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Original Article

Dextrose and Morrhuate Sodium Injections (Prolotherapy) for Knee Osteoarthritis: A Prospective Open-Label Trial

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Abstract

Objectives: This study determined whether injection with hypertonic dextrose and morrhuate sodium (prolotherapy) using a pragmatic, clinically determined injection schedule for knee osteoarthritis (KOA) results in improved knee pain, function, and stiffness compared to baseline status.
Design: This was a prospective three-arm uncontrolled study with 1-year follow-up.
Setting: The setting was outpatient.
Participants: The participants were 38 adults who had at least 3 months of symptomatic KOA and who were in the control groups of a prior prolotherapy randomized controlled trial (RCT) (Prior-Control), were ineligible for the RCT (Prior-Ineligible), or were eligible but declined the RCT (Prior-Declined).
Intervention: The injection sessions at occurred at 1, 5, and 9 weeks with as-needed treatment at weeks 13 and 17. Extra-articular injections of 15% dextrose and 5% morrhuate sodium were done at peri-articular tendon and ligament insertions. A single intra-articular injection of 6 mL 25% dextrose was performed through an inferomedial approach.
Outcome measures: The primary outcome measure was the validated Western Ontario McMaster University Osteoarthritis Index (WOMAC). The secondary outcome measure was the Knee Pain Scale and postprocedure opioid medication use and participant satisfaction.
Results: The Prior-Declined group reported the most severe baseline WOMAC score ($p = 0.02$). Compared to baseline status, participants in the Prior-Control group reported a score change of 12.4 ± 3.5 points (19.5%, $p = 0.002$). Prior-Decline and Prior-Ineligible groups improved by 19.4 ± 7.0 (42.9%, $p = 0.05$) and 17.8 ± 3.9 (28.4%, $p = 0.008$) points, respectively; 55.6% of Prior-Control, 75% of Prior-Decline, and 50% of Prior-Ineligible participants reported score improvement in excess of the 12-point minimal clinical important difference on the WOMAC measure. Postprocedure opioid medication resulted in rapid diminution of prolotherapy injection pain. Satisfaction was high and there were no adverse events.
Conclusions: Prolotherapy using dextrose and morrhuate sodium injections for participants with mild-to-severe KOA resulted in safe, significant, sustained improvement of WOMAC-based knee pain, function, and stiffness scores compared to baseline status.

Introduction

Knee osteoarthritis (KOA) is a common chronic disease resulting in joint stiffness, pain, and decreased function; it is common, expensive, and age-related. By age 65, the majority of the population has radiographic evidence of osteoarthritis.[1,2] Sources of pain include supportive extra-articular and intra-articular tissues.[3,4] Standard-of-care is multidisciplinary, but a recent systematic review reported no clear benefit of any one therapy.[5] Several alternative therapies have been evaluated but are also without clear efficacy. The Agency for Healthcare Research and Quality has called for the development of new therapies to prevent and treat KOA.[5]

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Prolotherapy is an injection therapy for chronic musculoskeletal conditions[6,7] including KOA,[8] targeting multiple pain generators in and around the knee. It emerged in 1937; the first substantive allopathic report referred to ''sclerotherapy'' due to the scar-forming properties of early injectants.[9] Current injection techniques were formalized in the 1950s; the term ''prolotherapy'' (from ''proliferant therapy'') was adopted when early researchers noted that ligamentous tissue exhibited an enlarged cross-sectional area after prolotherapy injections in animal models.[10] Literature of modest methodological rigor from the 1930s to the early 2000s reported positive clincal outcomes.[11] Contemporary hypotheses suggest that prolotherapy stimulates local healing of chronically injured tissue, although definitive evidence is lacking.[6]

