

POST INJECTION REST IN OSTEOARTHRITIS OF
THE KNEE: EFFECT ON PAIN RELIEF AND
KNEE FUNCTION AFTER INTRA-ARTICULAR
CORTICOSTEROIDS
A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL

CENTRE FOR NEWFOUNDLAND STUDIES

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**Post Injection Rest in Osteoarthritis of the Knee: Effect on Pain Relief and Knee
Function After Intra-Articular Corticosteroids
A Prospective Randomized Controlled Trial**

by

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A thesis submitted to the

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ABSTRACT

Primary osteoarthritis (OA) of the knee is a common clinical problem. One non-operative modality commonly used for symptomatic pain relief is an intra-articular corticosteroid injection. In rheumatoid arthritis patients, a period of rest post-corticosteroid injection (i.e. decreased weight bearing on the extremity), has been shown to improve clinical response. This question has yet to be addressed for patients with primary OA of the knee.

A twelve week randomized controlled trial was conducted in knee OA patients requiring an intra-articular corticosteroid injection into the knee. Forty-three patients were randomized to the rest group and forty-three to the no rest group. Patients in the rest group were instructed to keep weight bearing activities to a minimum for twenty-four hours after the injection. The no rest group had no physical restrictions placed on them. The primary outcome measure was the total WOMAC Index, which incorporates components of pain, stiffness and function. The WOMAC was measured at two, six, and twelve weeks post-injection. Repeated measures ANCOVA was used to analyze the primary outcome.

This trial failed to demonstrate any short term clinical benefit of post-injection rest after an intra-articular corticosteroid injection in patients with primary osteoarthritis of the knee.

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CHAPTER 1 INTRODUCTION

1.1 Background

Primary osteoarthritis (OA) of the knee is a significant clinical problem and as the population ages, the burden of this disease will increase. Primary osteoarthritis is a progressive “wear and tear” arthritis that increases in prevalence after age 50. It is estimated that 25 – 30% of people aged 45 to 64 and more than 85% of people older than 65 years of age have OA of the knee identifiable on radiographs (Cole et al). In comparison, secondary OA occurs after a known insult to the joint. Some common causes of secondary OA include intra-articular fracture, varus or valgus malalignment, and ligament or meniscal deficiency.

Published in the proceedings of a conference sponsored by the American Academy of Orthopaedic Surgeons (AAOS) and National Institutes of Health was a definition of OA: “Osteoarthritis is the result of both mechanical and biological events that destabilize the normal coupling of degradation and synthesis of articular cartilage and subchondral bone. Although it may be initiated by multiple factors including genetic, developmental, metabolic and traumatic, OA involves all the tissues of a diarthrodial joint. Ultimately, OA is manifested by morphologic, biochemical, molecular and biomechanical changes of both cells and matrix. This leads to softening, fibrillation, ulceration, and loss of articular cartilage, sclerosis, and eburnation of subchondral bone, and formation of osteophytes and subchondral cysts. When clinically evident, OA is characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of local inflammation” (Keuttner et al.).

It is the inflammatory component of this disease, and its treatment, which are of most interest here. OA is considered primarily a degenerative arthritis, particularly when

compared to primary inflammatory arthropathies such as rheumatoid arthritis. The inflammatory component of OA is thought to be secondary to the articular cartilage degeneration, however histologically the changes in the synovium are similar.

These histologic changes vary, depending on the stage of disease. The acutely inflamed joint early in the disease process has synovium with marked hyperplasia and a dense cellular infiltrate composed mainly of lymphocytes and monocytes. Toward the later stages of the disease, in “burned out” joints, the synovial membrane is thickened by fibrotic tissue, with little cellular infiltrate. The histology of OA is similar to inflammatory arthropathies, with the degree of inflammatory changes less in the synovium affected with OA (Haraoui et al.).

This inflamed synovium can produce substances that directly degrade articular cartilage. This synovium expresses high levels of inflammatory cytokines such as TNF- α and IL-1. These two factors stimulate MMP's, COX-2, and nitric oxide synthetase that directly degrade articular cartilage. Nitric oxide has recently been implicated in the pathogenesis of OA. It produces free radicals that result in an increase in chondrocyte apoptosis and this decline in chondrocyte numbers impairs the ability of the articular cartilage to maintain homeostasis and promote repair. (Ulrich-Vinther et al.)

Patients with osteoarthritis of the knee present primarily for treatment of pain. Two components of the disease probably combine to cause this pain. Cartilage destruction causes mechanical or skeletal pain. The inflammatory component results in pain through a separate mechanism.

Bone is rich in afferent nociceptors. Recent opinion was that the vast majority, if not all, of these fibers exist in the periosteum of bone (Mundy). This rich bed of nerve

fibers would explain the severe pain that is present with a fracture in which the periosteum has been disrupted. As the intracapsular or articular component of the bone is devoid of any periosteum, the conclusion that joint damage and exposed ebernated bone in isolation may not be painful could be drawn. Recent work in a rat model (Mach et al.), has shown that bone and bone marrow have sensory fibers. With an antibody labeling technique, the presence of myelinated and unmyelinated sensory fibers was demonstrated. These fibers could have a coordinated role in the generation of bone pain in patients with OA. As cartilage is completely lost and subchondral bone is exposed, the presence of these nerve fibers in bone may explain one pathway for pain in these knees.

Pain also results from the significant inflammatory reaction that can be present in osteoarthritic knees. As the course of the articular cartilage component of the disease is one of slow, continuous deterioration, it is the pain due to inflammation that causes the waxing and waning pattern often seen. Periods of severe discomfort with joint swelling, warmth and erythema may be interrupted by periods when the joint is relatively pain free. This inflammation stimulates the abundant pain fibers within the synovium and joint capsule.

The goal of treatment for OA is to lessen the burden of this pain. Pain in a joint will negatively affect its role thus affecting overall patient functioning and quality of life. Secondary goals of treatment include improving range of motion, correcting deformity, and preventing/slowing disease progression. Although total joint arthroplasty has been successful, it is only needed in a small proportion of patients with knee arthritis. Most patients avoid or delay surgical treatment with the many non-operative modalities that are available. Despite the varying success in relieving pain, no medical therapies to date have

been shown to prevent or slow joint degeneration, i.e. change the natural history of the disease. (Ulrich-Vinther et al.)

Treatment regimes for symptomatic osteoarthritis address different components of the disease. Joint deformity, either congenital or secondary to cartilage destruction or traumatic joint injury, can be treated with bracing or corrective surgery (osteotomies). Replenishing lost or degenerated articular cartilage has proven to be a formidable task. Replacing lost articular cartilage with osteochondral graphs, either allographs or autographs, has had variable success. Replacing lost cartilage and chondrocytes with tissue grown in tissue cultures has some promise but remains far from clinical use. The inflammatory component of the disease is often treated with systemic modalities (NSAID's) or local modalities (intra-articular corticosteroids).

In 2000, the American College of Rheumatology published recommendations for the non-surgical management of OA. (American College of Rheumatology Subcommittee). Nonpharmacologic therapy include education, weight loss, exercise programs and physiotherapy, assistive devices (cane), bracing and shoeware modifications. Pharmacologic therapy often starts with a mild analgesic. Acetaminophen, up to 4 grams per day, is generally well tolerated and is effective in mild to moderate disease (Bradley et al.). More severe disease or failure of acetaminophen therapy requires the use of non-steroidal anti-inflammatory drugs (NSAID's). Multiple authors have demonstrated the effectiveness of these medications over both acetaminophen and placebo and the side effects are well known. (Wolfe et al., Pincus et al., Altman et al.) Gastrointestinal side effects are the most problematic for the traditional NSAID's but

newer selective COX-2 inhibitors have a lower incidence of these problems. (American College of Rheumatology Subcommittee)

If these initial treatment modalities fail to adequately control a patient's symptoms, intra-articular therapies are often the next step. Recently, an intra-articular injection of a hyaluronic acid analog has been used. Hyaluronic acid is a component of synovial fluid and has been shown to be present in a lower concentration in knees with osteoarthritis. An analog of hyaluronic acid has been synthesized and has been shown to temporarily decrease the symptoms of OA of the knee when injected into the joint (Altman et al., Dougagos et al, Scale et al., Wobig et al.). Most regimes involve three injections separated a week apart and can provide six months to a year of improvement in pain level and functioning (Watterson et al.).

Viscosupplementation is not without concerns. Drug regulating bodies have classified these injections as medical devices. Thus, they have not had to meet the stringent safety and efficacy requirements of a drug. Although some trials have shown a clinical benefit, others have not demonstrated any improvement over placebo (Dahlberg et al., Henderson et al., Lomander et al.). In a recent prospective, randomized trial (Leopold et al.), viscosupplementation has not been proven to provide any better clinical result than intra-articular corticosteroids.

