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Hypertonic Dextrose and Morrhuate Sodium Injections (Prolotherapy) for Lateral Epicondylosis (Tennis Elbow):

Results of a Single-blind, Pilot-level Randomized Controlled Trial

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Abstract

Objective—Chronic lateral epicondylosis (CLE) is common, debilitating and often refractory. Prolotherapy (PrT) is an injection therapy for tendinopathy. The efficacy of two PrT solutions for CLE was evaluated.

Design—3-arm randomized controlled trial. 26 adults (32 elbows) with ≥3 months of CLE were randomized to ultrasound-guided PrT with dextrose (PrT-D), PrT with dextrose-morrhuate (PrT-DM) or watchful waiting (Wait-and-see). The primary outcome was the Patient-Rated Tennis Elbow Evaluation (PRTEE; 100-points) at 4, 8 and 16 weeks, (all groups) and 32 weeks (PrT groups). Secondary outcomes included pain-free grip strength and magnetic resonance imaging (MRI) score.

Results—PrT-D and PrT-DM participants reported improved PRTEE composite and subscale scores at 4, 8 and/or 16 weeks compared to Wait-and-see ($p<0.05$). At 16 weeks, compared to baseline, PrT-D and PrT-DM groups improved composite PRTEE scores by 18.7±9.6 (41.1%) and

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17.5±11.6 (53.5%) points, respectively. Grip strength of PrT-D participants exceeded that of PrT-DM and Wait-and-see at 8 and 16 weeks ($p<0.05$). There were no differences in MRI scores. Satisfaction was high; there were no adverse events.

Conclusions—Prolotherapy resulted in safe, significant improvement of elbow pain and function compared to baseline status and wait-and-see control. This pilot study suggests the need for a definitive trial.

Keywords

Randomized Controlled Trial; Lateral Epicondylosis; Prolotherapy; Tennis Elbow

Chronic lateral epicondylosis (CLE, "tennis elbow") is a common, debilitating and expensive[1] condition accounting for 4-7 of every 1,000 primary care office visits annually. Among industrial workers, the prevalence of CLE reaches 30%,[2] with symptoms duration of six months to two years, regardless of therapy.[3, 4] While CLE is often self-limited, up to 20% of cases are refractory to conservative care.[5] CLE and other chronic tendinopathies are now understood to be non-inflammatory conditions[6] characterized by collagen degeneration, fibroblast proliferation, mucoid degeneration and neovascularization.[7-9] While the source of pain is not known, relative rest, physical therapy, non-steroidal anti-inflammatory drugs (NSAIDs), surgery and other forms of treatment have been assessed, but none is uniformly effective, and none has been shown to address the underlying degenerative pathophysiology.[10] Corticosteroid injections, while effective in the short term, may result in worse outcomes than watchful waiting in the long term.[11] Indeed, content experts have suggested that CLE is best viewed as self-limited condition and that "wait and see" may be a reasonable approach.[12]

Prolotherapy (PrT) is an injection-based technique for treatment of chronic musculoskeletal pain including tendinopathy.[13] Hypertonic dextrose and morrhuate sodium are common injectants[14] used in prior pilot-level RCTs.[15, 16] Preliminary evidence, although promising, is limited by lack of validated primary outcome measures, short follow-up or lack of comparison to a "wait-and-see" control group. Therefore, the study team conducted a 3-arm randomized controlled trial (RCT) to test the hypotheses that adults with symptomatic CLE receiving PrT with either hypertonic dextrose (PrT-D) or combined dextrose and morrhuate sodium (PrT-DM) will have greater improvement in elbow-related quality-of-life, biomechanical and MRI-based or ultrasound-based outcomes than those in a wait-and-see control group.

METHODS

The study protocol was approved by the University of University Wisconsin (UW) Health Sciences Institutional Review Board.

Eligibility Criteria and Participant Recruitment

Participants were recruited from the community and the UW Sports, Rehabilitation and Family Medicine clinics, and followed from June 2009 to September 2010. Inclusion criteria were: 18 to 65 years old, self-reported lateral elbow pain present for at least three prior months and rated as "4" or more on a 0-10 ordinal response scale ("What was the average level of your left/right elbow pain over the last week?"), presence of pain over the lateral epicondyle on palpation and with resisted wrist extension during physical exam (first author, DR),[17, 18] and having failed at least one of the three most common treatments for CLE (NSAIDs, physician initiated physical therapy or a corticosteroid injection). Exclusion criteria included: prior elbow PrT, other elbow injection-based therapies within the past

three months, other concurrent upper extremity pathology, prior upper extremity surgery, self-reported pregnancy, significant co-morbidity precluding participation, bleeding disorders, allergy or intolerance to study medication, use of chronic opioid, anticoagulant or immunosuppressive medication, and standard MRI-related exclusions at our institution (http://www.uwhealth.org/healthfacts/B_EXTRANET_HEALTH_INFORMATION-FlexMember-Show_Public_HFFY_1116338384058.html).If both elbows were affected, each elbow was assessed separately for eligibility. Interested, eligible persons attended an informational meeting, were consented and enrolled.

