Practical Indications for Sonography in Musculoskeletal Medicine- Knee Joint Injections (PRISMM-Knee)

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Purpose

This study will compare the accuracy and patient-oriented outcomes between various techniques for intra-articular knee injections. Historically, a joint line (intercondylar) technique of injection at the medial or lateral joint line, reliant solely upon clinical palpation, has been the most popular approach among primary care and orthopedic providers. Newer approaches, making use of ultrasound visualization to accomplish access to the intercondylar recess and the anterolateral suprapatellar pouch, have gained in popularity. Because of uncertain accuracy with the traditional approach, this study is designed to determine if sonographic visualization combined with either of these two newer techniques improves accuracy and affects patient-oriented outcomes.

Research Design

Double-Blind Randomized Clinical Trial

Methodology/Technical Approach

Upon determination of the need for an intra-articular knee injection series of viscosupplementation (hyaluronan) and before the receipt of such injections, patients will be recruited into the study. The series calls for three injections spaced approximately one week apart. All three injections must be completed within one months time frame. The participants will be randomized into one of four treatment groups which will determine which approach will be used as well as the inclusion/exclusion of ultrasound guidance:

Group 1: Joint Line Ultrasound Guided
Group 2: Joint Line Landmark Based (sham Ultrasound)
Group 3: Suprapatellar Ultrasound Guided
Group 4: Suprapatellar Landmark Based (sham Ultrasound)

The patients will be blinded to their group assignment prior to the first injection and will not be able to see which technique is employed. The provider performing the injections will not be blinded. The third injection (only) will be different in that contrast medium will be injected along with the hyaluronan. Following the third injection, fluoroscopy will be used to determine presence/absence of the contrast medium into the joint. The radiologist interpreting these images will be blinded to the technique employed. At 3 months following the third injection, the patients will be contacted by a surveyor blinded to the group assignment.

Objectives and Specific Aims

1. To compare the accuracy of injections into the knee joint with two different approaches, joint line and suprapatellar pouch
2. To determine if the addition of ultrasound guidance to traditional landmark-based techniques enhances the accuracy of these techniques
3. To examine differences in patient perceived pain and functioning of their knee joint following the injection series.

Medical Application

Injections into the knee joint are an exceedingly common procedure by a variety of specialists, primary care physicians, and non-physician clinicians. Knowledge of the most accurate and clinically effective injection technique will positively impact countless future patients. If we find that the addition of ultrasound guidance increases accuracy, as

we hypothesize, patient-oriented results should be better with fewer complications. This will allow the patient to return to activity quicker.

Background and Significance

Literature Review (as of 18 November 2010) and Preliminary Data and/or Findings.

Knee osteoarthritis is exceedingly prevalent. While the exact worldwide incidence of symptomatic knee osteoarthritis is unknown, it is of note that 10% of people over the age of 55 experience disabling pain from knee osteoarthritis.[1] Treatment of this disease process is multifaceted and often includes intra-articular injection of corticosteroids and viscosupplements. Viscosupplements, with a mechanism of action that remains largely theorectical, was approved by the Food and Drug Administration in 1997. There are numerous proprietary preparations available, all of which contain natural or synthetic sodium hyaluronate (hyaluronic acid). Anecdotally speaking, injection of the knee joint is one of the most common procedures done in primary and specialty-based care.

The tibiofemoral joint, colloquially referred to as the "knee joint" encompasses the area where the femur, tibia, fibula, and the patella come together. The knee joint space extends from approximately two to three centimeters above the patella (suprapatellar pouch) to under the patella and to the top of the tibia (i.e., the tibial plateau). There are a diversity of injection approaches for the knee joint used in clinical practice.

Surface landmark–guided joint line technique. Based on clinical practice, the most common technique involves injection at the physician-perceived tibiofemoral joint line, based on palpation (Figure 1). This can be done either medial or lateral to the patellar tendon. The joint line is commonly understood to be the anterior aspect of the synovial space between the femur and tibia. Depending on the anatomy of the patient, this standard joint line approach may be difficult to achieve. For example, severe osteoarthritis and obesity can complicate the accuracy of this procedure. Further, there are inherent risks in this traditional method (Reference: 5.2 Scientific Justification).

