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## The efficacy of prolotherapy for lateral epicondylitis: A pilot study

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### Abstract

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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 epicondylitis.

#### Setting

Outpatient Sport Medicine clinic.

#### Study Design

Double-blind randomized controlled trial.

#### Participants

Twenty-four adults with at least 6 months of refractory lateral epicondylitis.

#### 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 0.5mL injections were made at the supracondylar ridge, lateral epicondyle and annular ligament at baseline, 4 and 8 weeks.

#### Outcome Measures

The primary outcome was resting elbow pain (0–10 Likert scale). Secondary outcomes were extension and grip strength. Each was performed at baseline, 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 ( $4.5\pm 1.7$ ,  $3.6\pm 1.2$  and  $3.5\pm 1.5$  versus  $5.1\pm 0.8$ ,  $3.3\pm 0.9$  and  $0.5\pm 0.4$  at baseline, 8 and 16 weeks, respectively); at 16 weeks, these differences were significant compared to baseline scores within and between groups ( $p<.001$ ). Prolotherapy subjects also reported improvement extension strength compared to Controls ( $p<0.01$ ) and grip strength compared to baseline ( $p<0.05$ ). Clinical improvement in Prolotherapy 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 epicondylitis compared to Control injections.

**Keywords:** prolotherapy, lateral epicondylitis, injection therapy, tendinopathy

## INTRODUCTION

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Lateral epicondylitis (LE) (“tennis elbow”) is an important condition of the upper extremity with an incidence of 4–7/1000 patients per year in primary care settings.<sup>1–3</sup> 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 is lacking.<sup>4</sup> Cost and time away from job or activity are significant.<sup>5, 6</sup> 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 epicondylitis” is the preferred term.<sup>7–9</sup> While many non-surgical therapies have been tested for LE refractory to conservative measures, none have shown to be uniformly effective in the long term.<sup>10–12</sup>

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.<sup>13, 14</sup> Animal model studies suggest PrT using dextrose and sodium morrhuate may enlarge and strengthen ligament and tendon insertions, though the precise mechanism is unclear.<sup>15–17</sup> (Jensen 2007 Unpublished data) Injection protocols were formalized in the 1950s by George Hackett, MD, a general surgeon in the US.<sup>18</sup> Treatment generally includes injection of tender tendon and ligament attachments (entheses<sup>19</sup>), with small volumes of proliferant solution, in 3 to 5 treatment sessions at monthly intervals.<sup>18, 20</sup> Anecdotal reports indicate PrT is used in Sport Medicine and Primary Care practices for a variety of musculoskeletal conditions, including refractory lateral and medial epicondylitis.<sup>21, 22</sup> (Rabago Unpublished data) Several human randomized controlled trials (RCTs) assessing PrT have reported positive outcomes for low back pain compared to baseline status<sup>23</sup> and to control subjects,<sup>24, 25</sup> and for osteoarthritis,<sup>26, 27</sup> though methodological quality has varied.<sup>14, 28</sup> 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

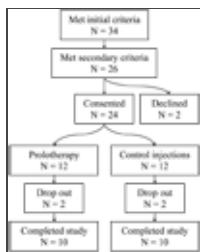
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The study protocol was approved by the institutional review board of Trinity Health Systems, Steubenville, Ohio.

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 one year. No RCTs of PrT for tendinopathy existed prior to 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 20–40% compared to baseline pain and disability conditions, <sup>23</sup> 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, 18 to 65 years old, 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 failed each of the following conservative care modalities: relative rest, physical therapy, non-steroidal anti-inflammatory drugs and two corticosteroid injections. Exclusion criteria included diabetes, corticosteroid elbow injection within 6 weeks and self-reported immuno-compromised 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, two declined participation and 24 were consented and 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 35mL sterile solution: 7.5mL 50% dextrose, 5mL of 5% sodium morrhuate, 2.5mL 4% lidocaine, 2.5mL 0.5% sensorcaine and 17.5mL 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 0.5mL 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 1.5mL. A peppering technique was not used. Injections occurred at baseline, 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 non-steroidal anti-inflammatory medications and starting new therapies.

