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Hypertonic dextrose injection (prolotherapy) for knee osteoarthritis: Long term outcomes

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Summary

Objective: Knee osteoarthritis (OA) is a common, debilitating chronic disease. Prolotherapy is an injection therapy for chronic musculoskeletal pain. Recent 52-week randomized controlled and open label studies have reported improvement of knee OA-specific outcomes compared to baseline status, and blinded saline control injections and at-home exercise therapy ($p < 0.05$). However, long term effects of prolotherapy for knee OA are unknown. We therefore assessed long-term effects of prolotherapy on knee pain, function and stiffness among adults with knee OA.

Design: Post clinical-trial, open-label follow-up study.

Setting: Outpatient; adults with mild-to-severe knee OA completing a 52-week prolotherapy study were enrolled.

Intervention and outcome measures: Participants received 3–5 monthly interventions and were assessed using the validated Western Ontario McMaster University Osteoarthritis Index, (WOMAC, 0–100 points), at baseline, 12, 26, 52 weeks, and 2.5 years.

Results: 65 participants (58 ± 7.4 years old, 38 female) received 4.6 ± 0.69 injection sessions in the initial 17-week treatment period. They reported progressive improvement in WOMAC scores at all time points in excess of minimal clinical important improvement benchmarks during the initial 52-week study period, from 13.8 ± 17.4 points (23.6%) at 12 weeks, to 20.9 ± 2.8 points, ($p < 0.05$; 35.8% improvement) at 2.5 ± 0.6 years (range 1.6–3.5 years) in the current follow-up analysis. Among assessed covariates, none were predictive of improvement in the WOMAC score.

Abbreviations: RCT, randomized controlled trial; BMI, body mass index; WOMAC, Western Ontario McMaster University Osteoarthritis Index; KPS, knee pain scale; MCII, minimal clinical important improvement.

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Conclusions: Prolotherapy resulted in safe, significant, progressive improvement of knee pain, function and stiffness scores among most participants through a mean follow-up of 2.5 years and may be an appropriate therapy for patients with knee OA refractory to other conservative care. © 2015 Elsevier Ltd. All rights reserved.

Introduction

Knee osteoarthritis (OA) is a chronic disease; knee pain, stiffness, and functional impairment are common sequelae. Knee OA is common and age-related;¹ 33.6% of those over 65 years of age will have knee OA,² conferring substantial expense for patients and society. The etiology of knee OA pain is multifactorial; pain generators include both intra-articular and supportive extra-articular structures.^{3,4} Standard-of-care is multidisciplinary; however, a recent systematic review reported no clear benefit of commonly used therapies.⁵ The Institute of Medicine has identified assessment of knee OA treatment strategies as a “top 100” comparative effectiveness research priority⁶ and the Agency for Healthcare Research and Quality has called for the development of new therapies to treat knee OA.⁵

Prolotherapy is a complementary and alternative medical (CAM) injection therapy for chronic musculoskeletal pain, including knee OA.^{7–9} It has been categorized as a *regenerative injection techniques for musculoskeletal pain by some researchers*.¹⁰ Small volumes of an irritant solution are injected at multiple tender ligament and tendon attachments and in adjacent joint spaces during several treatment sessions.⁷ The earliest description of prolotherapy to appear in the allopathic medical literature was in 1937 in a case report for temporomandibular joint, in which the modality was called ‘sclerotherapy’ due to the scar-forming properties of early injectants.¹¹ Contemporary injection techniques date from the 1950s when the more commonly used term ‘prolotherapy’ (from ‘proliferant therapy’) was adopted based on the observation that ligamentous tissue exhibited larger cross-sectional area after prolotherapy injections in animal models.¹² The mechanism of action remains unclear. Hypotheses include stimulation of local healing through inflammatory or sensorineural mechanisms,^{13–15} but definitive evidence is lacking.⁷ Hypertonic dextrose is the most commonly used injectant.⁷ Prolotherapy may be well-suited to address the multifactorial etiology of symptomatic knee OA because injections target multiple potential pain-generating sites in and around the knee joint; *positive one-year outcomes have been reported in three studies*,^{16–18} however the long term effects of prolotherapy in participants with knee OA are not known. We therefore enrolled participants from *one completed 52-week randomized controlled clinical trial*¹⁸ and *two completed 52-week non-controlled trials*^{16,17} in an open-label follow-up study to assess the hypothesis that adults with symptomatic knee OA who received prolotherapy will report progressive improvement on a validated assessment of knee pain, stiffness and function up to 3.5 years after initiating treatment.