Study Design

Participants were randomly assigned to blinded prolotherapy (PrT-D or PrT-DM) or Wait-and-see groups using a 1:1 computer-generated randomization. All participants were followed for 16 weeks post-entry; to aid participant retention, Wait-and-see participants were offered prolotherapy at 16 weeks and exited from the study. PrT participants were additionally evaluated at 32 weeks post-entry. PrT participants, and assessors of biomechanical and MRI outcomes were blind to the injection group status and timing of injections.

Interventions

Prolotherapy injections were performed under ultrasound guidance by the injector (KSL) at the UW Center for Musculoskeletal Ultrasound at 1, 4 and 8 weeks post-entry using either dextrose or dextrose-morrhuate sodium solutions (Table 1) prepared by the injector at the time of procedure. Tenderness at the lateral epicondyle was confirmed by palpation and participants underwent an ultrasound evaluation of lateral elbow structures using a Philips HDI 5000 US with specialized 12-5 MHz 38mm linear array scan heads and tissue-specific presets for imaging superficial tendons and ligaments. Analgesic skin wheals of 1% lidocaine were placed. Under continuous ultrasound evaluation, 0.5mL of the prepared PrT solution was injected onto the lateral epicondyle (22G, 1.5″ long needle). Then, up to 2.5 mL of the solution was “peppered” on bone along a short segment of the tendon and annular ligament at the areas of palpated tenderness and ultrasound-documented patholopgy. Post-injection, participants were offered 20 tablets of 325 mg acetaminophen for “as-needed” analgesia and were telephoned on day two to enquire about side effects or adverse events. They were advised on relative rest for 2-3 days post-procedure and progressive resumption of routine activity over one month.

Wait-and-see participants were counseled about CLE risk modification in daily living and work activities.

Adherence and Precautions

All participants were reminded at each contact to avoid NSAIDs and new therapies for CLE and to limit overuse of the elbow during the study period. They were encouraged to attend all treatment and assessment sessions. Wait-and-see participants were contacted by phone at the same intervals as PrT participants were seen during the 16 study weeks to minimize contact bias.

Outcome Measures

The primary outcome was the change in the composite score on the Patient-Rated Tennis Elbow Evaluation (PRTEE), a CLE-specific questionnaire evaluating disease-specific quality-of-life.[18, 19] The PRTEE’s elbow pain (5 items) and function (10 items) subscales show excellent reliability (interclass correlation coefficients, ICC: pain 0.96, function 0.92, and composite 0.96) and sensitivity to change.[18, 19] Scores range from 0 (good quality-of-

life, no pain or disability) to 100 (poor quality-of-life, extreme pain or disability). The minimal clinical important difference (MCID) was established for the PRTEE at 11-points or 37% improvement compared to baseline ('much better' or 'completely recovered').[20] The PRTEE was collected in person at baseline, 4, 8 and 16 weeks (all participants) and 32 weeks post-entry (PrT participants only). PrT participants provided the PRTEE data prior to their PrT procedures.

Secondary outcomes included pain-free grip-strength, a commonly used objective measure of CLE-related disability with good test-retest (Pearson correlation, $r \geq 0.8$) and validity (±3%)[21, 22] measures. For the grip-strength evaluation, participants sat in a chair with their shoulder flexed at 90°, elbow extended and forearm in the neutral position. All participants were instructed to squeeze the Baseline® (Fabrication Enterprises Inc., White Plains, NY) dynamometer set at 2 inches and cease squeezing prior to the onset of pain. The average of three replications performed prior to any procedure and separated by 60-second intervals was recorded at baseline, 8 and 16 weeks (all participants), and 32 weeks (PrT participants only) post-entry.

Secondary outcomes also included MRI and ultrasound elbow assessments. The study team used an ordinal 0-3 CLE severity grading based on the T1 and T2 MRI signal intensity at the common extensor tendon that corresponds to areas of collagen disruption, mucoid degeneration or neovascularization on histopathologic exam.[23, 24] Grade 1 consisted of tendon thickening and intermediate T1 and T2 signal intensity.[23, 24] Grade 2 corresponded to a partial-thickness tear. Grade 3 corresponded to a full-thickness tear. All participants were assessed using an Artoscan 0.2 Tesla MRI scanner at baseline and 16 weeks; PrT participants were also assessed at 32 weeks. MRI examinations consisted of an axial T1-weighted spin-echo sequence (TR/TE, 620/10 ms), an axial T2-weighted spin-echo sequence (TR/TE, 2200/80 ms), and a coronal T2-weighted spin-echo sequence (TR/TE, 2200/80 ms), all performed with a 15cm field of view, 192 × 160 matrix, and 3.5mm slice thickness. All MRI examinations were reviewed by a fellowship-trained musculoskeletal radiologist (RK). CLE severity at baseline and follow-up was further characterized by ultrasound of the common extensor tendon (CET) using published ordinal scales for hypoechogenicity, tendon thickness and neovascularity, which have been reported to be associated with tendinopathy as a biomarker and a potential source of pain.[25] Ultra-sound assessment also included acoustoelastography, a novel measure with the potential to objectively measure tendon tissue stiffness as a biomarker for baseline disease and response to therapy.[26] The ultrasound-based methods and results will be reported in a subsequent paper.