Hypertonic dextrose is the most commonly used prolotherapy injectant.[6] A recent open-label study and randomized controlled trial (RCT) reported improvement in KOA outcomes compared to baseline status,[12] and blinded saline injections and at-home exercise control therapies.[13] Both studies were limited by use of a single injectant (dextrose) or eligibilty criteria excluding participants with body–mass index over 42 g/m^2 or diabetes mellitus, risk factors for KOA, and immune compromise, respectively. While dextrose is a commonly used injectant, prolotherapists use other injectants in isolation or in combination with dextrose, including the sclerosant morrhuate sodium, and optimize the injection strategy to individual patient needs.[6,14,15] The effectiveness of prolotherapy for KOA using a pragmatic, multiple-injectant strategy has not been assessed. We therefore conducted an open-label study to test the hypothesis that a clinically guided dextrose and morrhuate sodium injection protocol improves knee pain, function, and stiffness during a 52-week follow-up period in participants with symptomatic mild-to-severe KOA.

Methods

The study was approved by the University of Wisconsin (UW) Health Sciences Institutional Review Board (IRB). The study sample was drawn from (1) control group participants of a prior RCT ($N=90$),[13] (2) persons who were eligible for but declined participation in the prior RCT, and (3) persons who were ineligible for the prior RCT (Fig. 1). All prospective participants were screened for the current study using eligibility criteria similar to the prior RCT. Inclusion criteria in the current study were the following: clinical criteria of KOA (American College of Rheumatology),[16] identification by a radiologist of KOA on an existing knee radiograph obtained within 5 years of the prior RCT enrollment, tenderness of one 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 on the question ''What is the average level of your left/right knee pain over the last week?'' (0–6 ordinal response scale). Exclusion criteria included the following: self-reported pregnancy, anticoagulation therapy, history of total knee replacement, prior knee prolotherapy, any knee injection within the past 3 months, inflammatory or postinfectious knee arthritis, daily use of opioid medication, allergy or intolerance to study injectants or pain medications (acetaminophen or oxycodone), body mass index (BMI) >45 kg/m^2, diabetes mellitus with hemoglobin A1C $>7.5\%$,