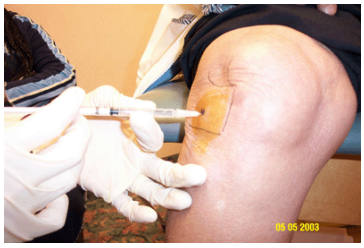


Figure 1: Tibiofemoral joint line technique for knee joint injection using the lateral joint line.[2]

Other techniques that have been described and used include the suprapatellar pouch (described below) and the patellofemoral joint line at the midpoint between the superior and inferior poles of the patella ("midpatellar"), either from the medial or lateral sides.

Surface landmark–guided suprapatellar approach. There has been a surge of interest in injection strategies that mitigate the difficulties of the surface landmark-guided joint line technique as described above. One such technique, one in which the needle is inserted into the suprapatellar pouch, takes advantage of the fact that the true joint space extends superior to the patella and anterior to the femur. This portion of the joint is commonly called the suprapatellar pouch (Figure 2). The potential advantage of this technique is that the needle does not contact the fragile articular cartilage. Its limitations are based on fact that in the absence of a knee effusion (fluid in the knee), the suprapatellar pouch is but a potential space that may be completely empty and collapsed and thus difficult to find with a needle tip. Even when a small effusion is present, it may be difficult to find, depending on its size and the palpatory skills of the provider.

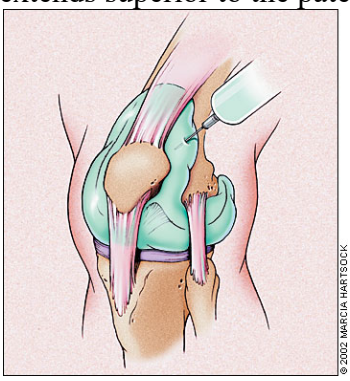


Figure 2: Suprapatellar Technique for Knee Joint Injection[3]

Technology may improve techniques. The advent of sonographic (ultrasound) visualization has made the suprapatellar approach infinitely easier. In the presence of an effusion, it is quite easy to do ultrasound-guided injection into the suprapatellar pouch. In the absence of an effusion, though, even ultrasound guidance into a potential tissue space can be challenging. Another newer approach uses ultrasound to guide a joint line (intercondylar) injection with the thought that visualization will enhance accuracy. While there are theoretical accuracy advantages with ultrasound-guided injections, the accuracy rates of these methods have not yet been evaluated. There are also monetary costs to adding the use of ultrasound visualization, and assembling the necessary equipment and supplies may increase the time to perform the procedure.

Studies have compared the accuracy of the landmark-based joint line approach to that of other injection approaches in the knee. One study compared the accuracy of anteromedial, anterolateral, and lateral midpatellar over a series of 240 injections.[6] All of these injections were landmark based (no ultrasound used for the procedure) and patients with an effusion were excluded from participation. The lateral midpatellar approach was found to be the most accurate (93%) compared to the anteromedial (75%) and anterolateral (72%) approaches.[4] Taken one step further, Esenyel et al compared the accuracy of four different approaches to knee injection in 78 cadaveric knees: anteromedial joint line, anterolateral joint line, lateral midpatellar, and medial midpatellar.[7] This particular study found the anterolateral approach to be the most accurate at 85% success versus 73% for anteromedial, 76% for lateral midpatellar, and 56% for medial midpatellar. Overall these studies show that the anterolateral aspect of the suprapatellar pouch may result in the highest accuracy for landmark-based injections.

