Original paper

RANDOMIZED PROSPECTIVE DOUBLE-BLIND PLACEBO-CONTROLLED STUDY OF DEXTROSE PROLOTHERAPY FOR KNEE OSTEOARTHRITIS WITH OR WITHOUT ACL LAXITY

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Context • *Use of prolotherapy (injection of growth factors or growth factor stimulators).*
Objective • *Determine the effects of dextrose prolotherapy on knee osteoarthritis with or without anterior cruciate ligament (ACL) laxity.*
Design • *Prospective randomized double-blind placebo-controlled trial.*
Setting • *Outpatient physical medicine clinic.*
Patients or other participants • *Six months or more of pain along with either grade 2 or more joint narrowing or grade 2 or more osteophytic change in any knee compartment. A total of 38 knees were completely void of cartilage radiographically in at least 1 compartment.*
Intervention • *Three bimonthly injections of 9 cc of either 10% dextrose and .075% lidocaine in bacteriostatic water (active solution) versus an identical control solution absent 10% dextrose. The dextrose-treated joints then received 3 further bimonthly injections of 10% dextrose in open-label fashion.*
Main Outcome Measures • *Visual analogue scale for pain and swelling, frequency of leg buckling, goniometrically measured flexion, radiographic measures of joint narrowing and osteophytosis, and KT1000-measured anterior displacement difference (ADD).*
Results • *All knees: Hotelling multivariate analysis of paired observations between 0 and 6 months for pain, swelling, buckling episodes, and knee flexion range revealed significantly more benefit from the dextrose injection (*P*=.015). By 12 months (6 injections) the dextrose-treated knees improved in pain (44% decrease), swelling complaints (63% decrease), knee buckling frequency (85% decrease), and in flexion range (14 degree increase). Analysis of blinded radiographic readings of 0- and 12-month films revealed stability of all radiographic variables except for 2 variables which improved with statistical significance. (Lateral patellofemoral cartilage thickness [*P*=.019] and distal femur width in mm [*P*=.021]. Knees with ACL laxity: 6-month (3 injection) data revealed no significant improvement. However, Hotelling multivariate analysis of paired values at 0 and 12 months for pain, swelling, joint flexion, and joint laxity in the dextrose-treated knees, revealed a statistically significant improvement (*P*=.021). Individual paired* t *tests indicated that blinded measurement of goniometric knee flexion range improved by 12.8 degrees (*P*=.005), and ADD improved by 57% (*P*=.025). Eight out of 13 dextrose-treated knees with ACL laxity were no longer lax at the conclusion of 1 year.*
Conclusion • *Prolotherapy injection with 10% dextrose resulted in clinically and statistically significant improvements in knee osteoarthritis. Preliminary blinded radiographic readings (1-year films, with 3-year total follow-up period planned) demonstrated improvement in several measures of osteoarthritic severity. ACL laxity, when present in these osteoarthritic patients, improved. (Altern Ther Health Med. 2000;6(1):68-80)*

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INTRODUCTION

Prolotherapy (*injection of growth factors or growth factor stimulators*) raises growth factor levels or increases growth factor effectiveness to promote tissue repair or growth. The most common solutions used for prolotherapy create a brief inflammatory response. Temporary cellular stress causes a release of cytokines and increased growth factor activity with migration of macrophages (white blood cells), and then multiplication of repair cells specific to the tissue. Unlike repair after an injury, disruption of architecture of tissue from injury does not occur, and new cells and matrix can be deposited in an organized fashion, with maturation of new tissue for 6 to 8 weeks.[1] Two double-blind studies have been performed on prolotherapy in low back pain using inflammatory solutions.[2,3] These studies both showed significant benefit from proliferant injection, but because the solutions were inflammatory there was some potential for impairment of double-blind protocol. The purpose of this investigation was to evaluate effectiveness of prolotherapy without using any inflammatory mechanism so that neither patient, research coordinator

nor primary investigator would have any way to determine patient group. Our specific plan was to study the effect of a non-inflammatory (10%) concentration of dextrose (D-glucose in water) on knee osteoarthritis patients via objective measures of knee cartilage, knee osteophytic status, and knee goniometric range, as well as by subjective measures of knee pain, knee swelling, and knee buckling.

Some patients in the study had anterior cruciate ligament (ACL) laxity, which is known to initiate and worsen knee osteoarthritis. A second purpose for this study was to observe the effect of proliferant injection on laxity of the ACL, as measured by an objective and reproducible measure (an electroarthrometer).

Elevation of extracellular glucose to as little as .5% (normal extracellular and cellular glucose is .1%) has been shown to raise levels of multiple polypeptide growth factors in a variety of human cells.[4-8] Exposure of several human cells to a hypertonic environment will also promptly result in a rise in DNA levels for growth factors within seconds to minutes.[9,10] Therefore, hypertonic dextrose solution has 2 mechanisms by which to increase levels of growth factors, potentially improving the status of critical cells in the joint such as chondrocytes (cartilage producing cells), osteocytes (bone producing cells), and fibroblasts (tendon/ligament/other soft tissue producing cells).

METHODS

Ads were placed for patients with knee arthritis to receive injection of a solution to reduce pain in knee osteoarthritis. Criteria for knee osteoarthritis included 6 months or more of pain in the knee, accompanied by either grade 2 or more joint narrowing or grade 2 or more osteophytic change. Grade 2 joint narrowing can be described as the presence of less than or equal to 3 mm of cartilage (found in only 8% without symptomatic knee osteoarthritis [OA]).[11] A grade 2 osteophyte can be described as a short, fat and obvious bone spur or a moderately long (10 mm or more), thin bone spur (found in only 14% without symptomatic knee OA.)[11] A standard radiographic atlas was used to determine joint narrowing and osteophytic grades, which was designed for that purpose.[12]

The ability to verify ACL laxity by any arthrometer requires testing of both knees for an anterior displacement difference (ADD) side to side. Using this method, the KT1000 (Medmetric Corporation, San Diego, Calif) has been shown to be equal to or more reliable than other arthrometers.[13-16] Based on extensive review of previous studies of the KT1000 an ADD of 2 is estimated to be 85% sensitive and 85% specific for ACL laxity.[15,17-19] Since this study was not funded to allow for magnetic resonance imaging (MRI) studies to rule out complete ACL tear, the number of patients with complete ACL tear could not be determined. Note that the objectivity of this electroarthrometer is found in its use of standard positioning of the knee within the device, audible indications when certain pressures are applied to the knee through the device, a precise readout easily visible for recording, and a routine to perform each reading 3 times to average all 3 readings.

Once the patients were found to meet radiologic and symptomological criteria for knee osteoarthritis, they were assigned serially to group 1 or 2 using a random number table by 1 of 2 data base coordinators always in the office. This group assignment was kept in a database blinded to the chief investigator and research coordinator.

The research coordinator obtained an estimate of arthritis medications taken and then demonstrated the use of a 100-mm visual analogue scale (VAS) and gave 3 examples of its use. The patients then self-scored their pain levels of knee pain at rest, knee pain walking on level surfaces, knee pain with stair use, and subjective swelling, and estimated the number of knee buckling episodes over the previous 2 months. Following this, the research coordinator obtained goniometric readings of joint flexion by the method described in a standard text.[20]

Patients who were taking any medication or oral supplement for osteoarthritis other than calcium, multivitamins, NSAIDS, acetaminophen, or occasional narcotic, were asked to discontinue them. The most common oral supplement discontinued was glucosamine/chondroitin sulfate.

Blood was obtained for sedimentation rate, rheumatoid factor, uric acid, and antinuclear antibody. Significant laboratory abnormalities led to referral to primary physician or rheumatologist for determination of the presence or absence of inflammatory arthritis. No patients required exclusion due to the laboratory battery after the initial phone screening.

Dextrose prolotherapy solutions for maximum safety have typically included bacteriostatic water, a small concentration of lidocaine, and dextrose. Because of the desire to maximize safety and comfort in this study and simulate typical prolotherapy solutions, the control was the usual bacteriostatic water with a very small amount of lidocaine, and the active solution was identical except for the inclusion of 10% dextrose.

At 0, 2, and 4 months solution was drawn up blinded to both chief investigator and research coordinator. Using a 27-gauge needle via an inferomedial approach, tibiofemoral injection was conducted with 9 cc of either 611.4 mOsm (10% dextrose and .075% lidocaine in bacteriostatic water) or 105.4 mOsm (.075% lidocaine in bacteriostatic water) solution. Bacteriostatic water consisted of .9% benzyl alcohol. The small dose of lidocaine was included for postinjection comfort. The solutions were identical in color and viscosity. Dextrose at 10% concentration is very slightly sticky if allowed to dry on the skin but Hibiclenz was used for glove and skin prep which masked any potential of noting any slight stickiness of solution.

Treatment continued beyond 6 months in the dextrose group with additional injections at 6, 8, and 10 months. Subjective variables, goniometric flexion, 2-view radiographs and KT-1000 ADD measurements were repeated at 1 year. Skier's (standing) views of the knee were used to determine tibiofemoral compartment status. Angle of knee flexion on skier's views, angle of radiograph beam to the knee, camera to film distance, power and duration of radiograph beam, and radiograph technician were identical at 0 and 12 months. Magnification on standing films was prevented by ensuring contact of patella with film plate. Skyline views of the patella

were used to determine patellofemoral compartment status, with similar measurements, including camera to knee and knee to film distance, to ensure an identical radiograph method.

Radiographs were read in double-blind fashion in the following way. The study coordinator obscured patients' names and labeled the film with a random patient number. The film date was obscured and a random number table was used to assign a number to the 0- and 12-month films. The 0- and 12-month films were then separated in different packets so that reading 1 film would not influence reading of the next. Osteophytic grade was measured in 6 compartments using a standard atlas with approximately 90% intra-reader agreement.[12] The compartments included medial femoral, medial tibial, lateral femoral, lateral tibial, medial patellofemoral, and lateral patellofemoral. Cartilage thickness was determined in 4 compartments in millimeters: medial tibiofemoral, lateral tibiofemoral, medial patellofemoral, and lateral patellofemoral. General hypertrophic change was evaluated as a width measurement in millimeters: distal femur width proximal to the intercondylar notch, distal femur width distal to the intercondylar notch, and proximal tibial width. Width measurements were made parallel with the film bottom edge through the area of largest width, including any osteophytes present. The x-rays were read by the chief investigator. A database coordinator loaded results onto the database.

Human subject research approval and monitoring was by the Institutional Review Committee of Bethany Medical Center in Kansas City, Kans. Procedures followed were in accordance with ethical standards outlined in the Helsinki Declaration Revision of 1983. The statistical analysis software was SPSS (Statistical Program for Social Science) version 7.5.3.

RESULTS

Blinding method problems were not identified. No treatment complications were noted. Seventy-seven patients had 1 or more knees that met study criteria for symptomatic osteoarthritis (OA). Nine patients dropped out over 12 months of followup, 4 due to lack of efficacy (3 in control group and 1 in active group), and 5 for unrelated medical reasons. This left 111 knees in 68 patients with OA.

At study onset 31 patients met arthrometric criteria for ACL laxity. Two dropped out over 12 months due to lack of efficacy and 4 for unrelated medical issues, leaving 25 for analysis.

Independent sample *t* tests were conducted to compare the active and control groups of OA knees. No significant differences were noted between groups for age, weight, pain levels, range of motion, buckling episodes, or radiographic findings. The same result was noted when *t* tests were conducted to compare active and control groups of knees with ACL laxity. The average knee OA patient in this study was 63 years of age and weighed 195 lb. Males comprised 58% of the study population.

Complications and Safety Issues

Discomfort after injection did not appear to vary between groups, typically lasting a few minutes to several days. Despite use of an allergy-size needle (27 gauge) and a single-insertion technique, some patients had pain with distension of the joint capsule even with this minimal volume (9 cc). The 9 cc volume for injection may be a bit excessive in that some patients were inhibited in flexion for several days. One person had a flare postinjection that appeared substantial, requiring interarticular steroid and then referral to an orthopedic surgeon. When blinding was broken she was found to have received control solution.

No allergic reactions or infections were noted.

Six-Month (Double-Blind Phase) Data Comparing Active and Control Solution for all Osteoarthritic Knees

Figure 1 presents a bar graph depicting improvements in pain (average of improvement in pain at rest, pain with walking, and pain with stair use) and swelling for the active and control groups at 6 months (after 3 injections of 9 cc of solution). Both active and hypotonic control solution administration resulted in considerable gains in VAS scores for pain.

Figure 2 shows improvement in knee flexion for both groups at 6 months. Both active and hypotonic control injections resulted in an improvement in goniometric knee flexion measures.