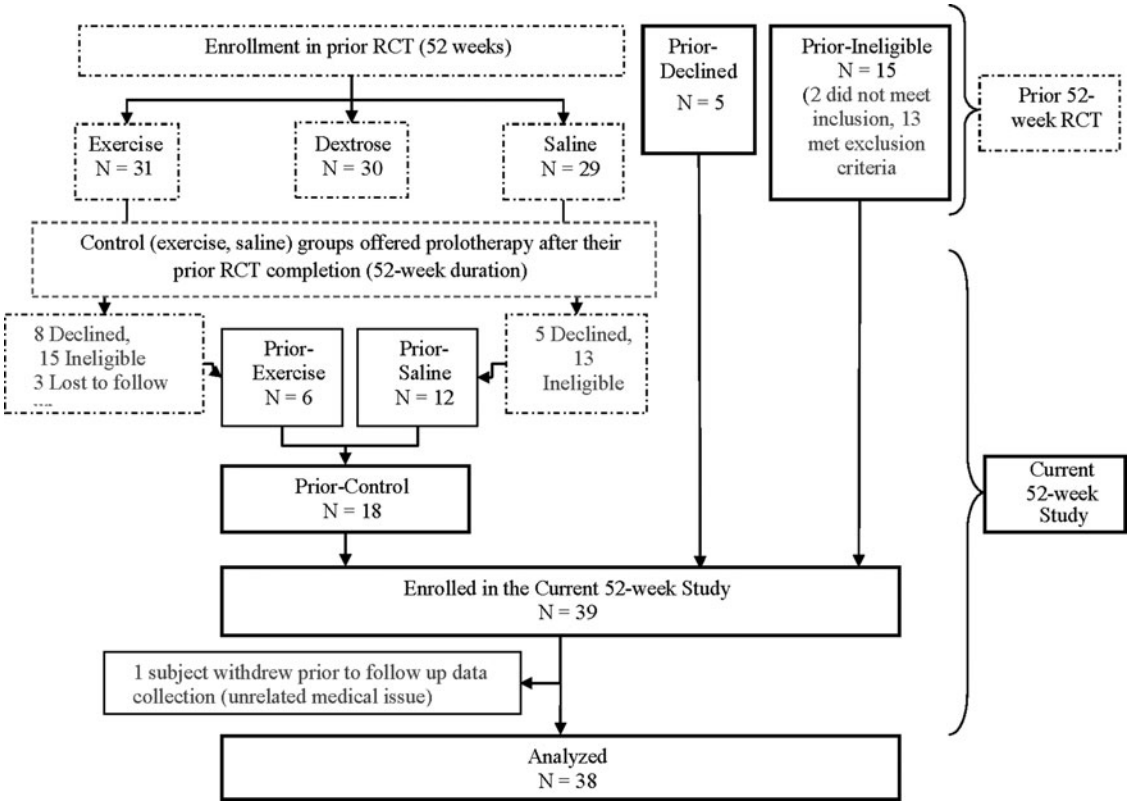

FIG. 1. Screening, enrollment and randomization dashed boxes indicate participation in prior study; solid line boxes indicate current 52-week intervention period.

or co-morbidity severe enough to prevent participation in the study protocol. Each knee was assessed separately for eligibility. Interested, eligible persons attended an informational meeting, were consented and enrolled ($N=38$), and were followed (2008–2009) for 52 weeks. The sample consisted of three groups: prior RCT-control group participants ($N=18$, ''Prior Controls''), prior RCT-declined participants ($N=5$, ''Prior Declined''), and prior RCT-ineligible participants ($N=15$, ''Prior-Ineligible'').

Intervention

All participants received dextrose prolotherapy at Session 1 (1 week postentry). Depending on individual treatment response and participant-preference, subsequent sessions used either dextrose or a combination of dextrose and morrhuate sodium at 5 and 9 weeks, with optional sessions at weeks 13 and 17, per injector recommendations and participant preference (Table 1). Participants with minimal or no improvement after the first session could receive the combined solution in each subsequent session. Participants were offered an optional 5-mg oxycodone tablet for injection-related analgesia prior to injection. The injector (JJP) examined the knee, marked tender anterior points, placed anesthetic skin wheals of 1% lidocaine, and performed prolotherapy injections according to an existing protocol (Table 1).[17] Postinjection, participants were offered acetaminophen and eight 5-mg oxycodone tablets as needed for 1 week and were advised on 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 KOA therapies during the study period.

Outcome Measures

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

Tertiary outcomes for injection participants included the following: (1) ratings of procedure-related pain severity using a 1–7 ordinal scale obtained immediately following and 2 days after each injection session, and (2) daily logs of opioid medication use (yes/no) during 7 days postinjection. 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 KOA like yours?'' (yes/no). All participants were able to make brief qualitative comments about their experiences.

Other measures

Demographics, self-reported weight and height, and severity of KOA on knee radiographs were collected at baseline to characterize the sample and to evaluate as covariates for statistical analysis. A fellowship-trained musculoskeletal radiologist (RK), using the 1–4-point Kellgren–Lawrence KOA scoring system,[22] evaluated existing, available knee radiographs. Attendance at injection sessions was tracked.

Analysis

The sample size was determined by convenience to match the intended size of the prior RCT study arms per UW-IRB stipulation.[23] Analysis was by intention-to-treat. Data were

Table 1. Injection Solutions and Technique

	Dextrose solution	*Dextrose–morrhuate solution*
Components	*Intra-articular:* 25% dextrose: 5 mL 50% dextrose 5 mL lidocaine 1% saline *Extra-articular:* 15% dextrose: 6.75 mL 50% dextrose 4.5 mL 1% lidocaine 11.25 mL 0.9% saline	*Intra-articular:* 25% dextrose: 5 mL 50% dextrose 5 mL lidocaine 1% saline *Extra-articular:* 5% morrhuate sodium/15% dextrose solution: 3 mL 50% dextrose 2 mL 5% morrhuate sodium 2 mL 0.9% saline 3 mL 1% lidocaine
Intervention	*Intra-articular:* 6.0 mL of solution in a single injection was performed using an inferomedial approach. *Extra-articular:* Up to 15 subdermal injections were placed and 0.5 mL of 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 solution.	

analyzed using SAS® 9.1 statistical software (SAS Institute Inc., Cary, NC). Distributional data characteristics were assessed; descriptive statistics were applied to describe outcomes at each time point; mean value ± standard deviation 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 at five time points over the 52 weeks. Mean values ± standard error were reported. Because the WOMAC evaluates participant's KOA-specific quality of life regardless of the number of knees (one or two) affected, the unit of analysis in the WOMAC model was the participant, 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 baseline score. The proportion of participants in each group who met the MCII benchmark of 12 points on the 0–100-point composite WOMAC was calculated.