Although ultrasound-guided injections are superior to surface landmark-guided techniques into the subacromial space (defined as the extra-articular area between the superior aspect of the humerus and the inferior surface of the acromion) of the shoulder; there are no consistent data regarding landmark-guided versus ultrasound guided

techniques for accuracy of injections specific to the knee joint. One study compared landmark-based and ultrasound-guided techniques in 184 patients receiving corticosteroid injections of their shoulder, elbow, wrist, knee, or ankle[3]. In aggregate, ultrasound-guided injections were found to be more accurate (83%) compared to clinical examination-guided injections (66%). However, this study was not powered to determine a difference in accuracy among the individual joints. Self-reported pain and function scores at two and six weeks following the injection were no different based on the technique employed. There was, however, a trend towards improvement in function based on a visual analog scale at two weeks post ultrasound-guided injection and a statistically significant improvement at six weeks post injection. Additionally, a trend was seen for improvement in pain (VAS scale) at two and six weeks post injection. Although there was lack of power to adequately reach a conclusion, this study suggests a potential therapeutic benefit with ultrasound-guided injections of the knee versus a landmark-based technique.

Wiler et al, compared the amount of fluid aspirated from 66 knee joints by emergency department physicians using an ultrasound-guided suprapatellar versus a landmark-based joint line approach.[4] This study found no difference in amount of fluid aspirated. However, participants reported significantly less pain when the ultrasound guided approach was used (3.71 versus 5.19 on a 10-cm VAS scale). Providers believed that the ultrasound approach was easier to perform (1.67 versus 2.11 units on a five-point scale) and the procedure time was shorter (10.58 versus 13.37 minutes). No analysis of target acquisition accuracy was obtained in this study.

One study showed increased accuracy of injections into the knee with ultrasound guidance, but the researchers used a medial midpatellar approach.[5] With this technique the patient lies supine and the needle is inserted medially at the patellofemoral joint line at the midpoint between the superior and inferior patellar poles . Among 89 injections, ultrasound guided medial midpatellar injections were found to have an accuracy rate of 95.6% compared to 77.3% with a landmark-guided medial midpatellar injection. However, the theoretical disadvantage to this technique in damage to the cartilage from the needle tip, a risk that typically precludes this approach from our standard practice.

Our clinical experience has been that ultrasound visualization of the suprapatellar injection plane is best accomplished with an anterolateral orientation and is made significantly easier by the presence of effusion. An effusion appears on ultrasound imaging as an easily identifiable homogenous black fluid pocket. We typically look for the presence of an effusion when performing suprapatellar knee joint injections since the effusion is our needle target. Visualization of an effusion was investigated in a small study on eight cadavers. In this study, Hong et al correlated five different ultrasound views of the suprapatellar pouch (longitudinal: medial, midline, lateral; transverse: medial, lateral) with varying amounts of solution (5, 10, 15, and 20 ml) used to simulate an effusion. Sensitivity was highest with at least 10ml of solution present and using a combination of lateral transverse and lateral longitudinal views.[8] We, therefore, hypothesize, that in the presence of approximately 10ml of fluid in the suprapatellar

pouch, the ultrasound-guided suprapatellar approach using a combination of lateral transverse and lateral longitudinal visualization will result in the highest accuracy.

Scientific Justification

We will examine three primary questions:
1. Whether there is a difference in the accuracy of injections into the knee joint using joint line approach compared to a suprapatellar pouch approach.
2. Whether the use of ultrasound guidance enhances the accuracy of these techniques.
3. Whether participants perceive a difference in pain and functioning depending on the technique.

To date, the data have not demonstrated that any of these four approaches (i.e., joint line approach without ultrasound, joint line approach with ultrasound, suprapatellar pouch approach without ultrasound, suprapatellar pouch approach with ultrasound) is the most accurate or should be the standard of care. By examining these questions we will determine the most appropriate approach to knee joint injections while balancing patient safety and accuracy of the procedure. This conclusion will be augmented by determination of patient-oriented outcomes following the procedure to include the WOMAC index (pain and function) as well as overall procedure satisfaction.

