The Efficacy of Prolotherapy for Lateral Epicondylosis: A Pilot Study

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Objectives: To assess whether prolotherapy, an injection-based therapy, improves elbow pain, grip strength, and extension strength in patients with lateral epicondylosis.

Setting: Outpatient Sport Medicine clinic.

Study Design: Double-blind randomized controlled trial.

Participants: Twenty-four adults with at least 6 months of refractory lateral epicondylosis.

Intervention: Prolotherapy participants received injections of a solution made from 1 part 5% sodium morrhuate, 1.5 parts 50% dextrose, 0.5 parts 4% lidocaine, 0.5 parts 0.5% sensorcaine and 3.5 parts normal saline. Controls received injections of 0.9% saline. Three 0.5-mL injections were made at the supracondylar ridge, lateral epicondyle, and annular ligament at baseline and at 4 and 8 weeks.

Outcome Measures: The primary outcome was resting elbow pain (0 to 10 Likert scale). Secondary outcomes were extension and grip strength. Each was performed at baseline and at 8 and 16 weeks. One-year follow-up included pain assessment and effect of pain on activities of daily living.

Results: The groups were similar at baseline. Compared to Controls, Prolotherapy subjects reported improved pain scores (4.5 ± 1.7, 3.6 ± 1.2, and 3.5 ± 1.5 versus 5.1 ± 0.8, 3.3 ± 0.9, and 0.5 ± 0.4 at baseline and at 8 and 16 weeks, respectively). At 16 weeks, these differences were significant compared to baseline scores within and among groups ($P < 0.001$). Prolotherapy subjects also reported improved extension strength compared to Controls ($P < 0.01$) and improved grip strength compared to baseline ($P < 0.05$). Clinical improvement in Prolotherapy group subjects was maintained at 52 weeks. There were no adverse events.

Conclusions: Prolotherapy with dextrose and sodium morrhuate was well tolerated, effectively decreased elbow pain, and improved strength testing in subjects with refractory lateral epicondylosis compared to Control group injections.

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INTRODUCTION

Lateral epicondylosis (LE), commonly known as tennis elbow, is an important condition of the upper extremity with an incidence of 4 to 7/1000 patients per year in primary care settings.[1–3] Its greatest impact is on workers with repetitive and high-load upper extremity tasks and on athletes. The most common cause of LE may be low-load, high-repetition activities such as keyboarding, though formal data are lacking.[4] Cost and time away from job or activity are significant.[5,6] The term "lateral epicondylitis" is often used indiscriminately to refer to chronic overuse lateral elbow injury. However, the vast majority of overuse tendon injuries, including LE, show no histopathologic evidence of inflammatory cells. Rather, they are chronic degenerative conditions. Therefore, "lateral epicondylosis" is the preferred term.[7–9] Although many nonsurgical therapies have been tested for LE refractory to conservative measures, none have been shown to be uniformly effective in the long term.[10–12]

Prolotherapy (PrT) is an injection-based treatment for chronic musculoskeletal pain, including tendinopathy. Dextrose (a form of glucose) and sodium morrhuate (an extract of cod liver oil) are two common PrT injectants.[13,14] Animal model studies suggest PrT using dextrose and sodium morrhuate may enlarge and strengthen ligament and tendon insertions, though the precise mechanism is unclear[15–17] (unpublished data; Jensen, 2007). Injection protocols were formalized in the 1950s by George Hackett, a general surgeon in the United States.[18] Treatment generally includes injection of tender tendon and ligament attachments (entheses[19]) with small volumes of proliferant solution in 3–6 treatment sessions at monthly intervals.[18,20] Anecdotal reports indicate PrT is used in sport medicine and primary care practices for a variety of musculoskeletal conditions, including refractory lateral and medial epicondylosis[21,22] (unpublished data, Rabago). Several human randomized controlled trials (RCTs) assessing PrT have reported positive outcomes for low back pain compared to baseline status[23] and to Control group subjects,[24,25] and for osteoarthritis,[26,27] though methodological quality has varied.[14,28] No RCT has assessed PrT for any tendinopathy. We therefore conducted a double-blind RCT to test the hypotheses

that PrT decreases elbow pain, improves resting grip strength, and improves isometric elbow extension strength in adults with LE refractory to standard of care therapy.

