Prolotherapy Versus Corticosteroid Injections for the Treatment of Lateral Epicondylosis: A Randomized Controlled Trial

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Objective: To compare the efficacy of prolotherapy versus corticosteroid injection for the treatment of chronic lateral epicondylosis.

Design: A prospective, randomized controlled, double-blinded study.

Setting: Academic, tertiary, outpatient, rehabilitation hospital.

Participants: Twenty-four subjects with clinically determined chronic (ie, lasting 3 months or longer) lateral epicondylosis were recruited. All subjects noted pain intensity levels significant enough to prevent the participation in activities, such as playing racquet sports or lifting heavy objects.

Methods: Subjects were assigned to receive either prolotherapy or corticosteroid injection for treatment of chronic lateral epicondylosis. Each subject underwent injection at baseline followed by a second injection 1 month later.

Outcome Measurements: Visual analog scale (VAS) self-rating of pain, quadruple visual analog scale (QVAS), and the Disabilities of the Arm, Shoulder, and Hand questionnaire (DASH) were measured at baseline and at 1, 3, and 6 months' follow-up.

Results: Within each group, the analysis demonstrated statistically significant improvements in both VAS and DASH within the prolotherapy group with significant changes noted from baseline to 3 months (VAS: Δ2.38; 95% confidence interval [95% CI] 1.04-3.71, $P = .004$ and DASH: Δ19.89; 95% CI 5.73-34.04, $P = .01$), and baseline to 6 months (VAS: Δ2.63; 95% CI 0.61-4.62, $P = .017$ and DASH: Δ21.76; 9% CI 7.43-36.09, $P = .009$) after initial treatment, as well as in the QVAS from baseline to 3 months. The steroid group demonstrated a clinically and statistically significant change for DASH only at both 3-month (Δ13.33; 95% CI 0.68-25.99, $P = .04$) and 6-month (Δ15.56; 95% CI 1.30-29.81, $P = .04$) follow-up. Comparison of the subjects completing the study revealed no significant differences between the prolotherapy and the corticosteroid group for change in VAS, QVAS, or DASH, although the study lacked sufficient power to draw conclusions from this finding. Eighty-three percent of the subjects were satisfied with their overall improvement during the course of the study, without significant differences revealed between groups. Aside from injection-associated pain, no adverse reactions were reported. Seventeen subjects completed study protocol.

Conclusions: Both prolotherapy and corticosteroid therapy were generally well tolerated and appeared to provide benefit of long duration. Small sample size precludes determining whether one therapy is superior to the other. Larger, controlled trials appear feasible and warranted on the basis of these findings.

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INTRODUCTION

Lateral epicondylosis (LE) is a painful enthesopathy or tendonosis of the common extensor tendon at the outer region of the elbow at the fibro-osseous junction [1-3]. Histological specimens from patients with chronic LE suggest that tendonosis is not an acute inflammatory condition but rather a failure of the normal tendon repair process associated with angiofibroblastic degeneration [4]. Evidence suggests that the predominant factor involved is a degenerative rather than an inflammatory process [5-8].

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Numerous treatment options have been described for LE. Traditional treatments include rest, activity modification, icing, nonsteroidal anti-inflammatory drugs, bracing, and physical therapy [9-13]. However, none of these treatments has proved to be generally effective [14].

Perhaps the most common treatment of LE is the corticosteroid injection, which is used to reduce inflammation in subjects with a variety of chronic tendonopathies [15]. However, because histologic studies have not found inflammation as a major feature in this condition, the rationale for corticosteroid injection appears misguided. There is some evidence to suggest that inflammation may actually be a useful component of the response to injury and healing process. Therefore, inhibiting this process may actually be counterproductive [16]. Several clinical trials have demonstrated limited efficacy for corticosteroid injections after 1 year [17-19]. Given the lack of evidence for long-term benefit from corticosteroid injection, there appears to be a need for the investigation of other injectable agents [20-23].

Prolotherapy has been defined as the iatrogenic stimulation of wound healing and tissue repair through the injection of an irritant solution into damaged ligaments and tendons. Prolotherapy solutions are purported to initiate an inflammatory cascade at the site of injection, which induces fibroblast proliferation and subsequent collagen synthesis, resulting in a tighter and stronger ligament or tendon [24]. Thus, although corticosteroid injections for chronic LE treatment are used to suppress inflammation, the primary mechanism of action of prolotherapy is to induce a small inflammatory response to promote adequate healing or more viable scar tissue formation that results in stronger fibrous tissue at the lateral epicondyle, which leads to improved function and reduced pain.