Materials and methods

Context

The study protocol is part of a larger body of work; each individual study was approved by the University of Wisconsin Health Institutional Review Board. The clinical trials identifier of the project as a whole is NCT00085722. *In two 52-week uncontrolled open label studies and one randomized controlled study, our group has reported improvement in self-reported knee OA-specific pain, function and stiffness compared to baseline status,^{16,17} and blinded saline control injections and at-home exercise therapy,¹⁸ in response to prolotherapy. The eligibility criteria and injection protocols of the three prior trials were nearly identical; the primary outcome measure in each was the Western Ontario McMaster University Osteoarthritis Index (WOMAC) questionnaire, a validated, responsive questionnaire evaluating knee OA severity using pain, stiffness, and function subscales.¹⁹ The improvement among participants receiving prolotherapy in each study was similar: 15.9 ± 2.5 points in ‘Open Label 1’,¹⁶ (Fig. 1) 12.4 ± 3.5 – 19.4 ± 7.0 points in Open Label 2,¹⁷ and 15.3 ± 3.5 points in the randomized controlled trial.¹⁸*

Study design

Post clinical-trial open-label follow-up study assessing self-reported outcomes among participants up to 3.5 years after enrollment in three prior studies.

Participants

The primary inclusion criteria *for the current study* were: receiving prolotherapy in one of three prior *studies* of prolotherapy for mild-to-severe knee OA;^{16–18} completion of 52 week follow-up assessment *in those studies*, and being 1.5 to 3.5 years from initial enrollment *in those studies* (Fig. 1). Details of the eligibility criteria of the prior studies have been published.^{16–18} Briefly, they included a diagnosis of knee OA based on clinical criteria,²⁰ augmented by radiologically demonstrated knee OA identified by a radiologist on an existing radiograph obtained within five years prior to initial enrollment; tenderness of one or more anterior knee structures on physical exam conducted by the first author (DR); and self-reported moderate-to-severe knee pain for at least 3 months, defined as a score of “3” or more in response to the question “What has been the average level of your left/right knee pain over the last week?” (0–6 ordinal response scale). *Potential participants were contacted sequentially, based on their 52-week exit date, from their*