METHODS

The study protocol was approved by the institutional review board of Trinity Health Systems, Steubenville, Ohio. Subjects were enrolled and treated from 1999 to 2002. Each subject was treated with blinded injections over an 8-week period, seen for in-person follow-up over 16 weeks, and was interviewed by telephone at 1 year. No RCTs of PrT for tendinopathy existed before the start of the current RCT, therefore we had no reported effect size of PrT for LE on which to base sample size calculations. A well done RCT reported an effect size of PrT for low back pain of 20% to 40% compared to baseline pain and disability conditions,[23] which is less than that observed in the lead author's (MS) clinical practice using PrT for LE. Final sample size for the current study reflected the assumption that we would improve on effect size for PrT seen in low back pain.

Eligibility Criteria and Subject Recruitment

The recruitment and subject participation scheme is shown in Figure 1. Adult patients (age, 18 to 65 years) were recruited from the sport medicine practice of the lead author (MS). Inclusion criteria were a diagnosis of LE and elbow pain for at least 6 months and failure of each of the following conservative care modalities: relative rest, physical therapy, nonsteroidal antiinflammatory drugs, and 2 corticosteroid injections. Exclusion criteria included diabetes, corticosteroid elbow injection within 6 weeks, and self-reported immunocompromised status. Eligible patients heard a brief explanation of PrT and were invited to participate. Thirty-four subjects who met initial clinical inclusion criteria were approached by study personnel; 26 were found to be eligible and were offered participation. Of these, 2 declined participation and 24 consented and were randomized to PrT or control injection groups. The 1:1 randomization scheme was prepared by the lead pharmacist of Trinity Health Systems; group assignment was determined by random number table and administered using sealed envelopes.

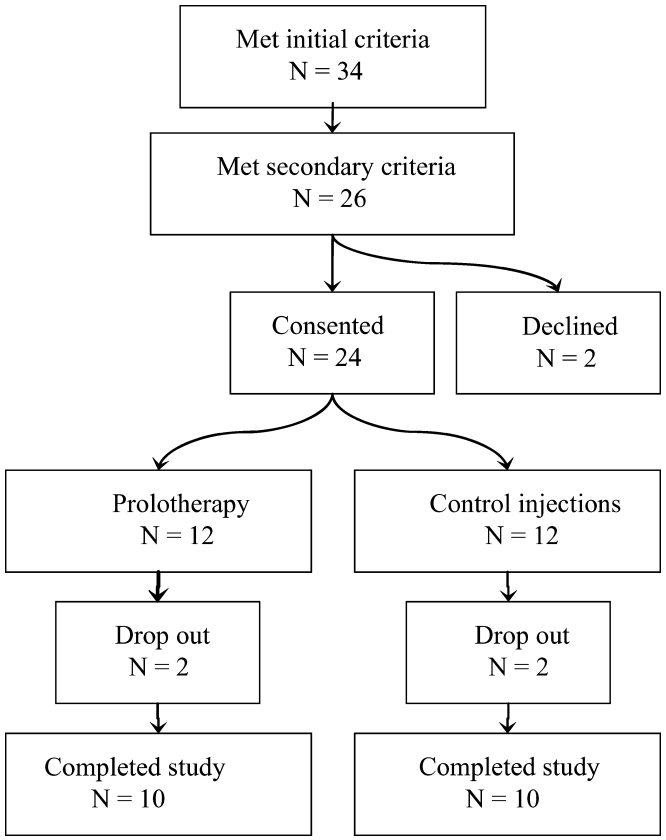

FIGURE 1. Subject participation.