To our knowledge, this is the first study that has directly compared prolotherapy versus the common practice of corticosteroid injection for the treatment of chronic LE of the elbow. Our hypothesis remains that prolotherapy and corticosteroid therapy are both well tolerated and have equivalent short-term efficacy for the treatment of LE. We believe that this study is of particular relevance, given the potential advantages of prolotherapy over corticosteroid injection. For example, prolotherapy may be preferable to patients who are apprehensive about receiving a corticosteroid injection because of known side effects, such as tendon rupture, fat pad atrophy, avascular necrosis, skin depigmentation, and, in patients with diabetes, hyperglycemia. Another major advantage of prolotherapy is that it may be more cost-effective in the long-term treatment of chronic LE compared with corticosteroid injection because of its theorized ability to alter the disease process itself, as opposed to merely treating symptoms. This would then lead to less additional health care–related expenditures, such as repeat doctor visits, prolonged treatment course (ie, repeat injections, physical therapy, medication use), and time taken from work.

MATERIALS AND METHODS

This study was approved by the Spaulding Rehabilitation Hospital Institutional Review Board. Subjects with chronic LE were recruited via advertisements at local tennis clubs and direct physician referral. Recruitment methods used in this study conform to the CONSORT RCT reporting guidelines [25,26] (Figure 1). Inclusion criteria included subjects between 18 and 75 years of age; a history of elbow pain in the region of the lateral epicondyle ranging in duration from 3 months to 2 years; pain on resisted extension of wrist and/or middle finger test (resisted extension of middle finger at the metacarpophalangeal joint); local tenderness to palpation at the lateral epicondyle; and the ability to read and write in English. Exclusion criteria included a history of steroid injection(s) within 6 months before study enrollment; other arm/forearm pathology, such as radial nerve compression; pregnancy/nursing; known thrombocytopenia, coagulopathy, or bleeding diathesis; history of diffuse pain syndrome; history of inflammatory arthropathy; workers compensation claim related to pain; chronic regional pain syndrome; subjects with litigation pending/planned related to pain; intolerance/allergy to local anesthetics or corticosteroids; untreated depression; and a history of narcotic use for pain management for more than 1 month or history of narcotic abuse. Previous prolotherapy injection was not part of the exclusion criteria, but no subjects reported undergoing this treatment before their enrollment in the protocol (Table 1).

Recruitment and Injection Methods

Subjects qualifying for the study, on the basis of telephone screening, were randomized by the use of a random numbers table to receive 1 of the 2 treatments. All subjects randomized provided consent and underwent injection at the first study visit. Subjects underwent physical evaluation by one of the study investigators (J.S.) before the first injection occurred, to confirm the diagnosis of chronic LE; the investigator used the criteria listed previously. A second investigator (A.C.) performed all of the injections in this study. The study was double-blind; the subjects, physicians administering the injections, and data management personnel were all blinded to the contents of the injectant.

Anecdotally, we have had success with these agents in our musculoskeletal medicine practice for the treatment of various conditions involving ligaments and tendons. The prolotherapy solutions were obtained from a single vendor. Both study medications were combined with a local anesthetic solution (procaine 0.9% NaCl preservative-free 1% solution). They were prepared by a pharmacist who was not otherwise involved with the study, and the subject's study identification number was affixed to the syringe. The contents of the syringes were obscured by the use of an opaque label to prevent inadvertent unblinding.