### Outcome measures

The outcome measures for all subjects were identical and were assessed at baseline, 8, 16 and 52 weeks. The

primary outcome was a resting elbow pain, recorded on a 0–10 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<sup>29, 30</sup> using a single grip at each of five different cylindrical diameters from 3.6 to 8.8cm, squeezed for 3–5 seconds with 60 seconds between grips. Isometric resistance strength was tested with Baltimore Therapeutic Equipment Primus (BTE)<sup>31</sup> device, using a single measurement with the wrist in extension, thumb up in neutral orientation, and the elbow flexed at 90 degrees. With the forearm in neutral position, the wrist was held in extension against the BTE; an isometric force was then applied by the subject and measured by the BTE.” Pre-and post- treatment magnetic resonance images were obtained at baseline and 16 weeks, however these data are not retrievable from the optical disk on which they are were stored and are assumed to be permanently unavailable. At 52 weeks, subjects were asked (by telephone) three 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/No) and whether they used other therapies for pain since completion of injections (Yes/No).

### Analysis

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, 10 in each group.

The 20 subjects were analyzed according to their randomized allocation. All subjects attended each of three injection sessions. Among collected data for 20 subjects, there was one 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.<sup>32</sup>

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

### Results

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The study sample consisted of 24 Caucasian adults (13 female) randomized to PrT (n=12) and Control (n=12) groups. Subjects’ ages ranged from 19 to 62 years, with a mean age of  $45.7 \pm \text{SD } 10.7$  years. Duration of elbow pain ranged from 0.5 years to 10 years ( $\pm \text{SD}$ :  $1.9 \pm 2.7$  years in the sample;  $1.1 \pm 1.1$  years and  $2.7 \pm 3.5$  years for the Control and PrT groups, respectively,  $p=0.2$ ). Baseline demographics, pain and function scores were comparable between the two groups. Two subjects in each group dropped out of the study after baseline data collection but before any injections had been performed. These four 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 three subjects (one PrT, two Control) dropped out due to pain after baseline data collection but prior to any injections. They went on to pursue surgery and were lost to follow-up. No follow-up data was collected about these four drop-outs.

Therefore, the subsequent analysis of treatment effects was performed for 20 subjects who received injections and completed follow-up outcome questionnaires. Among 20 analyzed subjects, one Control subject moved out of the study area after the 16-week assessment and was not available for the 52-week follow-up.

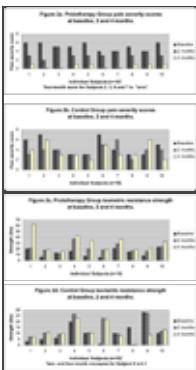
The 20 analyzed subjects were on average middle-aged ( $48.0 \pm SD 8.8$  years old) and suffered from moderate elbow pain ( $4.8 \pm SD 1.3$  points at rest). No significant baseline differences were found between the PrT (n=10) and Control (n=10) groups ([Table 1](#)).

	Controls	PrT	Total
	n=10	n=10	n=20
Female, % (n)	4 (40)	6 (60)	10 (50)
Age, yrs, mean (SD)	47.2 (8.0)	48.2 (8.5)	48.0 (8.8)
Duration of elbow pain, years (SD)	1.1 (1.1)	2.7 (3.5)	1.8 (2.7)
Pain at rest, points, mean (SD)	4.5 (1.7)	5.1 (1.8)	4.8 (2.0)
Isometric strength, lbs, mean (SD)	10.7 (6.3)	13.3 (6.7)	12.0 (7.4)
Grip strength, lbs, mean (SD)	32.2 (7.0)	30.1 (7.8)	31.2 (7.5)
Grip strength, % 1RM, mean (SD)	40.0 (22.8)	37.8 (20.1)	40.3 (21.6)
Grip strength, % 1RM, mean (SD)	40.4 (23.1)	38.1 (20.2)	40.0 (21.7)
Grip strength, % 1RM, mean (SD)	38.8 (20.8)	34.7 (21.3)	36.8 (20.4)
SD, lbs, % 1RM, mean (SD)	39.8 (20.8)	38.1 (20.2)	39.3 (19.8)
SD, lbs, % 1RM, mean (SD)	40.1 (21.0)	38.1 (20.2)	39.1 (20.6)