Hotelling multivariate analysis of paired observations between 0 and 6 months for active and control solution including all nonradiographic variables (pain at rest, pain with walking, pain with stair use, swelling, buckling episodes, and flexion range) demonstrated a statistically superior effect of active solution ($P = .015$). The results of individual paired *t* tests from 0 to 6

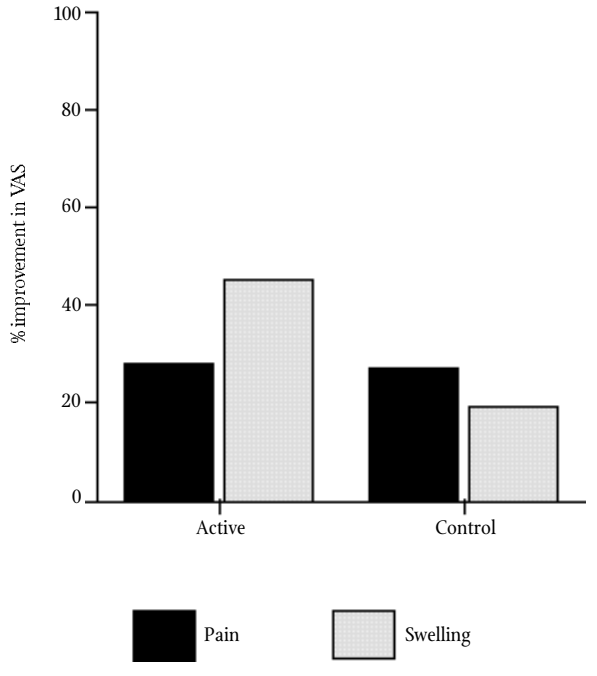

FIGURE 1 Percentage improvement in pain and swelling from study onset to 6 months for active and control solutions.

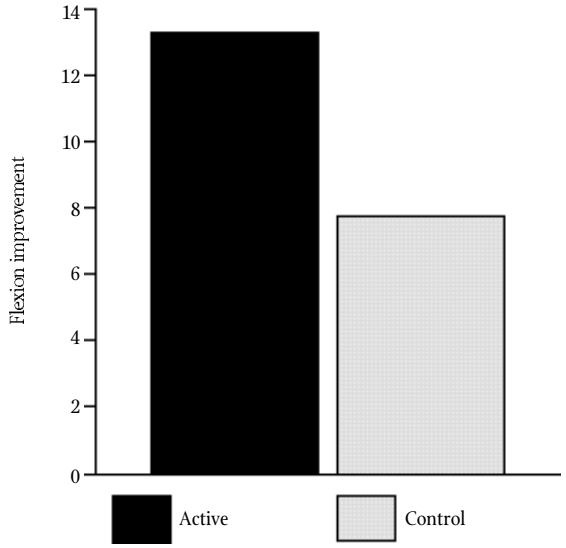

FIGURE 2 Degree improvement in knee flexion range of motion after 3 bimonthly injections of active or control solution.

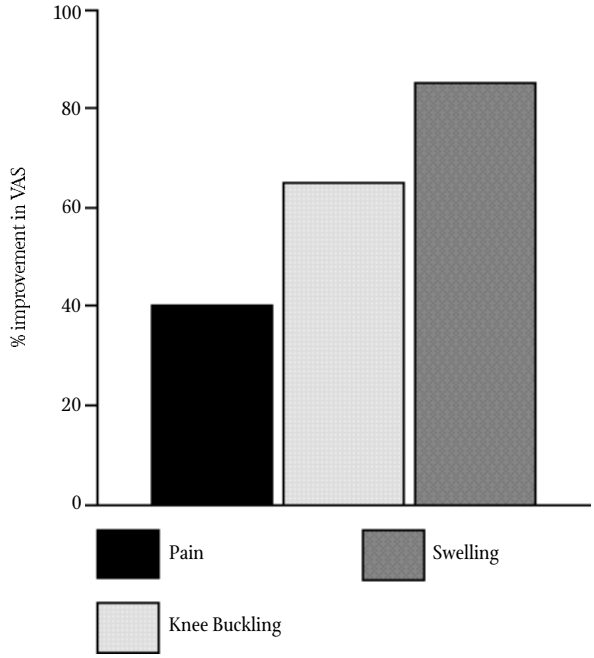

FIGURE 3 Percentage improvement in pain, subjective swelling and number of knee buckling episodes after 6 injections of active solution (at 1-year follow-up).

months for each of the variables are shown in Table 1. Although the active solution was superior statistically, highly significant improvement from 0 to 6 months was seen in pain with walking, pain with stair use, and flexion range of motion in both active and control groups.

The NSAID follow-up question was limited in its ability to determine a degree of change in level of intake, and no significant change between groups was noted. However, neither group had an increase in NSAID intake, which could explain improvement in pain levels or other variables.

One-Year Data (Nonradiographic) for Active Solution for Osteoarthritic Knees

Figure 3 shows percentage improvements in pain and swelling complaints and knee buckling in the dextrose group between 0 and 12 months (with 3 further bimonthly open label injections of dextrose). Pain improved by 40%, swelling by 63%, buckling episodes by 85%, and flexion by 14 degrees as compared with study entry.

Radiographic Data at 1 Year for Active Solution for Osteoarthritic Knees (Table 2)

Thirteen radiographic readings for each knee are shown in Table 2. These variables included medial femoral osteophyte grade (MFOG), medial tibial osteophyte grade (MTOG), lateral femoral osteophyte grade (LFOG), lateral tibial osteophyte grade (LTOG), medial patellofemoral osteophyte grade (MPOG), lateral patellofemoral osteophyte grade (LPOG), medial tibiofemoral cartilage thickness (MTFT), lateral tibiofemoral cartilage thickness (LTFT), medial patellofemoral cartilage thickness (MPFT), lateral patellofemoral cartilage thickness (LPFT), distal femur width proximal to the intercondylar notch (DFWP), distal femur width distal to the intercondylar notch (DFWD), and proximal tibial width (PTW).

Hotelling multivariate analysis of paired observations between 0 and 12 months for the dextrose-treated knees including all 13 radiographic variables revealed a statistically significant change (P=.028). Individual paired t tests showed the means for radiographic variables were all stable except for an improvement (increase) in lateral patellofemoral cartilage thickness (P=.019) and an improvement (decrease) in distal femur width including osteophytes (P=.021).

Data for Knees with ACL Laxity

The 6-month data showed no statistically significant differences between active and control solutions, nor significant changes in ACL laxity measurement. However, the dextrose-treated knees were given 3 additional injections of dextrose and data were collected at 1-year follow-up. Hotelling multivariate analysis of paired observations of the dextrose-treated knees comparing 0 and 12 months for VAS rest pain, VAS walking pain, VAS stair use pain, VAS swelling complaint, flexion range of motion, and KT1000 side-to-side difference showed statistically significant improvement over time (P=.021). The results of individual paired t tests from 0 to 12 months are shown in Table 3. Blinded goniometric range measurement improved by 12.8 degrees with a P value of .005 and KT1000 ADD improved by 57% with a P value of .025. Figure 4 is a bar graph showing the

TABLE 1 Means, standard deviations (SD), and individual paired *t* tests for change in nonradiographic variables from 0 to 6 months in all osteoarthritic knees for active and control solution

	Group	Mean (SD) 0 months	Mean (SD) 6 months	Mean diff 0-6 months	Standard error of mean diff	95% CI for the mean difference	Significance between means at 0 and 6 months
Pain at rest	Active	2.15 (2.24)	1.61 (1.71)	-.54	.24	-1.02 to -.06	.029
	Control	2.73 (2.02)	1.69 (1.73)	-1.04	.25	-1.54 to -.54	.00005
Pain with walking	Active	3.94 (2.82)	2.56 (1.97)	-1.39	.31	-2.01 to -.77	.00002
	Control	3.83 (2.20)	2.85 (2.20)	-.98	.32	-1.62 to -.34	.003
Pain with stair use	Active	5.33 (2.80)	3.96 (2.68)	-1.37	.32	-2.01 to -.73	.00004
	Control	5.83 (2.60)	4.60 (2.91)	-1.23	.32	-1.87 to -.59	.0002
Swelling	Active	2.44 (2.53)	1.35 (1.87)	-1.09	.25	-1.59 to -.59	.00003
	Control	3.12 (2.99)	2.52 (2.80)	-.60	.26	-1.12 to -.08	.022
Buckling episodes per 2 months	Active	7.78 (34.14)	2.54 (11.44)	-5.24	2.23	-9.70 to -.78	.020
	Control	1.00 (2.60)	.21 (.64)	-.79	2.27	-5.33 to +3.75	.729
Flexion range	Active	112.35 (19.54)	125.59 (8.63)	-13.24	2.15	+8.94 to +17.54	.00000001
	Control	117.75 (11.32)	125.44 (7.48)	-7.69	2.19	+3.31 to +12.07	.001

distribution frequency of laxity values (ADD) for dextrose-treated patients at time 0 and 12 months. Note that 8 of the 13 improved to the point that ADD was less than 2, such that they would no longer be considered lax, and this in a group of patients with one or more complete ACL ruptures.

DISCUSSION

Balance of Growth and Disrepair Factors in Bony Cortex, Cartilage, and Synovial Fluid

The balance of disrepair and repair in both bone and cartilage merit examination since degenerative changes in bone occur simultaneously with those in cartilage.[21,22]

Chief repair factors found in osteoarthritic subchondral bone or cartilage include insulin-like growth factor (IGF), transforming growth factor beta (TGF-β), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and platelet derived growth factor (PDGF).[21,22] Chief disrepair factors (factors that block growth factor effects or break down tissue or building blocks for tissue) for the bony surface or cartilage include interleukin-1 (IL-1) and tumor necrosis factor (TNF), which lead to a rise as much as 110-fold in metalloproteinases such as collagenase (which breaks down cartilage) in fibrillated cartilage and a rise as much as 24-fold in binding proteins (proteins that bind growth factors to keep them from functioning) in synovial fluid.[23-27]

TABLE 2 Means, standard deviations (SD), and individual paired *t* tests for change in radiographic variables from 0 to 12 months in osteoarthritic knees treated with active solution

Variable	Mean (SD) 0 months	Mean (SD) 6 months	Mean diff 0 - 12 months	Standard error of mean diff	95% CI for the mean difference	Significance between means at 0 and 6 months	Direction of change
MFOG	1.55 (1.07)	1.49 (1.02)	-.06	.11	-.28 to +.16	NS	Stable
MTOG	1.56 (.92)	1.53 (1.05)	-.03	.10	-.23 to +.17	NS	Stable
LFOG	1.65 (.91)	1.76 (.84)	+.11	.13	-.15 to +.37	NS	Stable
LTOG	1.22 (.95)	1.33 (1.00)	+.11	.13	-.15 to +.37	NS	Stable
MPOG	1.24 (.82)	1.25 (.82)	-.01	.12	-.25 to +.23	NS	Stable
LPOG	1.42 (.66)	1.40 (.66)	-.02	.08	-.18 to +.14	NS	Stable
MTFT	2.09 (2.18)	1.94 (2.14)	-.15	.13	-.41 to +.11	NS	Stable
LTFT	5.54 (2.06)	5.58 (2.32)	+.04	.17	-.30 to +.38	NS	Stable
MPFT	4.51 (1.63)	4.59 (1.41)	+.08	.19	-.30 to +.46	NS	Stable
LPFT	4.20 (1.54)	4.59 (1.34)	+.39	.16	+.07 to +.71	.019	Improved
DFWP	93.58 (7.23)	92.96 (7.07)	-.62	.26	-1.14 to -.10	.021	Improved
DFWD	90.18 (8.36)	90.60 (8.14)	+.42	.34	-.26 to +1.10	NS	Stable
PTW	89.18 (7.96)	88.53 (8.08)	-.65	.39	-1.43 to +.13	NS	Stable

Proliferation of Human Chondrocytes by Growth Factors in Culture and Chondrogenesis of Animal Cartilage by Injection of Growth Factors

Bujia[28] and Dunham[29] demonstrated that culturing human chondrocytes (nasal septum chondrocytes) in fluid containing TGF-β,[28] IGF-1,[29] or bFGF[28,29] resulted in proliferation. Injection of animal knees with a single injection of TGF-β,[30] bone metabolic protein-2 (BMP-2),[30] bFGF,[31] or hepatocyte growth factor (HGF)[32] has led to chondrogenesis,[30] enlargement of articular cartilage,[31] and repair of full thickness joint cartilage defects.[32] Implantation of gel or a collagen sponge saturated with growth factor or placement of a surgically placed small pump that delivers growth factors have led to repair of full thickness cartilage lesions in animal models, also.[33-35] However, demonstration of 3 weeks of proteoglycan synthesis after a single injection of TGF-β[30] and healing of full-thickness cartilage lesions with a single injection of growth factor[32] indicates that continuous exposure to growth factor may not be required for a prolonged growth factor effect. In established OA high levels of binding proteins or metalloproteinases may block the effect of a single growth factor