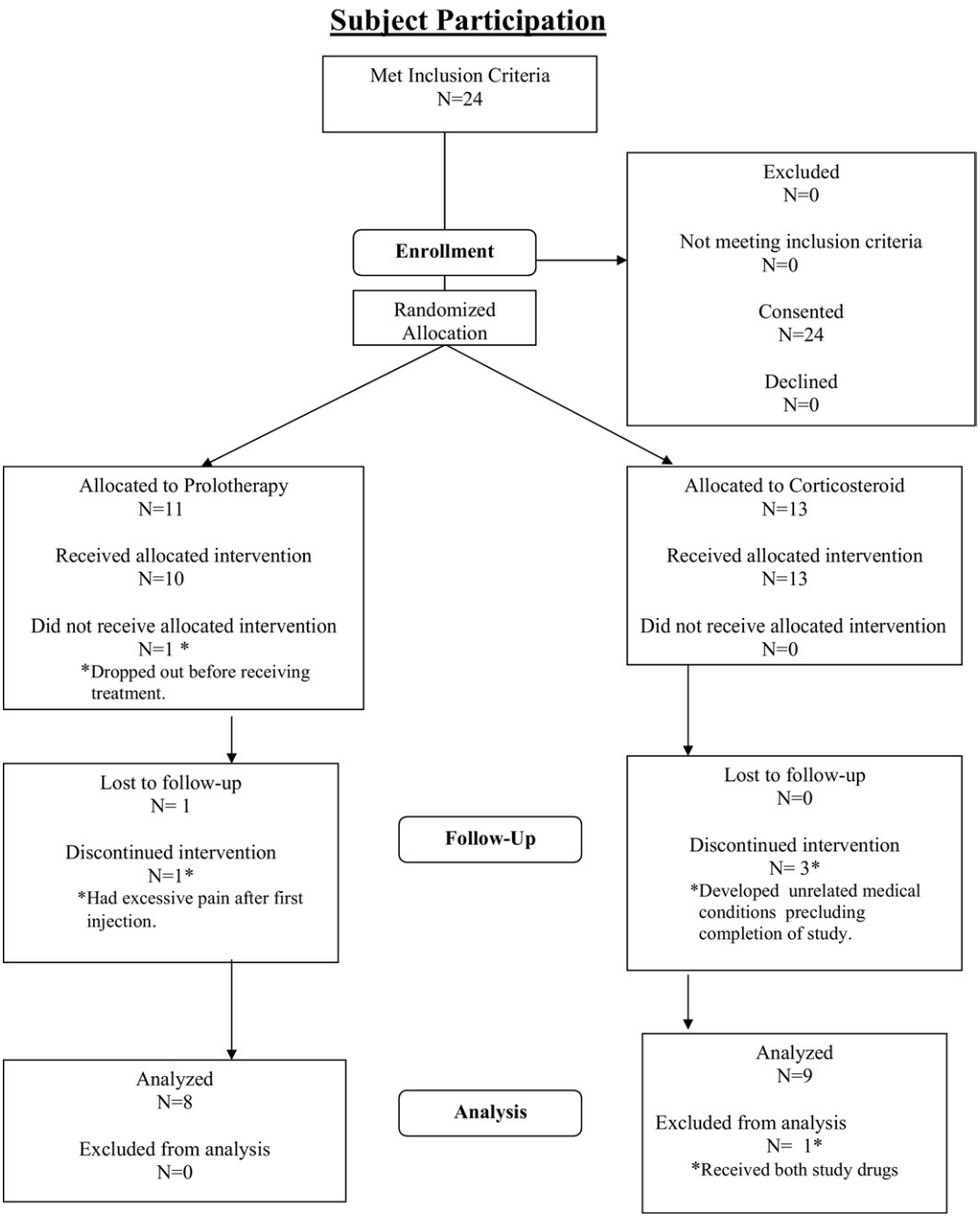

Figure 1. Subject participation.

All subjects received one of 2 study medications: (A) P2G (phenol 1.2%, glycerine 12.5%, and dextrose 12.5% in sterile water) plus sodium morrhuate, a combination of irritant, osmotic, and chemotactic agents [27]; or (B) methylprednisolone acetate injectable suspension (DepoMedrol; Pharmacia & Upjohn Company, Kalamazoo, MI), 40 mg/mL. For the prolotherapy injection (protocol A), each 3-mL syringe was filled with 1.0 mL of procaine, 0.9 mL of P2G, and 0.1 mL of of sodium morrhuate (Wellness Pharmacy, Birmingham, AL). For the corticosteroid group (protocol B), each 3-mL syringe was filled with 1.0 mL of procaine and 1.0 mL of DepoMedrol. A 27-gauge, 1.5-inch needle was used for all injections. The 2 solutions had a similar (ie, milky white) appearance.