[Table 1](#)

Baseline subject (n=20) characteristics. Results presented for the Control ("Controls"), Prolotherapy (PrT) groups and for the whole sample ("Total), as number (percentage) or mean value (standard deviation, SD).

Over time, PrT subjects, but not Control subjects, showed a significant improvement in pain scores (mean  $\pm$  SD:  $5.1 \pm 0.8$ ,  $3.3 \pm 0.9$  and  $0.5 \pm 0.4$  versus  $4.5 \pm 1.7$ ,  $3.6 \pm 1.2$  and  $3.5 \pm 1.5$  at baseline, 8 and 16 weeks respectively) ([Figure 2a](#) and [Figure 2b](#)). The PrT subjects' pain scores at 16 weeks significantly improved when compared both to their own baseline ( $p < .001$ ) and to the Control subjects' scores ( $p < .001$ ). All ten subjects in the PrT group reported that their pain score was one point or less at 16 weeks. No Controls reported scores of one point or less at 16 weeks. Control 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 the pain score was 6.68, corresponding to a large effect size; the absolute effect size was 3.6 points on the 0–10 pain scale. The number needed to treat to achieve a 2-point improvement on a 0–10 Likert pain scale was 1.4.



[Figure 2](#)

Variable	Group	Baseline	8 weeks	16 weeks	p value	p value	p value
		mean (SD)	mean (SD)	mean (SD)	vs baseline	vs control	vs control
Pain <sup>a</sup>	Ctl	4.5 (1.7)	3.6 (1.2)	3.5 (1.5)	NS	NS	NS
	PrT	5.1 (1.8)	3.3 (0.9)	0.5 (0.4)	<.001	<.001	<.001
	SD	NS	NS	<.001			
Isometric strength <sup>b</sup>	Ctl	10.7 (6.3)	10.7 (6.3)	10.7 (6.3)	NS	NS	NS
	PrT	13.3 (6.7)	21.1 (7.2)	30.5 (14.8)	<.001	<.001	<.001
	SD	NS	<.001	<.001			
Grip strength <sup>c</sup>	Ctl	32.2 (7.0)	32.2 (7.0)	32.2 (7.0)	NS	NS	NS
	PrT	31.2 (7.5)	30.5 (7.4)	30.5 (7.4)	NS	NS	NS
	SD	NS	NS	NS			

[Table 2](#)

Primary and Secondary Outcomes: Pain scores, Grip Strength and Isometric Strength of Prolotherapy (PrT) and Control (Ctl) Groups at baseline (0), 8 and 16 weeks. Results are presented as mean value (standard deviation, SD).

Similarly, scores for isometric strength testing showed significant improvement in the PrT group, increasing from  $13.3 \pm SD 6.7$  lbs at baseline to  $21.1 \pm SD 7.2$  and  $30.5 \pm SD 14.8$  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 2c](#), [Figure 2d](#)).

Grip strength data was less definitive. PrT subjects did not significantly differ from Control 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 subjects plateaued at 8 weeks, while it continued to improve among PrT 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 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 subjects reported using or seeking additional therapy. Fifty-two week follow up data on one of the Control subjects was not available due to loss to follow-up; ten percent ( $n=1$ ) of the Control subjects had no elbow pain and 80% ( $n=8$ ) reported elbow pain sufficient to interfere with ADLs at 52 weeks. Among 9 control subjects, four reported using additional therapies (surgery,  $n=2$ ; extracorporeal shock wave therapy,  $n=1$ ; acupuncture,  $n=1$ ).