Tertiary outcomes included PrT participant treatment satisfaction rating using 5-point (0=very dissatisfied, 5=very satisfied) scale. Demographics, duration of elbow pain and information on prior therapy for CLE were collected at baseline to characterize the sample, and to evaluate as covariates (age, gender, baseline CLE severity). Participants were queried about any new therapies for CLE and were able to make brief qualitative comments at all follow-up time points.

Analysis

The a priori sample size calculation was guided by an RCT reporting a 68% absolute effect size of PrT for severe CLE compared to saline injections.[15] Assuming a similar effect size on the PRTEE measure in PrT groups, minimal change in Wait-and-see controls and minimal loss to follow up, the sample size to detect this difference on the PRTEE between either PrT group and Wait-and-see group was 10 participants per arm (N=30; 80% power, two-sided $\alpha = 0.05$).

Data was analyzed with SPSS version 19.0 statistical software[27] by intention to treat. Descriptive statistics were used to describe baseline characteristics. The unit of analysis was the individual elbow. Quantitative data was assessed using a general linear model (GLM) at each time point holding the PRTEE composite or subscale scores as the dependent variable, with group and time as respective random factors. Age and symptom duration were evaluated as covariates in the model. Grip strength was analyzed using a similar GLM approach. Least-significant difference post-hoc analyses were carried out on the corresponding adjusted estimates for between group comparisons. Paired t-tests were used to estimate within-group differences. Statistical significance was assessed using two-tailed tests ($p<0.05$). Missing values were addressed using a "last value carried forward" strategy.[28] Ordinal MRI data are presented on a group-by-time basis.

RESULTS

Of the 134 persons screened by phone, 44 met eligibility criteria, and 31 persons were enrolled and randomized. Because 4 enrollees dropped out prior to completion of baseline data collection, 27 participants with 32 affected elbows were included in the analysis (Figure 1).

PrT-DM participants were slightly younger than those in other groups ($p=0.047$); there were no other significant differences between the groups (Table 2). The study sample was mostly (65%) male, 48.2±7.8 years old and reported more than three years of elbow pain. Baseline MRI was available for 29 out of 32 possible elbows; all MRI-imaged elbows showed detectable pathology, and 22/29 had features of moderate to severe disease. All 16 PrT participants (20 total elbows) received 3 planned PrT sessions.

Compared to baseline, PrT-D participants reported a statistically significant improvement in composite (at 16 and 32 weeks), pain (at 16 and 32 weeks) and function (at 32 weeks) PRTEE scores; PrT-DM participants reported a statistically significant improvement in composite (at 32 weeks), pain (at 16 and 32 weeks) and function (at 32 weeks) PRTEE scores (Table 3). Composite PRTEE score improvement for both PrT-D and PrT-DM were in excess of MCID at 16 weeks while improvement in Wait-and-see PRTEE scores were not.

Age- and symptom duration-adjusted between-group comparisons showed that both PrT groups outperformed ($p<0.05$) Wait-and-see on several PRTEE measures. At 8 weeks, participants in both PrT groups improved composite PRTEE scores compared to Wait-and-see ($p<0.05$). PrT-DM continued to outperform Wait-and-see at week 16 on the PRTEE composite score ($p<0.05$). PRTEE subscale scores followed a similar pattern. Participants in both PrT groups improved function subscale scores compared to Wait-and-see at 8 and 16-weeks ($p<0.05$), and PrT-DM participants improved pain subscale scores compared to Wait-and-see at 16-weeks ($p<0.05$). The PrT-D group also showed greater grip strength than either PrT-DM or Wait-and-see at 8 and 16 weeks ($p<0.05$) (Table 4). Grip strength did not change in Wait-and-see by 16 weeks and PrT-DM group by 16 or 32 weeks.

CLE severity was evaluated using existing MRI images in all participants for whom baseline MRIs were available (N=29). All participants had MRI-assessed disease at baseline; seven (23%) had Grade 1, 10 (33%) had Grade 2 and 12 (40%) had Grade 3 (Table 5). Over time, only minimal changes in MRI-assessed CLE severity grade were noted for each participant. There were no within or between group differences in MRI severity scores.

Six of eight (75%) PrT-D participants reported being "somewhat" or "very" satisfied; two participants (29%) reported "neutral" response (2/5) at 16 weeks; there was no change in satisfaction ratings at 32 weeks. At 16 weeks, seven of nine (78%) PrT-DM participants

reported being “somewhat” or “very” satisfied, 1 (11%) “neutral” and 1 (11%) “somewhat dissatisfied”; at 32 weeks, one participant was still “somewhat dissatisfied” but the remaining eight (89%) were “somewhat” or “very” satisfied. No participants reported starting new therapy for CLE. Inspection of qualitative comments showed all participants reported mild-to-moderate self-limited injection-related pain. This pain tended to resolve within 1 week in the PrT-D group. However, PrT-DM participants reported more severe and persistent injection-related pain taking up to 3 weeks to resolve. One PrT-DM participant’s 4-week PrT session was postponed by two weeks due to post-procedural pain. There were no unexpected or serious adverse events.

