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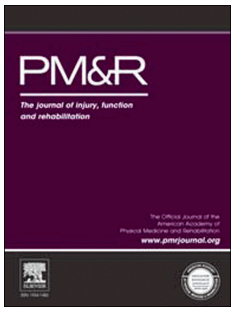

The Chondrogenic Effect of Intra-articular Hypertonic-dextrose (prolotherapy) in Severe Knee Osteoarthritis

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TITLE

The Chondrogenic Effect of Intra-articular Hypertonic-dextrose (prolotherapy) in Severe Knee Osteoarthritis.

ABSTRACT

Background: Dextrose injection is reported to improve KOA-related clinical outcomes, but its effect on articular cartilage is unknown. A chondrogenic effect of dextrose injection has been proposed**.**

Objective: To assess biological and clinical effects of intra-articular hypertonic dextrose injections (prolotherapy) in painful knee osteoarthritis (KOA).

Design: Case series with blinded arthroscopic evaluation before and after treatment.

Setting: Physical medicine and day surgery practice.

Participants: Symptomatic KOA for at least 6 months, arthroscopy-confirmed medial compartment exposed subchondral bone, and temporary pain relief with intra-articular lidocaine injection.

Intervention: Four to six monthly 10 mL intra-articular injections with 12.5% dextrose.

Main outcome measures: Visual cartilage growth assessment of 9 standardized medial condyle zones in each of 6 participants by three arthroscopy readers

masked to pre/post injection status (total 54 zones evaluated per reader); biopsy of a cartilage growth-area post-treatment, evaluated using H&E and Safranin-O stains, quantitative polarized light microscopy, and immunohistologic cartilage typing; self-reported knee specific quality of life using the Western Ontario McMaster University Osteoarthritis Index (WOMAC, 0-100 points).

Results: Six participants (1 female) with median age of 71, WOMAC composite score of 57.5 points and a 9-year pain duration received a median 6 dextrose injections and follow-up arthroscopy at 7.75 (4.5-9.5) months. In 19 of 54 zone comparisons all three readers agreed that the post-treatment zone showed cartilage growth compared with the pre-treatment zone. Biopsy specimens showed metabolically active cartilage with variable cellular organization, fiber parallelism, and cartilage typing patterns consistent with fibro- and hyaline-like cartilage. Compared with baseline status, the median WOMAC score improved 13 points (p=.013). Self-limited soreness after methylene-blue instillation was noted.

Conclusions: Positive clinical and chondrogenic effects were seen after prolotherapy with hypertonic dextrose injection in symptomatic grade IV KOA participants suggesting disease-modifying effects and the need for confirmation in controlled studies. Minimally invasive arthroscopy (single-compartment, single-portal) enabled collection of robust intra-articular data.

Key words: Chondrogenesis; osteoarthritis; knee; dextrose; intra-articular injections; prolotherapy.

Abbreviations:

Knee osteoarthritis (KOA)

Western Ontario McMaster University Osteoarthritis Index (WOMAC, 100 points)

Numerical Rating Scale (NRS, 0-10)

Insulin-like Growth Factor-1 (IGF-1)

Hematoxylin and eosin (H&E)

Quantitative polarized light microscopy (QPLM)

Body Mass Index (BMI)

Introduction

The Agency for Healthcare Research and Quality and the Institute of Medicine have called for evaluation of new knee osteoarthritis (KOA) therapies.[1,2] Hypertonic-dextrose injection (prolotherapy) is a treatment for chronic musculoskeletal pain, including KOA.[3] Functional and symptomatic benefit from hypertonic dextrose injection in knee osteoarthritis has been reported in three randomized controlled trials (RCTs) and three open-label studies, with stability of benefit at 30 month follow-up.[4-9] Animal and *in vitro* model data suggest cartilage-specific anabolic growth as a result of intra-articular dextrose injection.[10] A chondrogenic effect of intra-articular dextrose injection in human osteoarthritic knees has been hypothesized and assessed by radiograph and MRI, but not clearly demonstrated.[6,11]

Arthroscopy has been used for post-procedure “second-look” to evaluate the biological response of articular cartilage following stem cell injection and surgical procedures.[12,13] Direct visualization with arthroscopy and biopsy has the potential to detect subtle biological changes and may detect early cartilage change more accurately than MRI,[14] enabling the robust screening of potential chondrogenic effects in disease modification studies. We therefore tested the hypothesis that, among participants with severe symptomatic KOA, intra-articular hypertonic dextrose injections will be associated with chondrogenesis and clinical improvement compared with baseline status, as assessed by masked arthroscopic video review before and after treatment, post-treatment biopsy, and a disease-specific outcome questionnaire respectively.