The injection site was cleansed with 3 Betadine swabs followed by one alcohol pad. The injection procedure was as follows:

- The subject's arm was positioned on a firm surface with the elbow flexed and the palm down. One milliliter of study

Table 1. *Study inclusion and exclusion criteria*

Inclusion Criteria	Exclusion Criteria
1. Age >18 y and <75 y 2. History of pain >3 mo and <2 y 3. Pain on resisted extension of wrist and/or middle finger test (resisted extension of middle finger at metacarpophalangeal joint) 4. Local tenderness to palpation at lateral epicondyle 5. Ability to read and write in English	1. History of steroid injections within 6 mo before intervention 2. Other arm/forearm pathology. such as radial nerve compression 3. Pregnancy/lactation 4. Known thrombocytopenia, coagulopathy, or bleeding diathesis 5. History of diffuse pain syndrome 6. History of inflammatory arthropathy 7. Workers compensation 8. Chronic regional pain >2 y 9. Litigation pending/planned 10. Inability to return for follow-up 11. Intolerance/allergy to local anesthetics or injection corticosteroids 12. Fear of needles 13. Untreated depression 14. History of narcotic use for pain management >1 mo 15. History of narcotic abuse

solution was injected into the radial side of the annular ligament at the margin between the radial head and the ulna. A second injection of 0.5 mL of study solution was made into the attachment of the common extensor tendon at the lateral epicondyle. The needle was then "walked down" inferiorly, without removal, to reach the radial collateral ligament at the tubercle of the radius, where 0.5 mL of solution was injected (Figure 2).

- Subjects were monitored for one-half hour for an allergic reaction after injection and then informed that they might experience a postinjection flare in pain level. They were instructed to apply ice as needed, as well as take oral acetaminophen for pain control over the next several days. Each subject was given a 48-hour prescription for hydrocodone if needed for extreme pain. All anti-inflammatory medications were discontinued during the entire study period because of concerns that their anti-inflammatory action might interfere with the response to prolotherapy [28].
- All subjects were telephoned within 48 hours after each injection to ensure that no adverse events occurred.

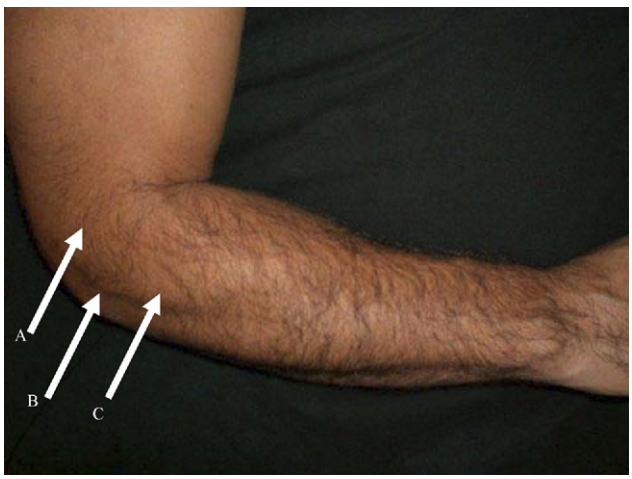

Figure 2. Surface anatomy of injection sites. (A) Common extensor tendon. (B) Radial collateral ligament. (C) Annular ligament, radial portion.

Subjects underwent 3 office visits and one telephone follow-up call (Table 2). The primary outcome measure was the visual analog scale (VAS), and the secondary outcome measures consisted of the quadruple visual analog scale (QVAS), the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire, and grip strength measurement. The VAS is a widely used and clinically validated scale of pain severity, with good reliability and sensitivity to change in pain symptoms [29,30] and has been validated in the LE population [31]. In this study, a 100-mm vertical line labeled with "no pain" on the bottom and "pain as bad as it could be" on the top was used to answer the question: "How would you rate your elbow pain?" A difference of 20 mm was significant as determined by the fact that this value correlates with 2 points on an 11-point VAS scale if each point represents 1 cm or 10 mm. It has been previously demonstrated by Farrar et al [32] that a change of pain intensity of 2 points on VAS (ie, 2 cm or 20 mm) is considered clinically significant on the basis of global assessment of change rating index.

