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Magnetic resonance imaging outcomes in a randomized controlled trial of prolotherapy for lateral epicondylitis

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Abstract

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Objective: To determine whether clinical improvement in lateral epicondylitis (LE) is associated with normalization of magnetic resonance images (MRI).

Methods: Twenty-four adults with refractory LE took part in a double-blind randomized controlled trial. Participants received prolotherapy or saline (control) injections at baseline, 4 and 8 weeks. Participants were assessed with clinical (0-10 visual analog scale) and functional (grip and isometric strength) measures and scanned using an Artoscan 0.2Tesla scanner, at baseline, 8 weeks and 16 weeks. The primary MRI outcome was an ordinal 0-3 severity grade based on common extensor tendon T1 and T2 signal intensity. Secondary MRI outcomes were the T2 area of pathology and a global impression of disease severity change.

Results: The clinical results have been published. Prolotherapy subjects, compared to controls, showed significant and clinically dramatic improvements in pain and biomechanical outcomes. In the current analysis, all participants showed similar MRI-demonstrated severity at baseline consistent with LE. While prolotherapy subjects clinically improved compared to controls, primary and secondary MRI outcome measures did not change compared to either baseline status or control participants.

Conclusions: There was a non-association between MRI-based severity and clinical severity at baseline and at 8-week and 16-week follow-up despite dramatic clinical improvement in response to PrT compared to control injections. Future studies may benefit from a stronger MRI and follow-up time of more than 16 weeks.

Key Words: lateral epicondylitis, magnetic resonance imaging, prolotherapy, tendinopathy

INTRODUCTION

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 settings¹⁻³ Auto industry workers have a prevalence of up to 16%.⁴ Cost and time away from job or activity are significant.^{5, 6} Treatment approaches for LE have historically varied widely and have included non-steroidal anti-inflammatory drugs, corticosteroid injections,^{7, 8} eccentric exercise,⁹ and other non-surgical therapies. None have been shown to be consistently effective.¹⁰⁻¹² The understanding of the pathophysiology of LE has changed in recent years.¹³⁻¹⁶ The hallmark of tendinopathy is now thought to be the presence of degenerative changes, including neovascularity and disorganized collagen fibers^{14, 17} which can be seen on histopathology, ultrasound (US) and magnetic resonance imaging (MRI).

The precise relationship of tissue degeneration and pain in patients with tendinopathy is unclear; US¹⁸⁻²⁰ and MRI²¹ have been used in an attempt to visually define the pathology for LE and other tendinopathies. While images using each technology show some association with elbow pain, no therapy has been shown to consistently modify the appearance of tendons on US or MRI. A more complete understanding of the pathophysiology of LE, including the nature of tendon healing in response to therapeutic intervention, is essential to guiding the development of future treatment. MRI may be an appropriate measure of disease modification in LE among patients with a positive clinical response to treatment. Chronic degeneration associated with LE changes the magnetic properties of molecules within the common extensor tendon (CET) that correspond to areas of mucoid degeneration and neovascularization.^{15, 22 23-25} However, the association between the degree of clinical improvement (pain and function) and MRI-based LE characteristics over time is not known.

Prolotherapy (PrT) is an injection therapy used for musculoskeletal conditions including osteoarthritis, low back pain and tendinopathies²⁶ which has been hypothesized to stimulate healing of chronic soft tissue injury.^{19, 27} We have recently reported dramatic clinical improvement for severe LE in response to PrT compared to control injections in an randomized controlled trial (RCT).²⁸ Briefly, 20 subjects with severe refractory LE and elbow pain for at least 6 months were treated with PrT or control saline injections. At 16 weeks, PrT subjects,

compared to controls, showed significant and clinically dramatic improvements in pain scores and biomechanical function outcomes. In the current study, we analyzed MRIs obtained prior to and after treatment for LE in participants of this trial to address the question: “is clinical improvement in severe LE at 16 weeks associated with normalization of MRI findings in participants receiving PrT compared to control injections?”