Side effects of injection therapy were minimal. All subjects ( $n=20$ ) experienced expected, self-limited post-injection pain; two PrT subjects experienced one episode each of local erythema, irritation and discomfort approximately one 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

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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 less than two consistent RCTs evaluating patient oriented evidence)<sup>37</sup> 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.<sup>13</sup> (Rabago unpublished data 2006) While sodium morrhuate is often clinically used in prolotherapy procedures (Rabago unpublished data 2006),<sup>13</sup> and its use has been reported in a case series,<sup>38</sup> 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 two points on a 0–10 Likert scale corresponded to a significant clinical difference across a variety of chronic pain conditions.<sup>39</sup> The difference between PrT and Control 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, suggesting a very meaningful clinical effect. Indeed, the number needed to treat to achieve a 2-point improvement on a 0–10 Likert pain scale using PrT in this study is 1.4. The pain score of four of ten PrT subjects at 16 weeks was “zero”.

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 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 subjects is consistent with findings from studies evaluating related injection therapies for tendinopathy. Lyftogt et al. used 20% dextrose in a study assessing PrT as a treatment for Achilles tendinopathy.<sup>40</sup> In this study, Doppler ultrasound-guided PrT injections were used to target and sclerose pathologic “neovessels” associated with tenderness.<sup>41</sup> Connel et al.<sup>42</sup> and Mishra et al.<sup>43</sup> used autologous blood and platelet rich plasma respectively as an injectant for lateral epicondylitis; they used a ‘peppering’ technique to fenestrate the tissue prior to 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<sup>41</sup> or collagen fibril disruption and subsequent healing response.<sup>42, 43</sup>

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;<sup>44, 45</sup> at high concentrations, sodium morrhuate in vitro is toxic to granulocytes, red blood cells, and endothelial cells.<sup>46</sup> This study used a relatively low concentration of dextrose (10.7%) for prolotherapy, although 10% has been reported in an RCT setting.<sup>26</sup> Stock 5% sodium morrhuate was used at 14.7% by volume in this study. This is a relatively high concentration of **SM** compared to anecdotally reported injection practices. (5%–20% by volume) (Jeff Patterson DO, Personal Communication 2007), though no rigorous assessment of injection patterns has been reported in existing surveys of prolotherapy practice patterns.<sup>13</sup> (Rabago, unpublished data 2006) When used to destroy neovessels in a procedure very similar to prolotherapy, the sclerosant polidocanol has been reported to reduce pain in lateral epicondyle,<sup>41, 47</sup> patellar<sup>48</sup> and Achilles<sup>49</sup> tendinopathies. Injections with dextrose and sodium morrhuate may have sclerosed neovessels and associated new nerves, though 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<sup>15</sup> and size (Jensen 2007 Unpublished data) 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 four randomized dropouts in the outcome analysis could have introduced bias. However, there are circumstances in which excluding drop-out is appropriate.<sup>50</sup> In the current study this was justified because: 1) the loss to follow-up was balanced in each group, 2) the four 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 was 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, though the 0–10 Likert scale is a standard measure of chronic pain.<sup>39</sup> A formal assessment of operator blinding was not performed, though 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 pre-filled blinded syringes. Grip strength assessment may have been compromised by non-standard technique; accuracy and reliability are enhanced when subjects perform grip testing 3 times at a given diameter.<sup>30</sup> Future studies should include a wrist strength rehabilitation program after pain control is achieved. One year follow-up questions were non-standard and while 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 subjects may have experienced greater post-injection pain than PrT subjects, though 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 Controls.

## Conclusions

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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 0–10 Likert pain scale is 1.4. This study provides level 1b evidence that PrT is an effective treatment for refractory lateral epicondylitis.<sup>37</sup> 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 lateral epicondylitis.

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