TABLE 3 Means, standard deviations (SD), and individual paired *t* tests for change in pain, swelling, flexion, and laxity variables from 0 to 12 months for active solution in knees with ACL laxity

	Mean (SD) 0 months	Mean (SD) 12 months	Mean diff 0-12 months	Standard error of mean diff	95% CI for the mean difference	Significance between means at 0 and 12 months
Pain at rest	2.31 (2.56)	1.38 (2.06)	-.93	.49	-1.91 to +.06	.082
Pain with walking	3.77 (2.77)	2.31 (2.72)	-1.46	.46	-2.38 to -.92	.008
Pain with stair use	5.54 (3.31)	4.15 (3.29)	-1.39	.47	-2.33 to -.45	.013
Swelling	2.77 (2.71)	1.54 (2.40)	-1.23	.66	-2.55 to +.09	.088
Flexion range	112.69 (16.93)	125.46 (6.89)	+12.77	3.77	+5.23 to +20.31	.005
KT1000 side to side diff	3.08 (1.32)	1.23 (2.24)	-1.85	.72	-3.29 to -.41	.025

injection, and there may be a need in humans to combine growth factors with agents that neutralize disrepair factors for optimum effectiveness in established osteoarthritis.[35]

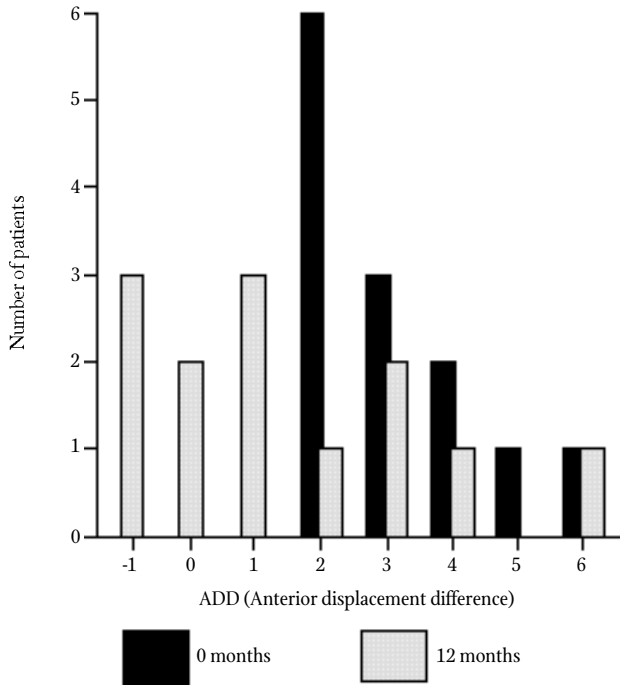

FIGURE 4 Frequency distribution of ADD in dextrose-treated knees. Comparison of 0 and 12 months.

Proliferation of Human Fibroblasts by Growth Factors in Culture

Human ACL ligament growth factors have not been fully elucidated, but Marui et al[36] demonstrated in cell suspension that collagen production by the human ACL ligament cell is increased by transforming growth factor beta (TGF-β) and epidermal growth factor beta (EGF-β), with EGF-β the most potent.

Effect on Human Cells of Exposure to Elevated Glucose

Elevation of extracellular glucose to as little as .5% has been shown to raise levels of IGF-1 in human mesangial (glomerular) cells,[7] IGF-2 in human mesangial cells,[7] TGF-β1 in human mononuclear cells[8] and human mesangial cells,[4,7] PDGF-B (platelet derived growth factor beta) in human mesangial cells[4] and human capillary endothelial cells,[37] bFGF in human gingival fibroblasts,[6] and connective tissue growth factor (CTGF) in human mesangial cells.[5] In addition, glucose in blood mononuclear cells has been found to suppress potential disrepair factors (interleukins such as IL-2, IL-6, and IL-10).[8] Cellular response to elevated extracellular glucose is swift. DNA levels for growth factor production rise within minutes to hours of cellular exposure to elevated glucose concentrations.[38] As many as 15 different genes are induced with exposure to elevated glucose concentration.[5]

Effect on Human Cells of Exposure to Osmolar Changes

Exposure of a cell to an osmolarity change as little as 50 mOsm has also been found to activate enzymes (phosphate donors, also termed kinases) in the cell similar to the growth factors mentioned above.[9,10,39-42] The mechanism appears to be via a

change in cell size, leading to kinase production via natural cellular responses to stress.[43,44] Although the kinases produced by osmolar change are not the same as with glucose elevation, proliferation response to a change in osmolarity has been demonstrated and at least 1 kinase produced is clearly a growth factor related to proliferation (PDGF).[10]

Potential Therapeutic Benefit of Bacteriostatic Water Solution or Anesthetic

The osmolarity of the bacteriostatic water solution used for the control injection was 105 compared to 611 for the active group. Information about the potential efficacy of hypotonic solution came out in the literature after our study began. This raised the question of whether the hypotonic control solution in this study was more than a placebo treatment. Review of placebo responses in recent double-blind studies of knee osteoarthritis revealed a range of pain reduction from 9% to 30%.[45-49] Review of studies on knee OA in which knee flexion measurements were obtained before and after treatment yielded few studies. A search over the last 30 years indicated a range of improvement in knee flexion in placebo groups from a -4.6 degree loss to a 1 degree gain.[50-53] The control group in this study improved by 28% in pain and 8 degrees in flexion range, suggesting more than a placebo effect. Since ligaments in different locations in animals respond to different growth factors there may be dissimilar findings for different joints.[54-56] Thus it is of interest that a concurrent finger OA study did show similar benefit with dextrose solution but the control solution did not show an appreciable benefit.[57]

It is possible that there was some therapeutic effect from inclusion of anesthetic in the solution as well, and if so this may explain some benefit in both groups. However, the concentration of lidocaine at .075% was quite low and was identical in both treatment solutions.

Magnitude of Clinical Benefit from Dextrose Solution Use Compared to Active Groups in Other Recent Studies

Pain improvement in the active treatment group by 40% through 1 year after 6 injections of 9 cc of simple dextrose solution approximated that of the active treatment group in recent studies on avocado soybean unsaponifiables,[48,58] chondroitin sulfate,[59] glucosamine,[47] and NSAIDs.[45,53,60,61] Range of motion improvement in flexion in the dextrose-treated knees (14 degrees) exceeded the range of flexion improvement (-2.6 to +12.5) in active treatment groups found in double-blind knee arthritis studies over the past 30 years.[50-53] No past studies could be found that quantified subjective swelling complaints or knee buckling frequency to compare with the 63% and 85% reductions demonstrated in the current study. Only 2 other studies indicated potential stabilization of radiograph findings similar to the current study.[62,63]

Previous Prolotherapy Injection Trials on Knee Ligament Laxity

Double-blind studies of injection prolotherapy with non-inflammatory solutions for knee osteoarthritis or knee ligament laxity have not been previously reported. However, stimulation of the inflammatory cascade produces growth factors, and temporary inflammation induction by sodium morrhuate has been shown in a double-blind study in rabbits to thicken and strengthen knee collateral ligaments.[64] The only human study on knee-ligament strengthening by inflammatory induction (using a 1.25% phenol 12.5% dextrose and 12.5% glycerine solution) had few patients and was unblinded.[65] However, despite the low patient numbers, highly significant improvement of laxity measurements by a Genucom knee arthrometer was noted.

Potential Applications and Future Study Implications

This study is 1 of 2 concurrent double-blind studies (along with a concomitant finger arthritis study)[57] to demonstrate that 10% dextrose alone is capable of a beneficial effect upon introduction into OA joints and that a treatment frequency of every 2 months is effective. Potential applications include patients too large or too young for total knee replacement, any patient in a third world country without replacement availability, patients who are symptomatic despite prescribed exercises or physical therapy or NSAIDs, or patients who are intolerant of NSAIDs.

This is the first study to demonstrate in double-blind fashion that simple 10% dextrose will correct ACL ligament laxity in an objectively-measurable fashion. Potential applications may include patients with laxity without rupture, post surgical repair to prevent the typical post-surgical gradual loosening, and large total joint patients with dislocation tendency.[66] The ability to intervene in a simple way for ACL laxity to limit the known complications of secondary arthritis should be of much interest. The broadness of application of dextrose injection in ligament/tendon treatment will depend on the cost of alternative treatments such as growth-factor-impregnated implants, direct stem cell injection, or injection of ACL ligament cells transfected with viruses whose genome has been altered to produce growth factors or to block growth factor inhibitors.[67-70] The safety and low cost of dextrose injection may make it suitable for study in prophylactic use for knee injection in athletes prone to ACL injuries or in those with injuries but intact ligament.

These study results with 10% dextrose use are intriguing in that clinical experience indicates that dextrose 25% is superior to 10% dextrose in the treatment of knee OA and ACL laxity. This author is currently investigating the ability of patients to tell the difference between 10% and 25% dextrose upon injection into the knee in preparation for direct study of 25% dextrose, to be certain that double-blind protocols would not be affected by the brief inflammatory effect of 25% dextrose. Future study protocols using dextrose for prolotherapy should consider different volumes of dextrose injection, as some have suggested that smaller volumes are equally effective and may allow 25% dextrose to be used without patient awareness. Other applications of injection prolotherapy and areas of past and current study are covered in 2 recent publications.[71,72]

If growth factor production results in more inexpensive and safe solutions for injection, this may be an alternative to stimulating growth factors by either brief inflammation or by dextrose

or by osmotic effects, and yet a likely outcome is that oral supplements, growth factor stimulant injection (prolotherapy), and direct growth factor provision by injection or other method will be complementary.

Frequency of treatment necessary for dextrose injection needs further evaluation, with current studies not designed to answer all questions about this. Clinical experience with 25% dextrose suggests that 2 to 3 bimonthly treatments are necessary prior to treatment taper.

For future studies on the ACL ligament, MRI availability to rule out complete ACL rupture and arthroscopy to confirm changes in cartilaginous surfaces would be ideal.

Now that the safety of dextrose in bacteriostatic water has been demonstrated in this study and a concomitant finger osteoarthritis study, future studies with dextrose should perhaps have dextrose in sterile water or saline versus an isotonic saline placebo.

Long-term radiograph follow-up data from the current study patients will be helpful to note net effect on cartilage and osteophytic change over a prolonged period, and patients are being followed for long-term radiographic findings.

CONCLUSIONS

Dextrose injection is clinically and statistically superior to bacteriostatic water in treatment of OA of the knee, with substantial improvements in joint pain, subjective joint swelling, flexion range of motion, and tendency for knee buckling. Anterior cruciate ligament tightening by objective measures was demonstrated with use of interarticular dextrose. Preliminary (1-year) radiographic findings show positive effects but 30- to 36-month followup radiography is planned for a clearer idea of the effect of proliferant injection on radiographic findings of OA. The inclusion of 38 knees in this study that were completely void of cartilage in at least 1 compartment, the long history of pain (8 years) in these knee OA patients, and their average size (195 lbs) strengthen the significance of the clinical outcomes demonstrated.

This study is remarkable in part because it represents an effective intervention with injection of as little as 9 cc of simple dextrose injection on 3 separate occasions. This study result, coupled with findings of a double-blind study on small joint (finger) OA, indicates that dextrose injection may have broad effectiveness in the treatment of joint and soft tissue.[57] Future studies using isotonic saline as placebo and using a higher concentration of dextrose solution will be important, although blinding may be more difficult for such studies. In the meantime prolotherapy with dextrose should be considered as one of the treatments for OA of knee and ACL laxity.