DISCUSSION

This RCT of adults with symptomatic CLE found substantial, consistent and significant improvements in composite or subscale PRTEE scores in response to two different prolotherapy solutions compared to Wait-and-see control at 16 week follow-up; improvement continued in the PrT groups to the 32 week follow-up. This study is the first robust assessment of 20% dextrose PrT for CLE, the first comparison of two different PrT solutions, and the first to compare either to natural history as represented by the Wait- and-see control group. At 16 weeks, improvement in the composite PRTEE score for both PrT groups substantially exceeded MCID on the PRTEE, while that of Wait-and-see participants did not; PrT group participants’ PRTEE scores continued improving through 32 weeks. Participants receiving PrT-D seemed to improve more quickly and with less post-injection pain than did the PrT-DM group; at 32 weeks however, there was no difference between PrT groups on any of the outcomes. Grip strength improved in PrT-D compared to both baseline and the two other groups.

These findings are consistent with those of multiple small RCTs, the methodologically strongest of which reported similar 16-week improvements on a 0-10 ordinal response pain scale and grip strength,[15] and non-significant MRI changes.[29] While the data cannot be directly compared, inspection suggests that the response to prolotherapy in Scarpone et al. was slightly more robust; methodological and baseline participant differences may account for this. The current study used a slightly lower concentration of morrhuate sodium, performed injections under ultrasound guidance, and enrolled participants with less severe and more variable baseline CLE severity. These findings are also consistent with clinical experience; morrhuate sodium injections are understood to hurt more and are typically reserved for more severe cases refractory to less irritating solutions such as dextrose alone. Direct comparison to prior studies and to studies involving steroid injections, laser or more conventional therapies is also difficult given methodological heterogeneity. While corticosteroid injections have been regarded as standard of care for CLE, recent evidence suggests that they provide inferior long-term outcomes than other treatments for CLE including ‘Wait and see’.[30] Overall, these findings suggest that PrT may improve upon standard of care for CLE for some patients, especially since most participants were refractory to prior conventional therapies. Whether PrT can modify the disease at the tissue level is not known; data from this study do not support such an effect discernable on MRI.

Prolotherapy is an evolving modality gaining popularity in sport, rehabilitation and family medicine, though its mechanism of action is unclear and likely multifactorial.[14] The injectants likely have independent biological actions; two recent RCTs report outcomes favoring PrT compared to blinded saline injections.[15, 31] The proposed biological mechanism of action has been reviewed.[14] Dextrose injections have been hypothesized to stimulate healing of chronically injured extra and intra-articular tissue;[32] animal model studies reported increased inflammatory markers[33] and significantly enlarged cross-sectional area in medical collateral ligaments.[34] Morrhuate sodium is a sclerosing agent. Animal

studies report a robust inflammatory response[33] and stronger medial collateral ligaments after injection with morrhuate sodium.[3536] The combined effect of the two agents has not been assessed in basic science studies, no prior studies have sought to optimize 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 PrT community. The potential of prolotherapy to stimulate release of growth factors promoting soft tissue healing and a positive neural effect have also been suggested. Needle trauma and volume expansion of local tissue may also produce a tissue-level effect.[37] The combined effects of needle trauma, volume expansion, and dextrose and morrhuate-specific mechanisms may explain positive findings for prolotherapy in this study.

The study is limited by small sample size and high data variability; however the response was robust enough to detect several between-group differences. The study does not include a blinded injection control, therefore some of the improvement reported by participants in active arms of the study may have resulted from being in an injection arm per se. However, a prior CLE PrT study reported improvement compared to blinded saline injections;[15] comparison to natural history as exemplified by a “wait and see” control arm is an accepted clinical trial strategy[11] and the challenge of selecting an appropriate control therapy in clinical trials assessing injection techniques has been noted.[37] The current study allows direct comparison to natural history and facilitates the study of PrT as a modifier of underlying degenerative disease through assessment of MRI and US measures (manuscript in process). The injector and assessor of PRTEE data were not blinded to injection type, and the blinding of injection participants, and biomechanical and MRI assessors was not formally assessed; data are therefore subject to potential injector and assessor bias. The 16-week follow-up portion of the RCT is relatively short; however, the primary outcome and grip strength data are consistent with a prior 16 week study, the positive results of which were also noted at 16 weeks and continued through 52 weeks.[15] Strengths include RCT design, validated patient-oriented outcomes, minimal missing data and a large, consistent effect size in the PRTEE score change in both PrT groups compared to Wait-and-see.