Interventions

Participants in the PrT group received injections of solution consisting of 50% dextrose, 5% sodium morrhuate and 4% lidocaine, and 0.5% sensorcaine. The study pharmacist mixed the following 35-mL sterile solution: 7.5 mL of 50% dextrose, 5 mL of 5% sodium morrhuate, 2.5 mL of 4% lidocaine, 2.5 mL of 0.5% sensorcaine, and 17.5 mL of normal saline. The solution is 10.7% dextrose and contains 14.7% sodium morrhuate by volume. The Control solution was normal saline. The syringe was blinded with an opaque paper sleeve. Using a 25 gauge 1.5-inch needle, the lead author injected 0.5 mL of either PrT or control solution into tendon insertions, with needle touching bone, at the supracondylar ridge, lateral epicondyl, and the annular ligament for a total of 1.5 mL. A peppering technique was not used. Injections occurred at baseline and at 4 and 8 weeks. The week 8 injection set occurred after the administration of the 8-week questionnaire. Neither prolotherapist nor participant was informed of group status during the study. Topical analgesia was not used. Participants in both groups were discouraged from using nonsteroidal anti-inflammatory medications and starting new therapies.

Outcome Measures

The outcome measures for all subjects were identical and were assessed at baseline and at 8, 16, and 52 weeks. The primary outcome was resting elbow pain recorded on a 0 to 10 Likert scale. Secondary outcomes included resting grip strength, isometric resistance strength, and follow-up questions at 52 weeks. Resting grip strength was assessed by a Jamar dynamometer[29,30] using a single grip at each of 5 different cylindrical diameters from 3.6 to 8.8 cm squeezed for 3 to 5 seconds with 60 seconds between grips. Isometric resistance strength was tested with the Baltimore Therapeutic Equipment Primus (BTE)[31] device using a single measurement with the wrist in extension, thumb up in neutral orientation, and the elbow flexed at 90 degrees. An isometric force was then applied by the subject and measured by the BTE. Pretreatment and posttreatment magnetic resonance images were obtained at baseline and at 16 weeks; however, these data are not retrievable from the optical disk on which they were stored and were assumed to be permanently unavailable. At 52 weeks, subjects were asked (by telephone) 3 follow-up questions: how much elbow pain they had (none, mild, moderate, or severe), whether elbow pain

affected their ability to perform activities of daily living (ADL) (Yes or No), and whether they used other therapies for pain since completion of injections (Yes or No).

Analyses

Randomization effects were assessed by comparing baseline characteristics of PrT and Control groups (n = 24). Two subjects from each group dropped out of the study before any follow-up data were collected (described in Results). Therefore, the analysis of treatment effects included 20 subjects with 10 in each group.

The 20 subjects were analyzed according to their randomized allocation. All subjects attended each of 3 injection sessions. Among collected data for 20 subjects, there was 1 missing quantitative value (isometric resistance strength at 16-week follow-up) in the Control group; the imputation technique of "last observation carried forward" was used for this missing value.[32]

Data were entered into the Excel database and analyzed with SPSS version 14.0 statistical software.[33] Descriptive statistics were used to describe baseline characteristics of the sample. Quantitative data were assessed using repeated measures analysis of variance[34–36] to test the primary and secondary hypotheses within and between groups (n = 20) at all time points. Differences between the 2 groups were then assessed with *t* test (paired or independent samples for within-group and between-group comparisons, respectively). Statistical significance was assessed using 2-tailed tests ($P < 0.05$). Analysis of the 52-week follow-up questions was by inspection.