The unit of analysis for the KPS 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.

For Prior-Control group participants, a paired *t*-test compared change in WOMAC score from baseline to 52-week follow-up in the RCT study to change in WOMAC score from baseline to 52-week follow-up in the current study.

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 study cohort was recruited from three sources (Fig. 1): (1) Eighteen (18) participants from the prior control groups (12 from Saline, 6 from Exercise) of the prior RCT met eligibility criteria and were enrolled. No statistically significant differences were found in baseline demographic and KOA severity variables, or time between the end of the RCT and the first prolotherapy session of the current study. The two groups were therefore pooled and analyzed as (1) one group (Prior-Controls, $N = 18$); (2) persons who were eligible for, but declined enrollment in the RCT (Prior-Declined, $N = 5$); and (3) persons ineligible for the prior RCT (Prior-Ineligible, $N = 16$) made up the second and third injection groups, respectively. An *a priori* decision was made to not pool these three groups because the recruitment source was substantively different for each. One participant (Prior-Ineligible) withdrew prior to the study intervention and collection of any follow-up data, and was not included, leaving 38 participants in the analysis (Fig. 1).

The study participants were 57.3 ± 5.5 years old with a BMI of 29.7 ± 5.7; the majority (74%) were either overweight (BMI ≥25–29.9 kg/m^2) or obese (BMI ≥30 kg/m^2) (Table 2). Women constituted 45% of the sample. On average, participants reported more than 5 years of KOA pain and most had failed at least one conservative therapy for KOA. While written radiograph reports identifying KOA were available for all included knees, administrative difficulties resulted in procurement of only 27 prestudy radiographs; Kellgren–Lawrence KOA radiological severity scores ranged from mild to severe. The three study groups were statistically similar at baseline except on KOA severity; participants in the Prior-Declined group had more severe KOA as assessed by composite WOMAC ($p = 0.02$) and knee stiffness ($p = 0.01$) scores.

Participants received 4.1 ± 1.1 injection sessions; 19 participants had both knees treated, and 19 participants had one knee treated (total 57 knees). The first prolotherapy session utilized dextrose solution only; from session 2–5, participants progressively selected the combination injectant (Table 3).

Participants in all groups reported improvement on the composite WOMAC measure in excess of the 12-point MCII (Table 4); Prior-Control participants reported a score change of 12.4 ± 3.5 points (19.5%, $p = 0.002$) compared to the baseline score of the current study. Compared to baseline status, participants in the Prior-Decline and Prior-Ineligible improved by 19.4 ± 7.0 (42.9%, $p = 0.05$) and 17.8 ± 3.9 (28.4%, $p = 0.008$) points, respectively; 55.6% of Prior-Control, 75% of Prior-Decline, and 50% of Prior-Ineligible participants reported score improvement in excess of 12 points MCII. There were no between-group differences ($p = 0.607$). KPS scores for this group followed a similar pattern (Table 5). No assessed covariates predicted overall improvement scores.

Participants generally reported consistent improvement across the WOMAC subscales, achieved near-maximum improvement by 24 weeks, and remained stable through 52 weeks. The most dramatic improvements were reported by Prior-Decline participants (Table 4). Regardless of the number of knees injected, KPS-based knee Pain Frequency (9–52 weeks, $p < 0.05$) and Severity (24 and 52 weeks, $p < 0.05$) were also significantly reduced (Table 5).