MATERIALS AND METHODS

The study protocol was approved by the institutional review board of Trinity Health Systems, Steubenville, Ohio and University of Wisconsin School of Medicine and Public Health. Participants with severe refractory LE took part in the study from 1999 to 2002. The methods and clinical results of the parent clinical study were published.²⁸ Figure 1 presents the participant flow in the parent study; Table 1 provides a brief description of participant eligibility criteria, study interventions, main outcome measures and clinical results. Briefly, subjects were randomized to receive injections with active PrT solution or saline control solution. The operator and participant were blinded to allocation. Subjects were assessed using a 0-10 visual analog pain scale and Isometric resistance strength using a Baltimore Therapeutic Equipment Primus (BTE)²⁹ device. Magnetic resonance images were obtained as part of the original study protocol but were not analyzed because the magnetic optical disc on which the images were stored was considered damaged; the radiographic images were assumed to be irretrievable. In 2008, undamaged elbow images were retrieved from the optical disc and transferred to compact disc.

Imaging Technique

An MRI examination of the symptomatic elbow was performed on participants using an Artoscan 0.2Tesla scanner at baseline, 8 weeks and 16 weeks. All 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 sequences were performed with a 15 cm field of view, 192 x 160 matrix, and 3.5 mm slice thickness.

Data Extraction

Images were initially saved to a magnetic optical disc and later transferred to compact disc by Extremity Imaging Partners. Images were viewed using Efilm software™. All MR elbow examinations were reviewed in random order by a fellowship-trained musculoskeletal radiologist (RK) who was blinded to the treatment allocation and participant clinical findings. He was aware of the images sequence for each participant.

MRI-based Outcome Measures

No validated metric correlates MRI findings with clinical disease severity for LE either at baseline or in response to clinical improvement; based on existing literature 3 scales were developed for this analysis. The primary outcome was an ordinal 0-3 severity grade. The scale is based on the T1 and T2 signal intensity at the common extensor tendon. Grade 1 disease corresponds to tendinopathy which consists of tendon thickening and intermediate T1 and T2 signal intensity within the tendon. Areas of intermediate T2 signal intensity within the diseased tendon have been reported to correspond to areas of collagen disruption, mucoid degeneration and neovascularization on histopathologic analysis.^{15, 30} Grade 2 disease corresponds to a partial thickness tear which consists of intermediate T1 and high T2 signal intensity within a portion of the tendon. Areas of high T2 signal intensity within the diseased tendon which been reported to correspond the areas of collagen disruption on histologic analysis. Grade 3 disease corresponds to a full thickness tear which consists of intermediate T1 and high T2 signal intensity within the entire tendon. We also developed two secondary measures, 1) a quantitative scoring metric based on the area of pathology on the common extensor tendon and 2) a global impression of disease severity change when baseline images were compared to 8 or 16 week images (no change, improved, worsened).

Analysis

Data was analyzed with SPSS version 15.0 statistical software.³¹ Study participants were analyzed according to their randomized allocation. Randomization effects were assessed by comparing baseline characteristics of PrT and Control groups. Ordinal data for the primary outcome are presented on a per subject basis (Table 3). Distributional characteristics of the data were evaluated. Most variables displayed a normal distribution; three continuous variables (MRI-

assessed T2 area at baseline, 8 weeks and 16 weeks) were not normally distributed. Descriptive statistics were used to describe baseline characteristics of the sample. Quantitative data was assessed using repeated measures analysis of variance³²⁻³⁴ for the normally-distributed variables 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); bivariate relationships were evaluated with Pearson correlation. For non-normally distributed variables, non-parametric tests (Friedman test for multiple related samples, Wilcoxon or Mann-Whitney tests for two related or independent samples, and Spearman correlation test) were used, respectively. Statistical significance was assessed using two-tailed tests ($p < 0.05$). Results are presented as mean $\pm$ standard deviation (SD), unless specified otherwise.

RESULTS

The clinical results of the parent study have been published.²⁸ Briefly, the study sample consisted of 24 Caucasian adults aged $45.7 \pm \text{SD } 10.7$ years with a duration of elbow pain ranging from 0.5 years to 10 years ($\pm \text{SD: } 1.9 \pm 2.7$ years. Baseline demographics, pain, function scores and MRI-related characteristics were comparable between the two groups. Two subjects in each group dropped out of the study prior to receiving injections but did not have significantly different baseline severity scores compared to participants who began the injection series. Analysis was carried out on all 20 subjects who began injection therapy; each underwent baseline and 8-week elbow MRI evaluation. Four participants (three PrT, one Control) did not complete their 16-week MRI testing; these 4 participants did not statistically differ from the rest of the sample on their baseline, 8-week, and available 16-week characteristics. One control subject who did not complete the 16-week MRI testing was the only control subject whose MRI-assessed global disease severity grade worsened (from “1” at baseline to “2” at 8 weeks).