RESULTS

The study sample consisted of 24 white adults (13 women, 11 men) randomized to PrT (n = 12) and Control (n = 12) groups. Subjects' ages ranged from 19 to 62 years, with a mean age of 45.7 ± SD 10.7 years. Duration of elbow pain ranged from 0.5 years to 10 years (±SD: 1.9 ± 2.7 years in the sample; 1.1 ± 1.1 years and 2.7 ± 3.5 years for the Control and PrT groups, respectively, $P = 0.2$). Baseline demographics, pain, and function scores were comparable between the 2 groups. Two subjects in each group dropped out of the study after baseline data collection but before any injections had been performed. These 4 subjects were not significantly different at baseline from subjects who received injections, with the exception of age; one of the drop-outs was significantly younger (19 years old) than the rest of the subjects (minimum age was 33 among the rest of 23 subjects). Among these early drop-outs, one PrT subject dropped out before baseline data collection, and 3 subjects (1 PrT, 2 Control) dropped out due to pain after baseline data collection but before any injections. They went on to pursue surgery and were lost to follow-up. No follow-up data were collected about these 4 drop-outs. Therefore, the subsequent analyses of treatment effects were performed for 20 subjects who received injections and completed follow-up outcome questionnaires. Among 20 analyzed subjects, 1 Control subject moved out of the study area after the 16-week assessment and was not available for the 52-week follow-up.

The 20 analyzed subjects were on average middle-aged (age, 48.0 ± 8.8 years) and suffered from moderate resting elbow pain (4.8 ± 1.3 points at rest). No significant baseline differences were found between the PrT (n = 10) and Control (n = 10) groups (Table 1).

Over time, PrT group subjects, but not Control group subjects, showed a significant improvement in pain scores (mean ± SD: 5.1 ± 0.8, 3.3 ± 0.9, and 0.5 ± 0.4 versus 4.5 ± 1.7, 3.6 ± 1.2, and 3.5 ± 1.5 at baseline and at 8 and 16 weeks, respectively) (Figure 2, a and b). The PrT group subjects' pain scores at 16 weeks significantly improved when compared both to their own baseline ($P < 0.001$) and to the Control group subjects' scores ($P < 0.001$). All 10 subjects in the PrT group reported that their pain score was 1 point or less at 16 weeks. No Control group subjects reported scores of 1 point or less at 16 weeks. Control group subjects did not significantly change their pain scores over the 16-week period (Table 2). The statistical effect size (Cohen's *d*) of the PrT treatment on

TABLE 1. Baseline Subject (n = 20) Characteristics. Results Presented for the Control and Prolotherapy Groups and for the Whole Sample (Total) as Number (percentage) or Mean Value (Standard Deviation, SD)

	Control (n = 10)	Prolotherapy (n = 10)	Total (n = 20)
Female, n (%)	4 (40)	6 (60)	10 (50)
Age, years, mean (SD)	47.7 (8.6)	48.2 (9.5)	48.0 (8.8)
Duration of elbow pain, years (SD)	1.1 (1.1)	2.7 (3.5)	1.9 (2.7)
Pain at rest, points, mean (SD)*	4.5 (1.7)	5.1 (0.8)	4.8 (1.3)
Isometric strength, lbs, mean (SD)†	10.7 (8.2)	13.3 (6.7)	12.0 (7.4)
Grip strength 1, lbs, mean (SD)‡	32.2 (17.0)	30.7 (18.5)	31.5 (17.3)
Grip strength 2, lbs, mean (SD)‡	49.0 (22.6)	37.6 (20.1)	43.3 (21.6)
Grip strength 3, lbs, mean (SD)‡	45.4 (23.1)	39.5 (23.2)	42.5 (22.7)
Grip strength 4, lbs, mean (SD)‡	38.8 (20.5)	34.7 (21.3)	36.8 (20.4)
Grip strength 5, lbs, mean (SD)‡	32.8 (20.6)	29.8 (18.0)	31.3 (18.9)
Grip strength 1–3, lbs, mean (SD)‡	42.2 (20.0)	35.9 (19.3)	39.1 (19.4)
Grip strength 4–5, lbs, mean (SD)‡	35.8 (20.4)	32.3 (19.4)	34.0 (19.5)

No statistically significant differences were detected between groups (ANOVA or chi-square test). *Pain at rest was assessed with 0 to 10 Likert scale. †Isometric strength was assessed by Baltimore Therapeutic Equipment Primus device and measured in pounds (lbs). ‡Grip strength, assessed by Jamar grip strength device and measured in pounds (lbs); a single grip was assessed at 5 different diameters. Grip 1–3 and Grip 4–5 are grip strength averages.