All injection group participants experienced expected mild-to-moderate postinjection pain. There were no other side-effects or adverse events. Fifty-five percent (55%) of all participants used oxycodone prior to injections, and 54% of all participants used oxycodone after injections. Postprocedure pain decreased from an average of 3.7 ± 1.7 points after injection to 2.5 ± 1.5 points by day 2. Twenty-nine (29) participants would recommend prolotherapy to other KOA patients; 3 were not sure and 3 would not. The use of periprocedural analgesics and satisfaction scores were not different between injection groups.

Qualitative comments showed that some participants reported dramatic improvement of knee-related quality of life by 9 or 12 weeks and subsequently overused their knees in sport or work-related activity. Participants in the Prior-Declined group reported they declined participation in the initial RCT because the impact of KOA on their overall

TABLE 2. BASELINE CHARACTERISTICS ($N=38$)

	Prior-control (n = *18*)	*Prior-declined* (n = *5*)	*Prior-ineligible* (n = *15*)	p-*Value*
Female, *n* (%)	9 (50.0)	1 (20.0)	7 (46.7)	0.482
Age, mean (SD)	57.1 (7.4)	54.8 (7.4)	58.5 (5.8)	0.414
Income				
< $50,000	1 (5.6)	0 (0)	3 (20.0)	
$50,000–$79,000	6 (33.3)	2 (40.0)	5 (33.3)	
$80,000+	11 (61.1)	3 (60.0)	7 (46.7)	0.624
Duration of knee pain, months (SD)	120.3 (101.6)	58.8 (42.9)	80.5 (79.1)	0.267
X-ray Kellgren–Lawrence OA Severity Score (0–4, %) of treated knees				
1–2 (mild OA)	9 (69.2)	2 (66.7)	4 (36.4)	
3–4 (moderate to severe OA)	4 (30.8)	1 (33.3)	7 (63.6)	0.250
BMI (SD)	29.8 (5.9)	26.0 (3.8)	30.9 (5.8)	
≤25	7 (38.9)	2 (40.0)	1 (6.7)	
26–30	3 (16.7)	2 (40.0)	9 (60.0)	
31+	8 (44.4)	1 (20.0)	5 (33.3)	0.074
Diabetes, *n* (%)	1 (5.6)	0 (0)	3 (20.0)	0.332
Prior knee intervention (%)[a]				
Arthroscopic surgery	7 (38.9)	1 (20.0)	6 (40.0)	0.703
Physical therapy	7 (38.9)	1 (20.0)	3 (20.0)	0.478
Hyaluronic acid injection	1 (5.6)	1 (20.0)	0 (0)	0.164
Corticosteroid injection	3 (16.7)	0 (0)	2 (13.3)	0.663
Glucosamine	5 (27.8)	3 (60.0)	8 (53.3)	0.287
WOMAC composite[b]	63.7 (12.6)	45.2 (10.9)	62.6 (13.4)	0.021
Pain	66.7 (14.2)	47.0 (5.7)	66.0 (12.0)	0.065
Stiffness[b]	60.4 (18.8)	37.5 (12.5)	56.7 (20.0)	0.011
Function	63.9 (13.3)	51.0 (17.8)	65.1 (14.5)	0.159

KPS	*Treated* (N = *27*)	*Untreated* (N = *9*)	*Treated* (N = *8*)	*Untreated* (N = *2*)	*Treated* (N = *22*)	*Untreated* (N = *8*)	
Pain frequency (SD)	3.30 (0.78)	1.54 (0.45)	3.67 (0.88)	2.25 (1.77)	3.17 (0.83)	1.88 (1.25)	0.337/0.600[c]
Pain severity (SD)	2.89 (0.88)	1.35 (0.41)	2.96 (1.01)	2.08 (1.53)	2.75 (0.78)	1.69 (0.93)	0.785/0.435[c]

The theoretical range of the WOMAC in this study is from 0 to 100, with higher values indicating better knee-related quality of life. 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.

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

[b]Participants in the Prior-Declined group reported more severe Composite and Stiffness scores than the other two groups. There were no other statistical differences between groups.

