients (68 per arm) will be recruited.

XIV. Treatment Groups:

1. Methylprednisolone taper – 21 x 4mg tablets at 6 weeks, qualifying for MUA if ROM <90° at 8 weeks
2. Placebo taper – 21 sugar tablets at 6 weeks with standard management, qualifying for MUA if ROM <90° at 8 weeks

XV. Risks and Benefits:

Most potential risks relate to medication side effects. Side effects can be categorized by organ system and include: dermatologic and appearance (skin thinning, weight gain, acne, hirsutism, alopecia, ecchymoses, Cushingoid appearance, striae), ophthalmologic (cataracts, increased intraocular pressure, exophthalmos), cardiovascular (fluid retention, hypertension, arrythmias, premature atherosclerosis, increased lipid levels), gastrointestinal (peptic ulcer disease, gastritis, gastrointestinal bleeding, steatohepatitis), bone and muscle (avascular necrosis, osteoporosis, myopathy), neuropsychiatric (mood disorders, insomnia, akathisia, psychosis, impaired memory), metabolic and endocrine (hyperglycemia, hypothalamic-pituitary-adrenal axis suppression), immune system (increased infection risk), and hematologic (leukocytosis).[31, 32]

However, risk of side effects are proportional to dose and chronicity of treatment, with many of the reported outcomes attributed to rheumatoid arthritis patients on chronic or high dose corticosteroids.[33, 34] Importantly, a methylprednisolone taper pack is defined as a low- and short-dose corticosteroid treatment, which is considered safe by the current literature.[23] A randomized controlled trial evaluating a 15-day oral prednisone taper versus placebo for radiculopathy due to a herniated lumbar disk found an increase in minor adverse events including insomnia, nervousness, increased appetite, indigestion, headache, joint pain, and sweating, but no difference in major adverse events was judged to be associated with corticosteroid use.[35] In this study, 49.2% of patients in the corticosteroid group reported at least one minor adverse event at three weeks, compared to 23.9% in the placebo group, with insomnia being the most commonly reported.[35]

Theoretical concerns remain regarding corticosteroid administration, including risk of infection, avascular necrosis, or hyperglycemia.[36] Despite theoretical concerns, large meta-analyses analyzing randomized controlled trials demonstrated there is no difference in major adverse outcomes following corticosteroid administration, including rates of postoperative infection.[37, 38] In fact, a significant decrease in pulmonary complications was found in the corticosteroid group as compared to placebo, while no significant differences were found between groups in regard to avascular necrosis, significant gastrointestinal bleeding, psychiatric complications, or death by any cause.[38] The effects of corticosteroids on blood glucose level seem to be inconsistent, with some studies reporting no difference in blood glucose levels following corticosteroid administration, while others report a significant increase up to one day postoperatively.[37] One study evaluated 98,390 patients that had received a single methylprednisolone taper pack over a 12 year period and found a low, but statistically significant, rate of osteonecrosis of .132% compared to 0.083% in controls, corresponding to a number needed to harm of 2041 patients.[39] In a survey completed by orthopaedic surgeons prescribing short-term oral corticosteroids to high school and college athletes, none reported any cases of osteonecrosis or infection following administration.[40]

As with all studies, a potential risk is a breach of confidentiality. Procedures for maintaining confidentiality are detailed below.

There is no current literature clearly establishing the role of methylprednisolone taper in patients with decreased ROM or delayed recovery following TKA. However, as described previously, corticosteroids have been shown to reduce pain and improve function in the immediate postoperative period following TKA, without an increase in adverse events. Therefore, we hypothesize that methylprednisolone taper at six weeks postoperatively in the appropriate patient cohort may improve ROM and recovery. However, because this is a double-blinded randomized controlled trial, there is approximately a 50% chance of being assigned to the placebo group. Furthermore, data from this study may help future patients who are experiencing delayed recovery in the postoperative period following TKA.

XVI. Procedures for maintaining Confidentiality:

All data, including any personally identifiable health information such as name and date of birth, will be stored on password-protected and encrypted spreadsheets on Microsoft OneDrive Cloud service. Microsoft OneDrive requires two-factor authentication. Only approved study staff, as

determined by the principal investigator, will have access to these stored data spreadsheets. All data collected for the purpose of this study will be de-identified for statistical analysis and publication.

XVII. Budget:

All costs for this study will be departmentally funded.

Item	Cost
Methylprednisolone Taper Packs	$3000
Placebo Taper Packs	$1500
Total	***$4500***

XVII: References

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Appendix 1: Dosing Schedule

	***Before* Breakfast**	***After* Lunch**	***After* Dinner**	***Before* Bedtime**
Day 1	2 capsules	1 capsule	1 capsule	2 capsules
Day 2	1 capsule	1 capsule	1 capsule	2 capsules
Day 3	1 capsule	1 capsule	1 capsule	1 capsule
Day 4	1 capsule	1 capsule	X	1 capsule
Day 5	1 capsule	X	X	1 capsule
Day 6	X	X	X	1 capsule