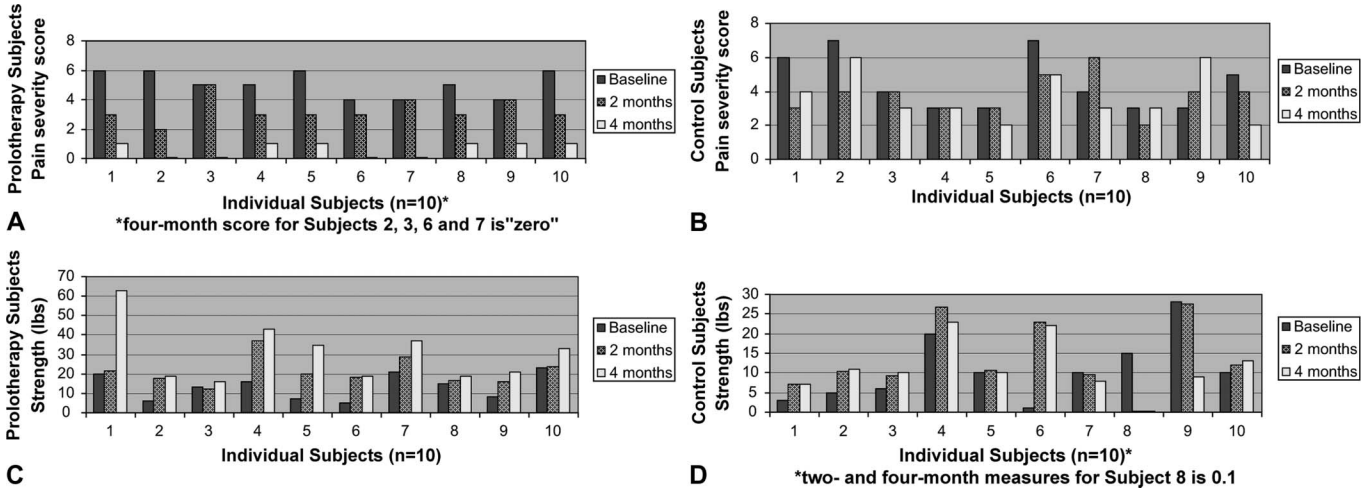

FIGURE 2. A, Prolotherapy group pain severity scores at baseline, 2 and 4 months. B, Control group pain severity scores at baseline, 2 and 4 months. C, Prolotherapy group isometric resistance strength at baseline, 2 and 4 months. D, Control group pain severity scores at baseline, 2 and 4 months.

the pain score was 6.67, corresponding to a large effect size; the absolute effect size was 3.6 points on the 0 to 10 pain scale. The number needed to treat to achieve a 2-point improvement on a 0 to 10 Likert pain scale was 1.4.

Similarly, scores for isometric strength testing showed significant improvement in the PrT group, increasing from 13.3 ± 6.7 lbs at baseline to 21.1 ± 7.2 and 30.5 ± 14.8 lbs at 8 and 16 weeks, respectively. The change in PrT group isometric strength was significant when compared to both PrT baseline scores ($P < 0.01$) and between Control and PrT groups at 16 weeks ($P < 0.01$). Control group subjects did not make significant isometric strength gains over time (Table 2; Figure 2, c and d).

Grip strength data were less definitive. PrT group subjects did not significantly differ from Control group subjects at any time point for any individual grip diameter or the average of grips 1–3 and 4–5. Compared to their own baseline, grip strength in both groups improved over 8 and 16 weeks ($P < 0.05$). However, grip strength improvement among Control group subjects plateaued at 8 weeks, while it continued to improve among PrT group subjects at 16 compared to 8 weeks ($P < 0.05$). There was high variability throughout the grip strength data. No demographic variable predicted differences in follow-up scores.