The QVAS is based on the VAS, which is a reliable and valid method for pain measurement [33]. The QVAS consists of 4 specific factors: (1) pain level at the time of the current office visit; (2) typical or average pain since the last visit (or since the initial visit or the onset of the condition, depending on the chronicity of the condition); (3) pain level at its best since the last visit, time of intake, or onset of the condition; and (4) pain level at its worst since the last visit, time of intake, or onset of the condition. In

Table 2. *Study design and outcome measures*

Time	Type of Visit	Outcome Measures	Procedures Performed
0	Initial (office)	VAS, DASH	GSD, injection 1
1 mo	Follow-up (office)	VAS, DASH	GSD, injection 2
3 mo	Follow-up (office)	VAS, QVAS, DASH	GSD
6 mo	Follow-up (telephone)	VAS, QVAS, DASH	

DASH = Disabilities of the Arm, Shoulder, and Hand questionnaire; GSD = grip strength dynamometry; QVAS = quadruple visual analog scale; VAS = visual analog scale.

expanding upon the VAS, the QVAS allows a more qualitative interpretation of pain score within a unit of time. Therefore, we decided to include this scale as a secondary outcome measure.

The DASH is a multidimensional disease-specific, brief, self-administered measure of symptoms and functional status among subjects with upper limb disorders. The DASH is intended to measure how much difficulty a subject has when performing common functional tasks and activities. The DASH consists of a 30-item questionnaire with 5 response options for each item with a scale ranging from 0, which indicates "least disability," to 100, which indicates "most disability." It incorporates questions related to functional limitations, symptoms, and psychosocial problems. The DASH has been well validated and has a smaller standard error of measurement and a validity comparable to that of joint-specific measures [34]. A change in 12.7 DASH score points is considered to represent clinically significant functional improvement [35].

We used grip strength as measured by a hand dynamometer as another secondary outcome measure of treatment. Forearm muscle contraction, specifically wrist extensor muscle contraction, occurs during strong grip, and LE has been shown to adversely affect grip strength [36]. Grip strength was assessed with a Jamar dynamometer (Asimow Engineering, Santa Fe Springs, CA; Figure 3) [37-40]. In a previous work, Stratford et al [31] have demonstrated that pain-free grip strength was more sensitive than maximal grip strength for demonstrating range after LE. For this reason, both pain-free and maximum strength were measured in this study. An average of 3 trials were used for grip strength measurements. Subject positioning and instruction were standardized on the basis of the recommendations of the American Society of Hand Therapists (Figure 4) [41].

For the actual testing procedure, pain-free grip strength measurements of the involved limb were conducted first. The subject was instructed to slowly squeeze the dynamometer and to stop the instant that discomfort was experienced. Three repetitions were performed, separated by a 20-second rest interval. Maximum grip strength measurements were then performed on the uninvolved limb, followed by maximum grip strength measurements of the involved limb.

At the 1-month follow-up, the subject underwent repeat physical examination and completion of outcome measures, including VAS, DASH, and grip strength dynamometry. All subjects underwent repeat injection with either a corticosteroid or prolotherapy solution, on the basis of their group assignment.

Figure 3. Jamar dynamometer.

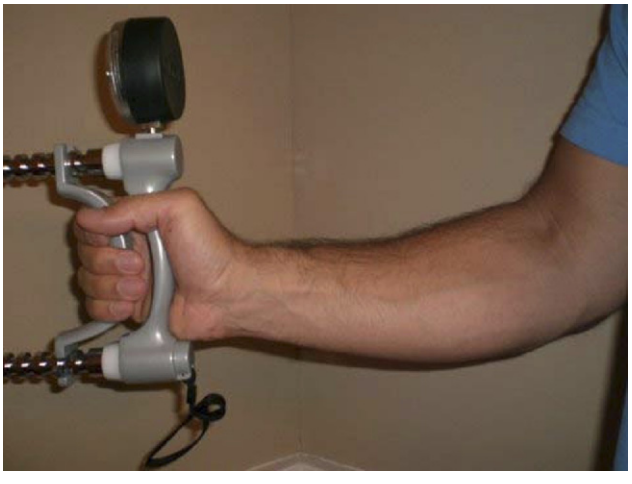

Figure 4. Standard positioning for grip strength dynamometry testing.

Subjects were reassessed again at 3 months after study entry, at which time the VAS, QVAS, DASH, and grip strength dynamometry were repeated. No further injections were performed. Subjects were then contacted 6 months later with a telephone follow-up. Before the 6-month telephone follow-up, the subject was mailed the VAS and DASH measures and asked to complete them within 48 hours before the scheduled follow-up call. Other data collected at baseline included age, gender, side of involvement, and time since onset of symptoms.