Methods

The study protocol was approved by the Bioethics Committee of the National University of Argentina in Rosario, Argentina. Due to the self-funded and preliminary nature of this study, enrollment was limited to six participants.

Eligibility criteria and participant recruitment

Inclusion criteria included knee pain for at least six months, clinically diagnosed KOA,[15] a weight bearing x-ray consistent with high grade medial compartment cartilage loss (Kellgren-Lawrence Grading Scale level IV; Figure 1), and confirmation of exposed subchondral bone by high resolution knee ultrasonography.[16] Exclusion criteria included anticoagulation therapy,

inflammatory or post-infectious knee arthritis, systemic inflammatory conditions, knee flexion of less than 100 degrees, knee extension of less than 165 degrees, any valgus, varus deviation greater than 20 degrees, or less than 90% acute pain relief after intra-articular injection of 10 ml of 0.2% lidocaine.

Assessment

Age, pain duration, prior knee interventions, and body mass index (BMI) were recorded at study entry. Biological, clinical and functional assessment occurred at a single follow-up time point after completion of treatment. Biological assessment included methylene blue stain for cartilage at arthroscopy, followed by a pre- and post-treatment zone-by-zone videography of the medial condyle and a post-treatment biopsy with histologic and immunohistologic evaluation, as described below. Clinical and functional assessment included knee range of motion measurement using a goniometer,[17] disease specific quality-of-life score (composite Western Ontario McMaster University Osteoarthritis [WOMAC,0-100 points])[18] and knee pain severity with walking (0-10 numerical rating scale [NRS]).[19]

Pre-Treatment Arthroscopy, Treatment, Post -Treatment Arthroscopy, Biopsy, and Histology

A single orthopedic surgeon (LAP) performed all arthroscopies in an outpatient hospital setting. Analgesia for arthroscopy consisted of intra-articular injection of 20 mL 0.5% bupivicaine with epinephrine, 20 mL of 2% lidocaine with epinephrine, and 20 mcg of fentanyl in 20 mL of sodium chloride. The procedure

was minimally traumatic using one entry port; inspection was limited to the medial femoral condyle without flipping the scope to view the patellar surface. Sixty mL of 0.14% methylene blue solution was instilled and left in place for 10 minutes; the knee was then flushed with 4 liters of sterile water. A video of the entire medial compartment was then made with standardized zone-by-zone scope movement through each of 9 portions of the medial condyle (Figure 2a; A-I).[20] Each of the 9 portions was labeled with the appropriate letter using video editor software (AVS Video Editor 6.1.2.211- Online Media Technologies Ltd) and the video was then libraried.

Treatment consisted of sterile preparation with chlorhexidine gluconate, followed by intra-articular injection of 12.5% dextrose (5 mL of 25% dextrose, 5 mL of normal saline) via a lateral approach to the supra-patellar pouch under ultrasound guidance.[21] Participants were asked to avoid taking glucosamine and chondroitin and to minimize weight bearing for 3 days after injection by using support of arms and opposite leg when rising from a chair and to avoid running and squatting during the remainder of the study. Assistive devices such as canes or crutches were not required.

The original protocol called for four monthly intra-articular dextrose injections (baseline, 1, 2 and 3 months) followed by arthroscopy at 4 months post-baseline injection. However, after the first participant completed injection and follow-up arthroscopy, and while participants 2-6 were receiving injections, an unforeseen

133 construction project closed the arthroscopy facility for several months. This
134 delayed the acquisition of arthroscopy for participants 2-6. Because the
135 investigators were concerned that weight-bearing ambulation for several months
136 in the absence of monthly injections could eliminate evidence of a dextrose-
137 related chondrogenic effect should one exist, we requested and received
138 permission from the human subjects committee to increase the number of
139 injection sessions from 4 to 6. While this created a difference in the planned
140 number of injections between participant 1 (four injections) and participants 2-6
141 (six injections), our intention was to obtain all arthroscopies within three months
142 of the final injection.
143
144 Video recordings from the first arthroscopy were reviewed by the lead surgeon
145 prior to the follow-u p arthroscopy, who then repeated the method of the index
146 procedure; a biopsy was obtained from an area of potential new growth, as
147 defined by a new area of methylene blue dye uptake on the base of the exposed
148 subchondral bone. The same single portal was used to place the 11-gauge 10
149 cm Jamshi needle (Cardinal Health DJ4011X). A photograph of the biopsy site
150 was taken pre- and post-biopsy. The biopsy was subjected to 1% Safranin-O and
151 hematoxylin and eosin (H&E) staining (RG, Anatomopathology Consultation
152 Clinic in Rosario, Argentina) according to standard histotechnologic methods.[22]
153 Quantitative polarized light microscopy (QPLM) was performed (Department of
154 Bioengineering at the University of California, San Diego) along with timed