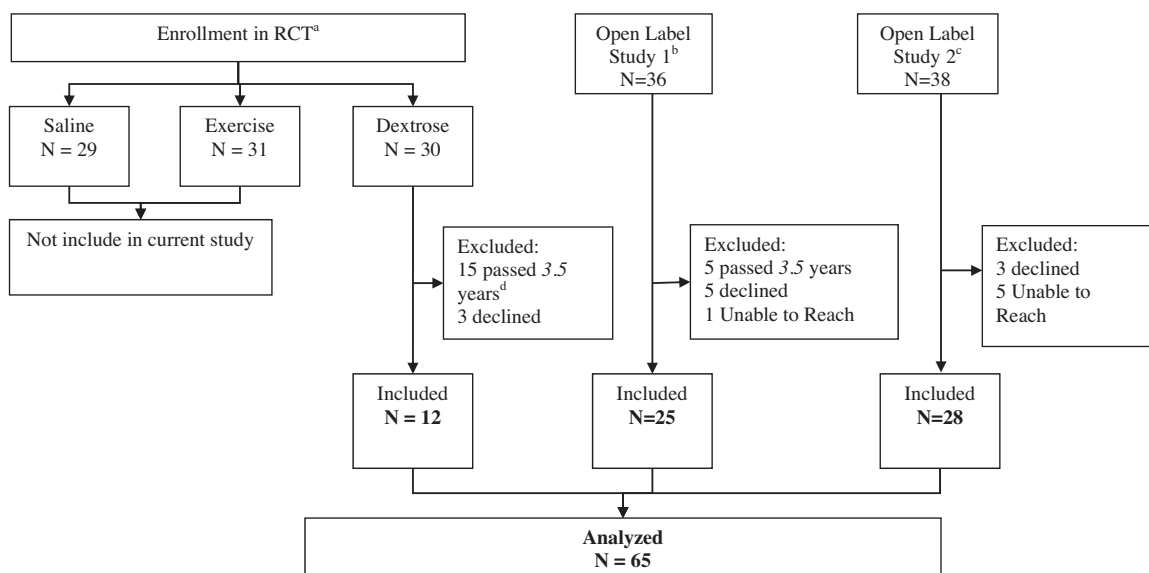


Figure 1 Participant recruitment. a: RCT, randomized controlled trial from which participants were recruited;¹⁸ b: the first uncontrolled study from which participants were recruited;¹⁶ c: open label 2, the second uncontrolled study from which participants were recruited;¹⁷ d: participants who were more than 3.5 years from initial recruitment in any of the 3 initial studies were not eligible for the current study.

initial study and assessed for eligibility in the current study from April 26, 2010 to November 22, 2010 (Fig. 1).

Intervention

The intra- and extra-articular prolotherapy injection protocol used in each of the three initial studies has been published.¹⁶ Briefly, participants received prolotherapy at 1, 5 and 9 weeks. Optional sessions were provided at weeks 13 and 17 per injector recommendations and participant preference. The injector examined the knee, marked tender anterior points, placed anesthetic skin wheals of 1% lidocaine and performed prolotherapy injections. Six mL of 25% dextrose was injected in the intra-articular space using an infero-medial approach and 22 mL of 15% dextrose was injected at extra-articular soft tissue attachments. Post-injection, participants were advised on relative rest for 2–3 days, with progressive resumption of routine activity over one month. They were discouraged from using non-steroidal anti-inflammatory medications (NSAIDs) and from starting new knee OA therapies during the initial-study follow-up period.

Outcome measures

The primary outcome measure was the same as that of the initial 52-week studies, change in knee-related quality-of-life as assessed by the composite score of Western Ontario McMaster University Osteoarthritis Index (WOMAC). We used a composite score, constructed as the weighted average of the three subscale scores, ranging from 0 (worst) to 100 (best) knee-related quality-of-life. The minimal clinical important improvement (MCII) on the WOMAC for knee OA has been reported as 12 points of change on a 0–100 mm visual analog scale.²¹ The secondary outcome, knee pain

scale (KPS),²² a validated questionnaire assessing knee pain severity (0–5 ordinal scale) and frequency (0–4 ordinal scale) was also used in this and the prior studies; higher scores indicated worse symptoms. KPS data were collected separately for each of the two knees, regardless whether the knee received prolotherapy (“treated knee”) or not (“untreated knee”). The WOMAC and KPS data were collected in person, before the procedure, at baseline and 12 weeks, and by phone at 26 and 52 weeks. In the current study, all long-term follow-up data were collected by phone.

Other measures

Demographics, self-reported weight and height, and severity of knee OA on knee radiographs were collected at baseline and analyzed for the current participants to characterize the sample and to evaluate as covariates for statistical analysis. Participants could make brief qualitative comments at each assessment point and were asked if they used other KOA therapies between 52 week and final follow-up. A fellowship-trained musculoskeletal radiologist using the 1–4 point Kellgren–Lawrence knee OA scoring system,²³ evaluated existing, available knee radiographs in the initial studies. The number of attended prolotherapy sessions was also tracked.

Analysis

Data were analyzed using SAS® 9.2 statistical software (SAS Institute Inc.: Cary, NC). Distributional data characteristics were assessed; primary and secondary continuous variables were normally distributed. Descriptive statistics were applied to describe outcomes at each time point; mean value ± standard deviation (SD) was reported unless otherwise specified.

Repeated measures analysis of variance compared baseline to follow-up scores (four time points over the follow-up period) of the WOMAC and the KPS. Individual participant data from the prior three 52-week studies was re-analyzed in a single longitudinal model in the current study. Because WOMAC evaluates participant's knee OA-specific quality of life regardless of the number of affected knees (one or two) the analysis of the WOMAC scores was on a "per participant" basis, regardless 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, body mass index (BMI), race, education, income, tobacco use, diabetes, prior knee surgery, Kellgren–Lawrence radiographic knee OA severity, duration of knee pain, and duration of follow-up. Percent improvement in WOMAC scores was calculated as the percentage change in total WOMAC score from baseline. The proportion of participants in each group who met the MCII benchmark of 12 points on the 0–100 point composite WOMAC was also calculated. 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 KPS-scores 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 which were not treated during the study. The model included KPS scores of untreated knees for individuals who only received treatment on a single knee. Two-tailed p -value <0.05 was established as a statistical significance level.