Adverse reactions of viscosupplementation have been reported. A local inflammatory reaction has been seen in up to eight percent of patients. This reaction is often severe, resembling a septic joint. Reactions are usually transient and no systemic effects have been reported. (Watterson et al., Lussier et al., Pyron et al.) Cost is often a prohibitive factor. A course of injections can cost hundreds of dollars.

Total joint arthroplasty (TJA) had revolutionized the treatment of end stage OA of the hip and knee and its success is well documented (Hanssen et al.). In patients who have failed non-operative treatment, TJA frequently results in a dramatic decrease in joint pain and an improvement in overall functioning. This procedure, despite its overall success, is not without its concerns. Deep infection and component dislocation can be serious problems and the devices do not have an infinite lifespan. Total joint arthroplasty is a less attractive option in patients younger than sixty years of age. (Ranawat et al.) These patients are more active and “wear out” their artificial joint at a faster rate than an elderly, more sedentary individual. Revision or redo surgery for a failed total joint arthroplasty produces inferior results compared to the primary procedure. (Ewald et al.) Younger arthroplasty patients will frequently require multiple complicated surgeries years after the index procedure. (Hanssen et al.) It is these concerns that leaves TJA for end stage disease in patients that have exhausted all non-operative modalities.

1.2 Intra-articular corticosteroid and knee OA

1.2.1 Prevalence and mechanism of action

A mainstay of treatment for OA of the knee has been intra-articular corticosteroid injections. First described in 1951, these injections have been used very commonly with some benefit and minimal risks. One survey of 223 orthopaedic surgeons revealed that each used intra-articular steroids on average 150 times per year (Fadale et al).

The mechanism of action of corticosteroids has been well documented. Corticosteroids are naturally occurring substances. They are synthesized from a

cholesterol foundation in the adrenal cortex. Corticosteroids produce an effect, to varying degrees, on most metabolic processes within the body.

These substances pass freely through the cell membrane and bind to receptors within the cytoplasm. This steroid – receptor complex can then enter the cell nucleus and alter RNA synthesis. The end result is an alteration of enzyme production and thus can have effects on all systems of the body.

Of most interest here is the effect of corticosteroids on inflammation.

Inflammation is the first of four stages in the healing process. Inflammation clinically is characterized by pain, stiffness, redness, swelling and heat. During this inflammatory phase, there is increased cellular membrane permeability and edema results. Leukocytes and macrophages are drawn to the area by chemical mediators. Macrophages remove dead cellular material and the leukocytes release hydrolytic enzymes producing arachidonic acid by hydrolysis of cell membrane phospholipids. It is the production of arachidonic acid that is altered by the corticosteroids.

Corticosteroids inhibits phospholipase A₂. Phospholipase A₂ catalyzes the breakdown of membrane phospholipids to arachidonic acid thus disrupting the inflammatory cascade. The latter three steps in the healing process, repair, remodelling, and maturation phases are less affected (Fadale et al.).

1.2.2 Review of efficacy of corticosteroid knee injections

The pain relieving benefits of intra-articular injections have been previously studied. Several randomized trials have been conducted and have showed either a mild, temporary benefit (1-2 weeks) (Dieppe et al., Friedman et al.) or no benefit over placebo

(Cederlof et al). Recently a meta-analysis of intra-articular steroids for OA of the knee has been completed (Towheed et al.). It demonstrated a role for intra-articular steroids in the short-term management of OA of the knee. No evidence has shown a lasting benefit (> 1 month) from these injections.

Many different corticosteroid preparations are available for intra-articular injection but there are no firm guidelines on deciding which drug to use. Water solubility seems to affect duration of action with the more water soluble compounds having a shorter duration of action. Water insoluble preparations are often used for chronic inflammatory conditions and more water-soluble used for more acute conditions. No clinical literature is available to support these trends with drug choice based solely on these theoretical principles (Fadale et al.).

Dosage of steroid used also lacks firm recommendations. In current clinical practice, the amount of steroid used is proportional to the size of the joint to be injected. Presently, the clinical practice at our institution is to use 40 mg of methylprednisolone acetate (Depo-Medrol) in a knee joint. Methylprednisolone acetate is cheap, readily available and is only slightly water-soluble (Fadale et al.).

There is debate about the safety of these drugs used intra-articularly. Although there is contradictory evidence (Pelletier et al.), it is felt by some investigators, based mainly on animal model work, that intra-articular steroid is deleterious to articular cartilage. In an animal model it has been shown that the steroid causes a decrease in cartilage – matrix production (Behrens et al., Mankin et al.). The drug inhibits chondrocyte proliferation and decreases matrix synthesis and it blunts the response to important growth factors such as TGF- β . There is no firm evidence, however, to show in

humans that intra-articular steroids, while relieving pain, speeds articular surface deterioration. This may be impossible to determine, as it will be difficult to show the steroid has a clinically relevant negative effect on articular cartilage structure when the natural course of the OA is progressive cartilage destruction.

The best evidence that addresses the clinical safety of intra-articular corticosteroid injections is recent work performed in Montreal (Raynauld et al.). This was a randomized, double blind, placebo controlled trial of intra-articular corticosteroids for OA of the knee. The investigators compared saline injections to corticosteroid injections every three months (regardless of pain relief) for two years. Radiographic loss of joint space was the primary outcome measure. The investigators felt that increased articular cartilage destruction secondary to these frequently administered corticosteroid injections would cause a decrease in the radiographic joint space. The trial failed to show any significant difference in the rate of joint space loss between the experimental and control groups. Thirty-four patients were in the experimental group and no adverse effects, either clinical or laboratory, were reported.

These joint injections are not truly local therapy. There is some systemic absorption of the intra-articular corticosteroid injection. The water solubility of the preparation is proportional to the amount of systemic absorption and suppression of the hypothalamus - pituitary – adrenal axis for two to seven days has been shown with high doses. Therefore only one large joint should be treated per visit and injections should be spread out over as long a time period as possible (Gray et al.).

This systemic absorption of the steroid may be responsible for reports of pain relief in joints other than the one injected. This is known as the “spill over effects” and is reported mainly in patients with primary inflammatory arthropathies.

Despite the theoretical concerns, side effects are very unusual and allergic reactions have been rare. This form of therapy has been used for at least thirty years and has a proven to be effective and safe (Kumar et al.). Unlike hyaluronic acid injections, cost is not a prohibitive factor.

Indications, contraindications, and method of injection cause little debate. Indications would include an osteoarthritic knee, diagnosed on clinical history, physical exam and plain radiographs, that has failed management with less invasive therapy such as NSAID’s, physiotherapy, activity modification and walking aids. Contraindications would include known hypersensitivity to the corticosteroid or an active infection at the injection site.

The post injection management for these patients varies between physicians. Some suggest the patient remain non-weight bearing for a period of time (24-48 hours) post-injection and others allow the patient to be as active as the pain allows without any specific restrictions. The physicians who restrict their patients claim an improved symptomatic response to the injection and a longer duration of benefit. Others argue that restricting the patient’s activity will not provide any appreciable improvement in outcome.

1.3 Rest and its Effect on Arthritis

Rest has been a form of treatment for arthritis for centuries. During the 1970's and early 1980's, patients with acute exacerbations of arthritis would routinely be admitted to hospital for strict bed rest for weeks or months. Joints would be immobilized with splints or casts. This regime was most frequently used for patients with inflammatory arthropathies. There are some theoretical benefits of rest in patients with inflammatory arthropathy. This has been mainly broken down into inflammatory and mechanical factors.

The intensity of the inflammatory response in an affected joint is worsened with activity. In both a rat and a rabbit model (Smith et al.), activity increased synovitis and inflammation compared to immobile joints. Increased motion also seems to increase joint effusions. Intra articular pressure is increased as well as synovial collagenase activity. This is thought to accentuate articular cartilage destruction, bony erosions and subchondral cyst formation.

Mechanical factors influenced by rest also have a role. Shear, torsion and tension are harmful to articular cartilage but are lower in magnitude than compressive force caused by weight bearing. Unloading the joint with bed rest reduces these forces.

Along with the theoretical benefits, proponents of rest treatment cited evidence demonstrating the safety of joint immobilization for up to four weeks and that patient's acute exacerbation settled more quickly with rest (Partridge et al.). It was also felt, without good evidence, that rest may decrease the constitutional manifestations of the disease (Partridge et al.).

Rest is not benign, cheap or easy to enforce. Prolonged rest results in muscle atrophy, osteopenia, and joint stiffness. There is an increased risk of thromboembolic disease, pneumonia, and skin problems. Not to be ignored are the psychological effects of this treatment. Direct financial cost is incurred with forced rest. Hospital beds and nursing care are expensive and in short supply. Missed work by patients results in significant indirect costs and compliance is difficult to enforce (Smith et al.).