immunohistologic stain applications for Type I and Type II cartilage of the specimens and normal human cartilage controls.[23]

Comparative Zone-by-Zone Readings of Libraried Arthroscopies

Three orthopedic surgeons (VOG, YUK, AC) otherwise uninvolved with the Study and its participants, and with 14,16 and 20 years of experience performing knee arthroscopies respectively, volunteered to be outside reviewers. They performed comparative zone-by-zone readings of the arthroscopies and were masked to the date on which the arthroscopy was obtained. Computer randomization prepared by the statistician (ALC) was used to assign the pre-treatment arthroscopy to either "Arthroscopy A" or "Arthroscopy B"; then the same assignation was performed for the post-treatment arthroscopy, and both were loaded onto the timeline of the video editing program, saved in that randomized order, and reviewed independently by each reviewer. The reviewers were asked to view each zone A-I, moving the video timeline back and forth between Arthroscopy A and B and answer the following question: "Comparing arthroscopy A with arthroscopy B, which zone has the appearance of additional cartilage growth, A, B, or N(neither)." Reviewers completed a table with 54 responses (9 zones for each of 6 participants). Unblinding occurred after the arthroscopies were scored.

Analysis

The results of section-by-section arthroscopic video analysis of each of 9 sections of the medial condyle in all 6 participants by each surgeon-reader were

summarized for display on a medial condyle map, and compared for inter-reader reliability using a Fleiss' kappa statistic.[24] Histologic findings were summarized using photos in a per-participant manner. Non-arthroscopic data were analyzed using PASW 18 (Predictive Analytics Software 18.0.0, IBM). Descriptive statistics (median and interquartile range); or number / percent) described non-arthroscopic data at baseline and each follow-up time point. A paired-samples T-test was utilized to compare the WOMAC scores, 0-10 NRS pain scores, and knee flexion and extension measures at baseline to those collected before the second arthroscopy.

Results

Enrollment and follow-up occurred from February 2010 to June 2013. Twenty potential participants were referred to the study team (Figure 1). Eight met initial eligibility criteria. One declined arthroscopy and one was disqualified due to severe hypertrophic synovitis confirmed by multiple synovial proliferation folds. Thus, six participants were enrolled with one assessed knee each; data from two right knees and four left knees were included in the analysis.

The study sample consisted of five men and one woman with median age of 71, BMI of 26.25, and knee pain duration of 9.6 years (Table 1). A median initial composite WOMAC score of 57.5, and limitation of knee flexibility suggested moderate to severe baseline symptomatic KOA.

Ultrasound imaging showed a partially denuded medial femoral condyle as well as cortical irregularities (Figure 3; column 1). All participants showed baseline multi-compartmental osteoarthritis on lateral and AP films (Fig. 3; columns 2 and 3). Exposed subchondral bone was confirmed in each participant on initial arthroscopy.

Participant 1 received 4 injections and participants 2-6 received 6 injections prior to the follow-up arthroscopy at a median 7.75 (range 4.5-9.5) months.

Arthroscopic Zone-by-Zone Outcomes

In 19 of 54 zones evaluated (35%), all three readers agreed that the post-treatment zone showed cartilage growth compared with the pre-treatment zone. In 35 of 54 zones assessed, the three readers did not all agree, consistent with a low Fleiss' kappa value of inter-reader agreement of .007. Figure 2a shows the zones of the medial condyle for orientation and figure 2b shows the number of zones for which all 3 reviewers agreed on growth. For example, all reviewers rated zone I to show more growth in 3 of the 6 participants. In addition, all participants showed areas of growth; specifically, all three reviewers agreed that at least 2 zones showed cartilage growth in each participant.

Arthroscopic Documentation of Biopsy Locations

To confirm that the biopsy was taken from an area of new growth, the pre- and post-arthroscopy pictures are provided (Figure 4; columns 2 and 3), the area of

biopsy is outlined by a red box (column 4), and the post biopsy defect is shown. Although the biopsy for participant 3 cut across an area which may have included some previous cartilage in addition to new growth, all others were from exclusively new growth areas.