Results

The recruitment and participation scheme is given in Fig. 1. Of the 82 potential participants who met the eligibility criteria, 10 declined due to lack of interest, one was unable to participate due to chronic illness, and six were unreachable. Sixty-five participants agreed to participate, provided self-reported data and were included in the long-term outcome analysis. Of these, 12 participants were recruited from the initial RCT, and 53 from either one of two open label studies.^{16–18} The study sample ($N=65$) consisted of predominantly female ($N=38$) Caucasian adults ($58.7 \pm SD 7.4$ years old, with 77% reporting BMI over 25 kg/m^2 (Table 1). Participants reported an average duration of 97.7 ± 91.2 months of knee pain prior to receiving prolotherapy. Most participants had tried and failed one or more conservative measures. Radiographic evaluation prior to receiving prolotherapy suggested that most (47/65) participants had mild OA (Kellgren–Lawrence score of 1 or 2) at baseline. *Two participants received hyaluronic acid injection therapy between 52 weeks and their final follow up time point.*

Participants received an average of 4.6 ± 0.7 prolotherapy sessions per injected knee in the initial 52-week studies; 30 participants had both knees treated, thus contributing 60 knees to the KPS analysis. Thirty-five participants had only one knee treated. The total sample size for the WOMAC and

KPS analyses of treated knees was therefore 65 participants with 95 knees, respectively. Thirty-five knees were included in the KPS analysis of untreated knees.

WOMAC

The average follow-up time from enrollment in the initial studies was 2.5 ± 0.6 years (range 1.6–3.5 years). Repeated measures analysis showed progressive improvement in the composite and subscale WOMAC scores from baseline through 12, 24, 52 weeks and 2.5 years ($p < 0.001$; Table 2). The total improvement in WOMAC composite score was 20.9 ± 22.6 points or 35.6% at 2.5 years; 62% (40/65) of participants improved by 12 or more points. Covariate analysis over the extended follow-up showed no association between WOMAC score change and sex, age, BMI, recruitment source, number of received injection sessions, injection of one or both knees, duration of knee OA pain, prior knee OA therapies, tobacco use, follow up time duration or the pre-treatment Kellgren–Lawrence scores.

A post hoc sub-analysis revealed that the majority of participants (53/65, 82%) reported improved composite WOMAC scores at the long-term follow-up compared with baseline ("responders"); their mean composite WOMAC score increase was 28.3 ± 17.5 points. A minority of participants ("non-responders", 12/65, 18%) did not report improved composite WOMAC scores at long term follow-up. They had smaller WOMAC score improvements at all time points through 52 weeks compared with responders, and a loss of 12.1 ± 7.9 points at 2.5 years compared with their baseline (Fig. 2) scores. Qualitative comments from 12 participants revealed that 4 of the non-responders engaged in early strenuous physical activity after two or more prolotherapy treatment sessions. Assessed covariates did not predict responder status.

KPS

Similar to the WOMAC, KPS scores improved progressively through the 2.5 year study period (Table 3; $p < 0.001$) in injected knees ($n=95$), regardless of the number of knees injected. Participants reported less severe baseline KPS-specific knee pathology in uninjected knees ($n=35$) but of note, reported a substantial, statistically significant improvement in KPS scores for both pain frequency (52%, $p < 0.05$) and severity (63%, $p = 0.05$) in those uninjected knees at 2.5 ± 0.6 years (Table 3).

Subjective percentage change

Eighty-six percent of participants (56/65) indicated that they had decreased knee pain, reporting an average of $71\% \pm 26\%$ less pain at the long-term follow up compared with baseline. Fourteen percent (9/65) reported that prolotherapy had no effect at the long-term follow-up.