Several investigators have attempted to answer the question whether or not forced rest has any clinical benefit, both short and longer term, in patients with inflammatory arthropathies. Prior to the 1970's, no good evidence existed for its use. Rest was commonly included in treatment regimes but was never studied as an isolated variable. Mills et al. performed a single blind randomized controlled trial that used rest as the only independent variable. Included were hospitalized patients with RA who continued with their usual medical management throughout the trial. Outcome measures included joint range of motion, number of swollen and tender joints, grip strength, walking time, ring size and sedimentation rate. The investigators could not demonstrate a statistically significant difference between the rest and activity groups in any of the outcome measures.

1.4 Review of the Literature

Very little research has been completed on the combination of a rest and intra-articular steroids use in arthritis. This paucity of evidence has resulted in the wide variety of post injection regimes in clinical practice. One paper by Chakravarty et al., tackled the question of efficacy of rest after an intra-articular corticosteroid injection into the knee.

This was performed in patients with an inflammatory arthropathy. It was a randomized controlled trial of ninety-four patients who had a steroid injection into the knee for pain non-responsive to other non-invasive modalities. Patients who were randomized to the rest group were admitted to hospital for twenty-four hours of strict bed rest while the control group were sent home with no particular restrictions on their activity. The groups were randomized using random number tables and appeared similar in some common variables (age, sex, duration of disease, and type of inflammatory arthropathy). The entire group would reasonably represent this patient population and no patients were lost to follow-up.

No validated scoring system was utilized as an outcome measure. Pain and stiffness was assessed using a ten centimetre visual analog scale. Knee circumference and fifty foot walking time was also measured. Laboratory assessments included a complete blood count, erythrocyte sedimentation rate and C-reactive protein. These outcome measures were collected at the time of injection and three, six, twelve, and twenty-four weeks post injection.

Using a statistical measurement tool by Matthews et al., the investigators found that the overall improvement of each outcome measure during the time frame of the study was better in the rest group compared to the no rest group. These findings were statistically significant ($p < 0.05$). Erythrocyte sedimentation rate and C-reactive protein also demonstrated an overall improvement in the study group. Pattern of improvement was not explicitly explained. The paper includes graphs of scores for each outcome measure for ten “representative” patients. It appears from the graphs that improvement

early (3 and 6 weeks) was similar for both groups, but at later times (12 and 24 weeks) the rest group fared better.

Seventeen percent of the patients did not complete the trial. These patients required a change in treatment for their knee synovitis due to a recurrence of their pain during the treatment period. This change in treatment was defined as a change or addition to their medical treatment, the necessity of a repeat steroid injection into the study knee, or an injection into another joint. A greater number of patients from the non-rest group had to withdraw, but this finding was not quite statistically significant ($0.05 < P < 0.1$).

There are some criticisms of this paper. Firstly, the assessors were not blinded in this study. Although blinding would have been ideal, most of the outcome measurements were completed by the patients (i.e. the visual analog scales and fifty foot walking times) or were objective lab values. This is probably not a fatal flaw in the study design.

This paper used non-standardized outcome measures which introduces two concerns. It makes comparison of the results of this paper to others difficult such as in a meta-analysis. Also the reader is not certain if the outcome measures used are sensitive enough to pick up a clinically relevant difference.

Another problem with extrapolating the results of the previous study in RA to our study in primary OA is that these are two different disease processes. The outcome measures selected in the above study are not relevant for primary knee OA .

The most significant limitation of this paper was the practicality of the intervention that is being proposed. The effect size of the improvement is likely to be small and thus the impact regarding cost effectiveness minimal. In our present Canadian health care system, forced and monitored rest for twenty four hours in a hospital setting

for all arthritis patients after a corticosteroid injection into the knee would likely not be feasible.

The concerns raised with the use non-standardized outcome measurement tools have spawned the development of standardized, validated outcome measures that are often disease specific. The measurement tool selected for this trial was the WOMAC, the Western Ontario, McMaster Osteoarthritis Index (Appendix 2). Its purpose is to measure clinically significant, patient relevant symptoms of pain, stiffness, and physical function in patients with osteoarthritis of the knee following intervention. (Bellamy et al.). Using a twenty four item questionnaire, three dimensions are measured, with subscales of pain, stiffness and function. All questions relate to the patient's experiences over the past forty-eight hours.

There are two versions available, a five point Likert scale and a 100mm horizontal visual analog scale. The Likert scale chosen here uses descriptive adjectives: none, mild, moderate, severe and extreme, which are translated into a numeric, ordinal scale (0-4). Total WOMAC score is a continuous variable representing an average of each subscale. Lower scores indicate a lower level of dysfunction. (Bellamy et al.)

Reliability, validity, and sensitivity/responsiveness to change has been extensively studied and results are generally positive. The pain and function subscales exhibit comparable or greater responsiveness than similar dimensions on the SF-36. (Rogers et al.) Not unlike other disease specific scales, the WOMAC is not immune to influence by other patient factors. Fatigue, depression, symptom counts, and low back pain, though not directly measured by the scale, seem to influence scores. (Wolfe) This measurement tool has been extensively used in the orthopedic and rheumatology literature.

A literature search revealed no randomized trials that attempted to answer the rest versus no rest question in patients with primary knee osteoarthritis. With the demonstrated clinical success of corticosteroid injections in OA patients, the recognition of the inflammatory component of osteoarthritis and the evidence to suggest that post injection rest is helpful in inflammatory arthropathies, many clinicians today recommend a period of rest in OA patients after injection. However, there is no direct evidence to support this practice. RA and OA are different disease processes and extrapolating the results of Chakravarty et al. to OA patients may not be valid. Thus a trial was designed to answer our research question.

1.5 Research Question

“Does a rest period of twenty four hours after an intra-articular steroid injection improve the magnitude and duration of pain relief in patients with osteoarthritis of the knee.”

CHAPTER 2 MATERIALS AND METHODS

The research question was addressed with a randomized controlled trial. Patients with primary osteoarthritis of the knee who had failed traditional non-invasive treatment were recruited for the study. They were randomized to either a period of rest (study group) or to non-restricted activity (control group) after an intra-articular steroid injection.

2.1 Subject Selection

Patients were recruited from outpatient Orthopaedic clinics. Patients were approached and asked to participate in our study if they met inclusion and exclusion criteria that had been established.

2.1.1 Inclusion Criteria

1. Primary osteoarthritis of the knee. Diagnosis based on clinical and radiographic findings and AAOS definition of OA. The diagnosis was made by the attending physician.
2. Non-invasive modalities of treatment, i.e. activity modification, NSAID's, have failed to satisfactorily control symptoms of pain and swelling. The attending physician has decided on treatment with an intra-articular corticosteroid injection.
3. Patient available for follow up during the study period.
4. Patient's informed consent expressed via signature on consent form.

2.1.2 Exclusion Criteria

1. Contraindication to intra-articular corticosteroid injection. (i.e. undesirable reaction to previous injection or active infection at the injection site.)
2. Inability to comply with a period of rest. (Reasons may include occupation or personal commitments that would make this rest period unacceptable.)
3. Inability or unwillingness to provide informed consent.

2.2 Randomization and Sample Size Calculation

Patients were randomized to the study or control group by the use of a coin toss as each subject is recruited. Heads – study group, tails – control group.

Our primary outcome measure was the total WOMAC score. Previous studies have reported a mean score of 10.3 with a standard deviation of 4.4, among patients with primary OA. We set a clinical difference of 20% as being clinically relevant. With $\alpha = 0.05$ and $\beta = 0.20$, a sample size of 39 patients per group was calculated for each group. Assuming a dropout rate of 10%, 43 patients per group (86 total participants) were required to answer our research question.

2.3 Intervention

When the inclusion criteria were met and informed consent was obtained (Appendix 1), the patient was either assigned to the control or experimental group. Regardless of assignment, the attending physician carried out a corticosteroid injection into the affected knee using 40 mg of methylprednisolone acetate (Depo-Medrol). The treating physician was not aware which of the two groups a patient was allocated.

With an assignment to the control group, the patient was discharged from the clinic with no restrictions on their activity. They were informed to perform any desired activity within the limits of their discomfort.

With assignment to the study group, patients were asked to rest for twenty-four hours after injection. Rest was defined as only the necessary walking required for the trip home (i.e. from the clinic to the car and from car to house) and the walking at home necessary for meals and personal hygiene.