The primary end points of the study were pain at 3 months, as assessed by the VAS, and disability, as measured by the DASH. Six-month follow-up outcomes were obtained as a secondary outcome because of previous studies on the use of corticosteroid injection treatment in LE that have shown loss of early therapeutic benefit at follow-up intervals ranging from 3 to 12 months [20-22].

Statistical Analysis

A change of 2 for VAS [29,30] and 12 for DASH [34,35] was considered clinically significant. A power analysis before study initiation revealed that approximately 56 subjects would be needed to detect a statistically significant difference between prolotherapy and corticosteroid injection therapy with 80% power. An insufficient number of subjects was recruited into this study, and therefore, a direct comparison of the 2 injection techniques could not be statistically assessed. An exploratory analysis was nonetheless performed to compare the change in scores for both VAS and DASH between the 2 groups. Within each study group, analysis was performed by the use of paired *t*-tests to determine whether each group showed improvement from baseline to the 3-month follow-up. A *P* value of $< .05$ was considered statistically significant. The same procedure was used to determine change in VAS, QVAS, and DASH from baseline to the 6-month follow-up as a secondary endpoint. Paired *t*-test analysis was also performed on the grip strength data for baseline and 3-month follow-up. Because of the small sample size and significant loss to follow-up, variability in the data was high, and an intent-to-treat analysis was not used. Instead, a per-protocol approach was used; statistical analysis was performed on data of those subjects who completed the protocol and follow-up assessments.

RESULTS

Despite the initial goal to enroll 56 subjects to complete this study, only 24 subjects were actually enrolled, of whom 17 completed the study. Enrollment was stopped because of limited resources, including investigators who could not continue to conduct the study for logistical reasons and lack of funding. Of the 24 patients who enrolled, one subject was discharged from the study before receiving treatment after onset of symptoms consistent with concomitant cervical radiculopathy, thus complicating interpretation. Three subjects withdrew because of unrelated medical or orthopedic conditions. One subject receiving prolotherapy reported excessive pain after injection and chose not to return. One subject was lost to follow-up, and another subject received one treatment each of prolotherapy and corticosteroids because of a protocol error and was excluded from further analysis.

Table 3. *Characteristics of the 2 treatment groups*

Characteristic	Steroid Group (n = 9)	Prolotherapy Group (n = 8)
Age, y, average (SD)	46 (5.3)	49 (56.2)
Range	35–50	42–57
Baseline VAS score, mm, average (SD)	3.28 (2.64)	3.63 (2.00)
Range	0–7.0	1.0–3.5
Baseline DASH score, average (SD)	26.48 (15.95)	30.41 (13.21)
Range	9.17–48.33	15.0–50.83
Baseline pain-free grip strength, kg, average (SD)	34.74 (13.53)	32.59 (7.80)
Range	14.8–60	25.0–47.33

Thus, analysis was performed with the use of data from the 17 patients who completed the study. Eight study subjects received prolotherapy and 9 received corticosteroid injection. Eleven subjects who completed the study were women. Patients ranged in age from 35 to 57 years (mean, 46 years; Table 3). Symptoms of LE were present for more than 3 months in all participants. All participants enrolled were working full time and had attained an educational background at the university level or greater. Table 3 lists characteristics of the 2 treatment groups.

Within each study group, analyses revealed reduction in pain, as measured by the VAS, from baseline to 3 months of 2.38 ± 1.60 SD ($P = .004$) and to 6 months of 2.63 ± 2.39 ($P = .017$). The corticosteroid group experienced a trend toward improvement on the VAS of 1.83 ± 2.85 ($P = .09$) at 3 months and 1.72 ± 4.41($P = .28$) at 6 months. The QVAS scores showed similar improvements in the prolotherapy group (10.63 ± 8.50 difference, $P = .01$, at 3 months, and 8.38 ± 8.96, $P = .03$, at 6 months). The steroid group showed improvement in the QVAS at 6 months (8.78 ± 8.74, $P = .017$) but not at 3 months (5.33 ± 9.25, $P = .122$). The DASH scores improved by 19.89 ± 16.93 points in the prolotherapy group at 3 months ($P = .0013$) and by 13.33 ± 16.46 points in the corticosteroid group ($P = .04$). These improvements in DASH scores were maintained at 6 months. No significant differences in the amount of change were

Table 4. *Study outcome data for corticosteroid (n = 9) and prolotherapy (n = 8) groups*