Human Use Justification

It is appropriate to use human subjects as research volunteers for this study. As this is a clinical trial, it would be impossible to do the study without human subjects. Due to the variation of ultrasound appearance and palpatory feedback used during an injection between live versus preserved tissue, it is not preferable to perform this trial on cadaveric subjects. Further, this study seeks patient oriented outcomes to further elucidate the applicability of these techniques. All of the techniques described above are currently used in clinical practice and will be recommended as part of the treatment plan per usual standard of care. As such, there are no additional risks associated with completion of this study other than reaction to the contrast agent.

Type of the Subject Population

Male and female subjects age 18 to 90 years presenting to a sports medicine clinic with knee pain justifying injection of a hyaluronic acid product will comprise the study population. The decision to use one of these products does not typically follow an algorithm that takes into account duration of symptoms or failure of modalities. Instead, this procedure is typically performed after the risks and benefits of various treatment options are discussed with the patient and he/she elects to receive this injection in concert with or as opposed to any number of other treatment modalities for knee osteoarthritis.

Inclusion and Exclusion Criteria

a. Inclusion Criteria
1. Male or female, age 18 to 90
2. Clinician determined need for intra-articular knee injection

b. Exclusion Criteria
1. Allergy to contrast dye, shellfish
2. Allergy to egg products or hyaluronate
3. Allergy to lidocaine
4. Localized skin infection at planned site of injection
5. Inability to complete follow-up phone call three months following the injection

Recruitment

Any adult-aged individual that meets inclusion and exclusion criteria will be eligible to participate in the study. Due to the expected large cohort of participants already present within the patient population at the trial site, no advertising will be necessary for this study.

Compensation for participation

No compensation will be provided to subjects.

Consent Process

a. There will be a Research Coordinator at the trial site who will administer the consent and HIPAA authorizations. This will be performed with a standardized consent form (Appendix A), including a scripted discussion of the study procedures and a scripted discussion of risks inherent in the injection techniques

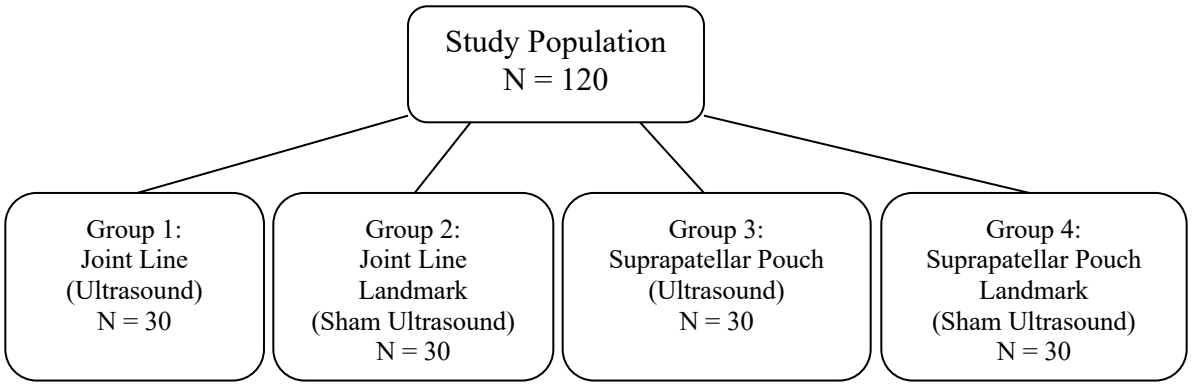
b. Upon completion of consent, the Coordinator will have the subject explain their understanding of the concept of treatment in their own words to ensure the subjects understand the consent.

Study Design

The study will be a randomized, double-blinded clinical study comparing four techniques for intra-articular knee injections.

The study investigators will receive a list of 120 computer generated random numbers from

one to four. No more than 30 will be in each group to ensure that each group is the correct size. Upon entry into the study, and prior to the first injection, subjects will randomized by selecting a sealed envelope from a box containing an equal number of envelopes for each of the four treatments groups. The envelope will be given, unopened, to the study doctor. The subject will be blinded to their study group assignment.