2.4 Outcome Measurement

The primary outcome measure was the total score of the WOMAC which includes the pain, stiffness and function subscales. A standardized questionnaire was administered to the patient, including demographic information, concomitant therapy, and disease related factors (appendix 2). Specifically, we recorded the age at the time of the study, sex, and analgesic use (i.e. NSAID's, acetaminophen, opiates, or natural remedies) in the 48 hours preceding injection as well as the number of previous steroid injections into the same knee. The parameters noted above were ascertained by a single study nurse who was well acquainted with the protocol. The patients then were provided the WOMAC questionnaire which was completed during the initial visit. Subsequent WOMAC measurements were retrieved by telephone at 2 weeks, 6 weeks and 12 weeks post injection. Adverse reactions, if any, were documented systematically in the study sheet. The patients were not prompted regarding any particular side effect. In an attempt to standardize the data collection procedure, a single study nurse was employed and a script was followed during collection of data over the telephone (Appendix 3).

Compliance with the intervention was assessed by asking the volunteers in the rest group, at the two week data collection point, if they indeed complied with the request to rest. As a broad measure for global satisfaction for both groups the volunteers at 2 weeks were asked if they had their time back, would they still have had the intra-articular injection performed.

Study design is summarized in Figure 1

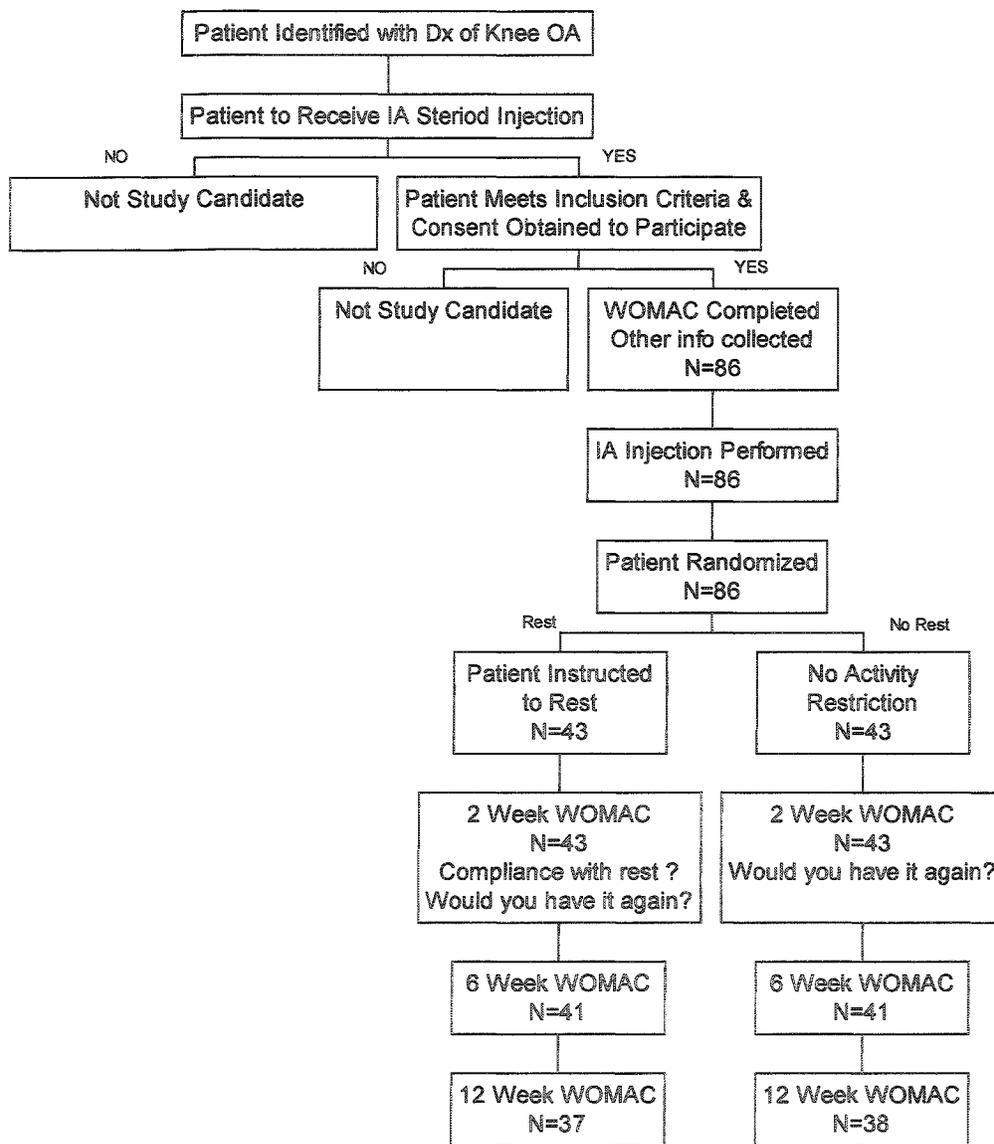


Figure 1 Study Design

2.5 Analysis

The two groups were compared to look at the similarity of the baseline parameters. Chi-squared analysis was performed for the following categorical variables as all the cells had at least 5 subjects: sex, side, previous corticosteroid injections, and use of any medication in the last forty-eight hours. For the continuous variables (age of subjects at time of study), student t-test was used.

Mean WOMAC scores were calculated for each subject at each of the four data collection points (immediately preceding injection, and 2, 6, and 12 weeks post injection). Statistical testing involved Repeated Measures Analysis of Co-Variance (ANCOVA) for both total WOMAC score and the pain subscale. The pain subscale was singled out as some investigators feel this is the most relevant parameter to assess efficacy of medical interventions as the treatment goals are primarily focused on limiting pain. (Robertsson et al.)

A multiple linear regression analysis was conducted to assess if any patient parameters helped predict response. The dependent variable was the change in the WOMAC score. The independent variables included, age, sex, number of previous cortisone injections, and analgesia use.

All statistical analysis was carried out using SPSS Version 11.0.1. (SPSS Inc. Chicago, IL.)

2.6 Ethical Issues and Consent

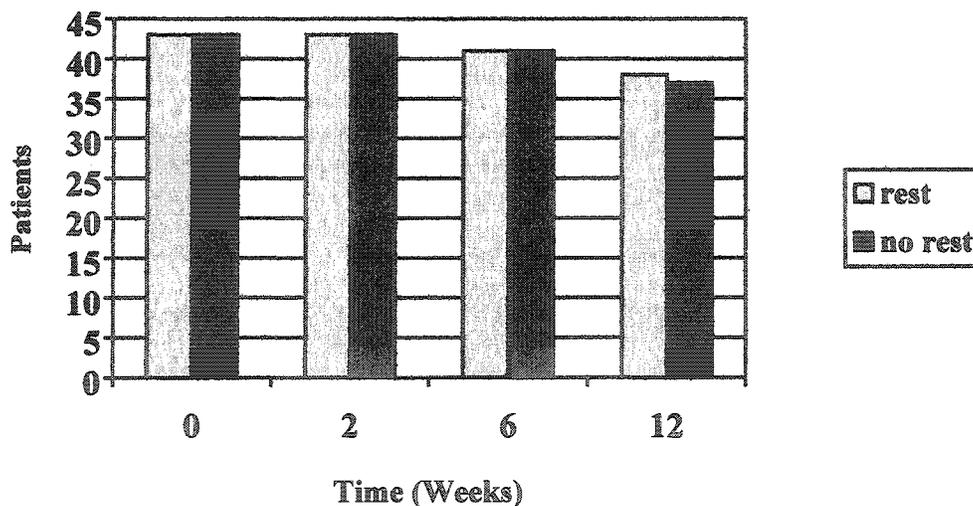
Study design and implementation met all the guidelines of the Tri-Council's policy statement of August 1998. Approval by the Human Investigations Committee at Memorial University of Newfoundland and Health Care Corporation of St. John's was granted (Appendix 4 & 5). Signed informed consent was obtained from all study subjects and subjects were reassured that they were free to leave the study protocol at any time. If a subject chose not to become involved in the study after the injection was given, post injection activity level was at the discretion of the attending medical staff.

Patient confidentiality was strictly protected. All patient records were treated as hospital charts and were stored safely under lock and key.

CHAPTER 3 RESULTS

Eighty-six patients were recruited to the study from outpatient orthopedic clinic between October 2001 and May 2002. Seventy-five (88.4%) patients completed the full twelve-week protocol. Eighty-two (95.3%) completed six weeks and all patients completed the two-week questionnaire (Figure 2). The reasons for withdrawal included: seven patients had repeat injections due to increase in symptoms, two patients had total knee replacements, one patient became incapacitated for medical reasons, and one could not be contacted.