[c]Baseline *p*-values for treated participants/baseline *p*-values for untreated participants.

SD, standard deviation; OA, osteoarthritis; BMI, body–mass index; WOMAC, Western Ontario McMaster University Osteoarthritis Index; KPS, Knee Pain Scale.

quality of life was too severe to accept the 67% chance of randomization to Exercise or Saline injection control groups.

Discussion

Participants with KOA in this prospective open-label study treated with a clinically determined prolotherapy protocol using dextrose and morrhuate sodium reported substantial, consistent improvement in knee pain, function, and stiffness at 52 weeks. The 12.4–19.4-point improvement in composite WOMAC scores exceeded reported MCII,[24] the smallest change in measurement signifying an important symptomatic improvement. MCII varies by KOA severity; patients with more severe KOA require more improvement to report a meaningful change. Participants in the Prior-Declined group, whose baseline WOMAC scores were the most severe, improved the most and met MCII improvement criteria for patients with severe KOA.[25] In all three groups, improvement was generally progressive in composite and subscale WOMAC scores through 52 weeks.

We did not find, nor did we expect, longitudinal differences between groups because each received active therapy. KPS ''per knee'' results were consistent with WOMAC findings. In general, there was a slight dip in some WOMAC measures at 12 or 24 weeks; scores rebounded by 52 weeks, perhaps because some participants overused their knees following substantial improvement earlier in the study.

TABLE 3. PROLOTHERAPY SOLUTION TYPE PER SESSION NUMBER IN SINGLE AND BILATERALLY TREATED KNEES

	Injection session				
Solution per knee	*1*	*2*	*3*	*4*	*5*
Single knee dextrose	43	21	11	3	1
Single knee morrhuate	0	6	13	17	17
Dextrose bilateral	12	22	8	4	4
Morrhuate bilateral	0	6	20	22	14
Total	55	55	52	46	36

Table 4. Western Ontario McMaster University Osteoarthritis Index Composite and Subscale Scores Over Time

	Pooled RCT exercise and saline injection control			*Current study*					
	Baseline RCT (N=18)	*Week 24 control (N=15)*	*Week 52 control (N=17)*	*Baseline case 5 Prior-Control (N=18) Prior-Decline (N=5) Prior-Ineligible (N=15)*	*Week 5 Prior-Control (N=18) Prior-Decline (N=4) Prior-Ineligible (N=15)*	*Week 9 Prior-Control (N=18) Prior-Decline (N=4) Prior-Ineligible (N=15)*	*Week 12 Prior-Control (N=18) Prior-Decline (N=4) Prior-Ineligible (N=15)*	*Week 24 Prior-Control (N=17) Prior-Decline (N=4) Prior-Ineligible (N=15)*	*Week 52 Prior-Control (N=17) Prior-Decline (N=4) Prior-Ineligible (N=14)*
WOMAC Composite score change, mean (SE)									
Prior-Control	61.9 (3.5)	69.9 (3.7)	68.4 (3.6)	63.7 (3.5)	66.6 (3.5)	72.6 (3.5)	69.4 (3.5)	71.4 (3.6)	76.1 (3.6)
Prior-Decline				45.2 (6.7)	64.5 (7.3)	70.2 (7.3)	69.3 (7.3)	63.6 (7.3)	64.6 (7.3)
Prior-Ineligible				62.6 (3.9)	63.7 (3.9)	76.3 (3.9)	73.1 (3.9)	75.0 (3.9)	80.4 (3.9)
Subscale score change, mean (SE)									
Pain									
Prior-Control	65.3 (3.8)	72.1 (4.0)	72.6 (3.8)	66.7 (3.8)	67.5 (3.8)	75.6 (3.8)	73.3 (3.8)	75.5 (3.8)	78.2 (3.8)
Prior-Declined				47.0 (7.2)	67.3 (7.8)	69.8 (7.8)	72.3 (7.8)	66.0 (7.8)	67.3 (7.8)
Prior-Ineligible				66.0 (4.1)	67.3 (4.1)	79.3 (4.1)	77.0 (4.1)	76.7 (4.1)	80.0 (4.1)
Stiffness									
Prior-Control	55.6 (4.8)	63.2 (4.5)	64.0 (4.5)	60.4 (4.3)	62.5 (4.3)	66.7 (4.3)	61.8 (4.3)	64.0 (4.3)	72.5 (4.3)
Prior-Declined				37.5 (8.1)	54.8 (8.9)	67.3 (8.9)	64.2 (8.9)	57.9 (8.9)	57.9 (8.9)
Prior-Ineligible				56.7 (4.7)	55.8 (4.7)	70.0 (4.7)	68.3 (4.7)	70.8 (4.7)	75.3 (4.7)
Function									
Prior-Control	64.9 (3.8)	74.7(4.0)	68.7 (3.8)	63.9 (3.8)	69.7 (3.8)	75.5 (3.8)	73.0 (3.8)	74.7 (3.8)	77.6 (3.8)
Prior-Declined				51.0 (7.1)	71.6 (7.8)	73.8 (7.8)	71.6 (7.8)	66.9 (7.8)	68.6 (7.8)
Prior-Ineligible				65.1 (4.2)	68.0 (4.2)	79.4 (4.2)	74.6 (4.2)	77.4 (4.2)	81.9 (4.2)