Discussion

Dextrose prolotherapy resulted in progressive improvement of 20.9 ± 22.6 points among participants in the cohort as a

Table 1 Baseline participant ($n=65$) characteristics.

Female, n (%)	38 (58)	
Age, years, mean (SD) ^a	58.7 (7.4)	
Income, n (%)		
<\$50,000	12 (18)	
\$50,000–\$79,000	18 (28)	
\$80,000+	35 (55)	
Duration of knee pain, months, mean (SD)	97.7 (91.2)	
BMI (kg/m) ^b , n (%)		
≤25	15 (23)	
26–30	25 (39)	
31+	24 (38)	
Prior knee intervention, n (%) ^c		
Arthroscopic surgery	26 (40)	
Physical therapy	18 (28)	
Hyaluronic acid injection	3 (5)	
Corticosteroid injection	7 (11)	
Diabetes, n (%)	4 (6)	
WOMAC ^d total score, points (SD)	58.4 (15.3)	
Pain	61.8 (15.2)	
Stiffness	51.9 (20.5)	
Function	61.4 (16.4)	
KPS ^e	Treated knees (SD)	Untreated knees (SD)
Pain frequency	2.51 (0.91)	1.22 (1.20)
Pain severity	1.98 (0.93)	0.87 (0.99)
X-ray Kellgren–Lawrence OA ^f severity score (0–4) of treated knees ^g ; n (%)		
1–2 Score (mild OA)	47 (72)	
3–4 (moderate to severe OA)	18 (28)	

^a SD, standard deviation.

^b BMI, body mass index.

^c Percentage does not sum to 100 due to participants' varied use of conventional therapies.

^d WOMAC, Western Ontario McMaster University Osteoarthritis Index; The theoretical range of the WOMAC in this study is from 0 to 100 with higher values indicating better knee related quality of life.

^e KPS, knee pain scale; The theoretical range of KPS scores for knee pain frequency is 0–4 and for knee pain severity is 0–5 with higher values indicating worse symptoms.

^f OA, osteoarthritis.

^g Existing knee radiographs were obtained for the more severely affected injected knee in each participant.

whole, in excess of MCII for the WOMAC, in knee specific quality of life among adults with symptomatic mild-to-severe knee OA over a mean follow-up of 2.5 ± 0.6 years. Mean score change was progressive throughout the study period, and consistent across the three WOMAC subscales

(pain, stiffness and function). Subjective participant perception of the change in knee OA-related quality of life indicated even larger gains. However, response to prolotherapy was divided; while the majority of participants continued to improve, a minority who had reported lesser

Table 2 WOMAC Composite and Subscale Scores.

Measure	Baseline ($N=65$)	Week 12 ($N=63$)	Week 24 ($N=64$)	Week 52 ($N=65$)	2.5 ± 0.6 Year ^b ($N=65$)
WOMAC composite (SD) ^a	58.4 (15.3)	+13.8 (17.4)	+13.5 (16.9)	+17.1 (19.6)	+20.9 (22.6)
WOMAC subscales (SD) ^a					
Pain	61.8 (15.2)	+13.5 (16.8)	+13.8 (18.2)	+16.1 (20.5)	+20.6 (22.3)
Stiffness	51.9 (20.5)	+14.1 (23.3)	+12.7 (20.3)	+18.1 (24.6)	+21.7 (27.8)
Function	61.4 (16.4)	+13.9 (17.4)	+14.1 (17.4)	+17.0 (18.5)	+20.3 (22.4)

Abbreviations: N, number; WOMAC, Western Ontario McMaster University Osteoarthritis Index; SD, standard deviation. Repeated measures analysis of variance compared baseline to follow-up scores.

^a $p < 0.001$ at all follow-up time points.

^b Range 1.6–3.5 years.