Figure 2
Patients completing Follow-up



Forty-three patients were allocated to each group. Using a Chi-Square analysis, the groups were compared for homogeneity. (Table 1)

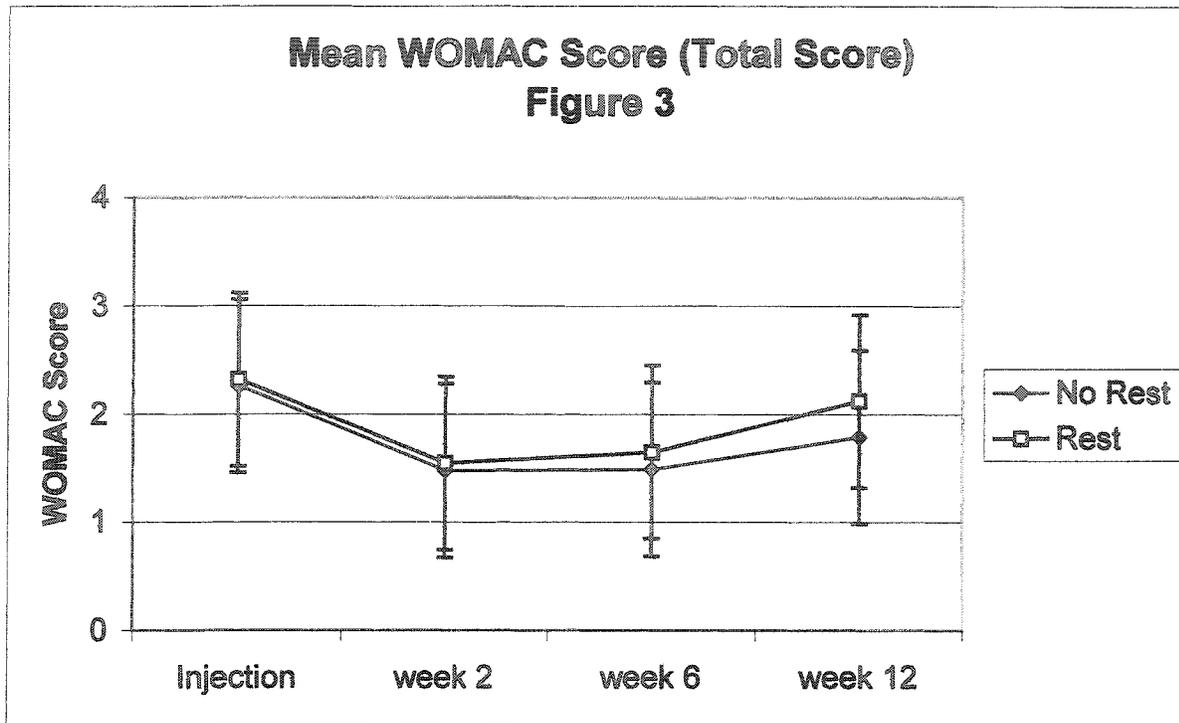
<u>Table 1</u>	Rest	No Rest	P value
# of Patients	43	43	
Mean Age (S.D.)	63.5 (14.2)	63.8 (13.0)	0.913
Side (R or L)	R 21 L 22	R 22 L 21	
Meds Taken last 48h	28 (65.1%)	30 (69.8%)	0.700
Previous Injection	25 (58.1%)	22 (51.2%)	0.451

Patient Baseline Characteristics

Total WOMAC scores were then analyzed (Table 2 and Figure 3).

<u>Table 2</u>	Injection	2 weeks	6 weeks	12 weeks
Rest (S.D.)	2.32 (0.829)	1.54 (0.961)	1.65 (0.775)	2.12 (0.942)
No Rest (S.D.)	2.26 (0.780)	1.48 (0.879)	1.49 (0.957)	1.79 (1.064)

Mean WOMAC scores (Total)



Efficacy of the injections was considered. The mean WOMAC score improved in both groups that maximized at week 2 but continued even until week 12. Paired T-tests were performed comparing week 2, 6, and 12 to the baseline score at injection for each group. These tests do not take into account the time line; it was performed to demonstrate that the injections do provide a clinical benefit (reduction in the WOMAC score) at most of our data collection points in both groups. At 12 weeks the no rest group score was slightly above statistical significance when compared to score at injection. (Table 3)

Table 3	P value on Paired Samples T-test (Rest Group)	P value on Paired Samples T-test (No Rest Group)
Injection – 2 weeks	P<0.001	P<0.001
Injection – 6 weeks	P<0.001	P<0.001
Injection – 12 weeks	P=0.020	P=0.074

Baseline Comparison (Total WOMAC Score)

To answer our research question, a comparison of the total WOMAC score of the study and control group was then completed with a Repeated Measures analysis of covariance (ANCOVA) which produced a p value of 0.506.

The primary purpose of intra-articular steroid is pain relief and relief of pain correlates well with patient satisfaction (Robertsson et al). We reanalyzed the groups using only the pain subscale of the WOMAC with an ANCOVA test and again failed to demonstrate a difference between the study and control groups (p=0.710). The paired samples t-test was repeated for the pain subscale and it demonstrated a reduction of pain in both groups at each data collection point (Tables 4, 5 and Figure 4)

<u>Table 4</u>	Injection	2 weeks	6 weeks	12 weeks
Rest (S.D.)	2.15 (0.932)	1.35 (1.01)	1.34 (0.858)	1.75 (1.11)
No Rest (S.D.)	2.28 (0.931)	1.23 (0.947)	1.44 (1.09)	1.88 (1.23)

Mean WOMAC scores (Pain Subscale)

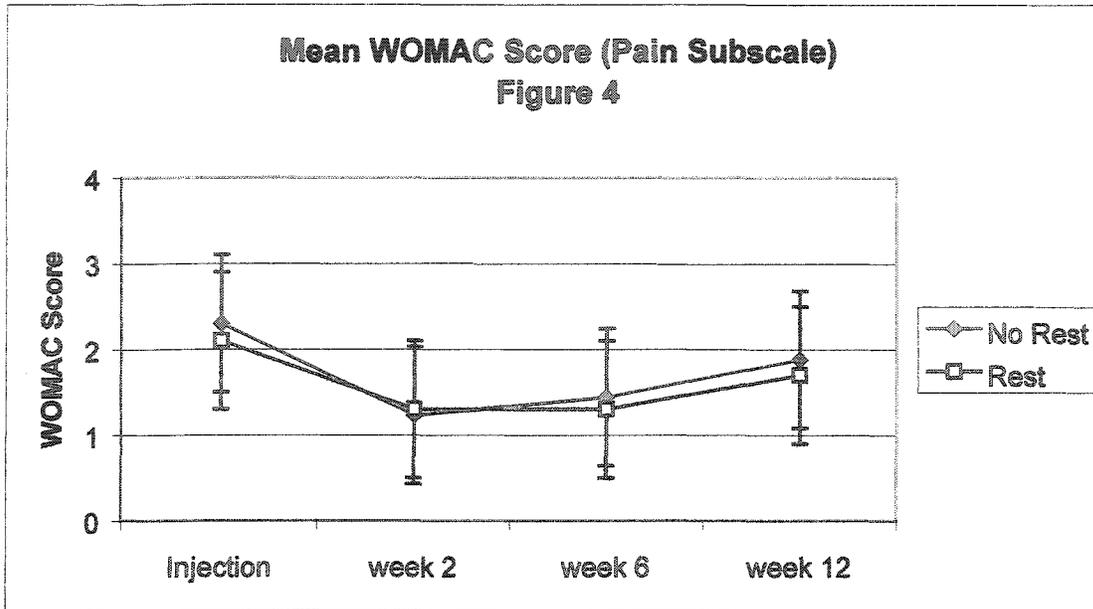


Table 5	P value on Paired samples T-test
Injection – 2 weeks	P < 0.001
Injection – 6 weeks	P < 0.001
Injection – 12 weeks	P = 0.008

Baseline Comparison (Pain Subscale WOMAC Score)

The ANCOVA accounts for the fact that the data was repeatedly collected at various points in time on the sample subjects. T-tests were performed at each data collection point to simply compare the study and control groups at each point in time for both the total WOMAC score and the pain subscale. No statistically significant results were demonstrated. These findings are summarized in Table 6.

Table 6	Week 2	Week 6	Week 12
Rest vs No Rest (Total WOMAC)	P = 0.764	P = 0.598	P = 0.542
Rest vs No Rest (Pain Subscale)	P = 0.600	P = 0.665	P = 0.643

Comparison of Study and Control Group (Total Score and Pain Subscale)

The re-injected patients were analyzed. Of the seven patients, three were from the No Rest group and four from the Rest group. This small group was then compared to the rest of the entire sample using an independent samples t-test and no significant difference was found in WOMAC scores at baseline ($p=0.385$), week 2 ($p=0.518$), or week 6 ($p=0.594$).