Basic Stains and Immunohistology for Cartilage Type

Figure 5 shows histological and immunohistologic findings for the medial condyle biopsy site. All Safranin-O stained slides showed orange stain uptake indicating the presence of negatively charged molecules in the matrix, consistent with glycosaminoglycans, and consistent with normal cartilage cell function. All H&E stained slides, assessing the presence of organized tissue growth on formerly denuded bone, showed a mixture of organized and disorganized tissue. QPLM assessment for fiber parallelism index showed areas of high fiber parallelism (orange or red areas), consistent with organized hyaline-like cartilage, in all but one participant (participant five). Positive uptake for Type I immunohistologic stain was noted in biopsy specimens from all participants, confirming that each specimen contained a fibrocartilage component. Positive uptake of Type II immunohistologic stain was noted in all biopsy specimens except participant 5, consistent with the presence of hyaline-like cartilage.

Clinical Outcomes

Median composite WOMAC scores improved from baseline to arthroscopic follow-up by 13 points (p=.013; Table 2). Median NRS-assessed pain severity

247 decreased by 3.7 points (p=.013). Median knee flexion improved 7.5 degrees
248 (p=.034); median knee extension deficit improvement was not significant (2.5
249 degrees; p=.086).
250
251 **Side effects and adverse events**
252 There were no adverse events associated with the injection procedures or with
253 arthroscopies. All participants noted self-limited mild-to-moderate, delayed-onset
254 aching pain lasting hours to 3 weeks after arthroscopy. This was greater than
255 that noted among non-study post-arthroscopy patients not receiving methylene
256 blue, and was thought to be related to a reaction to residual methylene blue after
257 irrigation.
258
259
260 ## Discussion
261 This study assessed the hypotheses that intra-articular hypertonic dextrose
262 injection is 1) associated with chondrogenesis and 2) provides a clinical benefit
263 compared to baseline status in participants with severe symptomatic KOA.
264
265 The evidence favoring chondrogenesis includes agreement by all three reviewers
266 of cartilage growth in 35% of possible evaluated zones and
267 histological/immunohistological presence of new cartilage in all 6 participants,
268 with a hyaline-like component in 5 of 6 biopsies from photographically-confirmed
269 areas of new methylene blue uptake. Mapping of growth zones confirms that this

growth occurred in both non-weightbearing and weightbearing areas. These outcomes were obtained post-procedure without use of weight-reducing devices such as off-loading braces. Unloading of the knee remains best care after cartilage repair procedures;[25] therefore, these data may underestimate the potential effect of the procedure in the presence of unloading. The improvement in clinical measures was statistically significant and clinically important, and consistent with three open-label studies and three RCTs of hypertonic dextrose prolotherapy injections for knee OA.[4-9]

These changes may result from the procedure tested; the small volume of methylene blue and subsequent saline lavage are not chondrogenic,[26-28] and neither is expected to result in the observed clinical benefit. Though the cartilage growth was limited to a relatively small portion of the denuded surface, these are the first objective data to support the hypothesis that hypertonic dextrose injection may stimulate the growth of cartilage in the human knee.

While this study suggests cartilage growth and self-reported clinical improvement may be effects of hypertonic dextrose injection, we are not able to determine whether a single mechanism is responsible for either outcome, or whether the two outcomes are related. Several hypotheses for the mechanism of action of hypertonic dextrose injection have been advanced. The traditional view is that hypertonic dextrose initiates a brief inflammatory cascade stimulating native healing and subsequent tissue growth; clinical improvement then results from a

restoration of tissue integrity.[29] Animal model studies have reported increased cross sectional area of MCL ligament in a rat model[30] and an increase in organized connective tissue width, thickening of collagen bundles, increase in energy absorption and of load-before-rupture in a rabbit model[31,32] in response to hypertonic dextrose injection. Ultrasound data suggest that hypertonic dextrose injection is followed by tissue regeneration in ligamentous tissue[33,34] however, analogous cartilage-specific data are lacking.

A direct pain-modulating effect has also been hypothesized. Recent clinical trial data suggest hypertonic dextrose may decrease pain via a sensori-neural mechanism through direct exposure of dextrose to multiple intra-articular KOA pain generators, including the fat pad, synovium and menisci. Two recent RCTs have suggested that sugar (dextrose) and a sugar alcohol (mannitol) have an analgesic effect in low back pain[35] and a capsaicin pain model[36] respectively, consistent with a potential sensori-neural mechanism of these agents.