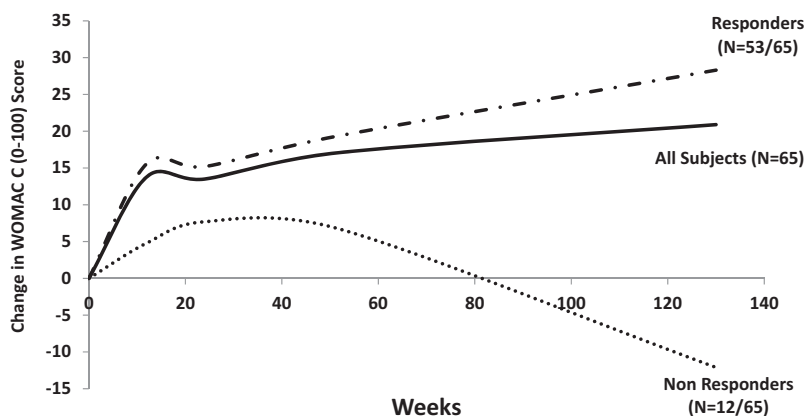


Figure 2 Mean change in WOMAC^a score of the cohort as a whole, responders^b and non-responders^c over 2.5 ± 0.6 years. ^a WOMAC, Western Ontario McMaster University Osteoarthritis Index; ^b Responders were defined as those participants who reported improved composite WOMAC scores at a mean of 2.5 ± 0.6 years compared to baseline status; ^c Non-responders were defined as those participants who reported worse composite WOMAC scores at 2.5 ± 0.6 years compared to baseline status.

gains through 52 weeks continued to report decreased (worsened) WOMAC scores at long-term follow-up compared with baseline. KPS-based results were consistent with WOMAC findings for injected knees; participants also reported improved KPS scores of uninjected knees.

Limitations of this study include a lack of comparison group between 52 and 130 weeks; participants after 52 weeks may have been biased in favor of the intervention. However, the response to prolotherapy among participants in all three initial trials (one blinded RCT, two uncontrolled open label) was very similar, suggesting limited intervention bias. Generalizability may be limited by numerous initial eligibility criteria and a relatively low mean age. The self-assessment of percentage improvement was relatively informal and, therefore, subject to bias. *The open-ended qualitative assessment of the use of other KOA therapy between 52 weeks and long-term follow-up may have been subject to recall bias, and weight was not assessed at follow-up; a potential positive effect of either other therapies or weight loss may account for some of the reported improvement.* Strengths include pragmatic assessment using validated patient-oriented outcome measures

during a long-term follow-up, and robust, consistent results reported by a majority of participants.

Improvement of injected knees in the short term is consistent with the results of *three* RCTs^{18,8,24} and two open label studies^{15,16} documenting positive effects of prolotherapy through a maximum of 52 weeks. Dumais et al. used the WOMAC measure and nearly identical injectants and injection protocols, and reported similar improvement attributable to injection. Current data are also consistent with one open label long-term study.²⁵ The ability to compare the current study to those by Reeves et al.^{8,25} and to studies of hyaluronic acid injection or other therapies is limited given the heterogeneity of study eligibility criteria, overall health status, patient expectation, baseline knee OA severity and outcome assessment methodology.²⁶ The current study improves upon prior long-term studies²⁵ through its use of validated outcome measures.

Improvement in uninjected knees is consistent with a prior open-label 52-week study.¹⁶ A reduction in compensatory mechanisms of the uninjected side may explain this effect. Individuals with knee OA have reduced knee and hip motion on the affected side compared with non-knee OA

Table 3 Longitudinal comparison of knee pain scales (KPS) of treated and untreated knees.

Treated knees (N = 95)					
Measure	Baseline (N = 95)	Week 12 (N = 92)	Week 24 (N = 93)	Week 52 (N = 95)	2.5 ± 0.6 Year ^b (N = 95)
KPS pain frequency (SD) ^a	2.51 (0.91)	-0.79 (1.10)	-0.81 (0.90)	-0.84 (1.14)	-1.07 (1.40)
KPS pain severity (SD) ^a	1.98 (0.93)	-0.83 (1.03)	-0.77 (1.11)	-0.83 (1.22)	-0.95 (1.21)
Untreated knees (N = 35)					
Measure	Baseline (N = 35)	Week 12 (N = 34)	Week 24 (N = 35)	Week 52 (N = 35)	2.5 ± 0.6 Year ^b (N = 35)
KPS pain frequency (SD) ^c	1.22 (1.20)	-0.59 (1.01)	-0.64 (1.11)	-0.64 (0.95)	-0.63 (1.31)
KPS pain severity (SD) ^c	0.87 (0.99)	-0.44 (0.92)	-0.48 (1.02)	-0.49 (0.82)	-0.54 (1.03)

Abbreviations: knee pain scale (KPS) SD, standard deviation; N, number. Repeated measures analysis of variance compared baseline to follow-up scores.