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Hypertonic Dextrose Injections (Prolotherapy) for Knee Osteoarthritis: Results of a Single-Arm Uncontrolled Study with 1-Year Follow-Up

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Abstract

Objective: The objective of this study was to determine whether prolotherapy, an injection-based complementary treatment for chronic musculoskeletal conditions, improves pain, stiffness, and function in adults with symptomatic knee osteoarthritis (KOA) compared to baseline status.
Design: This was a prospective, uncontrolled study with 1-year follow-up.
Setting: The study was conducted in an outpatient setting.
Participants: Adults with at least 3 months of symptomatic KOA, recruited from clinical and community settings, participated in the study.
Interventions: Participants received extra-articular injections of 15% dextrose and intra-articular prolotherapy injections of 25% dextrose at 1, 5, and 9 weeks, with as-needed treatments at weeks 13 and 17.
Outcome measures: Primary outcome measure was the validated Western Ontario McMaster University Osteoarthritis Index (WOMAC). Secondary outcome measure was the validated Knee Pain Scale (KPS). Tertiary outcome measure was procedure-related pain severity and participant satisfaction.
Results: Thirty-six (36) participants (60 ± 8.7 years old, 21 female) with moderate-to-severe KOA received an average of 4.3 ± 0.7 prolotherapy injection sessions over a 17-week treatment period and reported progressively improved scores during the 52-week study on WOMAC and KPS measures. Participants reported overall WOMAC score improvement 4 weeks after the first injection session (7.6 ± 2.4 points, 17.2%), and continued to improve through the 52-week follow-up (15.9 ± 2.5 points, $p < 0.001$, 36.1%). KPS scores improved in both injected ($p < 0.001$) and uninjected knees ($p < 0.05$). Prescribed low-dose opioid analgesia effectively treated procedure-related pain. Satisfaction was high and there were no adverse events. Female gender, age 46–65 years old, and body–mass index of 25 kg/m^2 or less were associated with greater improvement on the WOMAC instrument.
Conclusions: In adults with moderate to severe KOA, dextrose prolotherapy may result in safe, significant, sustained improvement of knee pain, function, and stiffness scores. Randomized multidisciplinary effectiveness trials including evaluation of potential disease modification are warranted to further assess the effects of prolotherapy for KOA.

Introduction

Knee osteoarthritis (KOA) is a degenerative disease causing joint pain, stiffness, and decreased function.[1] It is common, expensive,[2] and age-related[3]; by age 65, the majority of the population has radiographic evidence of osteoarthritis and 11% have symptomatic KOA.[4] The etiology of pain and disability in KOA is not well understood. Sources of pain likely include the joint capsule, ligaments, synovium, bone, and in the knee, the outer edge of the menisci as well as supportive extra-articular ligaments and tendons.[5,6] Standard-of-care is multidisciplinary, often including physical therapy, anti-inflammatory medication, intra-articular viscosupplementation, and arthroscopic surgery. However, a recent systematic review reported no clear benefit of any one therapy.[4] Other conservative therapies[7] and oral supplements[8,9] have also been reviewed. While some support exists for their use, definitive evidence is lacking. Acupuncture was reported as efficacious in

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a rigorous randomized controlled trial (RCT), though results were limited by substantial missing data and short follow-up period.[10] In light of high prevalence and substantial impact on individuals and society, and lack of effective treatment, the Agency for Healthcare Research and Quality has called for new approaches to prevent and treat KOA.[4]

Prolotherapy is a complementary injection therapy for chronic musculoskeletal pain, including knee osteoarthritis (KOA),[11,12] that has been hypothesized to stimulate healing of chronic soft-tissue injury. Hypertonic dextrose is a commonly used prolotherapy injectant.[11] A single randomized controlled trial (RCT) reported significant improvement in KOA pain scores when treated with prolotherapy[13]; however, the effectiveness of prolotherapy for KOA using validated measures has not been assessed. Therefore, a prospective uncontrolled pilot study was conducted to test the hypothesis that dextrose prolotherapy improves knee pain, function, and stiffness compared to baseline status in participants with symptomatic moderate to severe KOA.

Methods

The study protocol was approved by the University of Wisconsin Institutional Review Board.

Eligibility criteria and participant recruitment

Adults 40–76 years old were enrolled and followed from July 2004 to July 2008. They were recruited from University of Wisconsin Sports, Rehabilitation and Family Medicine clinics, prior control groups of an ongoing RCT assessing prolotherapy for KOA and the community. Inclusion criteria were a diagnosis of KOA based on clinical criteria for KOA defined by the American Rheumatological Association,[14] identification by a radiologist of KOA on an existing knee radiograph within 5 years, tenderness of one or more anterior knee structures on physical examination conducted by the lead physician (DR), and moderate-to-severe knee pain for at least 3 prior months, defined by scoring "3" or more on the question "What is the average level of your left/right knee pain over the last week?" using a 0–6 ordinal response scale. Exclusion criteria included the following: pregnancy, significant comorbidity (including uncontrolled diabetes mellitus defined as glycosylated hemoglobin >7.5%), anticoagulation therapy, history of, or planned, total knee replacement, prolotherapy or any other knee injection within the past three months, inflammatory or postinfectious knee arthritis, daily use of opioid pain medication, allergy or intolerance to study medication, lack of x-ray report of the affected knee or body–mass index (BMI) > 45 kg/m^2. Each knee was assessed separately for eligibility. Interested, eligible persons attended an informational meeting and gave informed consent.

Outcome measures

The primary outcome measure was change in the total score of Western Ontario McMaster University Osteoarthritis Index (WOMAC), a validated quality-of-life instrument designed to evaluate KOA severity using pain, stiffness, and function subscales.[15] The WOMAC total score, constructed as the average of the three subscale scores, ranges from 0 to 100, with 100 indicating maximum (best) knee-related quality of life, and has been shown to be responsive to change. Minimal clinical important differences on the WOMAC for KOA have been reported as 12%[16]–25%.[17] Secondary outcomes included the Knee Pain Scale (KPS),[18] a validated questionnaire assessing pain and function of the individual knee. KPS assesses pain frequency using a 0–4 Likert scale, and pain severity using a 0–5 Likert scale, with higher values indicating worse pain frequency/severity. KPS data were collected separately for each treated knee as well as for untreated knees to evaluate whether unilateral prolotherapy could have bilateral effects on knee pain scores. To the authors' knowledge, the minimal clinical important difference has not been published for the KPS. The WOMAC and KPS were collected in person and prior to any procedure at baseline, 5, 9, and 12 weeks, and by phone at 26 and 52 weeks postentry.

Tertiary outcomes included procedure-related pain severity and patient satisfaction. Participants reported pain levels on a 1–7 ordinal response scale immediately following and 2 days after a given injection session. Opioid medication use was recorded (yes/no). Participant satisfaction was assessed by the question "Would you recommend the therapy you received in this study to others with KOA like yours?" (yes/no). Participants were able to make brief qualitative comments about their treatment and clinical response.

Demographics, self-reported weight and height and severity of KOA-related findings on knee radiographs were collected at baseline to characterize the sample and to evaluate as covariates (age, gender, BMI, and x-ray-based KOA severity score) for statistical analysis. A fellowship-trained musculoskeletal radiologist (RK) using the 1–4 Kellgren-Lawrence KOA scoring system[19] evaluated existing, available knee radiographs. Among participants for whom existing radiographs were available and who also received injections on both knees, the more severe of the two radiographs was obtained.

Intervention

Injections were performed at 1, 5, and 9 weeks postentry, with optional sessions at weeks 13 and 17, per physician (JJP) recommendations and participant preference. Participants were offered an optional single 5-mg oxycodone tablet for analgesia 30 minutes prior to injection. The injector (JJP) examined the knee, marked tender anterior points, placed anesthetic skin wheals of 1% lidocaine and performed injections according to an existing protocol (Fig. 1).[20] Extra-articular injections were done "on bone" at major tender tendon and ligament insertions through up to 15 skin punctures using a peppering technique and placing a possible total 22.5 mL of solution. The single intra-articular injection was 6 mL of 25% dextrose using an inferomedial approach. Postinjection, participants were offered acetaminophen and eight 5-mg oxycodone tablets to use as needed for up to 1 week and were advised to have relative rest for 2–3 days, with progressive resumption of routine activity over 1 month. They were discouraged from using nonsteroidal anti-inflammatory medications and from starting new therapies for knee pain during the study period.

Analysis

Data were analyzed using SAS® 9.1 statistical software (SAS Institute Inc., Cary, NC). Distributional data characteristics were assessed; primary and secondary continuous variables were normally distributed. Descriptive statistics

A

Injection type	Solution	Injection Technique
Intra-articular	25% Dextrose: 5 mL 50% Dextrose 5 mL Lidocaine 1%	6.0 mL of 25% dextrose in a single injection was performed using an inferomedial approach.
Extra-articular	15% Dextrose: 6.75 mL 50% Dextrose 4.5 mL 1% Lidocaine 11.25 mL 0.9% Saline	Up to 15 sub-dermal injections were placed and 0.5 mL of 15% dextrose solution was injected using a peppering technique with a 25-gauge needle at each ligament-bone insertion. Each puncture site allowed for placement of solution at as many as 3 ligament-bone insertions using the technique of skin sliding (withdrawing the needle to just below the skin and reinserting into an adjacent area without removing from the initial puncture site) allowing for the peri-articular placement of up to 22.5 mL of dextrose solution.

B

1. Medial Collateral Ligament
2. Pes Anserine attachment
3. Tibial Tuberosity
4. Coronary Ligaments
5. Patella
6. Lateral Collateral Ligament
7. Intra-articular injection

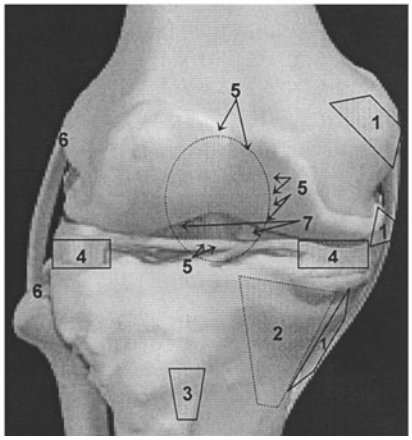

FIG. 1. **A.** Prolotherapy solutions and injection techniques. **B.** Injection locations (anterior right knee). Images © and courtesy of Primal Pictures Ltd.

were applied to describe outcomes at each time point; mean value ± standard deviation (SD) was reported at baseline unless otherwise specified.

Repeated-measures analysis of variance compared baseline to follow-up WOMAC total and subscale scores and the subscales of the KPS (five time points over the 52-week follow-up period). Mean values ± standard error was reported for this analysis. The unit of analysis in the WOMAC model was the participant. Because WOMAC evaluates participant's KOA-specific quality of life regardless of the number of knees (one or two) affected, the analysis of the WOMAC scores was on a "per participant" basis, regardless of whether one or both knees were injected. In addition to the unadjusted repeated-measures analysis, covariate analyses were also conducted, based on interaction of the covariates with the time-related trend in the model. Separate covariate analyses were conducted for participant age, gender, BMI, race, education, income, tobacco use, diabetes, prior knee surgery, Kellgren-Lawrence severity, and duration of knee pain. Percent improvement in WOMAC scores was calculated as the percentage change in total WOMAC score from baseline to 52 weeks relative to the potential improvement obtainable (100 minus the baseline). The number needed to treat (NNT) to achieve a minimal clinical important difference of 12% on the WOMAC total score,[16] and to achieve overall improvement of 25% and 50% were calculated.

The unit of analysis for the KPS model was the individual knee. Because KPS assesses each knee separately (that is, each participant completes two KPS questionnaires at each time point: one per knee), the KPS scores for each knee were analyzed individually. If a participant had both knees treated, that participant accounted for two knees in the treated-knees model. A hierarchical repeated-measures model corrected the standard errors for the interaction between the reports on two knees by the same individual.

A separate repeated-measures model analyzed KPS scores for knees that were not treated during the study. The model included untreated knees for individuals who only received treatment on a single knee. The significance test for change from baseline is reported for WOMAC scores and for KPS-assessed scores of treated and untreated knees. Two-tailed p-value < 0.05 was established as a statistical significance level.