Directions for Future Research

Determination of the clinical utility of PrT for CLE will require confirmation in a larger, longer effectiveness trial that includes biomechanical and imaging outcome measures to assess potential disease modification.

CONCLUSIONS

Among participants with CLE, PrT resulted in safe and significant improvements on validated CLE-specific quality-of-life, pain and function measures and grip strength compared to Wait-and-see control at 16 weeks, and compared to baseline status through 32 weeks. PrT may be an appropriate therapy for selected patients with refractory CLE.

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REFERENCES

1. Silverstein B, ViikariJuntura E, Kalat J. Use of a prevention index to identify industries at high risk for work-related musculoskeletal disorders of the neck, back and upper extremity. Am J Ind Med. 2002; 41:149–169. [PubMed: 11920960]
2. Bernard, BP. Musculoskeletal disorders and workplace fractures: a critical review of the epidemiological evidence for work-related musculoskeletal disorders of the neck, upper extremity and low back. National Institute for Occupational Safety and Health; Washington D.C.: 1997. NIOSH Publication 97-141
3. Hudak PL, Cole D, Haines T. Understanding prognosis to improve rehabilitation: example of lateral elbow pain. Arch Phys Med Rehabil. 1996; 77:586–593. [PubMed: 8831477]
4. Murtaugh JE. Tennis elbow. Aust Fam Physician. 1988; 17:90–95. [PubMed: 3358752]
5. Rineer CA, Ruch DS. Elbow tendiopathy and tendon ruptures: epicondylitis, biceps and triceps ruptures. J Hand Surg Am. 2009; 34:566–576. [PubMed: 19258160]
6. Khan KM, Cook JL, Kannus P, et al. Time to abandon the 'tendinitis' myth. BMJ. 2002; 324:626–627. [PubMed: 11895810]
7. Kraushaar BS, Nirschl RP. Tendinitis of the elbow (tennis elbow). Clinical features of histological, immunohistological, and electron microscopy studies. J Bone Joint Surg Am. 1999; 81-A:269–278.
8. Alfredson H, Ohberg L. Sclerosing injections to areas of neovascularization reduce pain in chronic Achilles tendinopathy: a double-blind randomised trial. Knee Surg Sports Traumatol Arthrosc. 2005; 13:338–344. [PubMed: 15688235]
9. Alfredson H, Ohberg L, Forsgren S. Is vasculo-neural ingrowth the cause of pain in chronic Achilles tendinosis? An investigation using ultrasonography and colour Doppler, immunohistochemistry, and diagnostic injections. Knee Surg Sports Traumatol Arthrosc. 2003; 11:334–338. [PubMed: 14520512]
10. Bisset L, Coombes B, Vicenzino B. Tennis Elbow. Clin Evid (Online). 2011:1117. PMID: 21708051. [PubMed: 21708051]
11. Bisset L, Beller E, Jull G, et al. Mobilization with movement and exercise, corticosteroid injection or wait and see. BMJ. 2006; 333:939. [PubMed: 17012266]
12. Szabo RM. Steroid injection for lateral epicondylosis. J Hand Surg [Am]. Dec 20.2009 34:326–330. 2008.
13. Rabago D, Best T, Beamsly M, et al. A systematic review of prolotherapy for chronic musculoskeletal pain. Clin J Sports Med. 2005; 15:376–380.
14. Rabago D, Slattengren A, Zgierska A. Prolotherapy in primary care. Prim Care. 2010; 37:65–80. [PubMed: 20188998]
15. Scarpone M, Rabago D, Zgierska A, et al. The efficacy of prolotherapy for lateral epicondylosis: a pilot study. Clin J Sport Med. 2008; 18:248–254. [PubMed: 18469566]
16. Glick, RM.; Day, RD.; Stone, DA., et al. Prolotherapy for the treatment of lateral epicondylitis: a double-blind pilot study. Paper presented at: Poster presented at: North American Research Conference on Complementary and Integrative Medicine; Edmonton, Canada. 2006 May 24;
17. Overend TJ, Wuori-Fearn JL, Kramer JF, et al. Reliability of a patient-rated forearm evaluation questionnaire for patients with lateral epicondylitis. J Hand Ther. 1999; 12:31–37. [PubMed: 10192633]
18. MacDermid JC. Update: the patient-rated forearm evaluation questionnaire is now the patient-rated tennis elbow evaluation. J Hand Ther. 2005; 07:407–410. [PubMed: 16271687]
19. Newcomer KL, Martinez-Silvestrini JA, Schaefer MP, et al. Sensitivity of the Patient-rated Forearm Evaluation Questionnaire in Lateral Epicondylitis. J Hand Ther. 2005; 18(4):400–406. [PubMed: 16271686]
20. Poltawski L, Watson T. Measuring clinical important difference with the Patient-Rated Tennis Elbow Evaluation. Hand Ther. 2011; 16:52–57.
21. Mathiowetz V, Weber K, Volland G, et al. Reliability and validity of grip and pinch strength evaluations. J Hand Surg Am. Mar. 1984; 9:222–226.