^a *p* < 0.001 at all follow-up time points.

^b Range 1.6–3.5 years.

^c *p* < 0.05 at all follow-up time points.

controls,²⁷ placing additional burden on the non-affected limb at a particular walking speed.²⁸ This may result in overuse, and subsequent pain and disability of the contralateral knee. Participants receiving prolotherapy may have relied less on the uninjected side due to post-injection improvement of the primarily affected knee, reducing overuse and improving bilateral knee function.

The mechanism of action for dextrose prolotherapy is not well understood; several hypotheses have been advanced. Hypertonic dextrose has been hypothesized to stimulate healing of chronically injured extra- and intra-articular tissue; the current outcomes suggest that an enduring effect may indeed follow prolotherapy among initial responders. Animal model studies reported significantly enlarged cross-sectional area in medial collateral knee ligaments,¹⁵ and increased inflammatory markers after dextrose injection;¹³ a recent human trial reported that cartilage volume stability, as assessed by magnetic resonance imaging, predicted improvement in WOMAC-based pain scores among prolotherapy recipients, suggesting a direct sensorneural neural effect of prolotherapy.¹⁴ Needle trauma, volume expansion of local tissue and bleeding may also produce tissue-level effects, separate from those of dextrose alone. The potential of prolotherapy to stimulate release of growth factors favoring soft tissue healing has also been suggested.^{8,29}

Clinically, these findings suggest that dextrose prolotherapy may provide meaningful primary treatment for well selected patients, with improvements sustained over the long term. The described procedure costs \$200 US per prolotherapy injection session in the lead author's practice; most patients pay out-of-pocket though some third-party payers cover prolotherapy on a prior authorization basis. Interest in prolotherapy among physicians and patients in the US appears to be high based on attendance at continuing medical education conferences and physician listings on relevant websites.⁷ Prolotherapy for knee OA is usually performed in the outpatient setting without ultrasound guidance; it is uncomplicated to learn and requires approximately 15 min to perform. Continuing medical education is provided in major university and national physician organization settings.⁷ These findings also suggest the need for further research to identify baseline characteristics of responders (e.g., biomarkers, radiographic features), whether objectively assessed outcomes (*physical function, MRI*) are consistent with self-report, whether prolotherapy is cost-effective compared to other therapy, and whether interim "booster" injection sessions, for example at 6 and/or 12 months, would improve effects among responders in whom initial effects have waned or among initial non-responders.

Conclusions

Among participants with knee OA, prolotherapy performed by a trained operator resulted in safe, meaningful and sustained improvements over an average 2.5 years on validated knee OA-specific pain, function and stiffness measures. Dextrose prolotherapy appears to be an effective long-term therapy for most patients with mild-to-severe knee OA who are refractory to conservative care.

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Conflict of interest statement

There are no conflicts of interest for all authors.

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References

1. Felson DT. Epidemiology of osteoarthritis. In: Brandt KD, Lohmander DM, eds LS, editors. *Osteoarthritis*. Oxford, England: Oxford University Press; 2003. p. 9–16.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008;**58**:26–35.
3. Felson DT. The sources of pain in knee osteoarthritis. *Curr Opin Rheumatol* 2005;**5**:624–8.
4. Felson DT. Osteoarthritis: new insights, Part 1: The disease and its risk factors. *Ann Intern Med* 2000;**133**:635–46.
5. Samson DJ, Grant MD, Ratko TA, et al. Treatment of primary and secondary osteoarthritis of the knee. In: *Agency for Healthcare Research and Quality (publication no. 07-E012): evidence report/technology assessment: prepared by Blue Cross and Blue Shield association technology evaluation center evidence-based practice center under contract no. 290-02-0026*. Rockville, MD: Agency for Healthcare Research and Quality; 2007. p. 157.
6. National Research Council. *Initial national priorities for comparative effectiveness research*. Washington, DC: The National Academies Press; 2009.
7. Rabago D, Slattengren A, Zgierska A. Prolotherapy in primary care. *Prim Care* 2010;**37**:65–80.
8. Reeves KD, Hassanein K. Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. *Altern Ther Health Med* 2000;**6**:68–80.
9. Fleming S, Rabago D, Mundt M, et al. CAM therapies among primary care patients using opioid therapy for chronic pain. *BMC Complement Altern Med* 2007;**7**(15). PMID: 17506893; PMCID: PMC1885447.
10. DeChellis DM, Cortazzo MH. Regenerative medicine in hte feild of pain medicine: prolotherapy, platelet-rich plasma, and stem cell therapy—theory and evidence. *Tech Reg Anesth Pain Manage* 2011;**15**:74–80.
11. Schultz L. A treatment for subluxation of the temporomandibular joint. *J Am Med Assoc* 1937;**109**(13):1032–5.
12. Hackett GS, Hemwall GA, Montgomery GA. *Ligament and tendon relaxation treated by prolotherapy*. 5th ed. Oak Park, IL: Gustav A. Hemwall; 1993.