Results

The recruitment and participation scheme is given in Figure 2. Thirty-eight (38) participants were enrolled. Two (2) participants withdrew consent after enrollment: 1 prior to injection due to scheduling difficulties and 1 after a single treatment session due to a herniated spinal disc unrelated to the study. Therefore, 36 participants were included in the analysis. Of these, 30 were recruited from community or outpatient clinics, and 6 from the former control groups of a

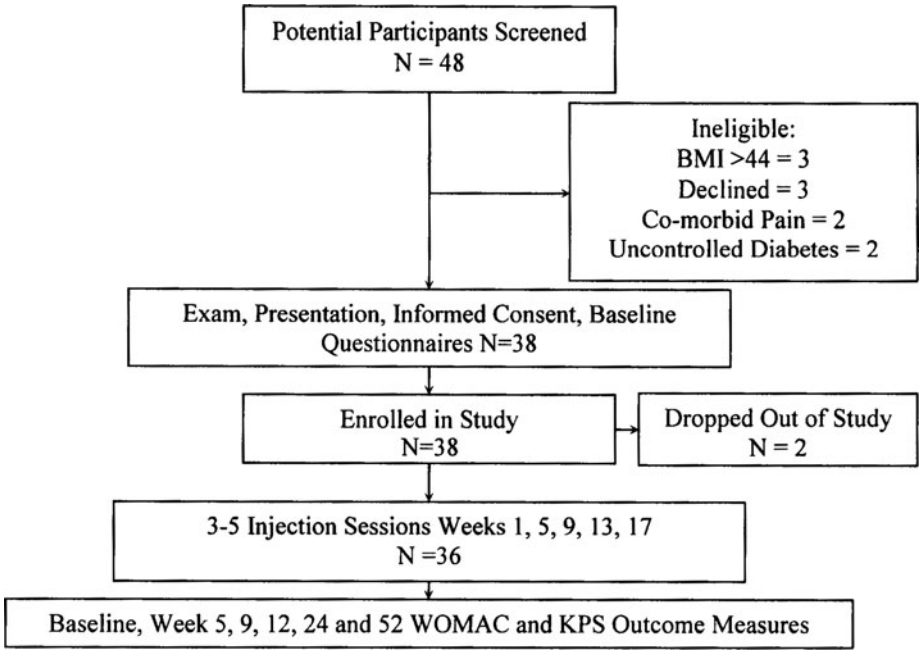

FIG. 2. Enrollment of participants and completion of the study. BMI, body–mass index; WOMAC, Western Ontario McMaster University Osteoarthritis Index; KPS, Knee Pain Scale.

prior prolotherapy RCT. The study sample ($N=36$; Table 1) consisted of white adults (60 ± SD 8.7 years old, range 46–71 years), the majority of whom were women ($N=21$) and who reported BMI over 25 kg/m^2. The reported duration of knee pain was 81.2 ± SD 72.9 months (range: 3–360). Most participants had tried and failed one or more conservative measures. Thirty-one (31) radiographs were available for evaluation; 0 radiographs were available for 5 participants, and 1 for each of the remaining 31 participants.

Prolotherapy intervention

Thirty-six (36) participants received an average of 4.3 ± 0.78 prolotherapy sessions; 22 participants had both knees treated, contributing 44 knees to the KPS analysis. Fourteen (14) participants had only one knee treated. The total sample size for the WOMAC and KPS analyses of treated knees was therefore 36 participants and 58 knees, respectively. The sample size of the KPS analysis of untreated knees was 14.

WOMAC

Repeated-measures analysis showed overall improvement in the total and subscale WOMAC scores (Table 2) during the study compared to baseline ($p<0.001$). The WOMAC scores progressively improved from baseline through 5, 9, and 12 weeks. Although a slight dip in the scores was noted at 24 weeks, they recovered by 52 weeks by which time participants reported a 36.1% (15.9 ± 2.5 points) improvement in the overall WOMAC score ($p<0.001$). Covariate analysis showed that female gender ($p=0.05$), age (46–65 years old, $p=0.04$), and a BMI ≤ 25 kg/m^2 ($p=0.04$) were associated with greater improvement in WOMAC scores. Improvement in the WOMAC scores was not related to the participant recruitment source, number of received injection sessions, injection of one or both knees, duration of KOA pain, prior KOA therapies, tobacco

Table 1. Baseline Subject ($N=36$) Characteristics

Variable	*Number (%)*	
Female, *n* (%)	21 (58%)	
Age, years, mean (SD)	60 (8.7)	
Income, *n* (%)		
<$50,000	7 (20%)	
$50,000– $79,000	11 (31%)	
$80,000+	17 (49%)	
Duration of knee pain, months, mean (SD)	81.2 (72.9)	
BMI, kg/m, *n* (%)		
≤25	8 (22%)	
26–30	15 (42%)	
31+	13 (36%)	
Prior knee intervention, *n* (%)[a]		
Arthroscopic surgery	15 (43%)	
Physical therapy	20 (61%)	
Hyaluronic acid injection	4 (12%)	
Corticosteroid injection	7 (21%)	
Diabetes, *n* (%)	2 (6%)	
WOMAC total score, points (SD)	55.9 (3.1)	
Pain	57.9 (17.5)	
Stiffness	51.7 (23.0)	
Function	58.1 (17.0)	
KPS score, points (SD)	Treated knees	Untreated knees
Pain frequency (0–4)	2.60 (0.90)	1.64 (1.24)
Pain severity (0–5)	2.08 (0.92)	1.19 (1.10)
X-ray Kellgren-Lawrence OA severity score (0–4) of treated knees[b]		
1–2 score (mild OA)	8 (22%)	
3–4 (moderate to severe OA)	23 (64%)	

[a]Percentage does not add up to 100 due to participants' varied use of conventional therapies.

[b]Existing knee radiographs were obtained for the more severely affected injected knee in each participant. Percentage does not add up to 100 due to missing data on five baseline knee radiographs.

SD, standard deviation; BMI, body–mass index; WOMAC, Western Ontario McMaster University Osteoarthritis Index; KPS, knee pain scale; OA, osteoarthritis.

Table 2. Change in WOMAC Scores Compared to Baseline Status

Measure	Score	Change in score compared to baseline					
	Baseline (n = *36*)	*Wk 5* (n = *36*)	*Wk 9* (n = *36*)	*Wk 12* (*n* = *33*)	*Wk 24* (*n* = *35*)	*Wk 52* (n = *34*)	p-*Value*[a]
Total and change in WOMAC score (SE)	55.9 (3.1)	+7.6 (2.4)	+11.6 (2.4)	+15.9 (2.5)	+13.9 (2.5)	+15.9 (2.5)	< 0.001
% Total score improvement	NA	17.2%	26.3%	36.1%	31.5%	36.1%	
WOMAC subscale scores (SE)							
Pain	57.9 (3.0)	+8.1 (2.6)	+10.8 (2.6)	+15.3 (2.6)	+14.6 (2.6)	+14.0 (2.6)	< 0.001
% Pain score improvement	NA	19.2%	25.7%	36.3%	34.7%	33.3%	
Stiffness	51.7 (3.3)	+5.6 (3.4)	+10.4 (3.4)	+15.6 (3.5)	+11.8 (3.4)	+16.5 (3.4)	< 0.001
% Stiffness score improvement	NA	11.6%	21.5%	32.3%	24.4%	34.2%	
Function	58.1 (2.9)	+9.3 (2.3)	+13.6 (2.3)	+16.9 (2.4)	+15.4 (2.4)	+17.1 (2.4)	< 0.001
% Function score improvement	NA	22.2%	32.5%	40.3%	36.8%	40.8%	

[a]Significance (*p*-value) is reported for overall treatment effect (repeated-measures model).
WOMAC, Western Ontario McMaster University Osteoarthritis Index; Wk, week; SE, standard error; NA, not applicable.

use, or diabetes. Improvement in WOMAC scores at 52 weeks was also not associated with pretreatment Kellgren-Lawrence scores (18.7 point improvement for participants with Kellgren-Lawrence scores of 1–2 and 11.7-point improvement for participants with Kellgren-Lawrence scores of 3–4; $p = 0.09$). The NNT to achieve the minimal clinical important difference of 12%[16] was 1.3; the NNT to achieve more robust overall improvements of 25% and 50% were 1.7 and 3.9, respectively. Thirty-eight percent (38%) of the participants achieved a 50% or greater improvement in the total WOMAC score at 52 weeks. The WOMAC score of 4 participants worsened over the 52-week study period, with no covariates being predictive. Qualitative comments revealed that three of these participants engaged in early strenuous physical activity after two or more prolotherapy treatment sessions. Overall, 15 participants reported engaging in strenuous physical activity earlier than recommended after clinical improvement at one or more points during the study.

KPS

Similar to the WOMAC, KPS scores improved progressively through the 52-week study period (Table 3; $p < 0.001$) in injected knees ($n = 58$), regardless of the number of knees injected. Participants reported less severe baseline KOA pathology in uninjected knees ($n = 14$) but interestingly, reported a statistically significant improvement in KPS scores even in the uninjected knees for both pain frequency (50%, $p < 0.001$) and severity (43%, $p = 0.001$) at 52 weeks (Table 3).

Procedure-related pain, satisfaction, and safety

As expected, all participants experienced self-limited postinjection pain, with 68% reporting oxycodone use prior to injections ("premedication") and 45% reporting oxycodone use after the injections. Ninety percent (90%) of those using oxycodone reported that it substantially decreased procedure-related pain. Participants reported that procedural pain waned by the second day after injection, from 3.8 ± 1.4 points to 3.1 ± 1.4 points on the 1–7 ordinal response pain severity scale. One (1) participant experienced local numbness distal to the knee that spontaneously resolved in 2 hours. Twenty-nine (83%) participants reported that they would recommend prolotherapy to patients with similar KOA. There were no adverse events.

Table 3. Change in KPS Scores Compared to Baseline for Treated and Untreated Knees[a]

	Treated knees (N = *58*)[b]		*Untreated knees* (N = *14*)[b]	
	Pain frequency	*Pain severity*	*Pain frequency*	*Pain severity*
Baseline score	2.60 (0.13)	2.09 (0.13)	1.64 (0.2)	1.19 (0.22)
Score change compared to baseline:				
Wk 5	−0.38 (0.12)	−0.39 (0.12)	−0.23 (0.23)	−0.08 (0.25)
Wk 9	−0.59 (0.12)	−0.56 (0.13)	−0.78 (0.23)	−0.54 (0.25)
Wk 12	−0.85 (0.12)	−0.78 (0.13)	−0.74 (0.25)	−0.66 (0.26)
Wk 24	−0.78 (0.12)	−0.70 (0.13)	−0.94 (0.24)	−0.67 (0.25)
Wk 52	−0.91 (0.12)	−0.76 (0.13)	−0.82 (0.23)	−0.51 (0.25)
% Improvement	35%	36%	50%	43%
p-Values[c]	< 0.001	< 0.001	0.001	0.028

[a]Results are presented as mean score (baseline) or mean score change (weeks 5–52) (standard error).
[b]Twenty-two (22) participants had both knees treated (44 knees) and 14 participants had one knee treated (14 knees) for a total of 58 knees treated and 14 knees untreated.
[c]Significance (*p*-value) is reported for overall treatment effect (repeated-measures model).
KPS, knee pain scale; Wk, week.

Discussion

This uncontrolled pilot study of participants with KOA found substantial, consistent improvement in knee pain, function, and stiffness at 52 weeks after treatment with prolotherapy. The 36% improvement on the validated WOMAC measure exceeded reported minimal clinical important difference of 12%[16]–25%[17] on the WOMAC; 38% of participants exceeded 50% improvement at 52 weeks.[21] While improvement was generally progressive over 52 weeks, there was a slight dip in scores in both the WOMAC and the KPS at 24 weeks, perhaps because some participants overused their knees following substantial improvement in knee pain at one or more time points in the study. These results may therefore underestimate the potential effect of prolotherapy in patients who adhere to recommendations for a gentle return to activity or sport following prolotherapy. These results provide level 3B evidence[22] that prolotherapy may be an effective treatment for pain and disability related to KOA.

Participants also reported significantly improved KPS scores on *uninjected* knees. This may represent a reduction in compensatory mechanisms of the uninjected side. Individuals with KOA have reduced knee and hip motion (i.e., angular velocity in the sagittal plane) on the affected side relative to controls,[23,24] thus placing additional burden on the unaffected limb when trying to maintain a given walking speed.[25,26] This may result in overuse, pain, and disability of the contralateral knee. Participants may have needed to compensate less on the uninjected side as a result of post-injection improvement of the primarily affected knee, sparing it from overuse and improving bilateral knee function. Overall, WOMAC and KPS data suggest that prolotherapy may improve upon standard of care for KOA, given that most participants were refractory to prior therapeutic measures. Such positive change may improve quality of life in the near term and delay progression of KOA in the long term. Clinical improvement may accrue preferentially to those who are of normal weight, female, and middle-aged.

These effects are consistent with another prolotherapy study, though comparison is limited by different injection protocols and outcome measures.[12] Direct comparison of these data to those in studies of hyaluronic acid injection and other conventional therapies is also difficult given the heterogeneity of reporting methods in many trials, but improvements of 20%–40% compared to baseline have been reported for conventional therapies and acupuncture.[4,8]

Prolotherapy is an evolving modality gaining popularity in sport and family medicine,[11,27] though its mechanism of action is unclear. Dextrose injections have been hypothesized to stimulate healing of chronically injured extra-articular and intra-articular tissue[28]; animal model studies reported increased inflammatory markers[29] and significantly enlarged cross-sectional area in medial collateral ligaments.[30] The potential of prolotherapy to stimulate release of growth factors favoring soft-tissue healing[12,31] and a positive neural effect have also been suggested.[32] Needle trauma and volume expansion of local tissue may also produce a tissue-level effect.[33] The combined effect of dextrose-specific effects, needle trauma, and volume expansion may explain positive results in this study. The source of pain in KOA is multifactorial. Prolotherapy injections target multiple potential nociceptors, including the relatively avascular articular cartilage and richly innervated intra-articular and extra-articular tissue including periosteum, periarticular ligaments, periarticular muscle, synovium, and joint capsule[6,34] and have been hypothesized to have intra-articular and extra-articular effects.[11,12,27]

Limitations and Strengths

Limitations of this study include small sample size and lack of comparison group. The assessment of participant satisfaction was indirect and subject to bias. Radiographs were not available for all participants, and the use of Kellgren-Lawrence criteria for baseline radiological assessment of KOA severity is controversial, given that scores have not been uniformly correlated to patient-centered outcomes. The Kellgren-Lawrence score, however, is likely to remain an important measure for gauging disease severity in symptomatic patients.[35] The enrollment of 6 participants who had completed a prior prolotherapy trial may have introduced bias, though participant recruitment source was not a significant covariate. Strengths include pragmatic assessment using validated, patient-oriented outcomes and robust, consistent results with minimal missing data.