22. Watanabe T, Owashi K, Kanauchi Y, et al. The short-term reliability of grip strength measurement and the effects of posture and grip span. J Hand Surg Am. 2005; 30:603–609. [PubMed: 15925174]
23. Potter HG, Hannafin JA, Morwessel RM. Lateral epicondylitis: Correlation of MR imaging, surgical and histopathological findings. Radiology. 1995; 196:43–46. [PubMed: 7784585]
24. Martin CE, Schweitzer ME. MR imaging of epicondylitis. Skeletal Radiol. 1998; 27:133–138. [PubMed: 9554003]
25. Maxwell NJ, Ryan MB, Taunton JE, et al. Sonographically guided intratendinous injection of hyperosmolar dextrose to treat chronic tendinosis of the Achilles tendon: a pilot study. AJR Am J Roentgenol. 2007; 189:W215–220. [PubMed: 17885034]
26. Ryan M, Lee K, Kobayashi H, et al. Abstract 990448 presented at the Annual Conference of the Association of Ultrasound in Medicine; Ultrasound-based Acoustoelastic Measurement of In Vivo Stiffness of the Common Lateral Elbow Extensor Tendon in Chronic Tendinopathy and Healthy Controls. Ultrasound Med. 2011; 30:S1. 2011;30:S1.
27. SPSS. SPSS for Windows, version 14.0 (statistical software). 2007. http://www.spss.com/spss/
28. Pledger GW. Basic statistics: importance of adherence. J Clin Res Pharmacoepidemiol. 1992; 6:77–81.
29. Rabago D, Kijowski R, Zgierska A, et al. Magnetic resonance imaging outcomes in a randomized controlled trial of prolotherapy for lateral epicondylosis. International Musculoskeletal Medicine. 2010; 32:117–123.
30. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. Lancet. 2010; 376:1751–1767. [PubMed: 20970844]
31. Rabago D, Miller DJ, Zgierska A, et al. (Poster Presentation) Dextrose prolotherapy for knee osteoarthritis: Results of a randomized controlled trial. Osteoarthritis Cartilage. 2011; 19(S1):S142–S143.
32. Banks A. A rationale for prolotherapy. Journal of Orthopaedic Medicine. 1991; 13:54–59.
33. Jensen K, Rabago D, Best TM, et al. Early inflammatory response of knee ligaments to prolotherapy in a rat model. J Orthop Res. 2008; 26:816–823. [PubMed: 18240327]
34. Jensen, KT. Healing response of knee ligaments to prolotherapy in a rat model [dissertation]. University of Wisconsin; Madison: 2006.
35. Liu YK, Tipton CM, Matthes RD, et al. An in-situ study of the influence of a sclerosing solution in rabbit medial collateral ligaments and its junction strength. Connective Tissue Research. 1983; 11:95–102. [PubMed: 6224646]
36. Aneja A, Spero G, Weinhold P, et al. Suture plication, thermal shrinkage and sclerosing agents. American Journal of Sports Medicine. 2005; 33:1729–1734. [PubMed: 16093538]
37. Rabago D, Wilson JJ, Zgierska A. Letter to the editor; platelet-rich plasma for treatment of achilles tendinopathy. JAMA. 2010; 303:1696–1697. [PubMed: 20442382]