Repeated-measures analysis of variance compared between-group total and subscale WOMAC scores.

Prior-Control participants reported greater WOMAC score change in the active portion of the study than in the control portion ($p=0.20$) compared to Control portion ($p=0.002$ compared to baseline of Active portion). Compared to baseline scores, participants in the Prior-Control ($p=0.002$), Prior-Decline ($p=0.05$), and Prior-Ineligible ($p=0.008$) reported improved WOMAC scores.

RCT, randomized controlled trial; SE, standard error.

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

	RCT waitlist and placebo injection control			*Current study*					
	Baseline RCT control (N=27)	*Week 24 RCT control (N=24)*	*Week 52 RCT control (N=26)*	*Baseline Prior-Control (N=27) Prior-Decline (N=8) Prior-Ineligible (N=22)*	*Week 5 Prior-Control (N=27) Prior-Decline (N=6) Prior-Ineligible (N=22)*	*Week 9 Prior-Control (N=27) Prior-Decline (N=6) Prior-Ineligible (N=22)*	*Week 12 Prior-Control (N=27) Prior-Decline (N=6) Prior-Ineligible (N=22)*	*Week 24 Prior-Control (N=26) Prior-Decline (N=6) Prior-Ineligible (N=22)*	*Week 52 Prior-Control (N=25) Prior-Decline (N=6) Prior-Ineligible (N=21)*
KPS Pain Frequency mean (SE) [*N*]									
Prior-Control	3.2 (0.2)	2.8 (0.2)	3.0 (0.2)	3.3 (0.2)	3.2 (0.2)	2.8 (0.2)	3.0 (0.2)	2.9 (0.2)	2.8 (0.2)
Prior-Decline				3.7 (0.3)	2.5 (0.4)	2.8 (0.4)	2.6 (0.4)	3.1 (0.4)	3.5 (0.4)
Prior-Ineligible				3.2 (0.2)	2.8 (0.2)	2.4 (0.2)	2.6 (0.2)	2.6 (0.2)	2.5 (0.2)
KPS Pain Severity mean (SE)									
Prior-Control	2.6 (0.2)	2.4 (0.2)	2.9 (0.2)	2.9 (0.2)	2.6 (0.2)	2.2 (0.2)	2.3 (0.2)	2.1 (0.2)	2.0 (0.2)
Prior-Declined				3.0 (0.3)	2.2 (0.3)	2.1 (0.3)	2.0 (0.3)	2.6 (0.3)	2.5 (0.3)
Prior-Ineligible				2.8 (0.2)	2.4 (0.2)	2.0 (0.2)	2.0 (0.2)	2.1 (0.2)	1.9 (0.2)

Repeated-measures analysis of variance compared between-group KPS scores.
Nine Prior-Control participants had both knees treated (18 knees) and 9 participants had one knee treated, resulting in a total of 27 individual knees for the KPS analysis.
Three Prior-Decline participants had both knees treated (6 knees) and 2 participants had one knee treated, contributing 8 individual knees to the KPS analysis.
Seven Prior-Ineligible participants had both knees treated (14 knees) and 8 participants had one knee treated, contributing 22 individual knees to the KPS analysis.
SE, standard error.