Directions for Future Research

Determination of clinical utility of prolotherapy for KOA will require assessment in a larger randomized multidisciplinary effectiveness trial that includes biomechanical and imaging outcome measures to assess for potential disease modification.[36,37]

Conclusions

Prolotherapy resulted in safe, significant, and sustained improvement on validated pain, function, and stiffness measures in participants with KOA. Prolotherapy performed by an experienced operator may be an appropriate therapy for selected patients with moderate-to-severe KOA who are refractory to conservative care.

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Disclosure Statement

No competing financial interests exist.

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Dextrose Prolotherapy for Knee Osteoarthritis: A Randomized Controlled Trial

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ABSTRACT

PURPOSE Knee osteoarthritis is a common, debilitating chronic disease. Prolotherapy is an injection therapy for chronic musculoskeletal pain. We conducted a 3-arm, blinded (injector, assessor, injection group participants), randomized controlled trial to assess the efficacy of prolotherapy for knee osteoarthritis.

METHODS Ninety adults with at least 3 months of painful knee osteoarthritis were randomized to blinded injection (dextrose prolotherapy or saline) or at-home exercise. Extra- and intra-articular injections were done at 1, 5, and 9 weeks with as-needed additional treatments at weeks 13 and 17. Exercise participants received an exercise manual and in-person instruction. Outcome measures included a composite score on the Western Ontario McMaster University Osteoarthritis Index (WOMAC; 100 points); knee pain scale (KPS; individual knee), postprocedure opioid medication use, and participant satisfaction. Intention-to-treat analysis using analysis of variance was used.

RESULTS No baseline differences existed between groups. All groups reported improved composite WOMAC scores compared with baseline status ($P < .01$) at 52 weeks. Adjusted for sex, age, and body mass index, WOMAC scores for patients receiving dextrose prolotherapy improved more ($P < .05$) at 52 weeks than did scores for patients receiving saline and exercise (score change: 15.3 ± 3.5 vs 7.6 ± 3.4, and 8.2 ± 3.3 points, respectively) and exceeded the WOMAC-based minimal clinically important difference. Individual knee pain scores also improved more in the prolotherapy group ($P = .05$). Use of prescribed postprocedure opioid medication resulted in rapid diminution of injection-related pain. Satisfaction with prolotherapy was high. There were no adverse events.

CONCLUSIONS Prolotherapy resulted in clinically meaningful sustained improvement of pain, function, and stiffness scores for knee osteoarthritis compared with blinded saline injections and at-home exercises.

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INTRODUCTION

Knee osteoarthritis is a chronic disease resulting in joint pain, stiffness, and decreased function.[1] It is common, expensive for patients[2] and society, and age-related[3]; by age 65 years, most of the population has radiographic evidence of osteoarthritis.[4] Sources of pain include intra-articular and supportive extra-articular structures.[5,6] Standard-of-care is multidisciplinary; however, a recent systematic review reported no clear benefit of any one therapy.[4] Conservative therapies[7] and oral supplements[8,9] have been evaluated but are without clear efficacy. The Agency for Healthcare Research and Quality has called for the development of new therapies to prevent and treat knee osteoarthritis.[4]

Prolotherapy is an injection therapy for chronic musculoskeletal injury, including knee osteoarthritis.[10-12] A core principle is the injection of small volumes of an irritant solution at multiple painful ligament and tendon insertions and in adjacent joint spaces over several treatment sessions.[10] Prolotherapy has been used in a form recognizable to contemporary prac-

titioners for at least 75 years; the earliest substantive report appeared in the allopathic literature when the technique was referred to as sclerotherapy as a result of the scar-forming properties of early injectants.[13] Contemporary injection techniques were formalized in the 1950s, when the more commonly used term *prolotherapy* (from *proliferant* therapy) was adopted based on the observation that a larger cross-sectional area of ligamentous tissue was seen after prolotherapy injection in animal models.[14] Literature of generally low methodological rigor from the 1930s to the early 2000s reported positive clinical outcomes.[15] The mechanism of action is unclear. Contemporary hypotheses suggest that prolotherapy stimulates local healing of chronically injured extra- and intra-articular tissue, though definitive evidence is lacking.[10] Hypertonic dextrose is a commonly used injectant.[10] Prolotherapy injections target multiple potential pain generators in and around the knee joint; it may be well-suited to address the multifactorial cause of knee pain from osteoarthritis. A single randomized controlled trial (RCT)[11] and 1 open-label study[16] reported improvement in outcomes in response to prolotherapy but were not methodologically rigorous. We therefore conducted a 3-arm RCT to assess the hypothesis that adults with symptomatic knee pain receiving prolotherapy will report greater improvement in knee-related quality-of-life than those receiving saline injections or at-home knee exercises.

METHODS

The study was approved by the University of Wisconsin (UW) Health Sciences Institutional Review Board. Adults aged 40 to 76 years were recruited from 2004 to 2009 from the community and University of Wisconsin family medicine, sports medicine, and rehabilitation clinics; each was then observed for 1 year. Inclusion criteria were a diagnosis of knee osteoarthritis based on clinical criteria (American College of Rheumatology),[17] identification of knee osteoarthritis by a radiologist on an existing knee radiograph obtained within 5 years of enrollment, tenderness of 1 or more anterior knee structures on physical examination, and self-reported moderate-to-severe knee pain for at least 3 months, defined as a score of 3 or more (0 to 6 ordinal response scale) on the question, "What is the average level of your left/right knee pain over the last week?" Exclusion criteria included pregnancy, diabetes, anticoagulation therapy, history of total knee replacement, prior knee prolotherapy, any knee injection within 3 months, inflammatory or postinfectious knee arthritis, daily use of opioid medication, allergy or intolerance to study medication, body mass index (BMI) greater than 40 kg/m^2, and comorbidity severe enough to prevent participation in the study protocol, including at-home exercise or attendance at scheduled injection appointments. Each knee was assessed separately for eligibility. Interested, eligible persons attended an informational meeting, gave consent for participation, and were enrolled.

Study Design

Participants were randomly assigned to 1 of 2 injection groups (dextrose or saline) or exercise using a computer-generated randomization scheme in forced blocks of 6 prepared by the UW Pharmacy Research Center. The injector, outcome assessor, principal investigator, and participants were blinded to injection group status.

Injection Intervention

Injections were performed at 1, 5, and 9 weeks with optional additional sessions at 13 and 17 weeks per the physician's (J.J.P.) recommendations and the participant's preference. Before the procedures the off-site UW Pharmacy Research Center prepared dextrose and saline syringes that were blinded using an opaque paper sleeve. Participants were offered an optional single 5-mg oxycodone tablet 30 minutes before injection. The injector (J.J.P.) examined the knee, marked tender anterior knee locations, placed anesthetic skin wheals of 1% lidocaine, and performed extra- and intra-articular injections according to a published protocol (Table 1).[16] Extra-articular injections were done on bone by palpation at major tender tendon and ligament insertions through up to 15 skin punctures using a peppering technique, placing a possible total 22.5 mL of solution; ultrasound guidance was not used. The 6-mL intra-articular injection was then delivered using an inferomedial approach. After the injection, participants were offered acetaminophen and 8, 5-mg oxycodone tablets to use as needed for up to 1 week and were advised on relative knee rest for 2 to 3 days with progressive resumption of routine activity over 1 month. They were discouraged from using nonsteroidal anti-inflammatory medications (NSAIDs) and from starting new therapies for their osteoarthritis during the study period.

At-home Exercise Intervention

Exercise group participants received an informational pamphlet about knee osteoarthritis (Visual Health Information, at http://www.vhikits.com/Default.aspx) depicting 10 at-home knee exercises demonstrated by the study coordinator at baseline. Participants were advised to begin exercises (3 sessions per week, 1 session daily, 10 repetitions per exercise), to gradually increase therapy as tolerated over 20 weeks (5 sessions per week, 3 times daily, 15 repetitions per exercise), and to continue them thereafter if desired.

Adherence and Precautions

Exercise group adherence was encouraged and assessed during telephone call reminders at the same interval that injection sessions occurred. Members of all groups were cautioned at each contact against knee overuse.

Outcome Measures

The primary outcome measure was change in knee-related quality-of-life as assessed by the composite score of Western Ontario McMaster University Osteoarthritis Index (WOMAC), a validated questionnaire evaluating osteoarthritis severity using pain, stiffness, and function subscales.[18] The WOMAC composite score, constructed as the weighted average of the 3 subscale scores, ranges from 0 (worst) to 100 (best) knee-related quality-of-life[19] and has been shown to be responsive to change.[18] The minimal clinical important difference (MCID) on the WOMAC for knee osteoarthritis has been reported as 12 points of change on a 0- to 100-mm visual analog scale.[20,21] Secondary outcomes included the knee pain scale (KPS),[22] a validated questionnaire assessing knee pain frequency (0 to 4 ordinal scale) and severity (0 to 5 ordinal scale), with higher values indicating worse symptoms. KPS data were collected separately for each treated knee and for untreated knees. The WOMAC and KPS scores were collected in person and before any procedure at baseline, 5, 9, and 12 weeks, and by telephone at 26 and 52 weeks.

Tertiary outcomes for injection participants included (1) ratings of procedure-related pain severity, using a 1 to 7 ordinal scale, obtained immediately after and 2 days after each injection session; and (2) daily logs of opioid medication use (yes/no) during the 7 days after each injection. Treatment satisfaction was assessed among all participants at 52 weeks with the question, "Would you recommend the therapy you received in this study to others with knee osteoarthritis like yours? (yes/no)." All participants were able to make brief qualitative comments about their experiences.

Demographics, self-reported weight and height, and severity of knee osteoarthritis seen on knee radiographs were collected at baseline to characterize the sample and to evaluate as covariates for statistical analysis. A fellowship-trained musculoskeletal radiologist (R.K.), using the 1- to 4-point Kellgren-Lawrence knee osteoarthritis scoring system,[23] evaluated existing, available knee radiographs. Attendance at injection sessions was tracked. Adherence to at-home exercises was assessed by the question, "In the past month, did you perform home exercises as directed? (yes/no)," administered by monthly mail-in logs for the first 20 weeks of the study. Blinding of the injector and injection participants was assessed at each injection session by asking each to identify the participant's group assignment using the items "dextrose," "saline," or "don't know."

Analysis

Two RCTs and clinical experience guided a priori sample size calculations. One RCT assessing prolotherapy for knee osteoarthritis reported a 44% effect size compared with baseline status on a visual analog scale.[11] A well-designed RCT reported a 20% to 40% effect size of prolotherapy for low back pain.[24] Assuming minimal change in the control groups and minimal loss to follow-up, 32 participants per arm would provide 80%

Table 1. Injection Solutions and Injection Techniques

Injection Type	Solution	Injection Technique
Dextrose		
Intra-articular 25% dextrose	In a 10-mL syringe: 5 mL 50% dextrose 5 mL lidocaine 1% saline	6.0 mL was injected using an inferomedial approach
Extra-articular 15% dextrose	22.5 mL distributed in 3, 10-mL syringes (7.5 mL each) using the following recipe: 6.75 mL 50% dextrose 4.5 mL 1% lidocaine 11.25 mL 0.9% saline	Up to 15 subdermal injections were placed, and 0.5 mL of 15% solution was injected using a peppering technique with a 25-gauge needle at each ligament-bone insertion. Each puncture site allowed for placement of solution at up to 3 ligament-bone insertions using a skin-sliding technique (withdrawing the needle to just below the skin and reinserting into an adjacent area without removing from the initial puncture site), allowing for the placement of up to 22.5 mL of solution
Saline control		
Intra-articular	5 mL 0.9% sodium chloride 5 mL 1% lidocaine	Injection technique identical to intra-articular injections above
Extra-articular	22.5 mL distributed in 3, 10-mL syringes (7.5 mL each) using the following recipe: 18 mL 0.9% sodium chloride 4.5 mL 1% lidocaine	Injection technique identical to extra-articular above

power to detect a 20% difference in mean composite WOMAC scores between control and dextrose participants at a significance level of 5%.