Table 7	Reinjected Group (Mean WOMAC Score)	Non-Reinjected Group (Mean WOMAC Score)	P Value
Baseline	2.52	2.24	P=0.385
2 weeks	1.22	1.45	P=0.518
6 weeks	1.69	1.49	P=0.594

Comparison of Reinjected and Non-reinjected Groups

Multiple regression analysis was then performed to determine if any variables were predictive of WOMAC Scores. The variables thought to be clinically relevant and possibly significant were, previous cortisone injection, age, and concomitant use of NSAID's. These three variables were tested at 2, 6 and 12 weeks using a multiple regression analysis and no statistically significant correlations was noted at 5% significance level.

All patients in the study group, when asked at the 2 week point, stated they had complied with the period of rest.

Eight-five of eight-six (98.8%) of patients at the 2 week point stated that if they had their time back, they still would have had the injection. Thus the injection was helpful for both the groups studied.

CHAPTER 4 DISCUSSION AND CONCLUSIONS

Discussion

Corticosteroid injections into the knee in patients with OA is a time honoured treatment that goes on countless times daily in orthopedic and rheumatology clinics throughout the world. There is research to suggest it is beneficial in the short term but its role in definitive treatment for OA is small. It gets patients through flare-ups of their OA and may be used repeatedly in older, unwell patients that are not candidates for arthroplasty.

Unlike inflammatory arthropathies such as rheumatoid arthritis, osteoarthritis is primarily a mechanical, degenerative disease, with a secondary inflammatory component. It is this known inflammatory component that explains the efficacy, at least in the short term, of intra-articular corticosteroids in patients with OA. Combining this therapy, with another known treatment for arthritis, namely rest, has been shown to be helpful in patients with inflammatory arthropathy. Despite the paucity of evidence to suggest it, the effectiveness of this combination has been extrapolated to include patients with a primarily degenerative arthritis. There is no evidence to scientifically allow this extrapolation.

In Chakravarty et al., the twenty four hour rest period was enforced by admission to hospital. Although this is the best way to assure compliance, we felt this was not possible both in our study protocol and more importantly, in today's Canadian health care system. Most clinicians who are advocates of rest post injection, simply tell their patients to rest if the injection is performed in the outpatient clinic. The clinicians understand this is not ideal however they also realize that the recourses do not exist to admit each and every injection patient to hospital for twenty four hours. For this reason, the intervention

in this trial was to ask patients to rest post injection. It was felt this was more representative of an intervention that had more real world practicality. Every patient in our study group, when asked at their two week follow-up, stated that they had complied with the twenty four hour rest period.

Telephone follow-up for the 2, 6 and 12 week collection points should not affect our results. The WOMAC has been validated for use over the telephone with excellent agreement between scores obtained in the office (face to face) and those obtained over the phone (Bellamy and Campbell et al.). With the local geography and climate, it was felt in-person interviews may result in a high number of patients lost to follow-up or less than accurate timing for each visit. To minimize confusion and inaccuracies, the first time (at injection) the WOMAC was completed in person with the study nurse. The patient was then given a blank WOMAC sheet to follow along with when the information was collected over the phone at the subsequent data collection points. A telephone script was used to maintain consistency.

Neither the patient nor the data collector was blinded in this study. With our intervention, blinding the patient was obviously impossible. However, both the rest and no rest group had an intervention (the injection). Thus, the satisfaction sometimes obtained from simply doing an intervention is negated.

Our primary outcome measure, the WOMAC, is designed to be straightforward which allows it to be self-administered.. The WOMAC questionnaire does not require subjective interpretation, the score is simply calculated from the answers given. For this reason, it was felt that unblinding the data collector, although not ideal, would not represent a major bias.

Some selection bias may be present in this study. All patients recruited were referred by a primary care physician for an orthopedic specialist assessment, thus possibly selecting out more severe cases of OA for the trial. However, mild cases of OA may respond to less invasive modalities (i.e. NSAID's) and not even require intra-articular steroids.

A common sub-group of OA is the inflammatory type. These patients present with a joint that more closely resembles a primary inflammatory arthropathy with more heat, erythema, and effusion. These patients may have a greater response to both the injection and the post-injection rest however we did not make this as an inclusion criteria or analyze these patients as a subgroup. As the disease is a continuum and without the presence of an objective method of selecting out these patients, it was decided to include all patients with OA.

The actual difference in the magnitude of the activity level between the study and control groups is unknown. Compliance in the study group seemed acceptable as all admitted they had complied with our instructions to rest. No attempt was made to determine how much activity the control group actually performed as this would have been very difficult to quantify.

The timing of the data collection points was not chosen randomly. Recent literature has shown little benefit after one month post-injection (Towheed et al.). The two-week interval would demonstrate any early benefit. The six-week point would measure the deterioration in symptoms that should occur. We felt this is when we may see an advantage in the rest group. The twelve-week measurement would demonstrate any longer term benefit, if it existed, of the rest. We felt at twelve weeks, most patients

would have returned to their pre-injection clinical symptomatology. This did not occur, however, with lower WOMAC score still evident at the twelve week point when compared to pre-injection.

The most common reason for missing data was due to re-injection. Patients returned to clinic before the trial was over, with either increased pain or return of discomfort and were re-injected. This was not planned for in trial design. It was felt unethical to deny this treatment due to involvement in the trial thus patients were re-injected at the discretion of their surgeon and further data collection was stopped. This group, however, could be insightful regarding the efficacy of the intervention. Where they all from the same group or was their WOMAC score higher at baseline? Of the seven patients re-injected, three were from the No Rest group and four from the Rest group. This small group of seven were then compared to the rest of the entire sample using an independent samples t-test and no significant difference was found in WOMAC scores at baseline, week 2, or week 6. The mean WOMAC mean at baseline was higher in the re-injected group (Table 7) but due to the small numbers in this group, no definite conclusions can be drawn.

A simple randomization technique was employed in this study. The patients were recruited from several clinics in two hospitals and the use of pre randomized envelopes was felt to be impractical. This technique did leave the possibility of having unequal numbers in our study and control groups which would have made statistical analysis more difficult. Fortunately, this problem did not occur, with exactly equal numbers assigned to each group. It appears, based on the obtained p values of the variables we

collected, that our group represented a random sample of the population with the groups being similar in the variables that were collected.

One of our WOMAC measurements (at Injection) is not affected by the intervention and both groups have similar scores at this point, due to our randomization. If simply included in a Repeated Measures ANOVA, it may diminish the magnitude of statistical difference between the rest and the no rest groups and may lead to a very conservative p-value . To account for this, the baseline data is analyzed as a covariate resulting in the test being better referred to as an Analysis of Co-Variance (ANCOVA) (Norman et al.) Using convention of $P < 0.05$ being the level of statistical significance, this trial failed to demonstrate any short term clinical benefit from a period of rest after an intra-articular corticosteroid injection in the knee for treatment of osteoarthritis.

Despite the reduction in WOMAC scores from baseline at all data collection points for both of the groups, this study does not provide evidence that corticosteroid injections provide relief of pain. This was not the objective of the study thus we did not include a placebo group to which to compare. We felt that withholding standard care in patients refractory to conventional therapy would be unethical. Also, there exist solid data that in the short term the steroid injections in the knee are helpful. These patients were recruited from a clinic which they were attending for the purpose of treatment for their OA. We did not deny anyone this safe, effective form of treatment.

It is conceivable that there is a trend for the group with no rest to have lower WOMAC scores (better outcomes), as numerically the scores were better at all three post injection time periods. It is possible that this gap may have continued to widen and at some point in time may have represented a statistically significant difference, if larger

number of subjects were tested and also if a longer period of follow-up was observed. Unfortunately, this trend was not known until all data was collected and analysed, making data collection at other collection points in time impossible.

This trend was noted approximately one year after the first patient had been entered in the trial. Although measurements at 4 and 6 months would have been ideal, it was decided to collect the WOMAC scores at one year post-injection. Only twenty-four patients at the one-year point had not had further intervention (i.e. another injection, arthroscopy, or total knee arthroplasty). Ten were from the rest group and fourteen from the no rest group and their WOMAC mean scores were 1.4 (S.D. 1.1) and 1.7 (S.D. 1.0) respectively. With the large dropout rate, no useful clinical conclusions could be drawn.

It is common for patients to state a decreasing clinical benefit with subsequent injections. The number of previous injections was recorded in hopes of demonstrating this, however the multiple regression analysis failed to prove it. Age and NSAID use also could not be shown to have an influence on outcome.

In recent work, there is both scientific and clinical evidence that rest can be detrimental in the quest to relieve pain. In a rat model Okamoto et al., demonstrated that sensory afferent fibres were sensitized in a similar fashion by both immobilization and inflammation. Highest afferent nerve activity was found in inflamed knees during the initiation of continuous passive motion after a period of rest. This may explain “starting pain” that patients with OA experience. The first few movements of an affected joint after a period of rest are the most painful, and with continued motion, the discomfort improves.