An alternative view is that glucose has direct anabolic effects.[37] In vitro data on glucose-specific effects on chondrocytes demonstrate proliferative effects that vary according to such factors as oxygen tension, osmolarity, and the source of the chondrocyte (osteoarthritic or non-osteoarthritic knees).[38-43] Synovial explants harvested from human donors and cultured in 0.45% dextrose demonstrated up to a fivefold elevation of IGF-1 gene expression and secreted IGF-1 into the tissue media.[44] Park et al. injected a solution that included 10% dextrose

316 compared to normal saline into ACL-transection-induced OA knee joints of New
317 Zealand white rabbits and reported decreased erosion of articular cartilage
318 overall compared to saline control, and minimal differences compared to normal
319 cartilage which did not undergo ACL transection.[10]
320
321 The current study is not able to identify the source of new cartilage. Progenitor
322 cells within the synovial joint environment may contribute to endogenous
323 cartilage repair.[45-47] Human synovium contains cells that, after culture expansion,
324 display properties of mesenchymal stem cells.[48] Another potential source of the
325 cartilage growth is cartilaginous aggregates within the exposed subchondral
326 bone. Zhang et al. documented the presence of cartilaginous deposit aggregates
327 in the subchondral bone in areas of the human osteoarthritic knee with exposed
328 bone.[49]
329
330 **Study Limitations**
331 The primary limitations of this study are small sample size and absence of a
332 control group. Potential conclusions are therefore modest. However, the cohort
333 was thoroughly evaluated; cartilage growth among all participants suggests a
334 modest but real chondrogenic response to hypertonic dextrose, and the
335 WOMAC-assessed response is consistent with blinded and non-blinded studies
336 of hypertonic dextrose injections for KOA.[6,7]. The low overall agreement rate
337 among arthroscopy reviewers masked to date of arthroscopy limits slightly the
338 confidence of our conclusions. Several aspects of the review process may

account for uncertainty and subsequent lack of agreement; these include: 1) very subtle growth, 2) No published guidelines on visual assessment of cartilage on exposed subchondral bone, and 3) review instructions that did not define exactly what constituted cartilage growth and were therefore open to interpretation by the reviewers.

Generalizability is limited by three factors. 1) Eligibility criteria included only the most severely affected knees; therefore, we are not able to address the potential effects of dextrose injection on patients with less severe KOA. While prior studies have enrolled participants with K-L I-III KOA,[4,7] we chose to include participants with KL IV and exposed subchondral bone because prior studies suggested positive clinical effects from prolotherapy on all grades of KOA,[4-9] and detection of cartilage growth is more clear on a denuded bone surface than on a cartilaginous surface. 2) The injection protocol varied slightly between one participant and the other five; however, both four and six injection sets fall within the clinically utilized number of injections. 3) Biopsy using a single entry port cannot obtain samples at the preferred angle of entry of 90 degrees. While this could affect precise assessment of tissue depth by layer, the use of QPLM allowed for an assessment of hyaline-like tissue quality via fiber parallelism, and photographic confirmation of biopsy site confirmed that the biopsy location was in an area of new methylene blue uptake.

Conclusions

Intra-articular hypertonic dextrose injections were associated with chondrogenesis in areas of exposed subchondral bone in participants with symptomatic grade IV osteoarthritic knees. Participants improved clinically in self-reported and objectively-assessed functional outcomes consistent with previous randomized clinical trials. Minimally invasive single-compartment single-portal arthroscopy enabled collection of robust data from a small number of participants, and may provide an attractive, cost-effective means with which to evaluate potentially disease-modifying therapy.

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Table and Figure Legends

Table 1: Baseline Participant Characteristics

[a] IR = Interquartile range

[b] Percentage does not sum to 100 due to participants' varied use of conventional therapies.

[c] 100 point WOMAC

Table 2: Median Baseline and Change in WOMAC Scores, NRS pain and flexibility

[a] Time until 2nd arthroscopy. Values obtained in week prior to arthroscopy.

[b] Significance (p-value) is reported compared to baseline status.

[c] IR = Interquartile range.