Data were analyzed using SAS 9.1 statistical software (SAS Institute Inc). Descriptive statistics describe outcomes at each time point; mean value and standard deviation (SD) were reported at baseline.

Analysis was by intention-to-treat. Repeated measures analysis of variance compared treatment groups on follow-up WOMAC total and subscale scores and KPS subscales after adjusting for baseline scores, age, sex, and BMI. Statistical significance between treatment groups was assessed at each time point (group × time interaction) and comprehensively for the entire time frame (main time effect). Because the WOMAC evaluates participant's knee-specific quality-of-life not considering the number of knees affected, the unit of analysis of the WOMAC scores was the participant regardless of the number of knees injected. Percentage improvement in WOMAC scores was calculated as the percentage change in total WOMAC score from baseline to 52 weeks relative to baseline score.[25,26] The proportion of participants in each group who met the MCID benchmark of 12 points on the 0- to 100-point composite WOMAC was calculated.

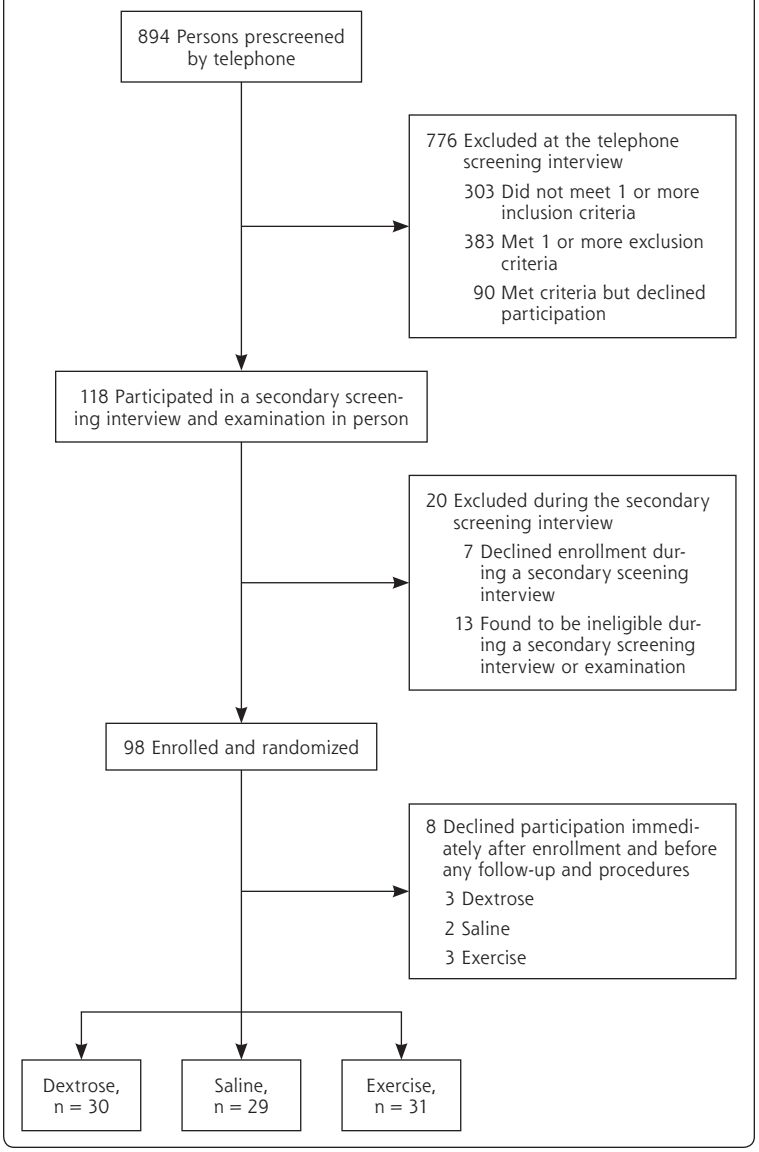
The unit of analysis for the KPS model was the individual knee. Because each participant completed 2 KPS questionnaires at each time point—1 per knee, the KPS scores for each knee were analyzed individually. If a participant had both knees treated, that participant accounted for 2 knees in the treated knees model. A hierarchical repeated measures model corrected the standard errors for the interaction between the reports on 2 knees by the same individual. A separate repeated measures model analyzed KPS scores for single untreated knees. The significance test for change from baseline is reported for WOMAC and KPS scores. A 2-tailed P value <.05 was established as a statistical significance level.

RESULTS

Of the 894 persons screened by telephone, 118 met initial eligibility criteria; 98 persons were enrolled and randomized. Eight enrollees dropped out before completion of any procedures or follow-up data collection. Ninety participants were therefore included in the analysis (Figure 1).

There were no significant baseline differences between groups (Table 2). The 8 enrollees who withdrew before the follow-up procedures were women; there were no other differences between the 8 women and the analyzed sample. The study sample consisted of 66% women with a mean age of 56.7 years (SD = 7.2 years); 74% were either overweight (BMI ≥25-29.9 kg/m^2) or obese (BMI ≥30 kg/m^2). Participants reported more than 5 years of knee pain, and most had failed at least 1 conservative therapy. Although radiograph reports identifying osteoarthritis were available for all included knees, administra-

Figure 1. Screening, enrollment, and randomization.



tive difficulties resulted in procurement of only 68 prestudy radiographs. The Kellgren-Lawrence scores ranged from mild to severe, and overall inclusion criteria, x-ray reports, and baseline WOMAC scores[19] suggest that on average, this cohort had moderate severity of knee osteoarthritis (Table 3).

Dextrose participants received 3.95 ± 1.0 injection sessions; 13 participants had both knees treated (26 knees), and 17 participants had 1 knee treated (total 43 knees). Saline participants received 3.71 ± 1.1 injection sessions; 13 participants had both knees treated and 15 participants had 1 knee treated (total 41 knees). Exercise participants returned an average of 22 (77.4%), self-assessments during the 20-week treatment period; 77% of participants reporting doing their at-home exercises as directed; 16 participants had both knees treated and 15 participants had 1 knee treated (total 47 knees). Fourteen participants reported using NSAIDS in the dextrose and saline groups, whereas 15 exercise participants reported NSAID use.

Between-group comparisons showed that dextrose participants at 52 weeks reported improved composite WOMAC scores (15.32 points, a 24% improvement compared with baseline status) compared with participants in the saline (7.59 points; $P = .022$) and exercise groups (8.24 points; $P = .034$). Fifty percent (15 of 30) of the dextrose participants improved by 12 or more points on the composite WOMAC score at 52 weeks compared with 30% (10 of 29) of saline participants and 24% (8 of 31) of exercise participants. Significant differences were also found at 9 weeks for dextrose compared with saline and exercise groups, 13.91 points compared with 6.75 points ($P = .020$) and 2.51 points ($P = .001$), respectively; and at 24 weeks, changes of 15.85 points compared with 8.12 points ($P = .021$) and 8.48 points ($P = .024$), respectively (Table 4, Figure 2).

Evaluation of the WOMAC subscale scores showed that dextrose participants generally reported consistent improvement across the subscales, achieved near-maximum improvement by 26

Table 2. Baseline Participant Characteristics by Treatment Group

Characteristic	Dextrose	Saline	Exercise	*P* Value
No.	30	29	31	
Female, No. (%)	19 (63)	20 (69)	21 (68)	0.82
Age, mean (SD), y	56.8 (7.9)	56.8 (6.7)	56.4 (7.0)	0.97
Duration of knee pain, No. (SD), mo	79.8 (62.9)	108.0 (99.5)	60.4 (71.6)	0.08
Body mass index, No. (%)				
≤25	10 (33)	8 (28)	6 (19)	
25-30	6 (20)	11 (38)	12 (39)	0.44
≥30	14 (47)	10 (34)	13 (42)	
Prior knee intervention, No. (%)				
History of arthroscopic surgery	7 (23)	5 (17)	7 (23)	0.84
Physical therapy	6 (20)	3 (27)	16 (52)	0.08
Hyaluronic acid injection	3 (10)	0 (0)	2 (6)	0.62
Corticosteroid injection	4 (13)	1 (9)	2 (6)	0.79
Glucosamine	7 (23)	5 (17)	8 (26)	0.82

Table 3. Baseline Participant Knee Osteoarthritis Severity Scores by Treatment Group

Characteristic	Dextrose		Saline		Exercise		*P* Value	
X-ray Kellgren-Lawrence osteoarthritis severity score[a]								
1-2 (mild osteoarthritis)	11		12		9		.35	
3-4 (moderate to severe osteoarthritis)	14		9		14			
WOMAC total score (SD) [range][b]	63.1 (15.0) [34.6-93.1]		62.7 (14.3) [34.3- 90.8]		60.5 (11.3) [35.7-77.0]		.73	
Pain score (SD) [range]	66.8 (14.9) [35.0-95.0]		66.7 (16.1) [30.0-95.0]		63.2 (13.1) [35.0-90.0]		.49	
Stiffness score (SD) [range]	57.1 (19.9) [25.0-87.5]		53.9 (14.2) [25.0-87.5]		55.3 (18.0) [12.5-100.0]		.73	
Function score (SD) [range]	65.2 (15.8) [39.7- 96.9]		67.6 (17.5) [35.3-100.0]		61.9 (12.7) [36.8-86.8]		.36	
Knee pain scale[c]	Treated Knee n = 43	Untreated Knee n = 17	Treated Knee n = 41	Untreated Knee n = 17	Treated Knee n = 47	Untreated Knee n = 15	Treated *P* Value	Untreated *P* Value
Pain frequency score (SD)	2.5 (0.9)	0.6 (1.1)	2.4 (0.9)	0.9 (0.9)	2.5(0.9)	0.7 (1.0)	.52	.69
Pain severity score (SD)	1.8 (0.8)	0.5 (1.1)	1.7 (0.7)	0.6 (0.8)	1.7(0.8)	0.4 (0.7)	.42	.74

WOMAC = Western Ontario McMaster University Osteoarthritis Index.

[a] Kellgren-Lawrence scores range from 1 to 4.

[b] The theoretical range in this study is 0 to 100, with higher values indicating better knee-related quality of life.

[c] The theoretical range of scores for knee pain frequency is 0 to 4 and for knee pain severity is 0 to 5, with higher values indicating worse symptoms.

Table 4. Change in the WOMAC Composite and Subscale Scores Over Time

Score	Week 5	Week 9	Week 12	Week 24	Week 52
WOMAC composite score change, mean (SE)					
Dextrose	7.94 (3.21)	13.91 (3.23)[a]	13.31 (3.32)[b]	15.85 (3.26)[a]	15.32 (3.32)[a]
Saline	5.22 (3.21)	6.75 (3.27)[a]	8.19 (3.37)[b]	8.12 (3.33)[a]	7.59 (3.36)[a]
Exercise	4.42 (3.21)	2.51 (3.26)[a]	4.26 (3.36)[b]	8.48 (3.28)[a]	8.24 (3.33)[a]
Subscale score change, mean (SE)					
Pain					
Dextrose	8.17 (3.49)	14.00 (3.52)[a]	11.78 (3.62)[b]	15.50 (3.56)[a]	14.18 (3.62)
Saline	3.28 (3.50)	5.29 (3.56)[a]	5.79 (3.67)[b]	6.40 (3.63)[a]	7.38 (3.67)
Exercise	4.53 (3.51)	3.44 (3.55)[a]	4.89 (3.66)[b]	8.07 (3.60)[a]	9.24 (3.63)
Stiffness					
Dextrose	7.08 (4.50)	14.17 (4.53)[c]	13.49 (4.67)[b]	14.85 (4.58)	15.55 (4.66)
Saline	8.62 (4.51)	9.12 (4.59)[c]	12.22 (4.73)[b]	10.40 (4.67)	9.97 (4.72)
Exercise	3.63 (4.51)	0.14 (4.58)[c]	3.13 (4.71)[b]	8.18 (4.61)	8.31 (4.68)
Function					
Dextrose	8.57 (3.27)	13.58 (3.30)[a]	14.61 (3.40)[a]	17.19 (3.33)[a]	16.25 (3.39)[a]
Saline	3.77 (3.28)	5.85 (3.34)[a]	6.63 (3.44)[a]	7.62 (3.40)[a]	5.46 (3.44)[a]
Exercise	5.10 (3.28)	4.00 (3.33)[a]	4.89 (3.43)[a]	9.30 (3.35)[a]	7.31 (3.40)[a]

WOMAC = Western Ontario McMaster University Osteoarthritis Index.