Variable	Group	Baseline to 3 mo (SD)	*P* Value, Baseline to 3 mo	Baseline to 6 mo (SD)	*P* Value, Baseline to 6 mo
VAS	Corticosteroid	1.83 (2.85)	.09 (−0.36 to 4.02)	1.72 (4.41)	.28 (−1.67 to 5.11)
	Prolotherapy	2.38 (1.60)	.004 (1.04-3.71)	2.63 (2.39)	.017 (0.63-4.62)
QVAS	Corticosteroid	5.33 (9.25)	.12 (−1.77 to 12.44)	8.78 (8.74)	.017 (2.06-15.5)
	Prolotherapy	10.63 (8.50)	.01 (3.52-17.73)	8.38 (8.96)	.03 (.88-15.87)
DASH	Corticosteroid	13.33 (16.46)	.04 (0.68-25.99)	15.56 (18.54)	.04 (1.30-29.81)
	Prolotherapy	19.89 (16.93)	.01 (5.73-34.04)	21.76 (17.15)	.009 (7.43-36.09)
Grip strength, lb	Corticosteroid	4.48 (7.24)	0.1 (−1.08 to 10.05)		
	Prolotherapy	6.99 (9.99)	.09 (−1.36 to 15.35)		
Maximum grip, lb	Corticosteroid	2.29 (4.53)	.17 (−1.19 to 5.77)		
	Prolotherapy	0.96 (2.07)	.72 (−7.07 to 5.14)		

Data in parentheses are 95% confidence interval unless otherwise noted. Values of $P < .05$ are considered significant.
SD = standard deviation.

observed between the prolotherapy and corticosteroid groups at 3 or 6 months with any of the 3 scales (Table 4).

No significant change in grip strength was seen within or between groups. Seven of 9 study participants receiving steroid therapy, and 7 of 8 participants receiving prolotherapy reported overall satisfaction with the outcome achieved upon completion of the study. One participant withdrew from the prolotherapy group because of excessive pain; no other adverse reactions were reported.

DISCUSSION

This randomized controlled trial (RCT) reports improvements within each of the 2 treatment groups over the course of the study, suggesting some degree of efficacy for both treatments. Improvements in the prolotherapy group were seen for both the primary outcome measure (VAS) and for one of the secondary outcome measures (QVAS), whereas improvements in the corticosteroid group were observed only in the VAS. Seven of 9 participants receiving steroid therapy, and 7 of 8 participants receiving prolotherapy, reported overall satisfaction with the outcomes achieved upon completion of the study. A diminution effect was observed by 6 months in the corticosteroid group, whereas a significant change in VAS score was maintained in the prolotherapy group. This finding could suggest longer efficacy duration for prolotherapy.

This is the second RCT to report findings for prolotherapy as a treatment for LE. In a recent double-blind, randomized controlled trial, Scarpone et al [42] examined the effect of prolotherapy on resting elbow pain, extension, and grip strength in 24 adults with at least 6 months of refractory LE. Results revealed that, compared with control subjects, those who received prolotherapy reported improved pain scores at each of the 3 reporting intervals. This finding was determined to be significant when compared with baseline. This effect was maintained at long-term follow-up. In our present RCT, subjects who received prolotherapy also reported improved extension strength compared with control subjects as well as improved grip strength compared with baseline, with no report of any adverse events.

Two recent pilot studies involving tendonopathy should be noted. Topol et al [43] examined the role of 12.5% dextrose for the treatment of chronic groin pain in 24 elite rugby and soccer players. At 17 months after initial treatment, 20 of 24 subjects had no residual pain, and 22 of 24 subjects were unrestricted with sport participation. Another study conducted by Maxwell et al [44] demonstrated a mean reduction in VAS pain scores of 78.1%-84% in 32 subjects injected with hyperosmolar (25%) dextrose under sonographic guidance for chronic Achilles tendonosis. Most recently, Yelland et al [45] conducted an RCT involving 40 subjects who demonstrated significant improvement over 12 months in symptoms related to Achilles tendinosis in subjects randomized to prolotherapy, eccentric loading exercises, and a combination group of prolotherapy and eccentric loading exercises. Participants who received the combined treatment seemed to do better than those given either treatment alone.

Despite limited evidence of long-term effectiveness, corticosteroids have been shown to be effective in acute time periods [19]. However, systematic reviews of the effectiveness of this form of injectable treatment for LE present conflicting results and report that many studies conducted in this area have poor methodologic quality [19,46].