Double-blinding will be done as follows: The subjects will be blinded to whether ultrasound was used to guide their treatment. The radiologist, who will review the fluoroscopic images after the injections, will be blinded to treatment group assignment. The injecting physician will not be blinded to the treatment group assignment. Treating physicians (injecting physicians) will perform the technique as detailed below based on the assignment of the participant. Subjects and the radiologists will both be asked to guess their treatment group at each point in the data collection to determine the effectiveness of the blinding process. The Surveyor will also be blinded to the treatment group allocation.

The injecting physicians will consist of orthopedic surgeons, sports medicine fellows, or sports medicine fellowship trained primary care physicians. All injecting physicians will receive a minimum of 2 hours of hands-on training specific to the procedures employed in this study. Additionally, they will be supervised for their first several ultrasound-guided procedures to assure competence with the techniques.

Study Methodology/Procedures

Appointment 1

1. Based on usual standard of care for knee pain, the treating physician will determine whether a series of viscosupplemental intra-articular knee joint injections is recommended. Patients who would likely benefit from the injections will be invited to participate in the study but will still receive usual care if they decide not to participate.

2. The informed consent document will be reviewed with and signed by interested patients.

Participants will complete the Western Ontario and McMaster Universities Arthritis Index (WOMAC), a validated, widely used instrument that measures self-reported pain, joint stiffness, and physical function. This index consists of 24 questions (5 pain, 2 stiffness, 17 physical function) and takes less than 5 minutes to complete. Raw scores are normalized to fit within a range of 0 (worst) to 100 (best). Additionally, there is a normalized raw Global Score that considers the variables of pain, stiffness, and physical function as a collective. The WOMAC will be issued four times during the study; prior to the three injections and again at the three month follow up phone call.

3. The injection procedure will be completed based on group assignment (see below). For the third injection in the series, all four groups will receive a "one needle, two syringe" injection as follows:
    a. A 21 gauge two inch needle attached to a 5 ml syringe filled with 5 ml of Omnipaque 300 ® (General Electric Healthcare, Princeton, NJ) contrast medium will be introduced into the skin at the predetermined site and directed either with or without ultrasound guidance based upon group assignment. Injection site, landmarks, and intended path of the needle are detailed further in the group description below.
    b. The entire contents of the syringe will then be injected. Following delivery of the contrast medium, the syringe will be removed while the needle remains in place.
    c. A second syringe with the pre-determined medication (Hyaluronic Acid) will be attached to the needle and this medication will be delivered.
    d. The needle and syringe will be removed from the knee and the injection will be bandaged.
4. The first and second injections will be performed based on the group assignment (see below) but will not include the use of contrast medium.

Group 1: Joint Line Ultrasound (JLUS)

The Joint Line Ultrasound (JLUS) group will receive a standard medial or lateral joint line injection aided by ultrasound guidance. Specifically, this technique will entail palpation by the clinician of the soft tissue triangle formed by the tibial plateau, border of the patellar tendon, and the distal femoral condyle as found on both the medial and lateral joint line with the patient sitting on the edge of an examination table. Their knees will be bent to 90 degrees of flexion. The decision between a medial versus a lateral approach will be made by the provider performing the injection and based on the patient's anatomy and the provider's determination of the most facile side in which to perform the injection, as is the traditional practice of performing this technique. The triangle felt to be most prominent (i.e. largest joint space) will be chosen as the injection site. The area will be prepped in the usual sterile fashion.

The injection will be performed as detailed above with real time ultrasound guidance. To accomplish this a 10 MHz linear array transducer from a standardized ultrasound unit (Logiq E ®, General Electric Healthcare, Chalfont St. Giles, United Kingdom) will be placed in an oblique orientation on the opposite soft tissue triangle from the intended injection site so that

the inner aspect of the opposite femoral condyle is visualized, but the ultrasound display will be positioned so that the patient cannot visualize the screen. The injection will occur through the soft tissue triangle and directed at a 45 degree angle to the inner aspect of the opposite femoral condyle, with the needle being advanced parallel to (in the longitudinal axis of) the US probe. When the needle is visualized to be adjacent to the articular cartilage, a small bolus of saline will be injected. When the provider is satisfied that the needle tip is underneath the synovium overlying the condyle, as evidence by the saline easily dispersing underneath the synovium and not accumulating adjacent to it, the viscosupplement will be injected followed by the contrast.