Figure 1: Enrollment of Participants and Completion of the Study

Legend 1: Eligibility and exclusion criteria, grade IV change on ultrasound of the medial femoral condyle and analgesia with lidocaine injection were required for candidacy. Methylene blue straining was used to visualize cartilage cells. Video recordings of the entire medial condyle were performed in a fixed sequence both before and after treatment. A biopsy was obtained of an area of visible growth

588 during the second arthroscopy. Changes in pain, flexibility, cartilage status,
589 histology, and Immunohistology were followed.

590 **Figure 2: Areas of Cartilage Growth on the Medial Femoral Condyle**

591 Legend 2: Left image shows the entire medial condylar surface of the left knee
592 divided into 9 sections (A-I) per International Cartilage Research Society (ICRS)
593 guidelines[28]. A cutout area is shown. A fraction is seen in each of the sections in
594 the right side magnified image. The denominator of each fraction is 6, the
595 number of knees evaluated arthroscopically before and after treatment. The
596 numerator is the number of knees that showed growth as agreed upon by all
597 three arthroscopists.

598 **Figure 3: Baseline Femoral Condyle ultrasound and AP and Lateral X-rays.**

599 Legend 3: The left column is an ultrasound image of the medial femoral condyle
600 showing at least focal full thickness loss of cartilage. AP radiographs were taken
601 in maximum extension with beam direction at joint height. Lateral compartments
602 were consistent with multicompartmental involvement.

603 **Figure 4: Arthroscopic Confirmation of Biopsy from an Area of Cartilage**
604 **Growth**

605 Legend 4: The darkened area in column one for each subject indicates the
606 section from which the biopsy was taken for each subject. A still photograph of
607 the area from which the biopsy was taken is shown from the first arthroscopy in
608 column two and at the time of the post treatment arthroscopy (column three).
609 Column four shows the area of biopsy within the red box and column five shows
610 the biopsy defect.

Figure 5: Safranin-O and H&E Stains, Quantitative Polarized Light Microscopy, and Immunohistology for Cartilage Type of Biopsy Specimens.

Legend 5: The normal positive uptake controls for immunohistologic stain for fibrocartilage and hyaline cartilage, respectively, were the perichondral (fibrous) region of nasal septal cartilage discarded at the time of routine nasal septal surgery and normal femoral condyle cartilage (cadaveric). An IgG stain of the same normal femoral condyle cadaver cartilage served as the negative control, since IgG will not be taken up by normal cartilage.

Table 1: Baseline Participant (n=6) Characteristics	
Female, n (%)	2 (40%)
Age, years, median (IR)[a]	71 (15)
Duration of Knee Pain, years, median (IR)	9.6 (10.8)
BMI, n (%)	
≤25	2 (33%)
26-30	3 (50%)
31+	1 (17%)
Prior Knee Intervention, n (%)[b]	
Physical Therapy	6 (100%)
Hyaluronic acid injection	1 (17%)
Corticosteroid injection	3 (50%)
Arthroscopic surgery	0 (0%)
WOMAC[c] median points (IR)	
Composite	57.5 (8)
Pain	57 (7)
Stiffness	57.5 (9)
Function	58 (8)
NRS pain, median (IR)	8.5 (3.25)
Flexibility	
Flexion Range, median, (IR)	112.5 (22)

Extension Deficit, median (IR)	**7.5 (11)**

[a] IR = Interquartile range

[b] Percentage does not sum to 100 due to participants' varied use of conventional therapies.

[c] 100 point WOMAC

Table 2. Median Baseline and Change in WOMAC Scores, NRS pain and flexibility			
Measure	**Baseline Score (n=6)**	**Improvement to a median 7.75 (Range 4.5 to 9.5 months)[a] (n=6)**	**P-Value[b]**
WOMAC Composite Score, median (IR)[c]	**57.5 (8.0)**	**-13 (22)**	**.013**
WOMAC Subscale Scores, median (IR)			
Pain	**57 (7.0)**	**-14 (21.0)**	**.010**
Stiffness	**57.5 (9.0)**	**-12.5 (23)**	**.017**
Function	**58 (8.0)**	**-13.5 (23)**	**.015**
NRS (0-10) Pain With Walking, median (IR)	**8.5 (3.25)**	**-3.7 (3.0)**	**.013**
Flexion Range, median (IR)	**112.5 (22)**	**+7.5 (13)**	**.034**
Extension Deficit, median (IR)	**7.5 (11)**	**-2.5 (7)**	**.086**

[a] **Time until 2nd arthroscopy. Values obtained in week prior to arthroscopy.**

[b] **Significance (p-value) is reported compared to baseline status.**

[c] **IR = Interquartile range.**