One of the most noteworthy clinical examples of the poor effect of rest on pain relief was work on bed rest and its usefulness as a treatment for acute back pain. (Malmivaara et al.). In a randomized trial, the investigators compared forty eight hours of bed rest, back-mobilizing exercises, and ordinary activity for treatment of patients with acute onset of non-specific low back pain. A more rapid recovery was found in patients who were permitted ordinary activity as tolerated than patients in either of the other two groups. Although the etiology of acute low back pain is much less understood than OA, there is some degenerative component present and this study demonstrates that rest is actually deleterious at relieving short-term pain.

One explanation for our findings may lie in the differing magnitude of the inflammatory component in OA and inflammatory arthropathies. With activity having been shown to worsen the inflammatory process in a joint (Smith et al.) and this inflammatory process being much more severe in RA than OA, one could see how rest for a primarily mechanical process such as OA would be less helpful than in patients with RA. This may partially explain the differing results obtained by this trial and Chakravarty et al. In this trial, the trend at all data collection points, was the total WOMAC index was higher (worse outcome) in the patients asked to rest.

Based on the previous work on rheumatoid patients, we hypothesized that resting after a steroid injection would be a simple intervention that may increase the duration and magnitude of relief. We were unable to prove that in this study. It is presently standard of care in our orthopedic department to discharge OA patients from clinic after a cortisone injection into the knee with no specific instructions for activity level. The result from this trial does not provide any evidence that will change this current practice.

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APPENDIX 1 CONSENT FORM

FACULTY OF MEDICINE - MEMORIAL UNIVERSITY OF NEWFOUNDLAND

AND

HEALTH CARE CORPORATION OF ST. JOHN'S

Consent To Participate In Bio-medical Research

TITLE: Does resting after a cortisone injection improve the pain relief?

INVESTIGATOR: Dr. Craig Stone, Dr. Proton Rahman

SPONSOR: Department of Surgery

You have been asked to participate in a research study. Participation in this study is entirely voluntary. You may decide not to participate or may withdraw from the study at any time without affecting your normal treatment.

Information obtained from you or about you during this study, which could identify you, will be kept confidential by the investigator. The investigator will be available during the study at all times should you have any problems or questions about the study.

Purpose of the Study:

Some doctors believe that resting for a short time (24 hours) after a cortisone injection improves the pain relief from your arthritis. Others believe it makes no difference and is not worth the inconvenience. This research project is designed to help answer this question.

Study Procedure:

You and your doctor have decided that a cortisone injection into your knee is the next step in your treatment. If you agree to enter our study, after your injection you will either be asked to “rest” for 24 hours *OR* to go about your usual routine. Rest will involve walking only to get home and to do necessary things at home like eating and going to the bathroom. You will be asked to fill out a questionnaire about the pain and function of your knee. You will be assigned to either the rest or no rest group by chance. You will have a 50 per cent chance of being asked to rest.

Duration of Participation:

The questionnaire will be repeated three times over the next several weeks. The later questionnaires can be completed over the phone. Your regular follow-up appointments with your doctor will not be affected.

Possible risks, discomforts, or inconveniences:

If you would be unable to rest for twenty-four hours due to important work or personal commitments, do not enter the study.

Treatment for those not entering the study:

If you do not choose to enter the study for any reason, your knee will be injected and your doctor will follow his/her usual suggestions about rest.

Liability Statement:

Your signature indicates your consent and that you have understood the information regarding the research study. In no way does this waive your legal rights nor release the investigators or involved agencies from their legal and professional responsibilities

Signature: _____

Date: _____

Witness: _____

APPENDIX 2 QUESTIONNAIRE / DATA COLLECTION SHEET

DATA FORM
Rest Post-Knee Injection Study
INITIAL VISIT
Clinic Assessment

Today's Date:

Patient's Name:

MCP #:

DOB:

Telephone #:

Occupation:

Knee (R/L):

Random allocation: Rest No Rest

Have you had any previous cortisone injection into THIS KNEE?

None 1 2 3 or more Unsure

Have you taken any medication for THIS KNEE in the last 48 hours? Yes No

NSAIDS Acetaminophen Chondroitin Sulphate Other _____

Complete WOMAC table for INJECTION VISIT (page 3)

WEEK 2
Via Telephone

Date Scheduled: _____

Date Completed: _____

Have you taken any medication for THIS KNEE in the last 48 hours? Yes No

NSAIDS Acetaminophen Chondroitin Sulphate Other _____

If you had your time back, would you have had the knee injection?

Yes No

(IF IN REST GROUP)

Did you rest after your injection? Yes No

Complete WOMAC table for WEEK 2 VISIT (page 3)

WEEK 6
Via Telephone

Date Scheduled: _____

Date Completed: _____

Have you taken any medication for THIS KNEE in the last 48 hours? Yes No

NSAIDS Acetaminophen Chondroitin Sulphate Other _____

If you had your time back, would you have had the knee injection?

Yes No

Complete WOMAC table for WEEK 6 VISIT (page 3)

WEEK 12
Via Telephone

Date Scheduled: _____

Date Completed: _____

Have you taken any medication for THIS KNEE in the last 48 hours? Yes No

NSAIDS Acetaminophen Chondroitin Sulphate Other _____

If you had your time back, would you have had the knee injection?

Yes No

Complete WOMAC table for WEEK 12 VISIT (page 3)

WOMAC Questionnaire

Please answer each of these questions on a scale of 0 to 4 where 0 is none and 4 is extreme.

Over the last 48 hours, how much pain do you have?

PAIN	Injection	Week 2	Week 6	Week 12
1. Walking on a flat surface				
2. Going up or down stairs				
3. At night while in bed				
4. Sitting or lying				
5. Standing Upright				

Please answer each of these questions on a scale of 0 to 4 where 0 is none and 4 is extreme.

In the last 48 hours...

STIFFNESS	Injection	Week 2	Week 6	Week 12
6. How severe is your stiffness, not pain, after first awakening in the morning?				
7. How severe is your stiffness, not pain, after sitting, lying, or resting later in the day?				

Please answer each of these questions on a scale of 0 to 4 where 0 is none and 4 is extreme.

Over the last 48 hours, what degree of difficulty do you have?

FUNCTION	Injection	Week 2	Week 6	Week 12
8. Descending Stairs				
9. Ascending Stairs				
10. Rising from sitting				
11. Standing				
12. Bending to Floor				
13. Walking on Flat				
14. Getting in and out of the car				
15. Going Shopping				
16. Putting on your Socks				
17. Rising from bed				
18. Taking off your socks				
19. Lying in bed				
20. Getting in and out of the bath				
21. Sitting				
22. Getting on and off the toilet				
23. Heavy domestic duties				
24. Light Domestic Duties				

APPENDIX 3 TELEPHONE FOLLOW UP SCRPT

Telephone Script:

Hello [participant]. This is [research nurse]. We are calling to follow up on our study of rest after your knee injection. You may remember the questionnaire that you completed in the clinic after your first knee injection. This is the same questionnaire that you completed in the clinic and we would like to complete it again now over the phone to see if there has been any improvement or worsening of your knee. It will take approximately 10 minutes. Would you care to complete this for us now? Please answer each of these questions on a scale of 0 to 4 where 0 is none and 4 is extreme.

Over the last 48 hours, how much pain do you have?

- Walking on a flat surface _____
- Going up or down stairs _____
- At night while in bed _____
- Sitting or lying _____
- Standing Upright _____

In the last 48 hours...

How severe is your stiffness, not pain, after first awakening in the morning? _____

How severe is your stiffness, not pain, after sitting, lying,
or resting later in the day? _____

Over the last 48 hours, what degree of difficulty do you have?

- Descending Stairs _____
- Ascending Stairs _____
- Rising from sitting _____
- Standing _____
- Bending to Floor _____
- Walking on Flat _____
- Standing _____
- Getting in/out car _____
- Going Shopping _____
- Putting on Socks _____
- Rising from bed _____
- Taking off socks _____
- Lying in bed _____
- Getting in/out bath _____
- Sitting _____
- Getting on/off toilet _____
- Heavy domestic duties _____
- Light Domestic Duties _____

*****Transfer results to data collection sheet*****

APPENDIX 4 HUMAN INVESTIGATIONS COMMITTEE APPLICATION

Human Investigation Committee - Application Form

Faculty of Medicine - Memorial University of Newfoundland

Health Care Corporation of St. John's

**Forward 20 copies of application and consent forms to:
Office of Research (HIC), Room 1759, Health Science Centre. (Phone 737-6974)**

1. Investigators.

	If a student, indicate program and name of supervisor Dr. P. Rahman
	Co-Investigators:

**2. Title of study. Include protocol number, if any.
dates.**

3. Starting and ending

Intra-articular steroid injection for Osteoarthritis of the knee: Effect of post injection rest on pain relief and function	Proposed start date: (at least 4 weeks from date of submission) September 2001 Anticipated completion date: June 2002
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4. Please fill in the appropriate information, if any.