Group 2: Joint Line Landmark (JLL)

The same determination of medial versus lateral approach as described in Group 1 will be made. The injection will be performed as described above. The ultrasound probe will be placed in an oblique orientation on the opposite soft tissue triangle from the intended injection site, but the ultrasound display will be positioned so that the patient cannot visualize presence or absence of the needle, and the image will be placed on "FREEZE" so that no active images are being viewed. The injection will be completed based strictly on tactile feedback from the injecting physician. The needle will enter the predetermined soft tissue triangle and directed toward the joint space. Once the injecting physician believes that the needle is positioned within the joint space, the viscosupplement will be injected followed by the contrast.

Group 3: Suprapatellar Ultrasound Guided (SPUS)

Real time ultrasound guidance using a standardized ultrasound unit with a 10 MHz linear array transducer (Logiq E ®, General Electric Healthcare, Chalfont St. Giles, United Kingdom) will be used to guide the injection for this group. The ultrasound display will be positioned so that the patient cannot visualize the screen. After sterile prep of the anteriolateral suprapatellar area (approximately 1 cm superior to the patella at a level approximating that of the lateral patellofemoral joint space), the suprapatellar pouch will be visualized. First, a longitudinal view capturing the proximal patella and the plane between the prefemoral fat pad (superficial to the femur) and suprapatellar fat pad (deep to the quadriceps tendon) will be obtained. Presence or absence of an effusion, visualized as a localized collection of anechoic material within this plane, will be noted. Next, the probe will be turned 90 degrees to a transverse view of the plane just proximal to the patella. Small adjustments in probe positioning will be done to create the best visualization of the suprapatellar pouch. After the desired visualization is achieved the needle will be inserted just lateral to the vastus lateralis in the longitudinal axis of the US probe and angled medially until the tip of the needle is within the suprapatellar pouch. Should an effusion be present, this will serve as the target landmark. In this instance, the effusion will be aspirated using a clean 5ml syringe prior to the injection. In the absence of an effusion, the target landmark will be the plane between the prefemoral and suprapatellar fat pads. In the absence of an effusion, injection of saline will be done first to dissect this plane further to assure that the needle tip is within the suprapatellar pouch. Once the injecting physician is confident of needle position with the pouch, the viscosupplement will be injected followed by the

contrast.

Group 4: Suprapatellar Landmark (SPL)

Patients randomized to the Suprapatellar Landmark (SPL) group will receive the same procedure as the Suprapatellar Ultrasound Guided (SPUS) group., with the exception of the sham ultrasound. To accomplish this, the ultrasound probe will purposely be positioned in the transverse plane of the suprapatellar area but the ultrasound display will be positioned so that the patient cannot visualize the screen, and the "FREEZE" button will be activated so that no active image is transmitted. The display will be positioned such that visualization by the patient will not be possible. The injecting physician will insert the needle lateral to the vastus lateralis toward the suprapatellar pouch. When the injecting physician believes the needle tip is in the pouch, the viscosupplement will be injected followed by the contrast.

It should be noted, that none of the participants in the study will be given the ability to visualize the ultrasound screen or injection procedure.

5. Following each injection, all patients will conclude their encounter with the injecting physician by being asked to rate on a scale of 0 to 10 their procedural pain from the procedure. For pain, a score of 0 will correspond to no pain and 10 will correspond to the worst pain they have ever experienced. After each injection, and at the three month follow up telephone call, the subjects will be asked to rate their overall procedure satisfaction on a 0-10 scale where "0" represents complete dissatisfaction and "10" represents complete satisfaction.
6. . After the third injection, and after answering these questions, the patient will proceed directly to the Radiology Department.