13. Jensen K, Rabago D, Best TM, et al. Early inflammatory response of knee ligaments to prolotherapy in a rat model. *J Orthop Res* 2008;**26**:816–23.
14. Rabago D, Kijowski R, Woods M, et al. Association between disease-specific quality-of-life and magnetic resonance imaging outcomes in a clinical trial of prolotherapy for knee osteoarthritis. *Arch Phys Med Rehabil* 2013;**94**(11):2075–82.
15. Jensen KT, Rabago D, Best TM, et al. Longer term response of knee ligaments to prolotherapy in a rat injury model. *Am J Sports Med* 2008;**36**:1347–57.
16. Rabago D, Zgierska A, Fortney L, et al. Hypertonic dextrose injections (prolotherapy) for knee osteoarthritis: an uncontrolled study with one-year follow-up. *J Altern Complement Med* 2012;**18**:408–14.
17. Rabago D, Patterson JJ, Mundt M. Dextrose and morrhuate sodium injections (prolotherapy) for knee osteoarthritis: the results of a prospective open label trial. *J Altern Complement Med* 2013;**20**(5):381–91. PMID: 24635447.
18. Rabago D, Patterson JJ, Mundt M, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. *Ann Fam Med* 2013;**11**(3):229–37.
19. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes in antirheumatic drug therapy in patients with osteoarthritis of the knee. *J Rheumatol* 1988;**15**:1833–40.
20. Altman RD. Criteria for classification of clinical osteoarthritis. *J Rheumatol Suppl* 1991;**27**:10–2.
21. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Ann Rheum Dis* 2005;**64**(1):29–33.
22. Rejeski JW, Ettinger WH, Shumaker S, et al. The evaluation of pain in patients with knee osteoarthritis: the knee pain scale. *J Rheumatol* 1995;**22**(6):1124–9.
23. Kellgren JH, Jeffrey MR, Ball J. *The epidemiology of chronic rheumatism. Atlas of standard radiographs of arthritis*. Oxford, UK: Blackwell Scientific Publications; 1963.
24. Dumais R, Benoit C, Dumais A, et al. Effect of regenerative injection therapy on function and pain in patients with knee osteoarthritis: a randomized crossover study. *Pain Med* 2012;**13**:990–9.
25. Reeves KD, Hassanein KM. Long-term effects of dextrose prolotherapy for anterior cruciate ligament therapy. *Altern Ther Health Med* 2003;**9**(3):58–62.
26. Singh J, Sloan JA, Johanson NA. Challenges with health-related quality of life assessment in arthroplasty patients: problems and solutions. *J Am Orthop Surg* 2010;**18**:72–82.
27. Brinkmann JR, Perry J. Rate and range of knee motion during ambulation in healthy and arthritic subjects. *Phys Ther* 1985;**65**:1055–60.
28. Messier SP, Loeser RF, Hoover JL, et al. Osteoarthritis of the knee: effects on gait, strength, and flexibility. *Arch Phys Med Rehabil* 1992;**73**:29–36.
29. Kim SR, Stitik TP, Foye PM. Critical review of prolotherapy for osteoarthritis, low back pain, and other musculoskeletal conditions: a physiatric perspective. *Am J Phys Med Rehabil* 2004;**83**:379–89.