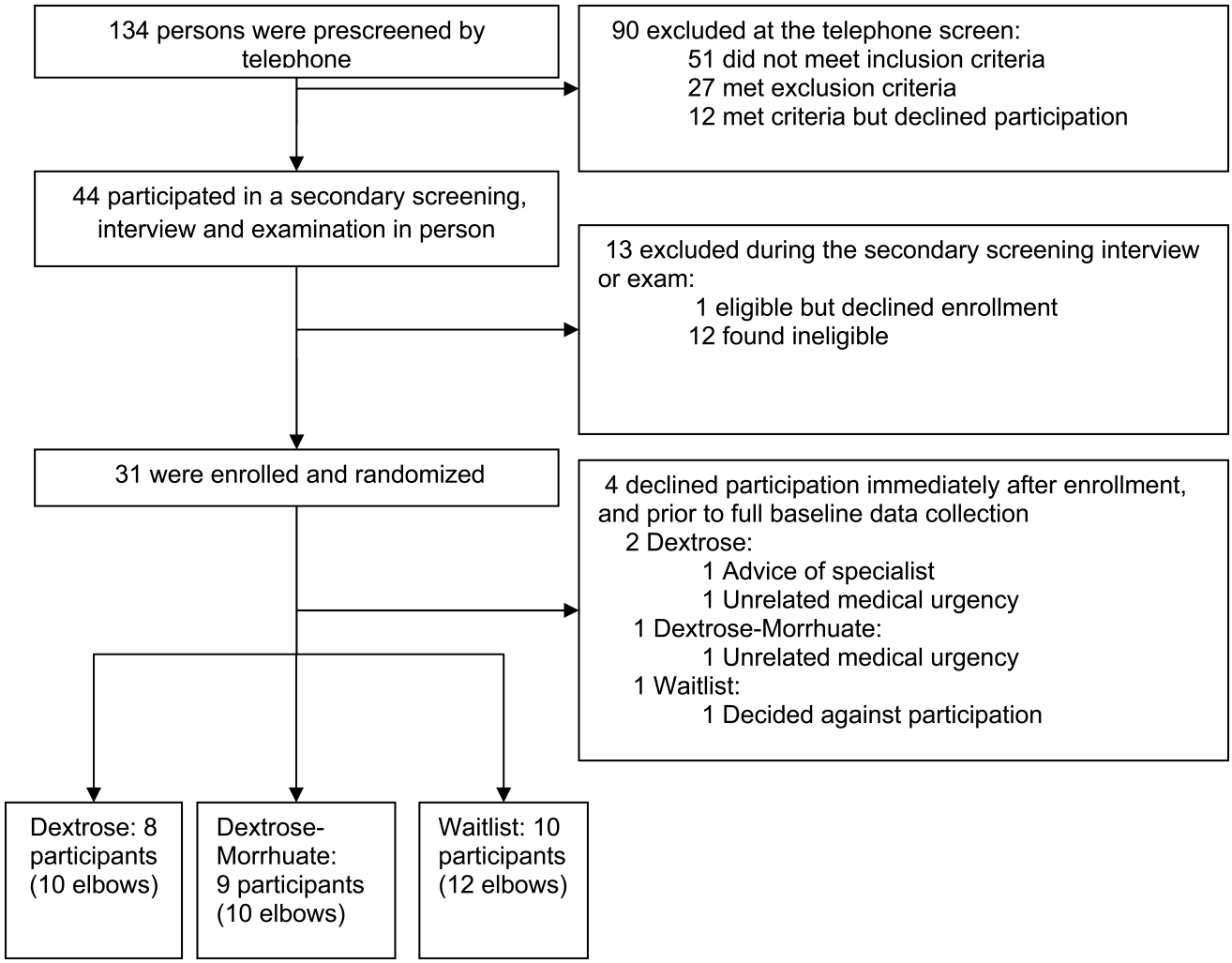

Figure 1.
Screening, Enrolment and Randomization

Table 1

Prolotherapy solutions and injection techniques

Injection type	Solution	Injection Technique
Analgesic skin wheel	3 mL 1% lidocaine (3 mL syringe)	Each PrT subject received a palpatory and US elbow exam. Analgesic skin wheals of 1% lidocaine were placed at areas of palpated tenderness.
Dextrose PrT	4 mL 50% dextrose + 4 mL 0.9% saline + 2 mL 1% lidocaine (10 mL syringe)	Under continuous US evaluation, 0.5mL of PrT solution was injected onto the lateral epicondyle; then up to an additional 2 mL of the solution was “peppered” on bone along a short segment of the tendon and annular ligament at the areas of palpated tenderness and US-documented patholopgy.
Dextrose & Morrhuate PrT	1 mL 5% morrhuate sodium + 1.5 mL 50% dextrose + 2 mL 1% lidocaine + 2.5 mL 0.9% saline (10 mL syringe)	Injection technique identical to above.
Post-injection procedures		Subjects were instructed to rest after the PrT injections for five minutes. Participants were given 100 tablets of 325 mg acetaminophen for “as-needed” analgesia, written instructions for aftercare and were then telephoned after 2 days to inquire about comments, questions, side effects or adverse events.

Abbreviations: PrT – prolotherapy; US - ultrasound

Table 2

Baseline Participant Characteristics

	Dextrose	Dextrose-Morrhuate	Waitlist Control
N (individuals)	8	9	10
N (Elbows)	10	10	12
Female, N (%)	1 (14)	4 (44)	4 (40)
Age, mean (SD)	50.4* (6.8)	42.6* (9.8)	51.7* (6.8)
Duration of Elbow Pain, months (SD)	61.7 (48.2)	40.0 (44.7)	55.5 (73.4)
Prior Elbow Intervention, N (%)			
Physical Therapy	6 (85.7)	7 (77.8)	9 (90.0)
Iontophoresis	1 (14.3)	1 (11.1)	2 (20.0)
Corticoteroid injection	2 (28.6)	5 (55.6)	6 (60.0)
Brace	5 (71.4)	5 (55.6)	2 (20.0)
PRTEE, score (SD)			
Composite	41.5 (6.4)	32.7 (7.1)	50.9 (6.1)
Pain	24.2 (2.7)	20.8 (3.0)	24.8 (2.6)
Function	16.4 (3.9)	18.1 (4.2)	26.0 (3.5)
Grip strength, Newton (SD)	299.4(61.7)	201.3(29.9)	181.7(42.6)
MRI-based CLE Severity Score			
None (Grade 0)	0	0	0
Mild (Grade 1)	2	3	2
Moderate (Grade 2)	3	3	4
Severe (Grade 3)	3	4	5

N, number; PRTEE, patient rated tennis elbow evaluation; SD, standard deviation; MRI, magnetic resonance imaging.