7. Images of the joint will be obtained following the third injection. These images will be analyzed by a radiologist blinded to the technique employed and used to determine presence of or absence of the contrast medium within the joint.

Appointment 4 (telephone)

8. Subjects will be contacted approximately three months after the procedure by a Surveyor and the WOMAC Osteoarthritis Index will be repeated. The patients will be asked to rate their procedural satisfaction and also detail other therapies they have employed since the injection. This will include supplements, exercise (frequency and duration), acupuncture, physical therapy, etc.

Data Collection

Data collection will occur at three points during the investigation:

- Initial evaluation: Screening instrument for first visit (history and physical, diagnostic and inclusion/exclusion criteria), WOMAC (prior to receiving each of the three injections), and intervention

The clinical staff will collect the following data:

- Name, email, phone number
- Demographics: age, gender, type and number of injections received previously
- Informed consent/HIPAA document
- WOMAC Osteoarthritis Index

- Post Procedure

  The Injecting physician will record the following data:

  - Group Assignment
  - Amount and type of therapeutic substance injected
  - Total time to complete procedure from sterilization to bandaging
  - Procedural Pain Score (0 to 10)
  - Procedural Satisfaction Score (0 to 10)
  - Complications

  In a separate electronic database, the radiologist will record the following data:

  - Name
  - Presence or absence of contrast material within the knee joint

- Three months after intervention (telephone)
  - WOMAC Osteoarthritis Index
  - Procedure Satisfaction Score (0 to 10)

Study Time Line

Assessment				
Study Day / Period	Initial Evaluation and First Injection	Second Injection	Third Injection With contrast	3 months Post Treatment
Screening	x			
Informed Consent, discuss Plan, etc.	x			
Randomization	x			
Demographics, History & Physical	x			
WOMAC (pre injection)	x	x	x	x
Treatment	x	x	x	
Procedural Pain (post injection)	x	x	x	
Procedural	x	x	x	x

Satisfaction (post injection)				
Fluoroscopic Analysis			x	
Complications (post injection)			x	

Statistical Consideration

Primary endpoints are presence/absence of contrast medium in the joint, the WOMAC osteoarthritis index, and overall satisfaction with the injection technique. Our statistical analysis of the WOMAC index will consider a mean change from baseline to post-injection with the variables of pain, stiffness, and function. We will also study the mean change of the Global Score from the WOMAC.

Data Analysis

Statistical analysis of the WOMAC score will consist of one-way analysis of variance (ANOVA) followed by Tukey's post-hoc multiple comparisons between the four groups with a 5%, two-sided familywise significance level (which allows for comparisons between all possible pairs of treatments). Chi square tests will be used to compare the percent accuracy among the four groups. We will also perform sub-analysis to determine if any trends can be linked to the type of medication (viscosupplementation) injected versus accuracy.

Safety Monitoring and Analysis Plan

Since treatments are provided at the onset of the study, "stopping rules" will not apply in this study. Since the primary outcome includes pain and functioning at baseline and 3 months following the intervention, the entire study must be carried out in order to gather the desired data. There have been no unexpected side effects other than local pain and swelling at the injection site that have been reported in the studies using these injection techniques, so we do not believe any other specific side effects will need to be monitored. Patients will not be included in the study if a contraindication applies to them. Of note, viscosupplementation is not contraindicated in pregnant patients.

Sample Size Estimation

For the comparison of accuracy, a two group chi square test with a 5% two-sided significance level will have 80% power to detect a difference of 33 percentage points between groups when the accuracy in the less-accurate condition is 60% and the sample size in each group is 25.

Previous studies have demonstrated an effect size of the WOMAC ranging from 0.5 to 1.0 when medication interventions were studies on patients with knee pain. A sample size of 25 in each group will have 80% power to detect an effect size of 0.809 using a two group t-test with a 5% two-sided significance level.