Notes: Numbers of participants for measurement points are as follows. Week 5: n = 30 dextrose, n = 29 saline, n = 28 exercise. Week 9: n = 30 dextrose, n = 26 saline, n = 27 exercise. Week 12: n = 27 dextrose, n = 24 saline, n = 25 exercise. Week 24: n = 28 dextrose, n = 25 saline, n = 27 exercise. Week 52: n = 26 dextrose, n = 25 saline, n = 26 exercise. Repeated measures analysis of variance compared between-group total and subscale WOMAC scores after adjusting for baseline scores, age, sex, and body mass index.

[a] Dextrose outperformed saline (P <.05) and exercise (P <.05); no statistically significant differences between saline and exercise.

[b] Dextrose outperformed exercise (P <.05); no statistically significant differences between dextrose and saline, and between saline and exercise.

[c] Dextrose outperformed exercise (P <.05); saline outperformed exercise (P <.05); no statistically significant differences between dextrose and saline.

weeks, and remained stable through 52 weeks. The most dramatic improvements were on the function subscale; dextrose participants reported significantly better function than both saline and exercise participants for a change of 16.25 compared with 5.46 (P = <.001) and 7.31 points (P = .009), respectively, at 52 weeks.

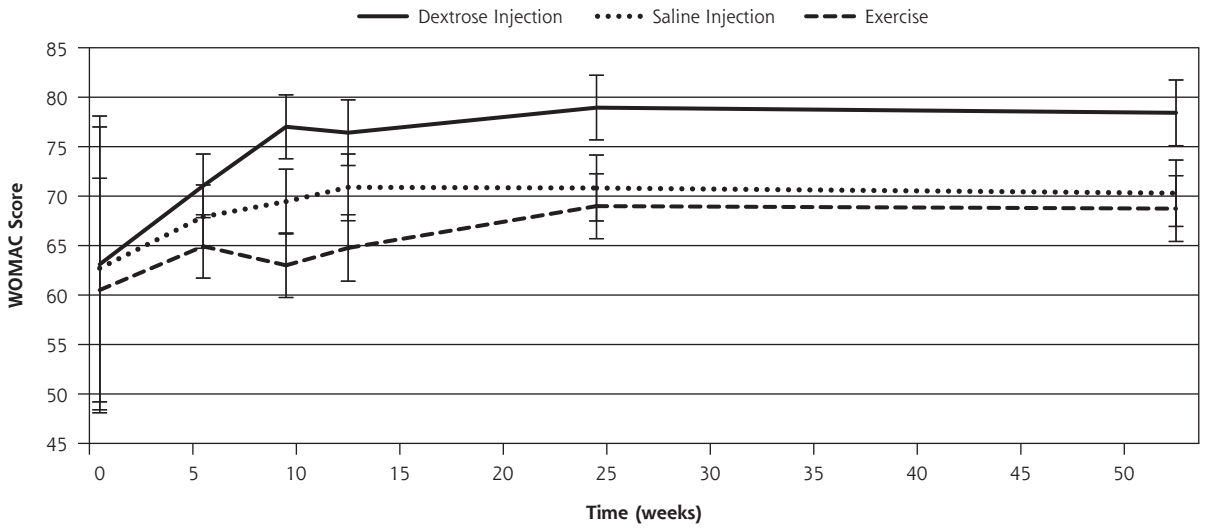
At 9 weeks, dextrose participants reported significantly better function than both saline and exercise, with a change of 13.58 compared with 5.85 points (P = .021) and 4.00 points (P = .004), respectively.

At 24 weeks, dextrose participants also reported significantly better functional change than both saline and exercise, with a change of 17.19 points compared with 7.62 points (P = .005) and 9.30 points (P = .018), respectively.

There was no correlation between exercise compliance in the exercise group and WOMAC composite improvements at 52 weeks (r = –0.11, P = .625).

Overall, the WOMAC scores of saline participants did not significantly differ from those of the exer-

Figure 2. Change in WOMAC composite scores over 52 weeks (± standard error).



WOMAC = Western Ontario McMaster University Osteoarthritis Index.

Note: WOMAC is scored on a range of 0 to 100 points, with higher scores indicating better knee-related quality of life. Nonoverlapping confidence intervals indicate significance of change in dextrose scores compared with change in scores of both saline (P <.05) and exercise (P <.05) groups.

Table 5. Change in Knee Pain Scale Pain Frequency and Pain Severity Scores in Individual Treated Knees Over Time

Measure	Week 5	Week 9	Week 12	Week 24	Week 52
KPS pain frequency score, mean (SE) [No.]					
Dextrose	−0.55 (0.26) [43]	−0.84[a] (0.25) [42]	−0.87[a] (0.27) [38]	−1.19[a] (0.25) [40]	−1.20[a] (0.21) [37]
Saline	−0.26 (0.26) [40]	−0.32 (0.25) [37]	−0.31 (0.27) [36]	−0.48 (0.25) [37]	−0.60 (0.21) [38]
Exercise	−0.15 (0.25) [38]	−0.22 (0.24) [40]	−0.12 (0.26) [37]	−0.49 (0.24) [39]	−0.40 (0.21) [38]
KPS pain severity score, mean (SE)					
Dextrose	−0.25 (0.26)	−0.48 (0.25)	−0.51 (0.27)	−0.92[a] (0.25)	−0.92[a] (0.21)
Saline	−0.07 (0.26)	−0.19 (0.25)	−0.16 (0.27)	−0.26 (0.25)	−0.32 (0.21)
Exercise	−0.07 (0.25)	−0.15 (0.24)	−0.06 (0.26)	−0.33 (0.24)	−0.11 (0.21)

KPS = knee pain scale.

Repeated measures analysis of variance compared between-group KPS scores after adjusting for baseline scores, age, sex, and body mass index.

[a] Change in dextrose score was greater than change in saline (P <.05) and exercise (P <.05) scores, and there were no statistically significant differences between saline and exercise scores.

cise group except for the stiffness scores at 9 (P = .047) and 12 weeks (P = .049), when the saline group fared better. Regardless of the number of knees injected, KPS-based knee pain frequency (9 through 52 weeks, P <.05) and severity (24 and 52 weeks, P <.05) were significantly reduced in the dextrose group compared with both comparison groups (Table 5). KPS scores of untreated knees improved slightly in all 3 groups compared with baseline but were not different between groups.

All injection group participants experienced expected mild to moderate postinjection pain; 3 participants in the dextrose group and 5 in the saline group experienced self-limited bruising. There were no other side effects or adverse events. The use of periprocedural analgesics was not different between injection groups. Sixty-three percent of saline participants used acetaminophen before or after injection compared with 74% of dextrose participants. Oxycodone was used before (63%) and after (47%) dextrose sessions and before (57%) and after (43%) saline injection sessions. Ninety-one percent of dextrose participants, 82% of saline participants, and 89% of home exercise participants reported they would recommend their respective interventions to other patients with knee osteoarthritis. Blinding was intact; the injector indicated "don't know" 93% of the time, and participants indicated "don't know" 91% (dextrose) and 93% (saline) of the time, with the remaining selections evenly divided between correct and incorrect answers (P = .77).

DISCUSSION

This RCT of adults with symptomatic knee osteoarthritis found substantial, consistent, and significant improvements in composite WOMAC scores at 26 and 52 weeks for the dextrose group compared with saline injections and at-home exercise groups. At 52 weeks, the average improvement on the WOMAC score was 15.32 ± 3.3 points or 24% compared with the baseline score; 50% (15 of 30) of the dextrose group reported improvement in the composite WOMAC score for the dextrose-treated participants, which exceeded the MCID of 12 points. Improvement in the dextrose group was consistent across the 3 WOMAC subscales, was nearly maximum by 26 weeks, and remained stable through 52 weeks. KPS-based results on a per knee basis were consistent with WOMAC findings.

These effects are consistent with findings of a single-arm prospective study (N = 36) using an identical injection protocol and similar eligibility criteria.[16] Participants in that study were slightly more symptomatic at baseline but reported similar overall effects at 52 weeks on WOMAC and KPS outcome measures; uninjected contralateral knees also showed significant improvement, suggesting that dextrose prolotherapy for more symptomatic knee osteoarthritis may also result in improvement of the uninjected side, likely through reduction in compensatory mechanisms. Our current findings are also consistent with a second prolotherapy RCT for knee osteoarthritis, though comparison is limited by methodological heterogeneity.[11] Direct comparison with studies of hyaluronic acid injection or other therapies is also limited given the heterogeneity of study eligibility criteria, overall health status, patient expectation, baseline osteoarthritis severity,[21] and WOMAC scoring methodology,[27] but improvements of 20% to 40% compared with baseline have been reported.[4,28]

The mechanism of action for dextrose is unclear. Hypertonic dextrose has been hypothesized to stimulate healing of chronically injured extra- and intra-articular tissue[29]; animal model studies reported

increased inflammatory markers[30] and significantly enlarged cross-sectional area in medial collateral ligaments.[31] The potential of prolotherapy to stimulate release of growth factors favoring soft tissue healing[11,32] and a positive neural effect[33] have also been suggested. In addition to dextrose-specific effects, needle trauma and volume expansion of local tissue may also produce tissue-level effects.[34]

Limitations of this study include a relatively small sample size, though the effect size of prolotherapy proved adequate to detect between-group differences. The study was not large enough to detect uncommon adverse events, such as intolerance to study medication or rare injection-related sequelae. Generalizability may be limited by numerous exclusion criteria, the relative youth of the cohort compared with those in some knee osteoarthritis studies,[35] and the relative lack of participants with very severe baseline WOMAC scores. The assessment of participant satisfaction was indirect and subject to bias. Radiographs were not available for all participants, and the use of Kellgren-Lawrence criteria for baseline radiological assessment of knee osteoarthritis severity is controversial. The Kellgren-Lawrence score, however, is likely to remain an important measure for gauging disease severity in symptomatic patients.[36] The exclusion of patients taking chronic opioids limits the generalizability of the results. Although clinical experience suggests that such patients may still benefit from prolotherapy, long-term (greater than 1 year) effectiveness and side effects are unknown. Strengths include pragmatic assessment using validated, patient-oriented outcomes and robust, consistent results.

These findings suggest that dextrose prolotherapy may improve upon standard care of knee osteoarthritis for certain patients. Its use in clinical practice is relatively uncomplicated; prolotherapy is performed in the outpatient setting without ultrasound guidance using inexpensive solutions. The knee protocol is easy to learn and requires less than 15 minutes to perform; continuing medical education is provided in major university and national physician organizations settings.[10] A prior study suggested that clinical improvement may accrue preferentially to those who are middle-aged, of normal BMI, and female.[16] For responders, whether prolotherapy results in sustained effect past 52 weeks, disease modification, or delayed definitive care, such as knee replacement, is not known. Clinical experience suggests that repeated sessions and tune-up sessions after 52 weeks improve outcomes and do not pose additional risk. The described procedure costs $218 per session in our clinic. Some third-party payers cover prolotherapy with authorization, but most patients pay out-of-pocket. Interest in prolotherapy among physicians and patients in the United States appears to be high based on attendance at continuing medical education conferences and physician listings on relevant websites.[10] Although the number of practitioners who perform prolotherapy in the United States is likely in the hundreds, no formal survey has been done since 1993.[37]

Prolotherapy for knee osteoarthritis has not been compared with other current therapy, including intra-articular corticosteroid and hyaluronic acid injections. Determination of clinical utility of prolotherapy will require confirmation in a larger effectiveness trial that includes biomechanical and imaging outcome measures to assess potential disease modification.[38,39] Clinical trials designed to optimize dose and assess biological mechanism of action are also warranted.

Prolotherapy performed by a trained operator resulted in safe, significant, and sustained improvements on validated, quality-of-life, pain, function, and stiffness measures compared with blinded (saline injections) and nonblinded (at-home exercise) comparison interventions. Prolotherapy may be an appropriate therapy for patients with knee osteoarthritis refractory to conservative care.

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Rabago D, Miller D, Zgierska A, Mundt M, Kijowski R, Belling J, Patterson, JJ; *Dextrose prolotherapy for knee osteoarthritis: Results of a randomized controlled trial* (Poster presentation); Osteoarthritis Research Society International (OARSI) World Congress on Osteoarthritis; San Diego California, September 15-17, 2011.

Rabago D, Zgierska A, Mundt M, Kijowski R, Belling J, Patterson, JJ; *Dextrose prolotherapy for knee osteoarthritis: Results of a randomized controlled trial* (Oral presentation); North American Primary Care Research Group (NAPCRG) 39th annual conference; Banff, Canada; November 12-14, 2011.

Clinical trials identifier: NCT00085722

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