At the 52-week follow-up, 60% (n = 6) of PrT group subjects reported "no elbow pain or impact on ADLs," 20% (n = 2) reported "mild pain with no impact on ADLs," and 20% (n = 2) reported "mild pain and disability with extreme grip only, and modest impact on ADLs." None of the PrT group subjects reported using or seeking additional therapy. Fifty-two–week follow-up data on 1 of the Control group subjects was not available due to loss to follow-up; 10% (n = 1) of the Control group subjects had no elbow pain, and 80% (n = 8) reported elbow pain sufficient to interfere with ADLs at 52 weeks. Among 9 Control group subjects, 4 reported using additional therapies (surgery, 2; extracorporeal shock wave therapy, 1; acupuncture, 1).

Side effects of injection therapy were minimal. All subjects (n = 20) experienced expected, self-limited post-injection pain; two PrT group subjects experienced 1 episode each of local erythema, irritation, and discomfort approximately 1 day after injection. These symptoms resolved with acetaminophen with codeine. This is consistent with an anecdotally reported occurrence rate (approximately 10%) of self-limited post-injection pain flares. There were no allergic reactions to sodium morrhuate.

DISCUSSION

This RCT reports significant reduction in pain and improved isometric strength scores in subjects with refractory LE treated with PrT using dextrose and sodium morrhuate compared to control injections. It provides level 1B evidence (high-quality RCT in a setting of fewer than 2 consistent RCTs evaluating patient-oriented evidence)[37] that PrT is an effective therapy for LE. This is the first RCT to report such findings for PrT as a treatment for any tendinopathy. Dextrose is the most commonly used PrT injectant[13] (unpublished data, Rabago, 2006). Although sodium morrhuate is often clinically used in prolotherapy procedures[13] (unpublished data, Rabago, 2006) and its use has been reported in a case series,[38] this is the first RCT to report the use of sodium morrhuate as a treatment for any tendinopathy. Pain scores and isometric strength testing are accepted clinical outcome measures of musculoskeletal conditions, including LE. While the Cohen's *d* of 6.7 suggests a statistically large effect size, the minimal clinically important difference for elbow pain is not established. However, a recent review concluded that a reduction of 2 points on a 0 to 10 Likert scale corresponded to a significant clinical difference across a variety of chronic pain conditions.[39] The difference between PrT group and Control group pain scores (absolute effect size) in the current study is 3.6 points at 16 weeks, a greater than 50% improvement compared to both baseline and Control group, suggesting a very meaningful clinical

TABLE 2. Primary and Secondary Outcomes: Pain Scores, Grip Strength, and Isometric Strength of Prolotherapy (PrT) and Control (Ctl) Groups at Baseline (0) and at 8 and 16 Weeks. Results are Presented as Mean Value (Standard Deviation, SD)