Check applicable boxes.

Hospital or Community Setting Involved	Involves		
	Patients or Residents	Records	Facilities
Health Science Centre	X		X
St. Clare's Mercy Hospital	X		X

5. List the main objectives of the investigation. Use only the space provided.

1. To determine if a short period of rest after an intra-articular steroid injection improves the level and duration of pain relief in patients with primary osteoarthritis of the knee.

6. Introduction to study.

(a) What is the scientific background to the study?

Osteoarthritis of the knee is a very common clinical entity. It is estimated that 25 – 30 % of people aged 45 to 64 and more than 85% of people older than 65 years of age have OA of the knee identifiable on radiographs. Intra-articular steroid injections have been used for over fifty years in the treatment of this disease. This treatment modality has been shown to provide relief of pain and improve function in these patients for a short period of time (1 month). It does not provide a cure or long lasting benefit.

Intra-articular steroids have been shown to be safe and have few systemic side effects. They are routinely used as a non-operative form of treatment in patients with osteoarthritis of the knee when less invasive modalities such as physiotherapy, non-steroidal anti-inflammatory drugs, and activity modifications have failed to provide satisfactory pain relief.

(b) What is the rationale for the study?

Physicians providing this form of treatment vary on their post injection recommendations. Some allow the patient to continue with their normal daily activities and others suggest to the patient to rest for a short period (24 hours). Proponents of post injection rest feel it results in a more significant and longer lasting pain relief. The proposed study will help to answer this clinical question.

(c) Summarize any relevant human or animal studies already conducted.

Many studies have been published documenting the excellent safety profile of this treatment. Allergic reactions have been rare and systemic absorption is minimal and causes few, if any, significant problems. One survey of 223 orthopaedic surgeons revealed that each used intra-articular steroids on average 150 times per year.

A recent meta-analysis of studies pertaining to the benefits of intra-articular steroids has demonstrated that short-term pain relief, up to one month, is provided with this treatment when compared with placebo.

Only one study exists in the literature that addresses the issue of post injection rest. A study of patients with rheumatoid arthritis demonstrated that a short period of rest post-injection improved both the duration and level of pain relief in the knee. No previous study has addressed this question in osteoarthritic patients.

7. Blood or other tissue sampling.

(a) List samples to be taken from participants. State type of sample, frequency and amount

NONE

Will any samples be kept after the **completion** of the study? Y / N If yes, include section 9 on consent form.

8. Research interventions.

(a) List any procedures, tests or substances to be administered to participants: e.g. imaging, special diets, drugs (state dose and frequency), isotopic tracers, ECGs etc. List only those that are not part of normal patient management. 40mg of Methylprednisolone Acetate will be injected into the painful knee of the patient under sterile conditions in the clinic setting.

(b) List questionnaires, interview scripts or chart audit forms to be used: Attach copies of each. The WOMAC (Western Ontario and McMaster Osteoarthritis Index). The pain, stiffness and function subscales will all be used.

9. For studies involving patients.

(a) What treatment do *YOU* now use for patients who would meet the inclusion criteria for this study? (i.e. How would you manage these patients if they did not go into this study?) For patients not involved in the study, the steroid injection will be administered and no period of rest will be suggested. The patients will be free to carry on with their routine daily activities.

(b) Is this an application for a clinical trial? Yes / No
If yes, what phase is this trial? I II III IV
What is the design of the trial (e.g. open, double blind, crossover etc.)?

10. In the space provided, give a brief description of the design of the study, including participant selection, interventions and outcome measurement. (Attach one copy of a protocol if available). Do not expand this box

The study group will consist of patients requested to rest. This will involve not returning to work, ambulating only to travel home and necessary ambulation at home (eating and bathroom). Twenty-four hours of rest will be requested. The control group will be injected and have no specific restrictions applied. It will be suggested that they carry on with their usual daily routine. Patients will be randomly assigned to each group after the injection is performed. Inclusion criteria will include 1. Primary osteoarthritis of the knee. Diagnosis based on clinical and radiographic findings and AAOS definition of OA. 2. Non-invasive modalities of treatment, i.e. activity modification, NSAID's, have failed to satisfactorily control symptoms of pain and swelling. 3. Patient available for follow up. 4. Patient's informed consent expressed via signature on consent form.

Exclusion criteria will include: 1. Contraindication to intra-articular corticosteroid injection. Common examples include undesirable reaction to previous injection and active infection at the injection site. 2. Inability to comply with a period of rest. Reasons may include occupation or personal commitments that would make this rest period unacceptable. The WOMAC will be administered immediately post-injection, and via telephone at 2 weeks, 6 weeks and 3 months post injection.

11. Participants.

Number of participants at this site. 94

Will pregnant women be excluded? YES

Is this part of a multi-center study? NO If Yes, what is the total number of participants at all sites? _____

How will participants be recruited?

Patients will be recruited from rheumatology and orthopaedic outpatient clinics in the Health Care corporation of St. John's. Patients who meet the inclusion criteria will be approached to participate in the study.

12. What is the basis for the choice of sample size? (Consider the total number of participants for multi-center studies).

The mean and standard deviation for the pain subscale of the WOMAC has previously been determined; mean ($X = 10.3$) and standard deviation ($sd = 4.4$). The investigators have decided a 20% change in the WOMAC score to be clinically relevant. With such a benign intervention as a period of rest, a small improvement in outcome would be clinically important and would justify the intervention. With $\alpha = 0.05$ (Type I error) and $\beta = 0.20$ (Type II error), a sample size of 39 patients per group is required. This was calculated using a two-tailed test comparing two independent groups. Assuming a dropout rate of 10%, 43 patients per group (86 total participants) will be required to answer our research question.

13. What risks, discomforts or inconveniences are involved?

(a) risks: The small risks associated with the injection. Infection and allergic reaction are exceedingly rare.

(b) discomforts: There is a small amount of discomfort associated with the injection. It is often described as similar to a routine blood test.

(c) inconveniences: The study group will be inconvenienced by the period of rest.

14. Benefits.

Are there any immediate benefits for the participants (including controls)? YES Please specify.

Patients in both groups may benefit with pain relief and improved function as a result of the intra-articular steroid injection.

(a) What steps will be taken to preserve confidentiality?

Patient confidentiality will be strictly protected. All patient records will be treated as hospital charts and will be stored safely under lock and key. Any publication or presentation resulting from the study will make no reference to patient identification.

(b) List names of all personnel who can access information that could be linked to individual participants.

Dr. N. Craig Stone

Dr. P. Rahman

Clinical Research Nurse - TBA

15. Confidentiality.

16. Consent process.

(a) Who will make the initial contact with the participant? Attending physician (orthopaedic or rheumatology)

(b) Who will obtain the consent of the participant? Clinical research nurse

(c) Explain procedure for obtaining consent.

When a patient is identified as a potential study participant, the protocol will be summarized with them. They will be given a consent form to read and time will be allowed for any questions or clarifications. The potential participant wished to discuss their consent form with others (i.e. family member, family doctor) the steroid injection will be delayed until the decision has been made. If this delay in treatment is unacceptable to the patient, the patient will have their injection performed and not included in the study.

17. Vulnerable populations.

Will participants include: Minors (less than 19yrs) ? **NO** or Persons incompetent to give consent? **NO**

If so, please justify. Outline the measures that will be used to protect their rights (attach separate sheet if required).

18. Debriefing.

Explain the mechanism, if any, for feedback to participants.

Participants will be assured that they can request a copy of any publication and/or presentation that results from the study.

19. Payments.

(a) Will participants receive: reimbursement for expenses incurred? NO payment for participation in the study? NO	Please specify on separate sheet according to "Guidelines for the Remuneration of Research Subjects."*
(b) Will there be any payment to a third party for referral of patients? NO	Please specify on separate sheet according to "Guidelines for Payment of Finders' Fees."*

* Available in the HIC office and on HIC web page.

20. Budget

Please enclose a copy of the budget for this study, including source of funding.

Will the budget be administered through the University Finance Office? **Y / N** If no, where?

Will any investigator receive financial or other benefit by virtue of conducting this study? **NO**

21. Ownership of data.

Is there any restriction on publishing the results of the study? NO
If yes, please explain?

22. Reminders.

We would like to remind you that it is your responsibility to ensure that permission is obtained from clinicians, departments, institutions or communities whose patients / residents will be involved in the study.
We would also like to remind you that you must read "Ethical Conduct for Research Involving Humans" (available in the HIC Office and on HIC Web Page.)

Signature of principal investigator.	Signature of supervisor, in case of student application.
Date	

Revised 2000-09-18

APPENDIX 5 APPROVAL LETTERS