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 treatment.

The improvement in WOMAC scores are consistent with those in two prior KOA studies using similar injection protocols and reported positive outcomes compared to baseline[12] and control status.[13] The current study adds three important findings. First, participants with mild-to-moderate (Prior-Control and Prior-Ineligible) and moderate-to-severe KOA (Prior-Declined) progressively selected the two-solution injectant over dextrose alone and met general MCII improvement criteria, suggesting that the current injection protocol effectively improves WOMAC and KPS-based outcomes. Second, it does so in a more generalizable population than reported in prior studies.[13] Third, improvement was also reported by the most severe group (Prior-Declined) of participants. The use of pre- and postinjection opioid pain therapy, injection-related pain, and overall satisfaction was similar to prior studies,[13] suggesting that this two-solution injectant is not substantively more painful.

Our current findings are also consistent with a third prolotherapy study for KOA, though comparison is limited by methodological heterogeneity.[8] Direct comparison to studies assessing hyaluronic acid injection and other therapies is also limited by the heterogeneity of study eligibility criteria, overall health status, patient expectation, baseline KOA severity,[20] and WOMAC scoring methodology,[26] but improvements of 20%–40% compared to baseline have been reported.[5]

Prolotherapy is an evolving modality gaining popularity in rehabilitation, sport, and family medicine; its mechanism of action is not known and likely multifactorial.[6] Dextrose and morrhuate sodium may have independent biological actions; two recent RCTs report outcomes favoring prolotherapy compared to blinded saline injections using a combined solution[15] and dextrose alone.[23] Proposed biological mechanisms of action have been reviewed.[6] Dextrose injections may stimulate healing of chronically injured intra- and extra-articular tissue[27]; animal model studies reported increased inflammatory markers[28] and enlarged cross-sectional area in medial collateral ligaments compared to saline injections ($p < 0.05$).[29] Morrhuate sodium is a sclerosing agent reported to produce a robust inflammatory response[28] and stronger medial collateral ligaments in animal models.[30,31] The combined effect of the two agents has not been assessed in basic science studies, prior studies have not optimized concentration of either dextrose or morrhuate sodium, and no governing body has published guidelines for optimal concentrations of these injectants. The injectant concentration and protocol used in the current study are consistent with those used in the prolotherapy community. The potential of prolotherapy to stimulate release of growth factors promoting soft-tissue healing and a positive neural effect have also been suggested.[32,33] Needle trauma and volume expansion of local tissue may also produce a tissue-level effect.[34] The combined effects of needle trauma, volume expansion, and dextrose and morrhuate-specific mechanisms may explain positive findings for prolotherapy in this study.

Limitations and Strengths

Limitations of this study include modest sample size and nonrandomized methodology. Participants were recruited from multiple sources whose baseline circumstances and severity were dissimilar; however, participant diversity was appropriately assessed within the analytic frame. Baseline diversity may add to the overall generalizability of these results. 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 but is likely to remain an important measure for gauging disease severity in symptomatic patients.[35] The enrollment of 18 participants who had completed a prior prolotherapy trial as control participants may have introduced bias, though analysis of recruitment source did not reveal significant covariance. 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 with a combined solution of dextrose and morrhuate sodium 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.

Conclusions

Prolotherapy with dextrose and morrhuate sodium resulted in substantial, significant, and sustained improvement on validated pain, function, and stiffness measures in participants with mild-to-severe KOA compared to baseline status. Prolotherapy performed by a trained operator may be an appropriate therapy for selected patients who have moderate-to-severe KOA and who are refractory to conservative care.

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Disclosure Statement

No competing financial interests exist.

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