Variable	Group	Baseline (0 weeks)	8 weeks	*P* (8 versus 0 weeks)†	16 weeks	*P* (16 versus 0 weeks)†	*P* (16 vs. 8 weeks)†
Pain, points, mean (SD)‡	Ctl	4.5 (1.7)	3.6 (1.2)	NS	3.5 (1.5)	NS	NS
	PrT	5.1 (0.8)	3.3 (0.9)	0.004	0.5 (0.4)	<0.001	<0.001
	*P**	NS	NS		<0.001		
Isometric strength, lbs, mean (SD)§	Ctl¶	10.3 (8.6)	15.1 (8.1)	NS	11.3 (6.8)	NS	NS
	PrT	13.3 (6.7)	21.1 (7.2)	<0.01	30.5 (14.8)	<0.01	<0.05
	*P**	NS	0.06		<0.01		
Grip strength 1, lbs, mean (SD)¶	Ctl	32.2 (17.0)	51.3 (24.7)	<0.05	59 (34.5)	<0.01	0.06
	PrT	30.7 (18.5)	43.3 (17.3)	NS	55.6 (18.6)	<0.01	<0.05
	*P**	NS	NS		NS		
Grip strength 2, lbs, mean (SD)¶	Ctl	49 (22.6)	79.8 (38.6)	<0.05	80 (39.5)	<0.05	NS
	PrT	37.6 (20.1)	59.3 (27.5)	0.06	70 (26.3)	<0.01	0.06
	*P**	NS	NS		NS		
Grip strength 3, lbs, mean (SD)¶	Ctl	45.4 (23.1)	77.3 (36.9)	<0.05	76.4 (37.2)	<0.05	NS
	PrT	39.5 (23.2)	59.8 (21.6)	<0.05	66 (23.2)	<0.01	NS
	*P**	NS	NS		NS		
Grip strength 4, lbs, mean (SD)¶	Ctl	38.8 (20.5)	69.3 (29.4)	<0.01	70.1 (32.5)	<0.05	NS
	PrT	34.7 (21.3)	52.1 (22.4)	<0.05	63.3 (23.5)	<0.01	<0.05
	*P**	NS	NS		NS		
Grip strength 5, lbs, mean (SD)¶	Ctl	32.8 (20.6)	59.6 (30.2)	<0.05	63.1 (29.9)	<0.01	NS
	PrT	29.8 (18.0)	46.4 (23.9)	<0.05	54.2 (23.4)	<0.01	<0.05
	*P**	NS	NS		NS		
Grip strength 1-3, lbs, mean (SD)¶	*Ctl*	42.2 (20.0)	69.5 (32.3)	<0.05	71.8 (35.7)	<0.05	NS
	PrT	35.9 (19.3)	54.1 (21.4)	0.06	63.9 (22.3)	<0.01	<0.05
	*P**	NS	NS		NS		
Grip strength 4-5, lbs, mean (SD)¶	Ctl	35.8 (20.4)	64.5 (29.6)	<0.01	66.6 (31.2)	<0.05	NS
	PrT	32.3 (19.4)	49.3 (22.9)	<0.05	58.8 (23.3)	<0.01	<0.05
	*P**	NS	NS		NS		

*Difference between the experimental (PrT) and Control (Ctl) groups at the same time points (independent-samples *t* test). †Differences within the group across different time points (paired-samples *t* test). ‡Pain at rest assessed with 0 to 10 Likert scale. §Isometric strength assessed by Baltimore Therapeutic Equipment Primus device and measured in pounds (lbs). ¶Grip strength assessed by Jamar grip strength device and measured in lbs; a single grip was assessed at 5 different diameters. Grip 1–3 and Grip 4–5 are grip strength averages. ||The control group had 1 missing value set, grip strength at 16-week follow-up.

effect. Indeed, the number needed to treat to achieve a 2-point improvement on a 0 to 10 Likert pain scale using PrT in this study is 1.4. The pain score of 4 of 10 PrT group subjects at 16 weeks was 0.

That both groups improved in grip strength suggests that clinical improvement may have been related to the passage of time, needle effects, or the placebo effect. However, the fact that Control group subjects seemed to plateau at 16 weeks at some Jamar diameters suggests that PrT also played a role in the improvement of grip strength. Grip strength data may also reflect unaddressed muscle-tendon unit deconditioning. Subjects were not prescribed formal physical therapy after injection therapy.

The positive effect of PrT compared to baseline status and to Control group subjects is consistent with findings from studies evaluating related injection therapies for tendinopathy. Lyftogt used 20% dextrose in a study assessing PrT as a treatment for Achilles tendinopathy.[40] In this study, Doppler ultrasound-guided PrT injections were used to target and sclerose pathologic "neovessels" associated with tenderness.[41] Connel et al[42] and Mishra et al[43] used autologous blood and platelet-rich plasma, respectively, as injectant for LE; they used a peppering technique to fenestrate the tissue before injection and an injection technique otherwise similar to the current study. These studies reported dramatic improvement in pain compared to baseline. Pain reduction was hypothesized to be related to the elimination of nerve fibers that are associated with neovessels[41] or collagen fibril disruption and subsequent healing response.[42,43]