*All baseline differences between groups were not significant except age; participants in the dextrose-morrhuate group were younger than those in the other two groups (p=0.047).

Table 3

Patient-Rated Tennis Elbow Evaluation (PRTEE) composite and subscale scores over time in prolotherapy with dextrose (PrT-D, N=10), prolotherapy with dextrose and morrhuate (PrT-DM, N=10), and Waitlist control (N=12) groups.

Measure	Baseline	Week 4	Week 8	Week 16	Week 32
Composite Score (SE)					
PrT-D group **raw score, mean (SE)**	41.5 (6.4)	27.4[b](5.3)	27.2[a](5.9)	22.8[c*](7.2)	17.8[**](5.55)
Mean (SE) and percent [%] change from baseline		14.1(6.5) [33.9]	14.3(8.7) [34.5]	18.7(9.6) [41.1]	23.7(8.4) [57.1]
PrT-DM group raw score, mean (SE)	32.7 (7.1)	31.0[b](6.0)	24.9[a](6.6)	15.2[c](8.1)	8.2[*](6.7)
Mean (SE) and percent [%] change from baseline		1.7(7.3) [5.2]	7.8 (10.5) [23.8]	17.5(11.6) [53.5]	24.5(10.6) [74.9]
Waitlist group raw score, mean (SE)	50.9 (6.1)	44.8[b](5.1)	46.7[a](5.6)	41.6[c](6.9)	NA
Mean (SE) and percent [%] change from baseline		6.1(7.2) [11.9]	4.2 (9.9) [8.2]	9.3(11.0) [18.3]	NA
Subscale raw score, mean (SE)					
Pain					
PrT-D	24.2 (2.7)	16.2 (2.6)	15.5 (3.0)	13.6[c*](3.6)	11.1[*](3.3)
PrT-DM	20.8 (3.0)	20.4 (2.9)	16.7 (3.4)	7.9[c*](4.0)	4.9[*](3.3)
Waitlist	24.8 (2.6)	22.4 (2.5)	23.2 (2.9)	20.9[c](3.5)	
Function					
PrT-D	16.4 (3.9)	11.1[b](3.0)	11.6[a](3.1)	9.1[a](3.7)	8.5[*](3.0)
PrT-DM	18.1 (4.2)	16.6[b](3.3)	13.3[a](3.5)	7.3[a](4.2)	5.0[*](3.0)
Waitlist	26.0 (3.5)	22.2[b](2.8)	23.2[a](3.0)	20.6[a](3.6)	

SE, standard error; N, Number;

Between group analysis at each time point used a general linear model, adjusted for age during the 16-week portion of study:

[a]x; Change in PrT-D score and PrT-DM score was greater than Waitlist ($p<0.05$); no significant differences between PrT-D and PrT-DM .

[b]x; Change in PrT-D score was greater than Waitlist ($p<0.05$); no significant differences between PrT-D and PrT-DM, and no significant difference between PrT-DM and Waitlist.

[c]x; Change in PrT-DM score was greater than Waitlist ($p<0.05$); no significant difference between PrT-D and PrT-DM,and no significant difference between PrT-D and Waitlist.

Within group analysis using paired t-tests compared scores at each time point to baseline status:

[**]x; Significant change from baseline ($p<.0.01$).

[*]x; Significant change from baseline ($p <0.05$).

Table 4

Grip strength for participants in prolotherapy with dextrose (PrT-D, N=10) and morrhuate (PrT-DM, N=10) and Waitlist control (N=12) groups.

Measure	Baseline	Week 8 (SE)	Week 16 (SE)	Week 32 (SE)
Grip Strength, Newtons, mean (SE)				
PrT-D (N=10)	299.4(61.7)	348.6(56.8)†◇	364.4(50.3)†◇*	368.9(49.9)*
PrT-DM (N=10)	201.3(29.9)	208.4(23.9)	202.2(21.5)	239.9(28.8)
Waitlist (N=12)	181.7(42.6)	210.1(40.2)	200.4(53.0)	NA

SE, Standard error; PrT , prolotherapy; D, dextrose; DM, dextrose-morrhuate; N, number; NA, not applicable.

*Improvement in grip strength compared to baseline status ($p<0.05$);

†Improvement in grip strength compared to Waitlist ($p<.05$);

◇Improvement in grip strength of the PrT-D group compared to the PrT-DM group ($p<.05$)

Table 5

Magnetic resonance imaging scores for the three groups over time. There were no changes between or within groups.

MRI Score	Baseline # participants	16 weeks # participants	32 weeks # participants
Control			
Grade 0	0	0	NA
1	2	2	NA
2	4	7	NA
3	5	2	NA
PrT-D			
Grade 0	0	0	0
1	2	3	3
2	3	3	2
3	3	3	3
PrT-DM			
Grade 0	0	0	0
1	3	3	3
2	3	3	3
3	4	2	2

MRI, magnetic resonance imaging; #, number; NA, not applicable; PrT-D, prolotherapy with dextrose; PrT-DM, prolotherapy with dextrose and morrhuate