Prolotherapy has been proposed as a potential therapy for chronic LE and is used by some physicians to treat this condition and other enthesopathies. Prolotherapy is believed to produce a controlled inflammatory response and to stimulate adequate fibroblastic proliferation and connective tissue repair [47]. This result has been shown in multiple studies in which the authors used different proliferants. For example, biopsy samples examined after use of proliferant containing 2.5% phenol, 25% dextrose, and

25% glycerin (P2G) demonstrated a transient inflammatory reaction sufficient to create a fibroblast response [48]. Microscopic evidence in multiple studies in which the investigators used P2G or 5% sodium morrhuate reveals thickening of individual collagen fibers [24,49], thickening of entire ligaments and tendons in human subjects and in rabbit models [24], enlargement of the tendino-osseous junction [49], and ligamentous strengthening [24]. In multiple studies, proliferant injection with either P2G or 10% dextrose into anterior cruciate ligament demonstrated tightening [50,51].

Other authors suggest that the use of 10% dextrose could be enough of a stimulus to cause the release of growth factors. They, in turn, postulate that this may play an important role in the therapeutic effects of proliferant therapy [52,53]. These studies, in which the investigators have used a variety of proliferant solutions and animal models versus human subjects, illustrate the basic mechanism of prolotherapy, in which injection of an irritant solution triggers a localized inflammatory cascade, similar to that which occurs in the normal healing process, whereby fibroblastic hyperplasia and collagen formation lead to tightening, thickening, and strengthening of the ligaments or tendons [49,54]. This, in turn, results in stronger connective tissue with improved biomechanics, joint function, and decreased pain [45,51,54].

To date, no specific prolotherapy guidelines exist, and published clinical studies show significant differences in treatment protocols, with little attempt at standardization. In addition to the use of different proliferant solutions, studies vary in the number of treatments given, treatment intervals, proliferant doses and concentrations, and adjunct therapies used [54]. Three solutions are commonly used in proliferant therapy, including D-glucose (dextrose), phenol-glucose-glycerin (P2G), sodium morrhuate [17,24], or combinations of these (dextrose and sodium morrhuate, in addition to mepivicaine and cyanocobalamine, known as Pomeroy solution) [48,54].

LIMITATIONS

The major weakness of our study was the small sample size, which limits conclusions that can be drawn from the data. The study was underpowered and not able to detect statistical significance between groups. Future studies may consider using multiple centers or less stringent inclusion criteria. We found it difficult to attract an adequate number of patients despite recruitment around a major metropolitan city.

Another limitation of the study was the limited number of injections given in the protocol. Two injections of prolotherapy were chosen because this study allowed a direct comparison of prolotherapy to the conventionally accepted treatment of corticosteroid injection. Many of the recommendations for the use of local corticosteroid injections are determined by anecdotal evidence. Although there is no consensus with respect to the safe number of injections or the appropriate interval between injections [55], in our musculoskeletal medicine practice, we try to limit corticosteroid injections to 3-4 per year. Therefore, it was thought that having subjects undergo 2 injections may thereby limit potential side effects of corticosteroids. Standard prolotherapy treatment consists of more than 2 injection sets if patients are not clinically improving. However, because a standard of care practice for the number of corticosteroid injections does not currently exist, the issue is raised here on the feasibility of conducting a study using more injection sets. Frankly, it would be difficult to justify the use of 3 or more corticosteroid injections for the sole purpose of an RCT.

The severity of symptoms from LE was also an issue in this RCT. Because LE was chronic in all study subjects, pain was most often more severe with repetitive use, such as while playing racquet sports. Therefore, the baseline/resting VAS was low in most cases, making the determination of a significant change from baseline difficult.

CONCLUSION

To our knowledge, this is the first RCT comparing prolotherapy with corticosteroid injection for the treatment of chronic LE and the second study to examine the use of prolotherapy for this patient population. Our results suggest that prolotherapy may be a useful alternative to corticosteroid injection, and may provide a basis for undertaking larger, more definitive studies.

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CME Question

In this study on injection treatments of lateral epicondylitis (LE), the efficacy of prolotherapy injections:

a. could not clearly be established due to small sample size.
b. is significantly better than non-injection treatments.
c. was not as good as corticosteroid injections in pain relief.
d. was significantly better in acute LE than chronic LE.

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