Improved outcomes in the current study may accrue from effects hypothesized in both the above studies. First, concentrated dextrose and sodium morrhuate have sclerosant qualities[44,45]; at high concentrations, sodium morrhuate in vitro is toxic to granulocytes, red blood cells, and endothelial cells.[46] This study used a relatively low concentration of dextrose (10.7%) for PrT, although 10% has been reported in an RCT setting.[26] Stock 5% sodium morrhuate was used at 14.7% by volume in this study. This is a relatively high concentration of sodium morrhuate compared to anecdotally reported injection practices (5% to 20% by volume; personal communication, Jeff Patterson, 2007), though no rigorous assessment of injection patterns has been reported in existing surveys of PrT practice patterns[13] (unpublished data, Rabago, 2006). When used to destroy neovessels in a procedure very similar to PrT the sclerosant polidocanol has been reported to reduce pain in lateral epicondyle,[41,47] patellar,[48] and Achilles[49]

tendinopathies. Injections with dextrose and sodium morrhuate may have sclerosed neovessels and associated new nerves, although we did not attempt to visualize neovascularity using ultrasound. Second, bleeding from needle trauma and tissue expansion in the potential space adjacent to tendon insertions may mimic the effect of fenestration and autologous blood injections reported in the Connel and Mishra studies. Finally, dextrose and sodium morrhuate have been shown to affect the strength[15] and size (unpublished data, Jensen, 2007) of stretch-injured ligaments in an animal model, perhaps by an inflammatory mechanism. Given that tendinopathies at various anatomical sites likely share pathophysiological mechanisms, PrT may be relevant treatment for tendinopathy other than LE.

There are several limitations of this pilot study. Excluding the 4 randomized drop-outs in the outcome analysis could have introduced bias; however, there are circumstances in which exclusion of drop-outs is appropriate.[50] In the current study this was justified because (1) the loss to follow-up was balanced in each group; (2) the 4 subjects were statistically similar at baseline to the 24-member cohort as a whole; (3) the loss to follow-up occurred before any follow-up data were collected; and (4) imputation is not justified when missing data would compromise the overall analysis. We did not use a validated disease-specific questionnaire as the primary outcome, although the 0 to 10 Likert scale is a standard measure of chronic pain.[39] A formal assessment of operator blinding was not performed, although the syringe was blinded and the operator (MS) was not consciously aware of group status. Control solution and PrT injectants are clear. Sodium morrhuate in high concentration has a slightly yellow tint and is slightly more viscous than saline. These issues are unlikely to affect blinding in the setting of prefilled blinded syringes. Grip strength assessment may have been compromised by nonstandard technique; accuracy and reliability are enhanced when subjects perform grip testing 3 times at a given diameter.[30] Future studies should include a strength rehabilitation program after pain control is achieved. One-year follow-up questions were nonstandard and, though clinically relevant, were difficult to relate to the quantitative data. The PrT solution contained local anesthetics, but the Control solution did not, which could have influenced the treatment effect. This discrepancy may also have affected blinding because Control group subjects may have experienced greater post-injection pain than PrT group subjects, although this was not observed by the injector. Strengths include double-blind design, multiple standard, patient-oriented assessments, minimal missing data and a large, consistent effect size for pain and isometric strength in the PrT group compared to the Control group.

CONCLUSIONS

Prolotherapy with dextrose and sodium morrhuate was well tolerated and dramatically improved pain and isometric resistance strength compared to control injections. The number needed to treat to achieve a 2-point improvement on a 0 to 10 Likert pain scale was 1.4. This study provides level 1b evidence that PrT is an effective treatment for refractory LE.[37] Further research in a larger more tightly controlled study, using Doppler ultrasound, with study arms including other injectants is warranted. Prolotherapy performed by a trained operator is a reasonable therapeutic option for patients with refractory LE.

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