Reference: Lenth, R. V. (2006-9). Java Applets for Power and Sample Size [Computer software]. Retrieved November, 2010, from http://www.stat.uiowa.edu/~rlenth/Power.

Reporting Adverse Events

Definitions:
Adverse events (adverse effects, adverse reactions): any occurrence of injury, dysfunction, disease, or abnormality of any organ or tissue that occurs in a subject enrolled in a clinical protocol. Manifestations of an adverse event may include symptoms, physical exam abnormalities, diagnostic study abnormalities, and/or death.

Expected adverse events: adverse events previously known or anticipated to result from: 1) the interventions and interactions used in the research (these events must be included as potential risks in the consent form); 2) the collection of identifiable private information under research (these events must be included as potential risks in the consent form); 3) an underlying disease, disorder, or condition of the human subjects; and/or 4) other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

Unexpected adverse events /Unanticipated problems: adverse events that 1) are not expected given the nature of the research procedures and the subject population being studied; and 2) suggest that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known or recognized.

Serious adverse event: an adverse event that is fatal, life-threatening, permanently disabling, require inpatient hospitalization, or result in congenital anomalies/birth defect, overdose or cancer, or any other adverse event that, based on appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above.

Expected Adverse Events from Research Risks and Reporting

- Rare but serious (Event Rate < 1%): infection at the site of injection; contrast dye allergic reaction.
- Likely (5% ≤ Event Rate < 10%): 8% incidence of pseudo-synovitis with the use of Synvisc® products.
- More likely (Event Rate ≥ 10%): bruising, swelling and increased pain at site of injection for several days to a few weeks.

Monitoring of adverse clinical events will be done during each of the two scheduled follow-up assessments. These will be managed as follows:

- Infection at injection site, or blood-borne infection: manage as clinically indicated based on assessment by physician.
- Contrast dye reaction: treat as clinically indicated based on severity.
- Pseudo-synovitis: NSAIDs, ice, compression, elevation.
- Bruising, swelling and increased pain at site of injection: treat with compression, ice, and prescribed pain medications (no NSAIDs), and patient reassurance that these resolve with time.

Reporting Serious and Unexpected Adverse Events to the IRB

Serious Adverse Events: The PI, within one working day, will report all serious adverse events (SAE) occurring in subjects enrolled in the study. This is accomplished by submitting an adverse event report memorandum to the IRB. Serious adverse events will be reported even if the PI believes that the adverse events are unrelated to the protocol.

Unexpected (but not serious) adverse events occurring in subjects enrolled in the study, in the opinion of the PI, are possibly related to participation in the protocol will be reported by the PI within 10 (ten) working days to the IRB using the same procedure.

For all serious and/or unexpected adverse events, the PI will forward a copy of the adverse event report to IRB. A summary of all serious or unexpected side effects also will be included in the APR.

Protected Health Information

All participant PHI and study results will be located in a password protected spreadsheet on a computer. The radiologist will also maintain a password protected spreadsheet on his/her personal work computer with password protected access and will provide this data as requested to the Principle Investigator. The Principle Investigator will maintain a central file of all PI and data on a password protected spreadsheet on a computer with password protected access.

Research documents that contain PHI will be destroyed when the study results have been published in a medical journal. Non-PHI results will be maintained indefinitely in the possession of the PI.

Reporting Protocol Deviations

Any protocol deviations during the course of the study will be promptly reported to the IRB and sponsor if applicable, through the medical monitor of the protocol if applicable. Examples of deviations include but are not limited to variances from the treatment schedule

for an individual patient, failure to use the most current consent form, and/or incomplete or lost records.

Reporting protocol deviation is accomplished by submitting a protocol deviation memorandum to the IRB.

Cost

The trial participants will not be charged any fees above the typical cost of their encounter with their physician and the cost of the injection of their medication. The expected cost of the Omnipaque 300 will be $6.25 per injection, totaling $750.00 for the entire study ($6.25 x 120 participants). Dr. Dorvault will provide accomplishment and interpretation of the fluoroscopic images at no additional charge.

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