The 20 analyzed participants were middle-aged ($48.0 \pm \text{SD } 8.8$ years old) and suffered from moderate elbow pain ($4.8 \pm \text{SD } 1.3$ points at rest). All had MRI proven LE as assessed by the primary outcome measure; 9 participants had Grade 1 (45%), 9 had Grade 2 (45%) and 2 (in the PrT group) had Grade 3 (10%), average (mean) Grade 1.7 ± 0.7 , median 2. (Table 3).

Clinical outcome results have been published;²⁸ over 16 weeks, PrT participants, but not Control participants, showed a significant improvement in pain and strength scores. (Table 1) PrT participants reported an absolute reduction in pain scores of 3.6 points on the 0-10 pain scale at 16 weeks (68% improvement compared to control injections) ($p < .001$). All ten participants in the PrT group reported that their pain score was one point or less at 16 weeks. Control participants did not significantly change their pain scores over the 16-week period (Table 3). 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 number needed to treat to achieve a 2-point improvement on the 0-10 Likert pain scale was 1.4.

Similarly, scores for isometric strength testing showed significant improvement in the PrT group. 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 participants did not make significant isometric strength gains over time. No demographic variable predicted differences in follow-up scores.

Primary MRI Outcome Results: Formal staging of the MRI-based disease severity showed that at baseline, in the PrT group, four participants were classified as Grade 1, four as Grade 2, and two as Grade 3; in the Control group five participants were classified as Grade 1 and five as Grade 2. (Table 3) At 8 weeks, 4/20 imaged participants changed their grade: two PrT participants improved (one of these did not complete 16-week imaging); worsening occurred in one subject from each group (the Control subject did not complete the 16-week imaging). At 16 weeks, 3/7 imaged PrT participants changed their Grade (one improved, two worsened); none of the 9 Controls changed grade. The MRI-based global disease severity changed in 9/20 participants at 8 weeks. One PrT and 3 Controls worsened and 3 PrT and 2 Controls improved. At 16 weeks, 8/16 participants had changed grade from baseline. Two PrT and 2 Controls improved and 2 PrT and 2 Controls worsened.

Secondary Outcomes: Overall, the MRI-determined T2 area of the common extensor tendon did not change significantly during the study (Table 4). While the average area of pathology in the PrT group showed a tendency to decrease slightly, area among Control participants appeared to

increase over time. However, variability was high and these trends were not statistically significant.

Comparison between the disease-specific grade change and the “global disease severity” change showed that about 1/3 of these results at both 8 and 16 weeks (7/20 and 5/16, respectively) were inconsistent; the discrepancy between the Grade change and “global disease severity” change did not follow any specific pattern and was not associated with a clinical change in pain severity or mechanical measures. There was no association between MRI grading and pain score at baseline. In addition, clinical grade at baseline was not predictive of clinical improvement at 8 or 16 weeks.

DISCUSSION

This is the first RCT to use MRI as an outcome measure of LE treatment response. All participants showed baseline pathology on MRI consistent with severe LE, though severity scores did not correlate with clinical severity scores for either group. We also found a lack of association between magnetic resonance severity scores and clinical severity scores among participants with severe LE at 8 and 16 weeks. While participants receiving PrT reported dramatic improvement in pain and function scores compared to Controls, scores on three different MRI severity assessments did not improve among PrT participants compared to Controls at either the 8 or 16 week follow-up points.

These findings are consistent with those of one other study, a non-randomized controlled study of MRI responsiveness to clinical outcomes.²¹ In this study, 30 participants with LE of unreported duration and severity improved clinically after treatment with wrist splint or corticosteroid injection. Magnetic resonance images showed baseline pathologic changes in 25 of the 30 participants compared to no change in 20 of 22 normal controls at baseline. Pathologic changes persisted at the 6-week MRI follow-up among LE participants in spite of clinical improvement. The degree of the clinical improvement and the use of functional assessment were not reported.

The results of both studies suggest a limited role for MRI in diagnosis and monitoring of LE in the routine outpatient context. While studies have reported that changes in the thickness of the common extensor tendon and areas of fluid-like signal intensity are associated with the clinical condition of LE,¹⁵ a clear, consistent relationship between such changes and clinical outcomes has not been reported. Savnik et al. suggested that MRI may have a role in monitoring treatment response in order to select a more specific therapy.²¹ However, given that MRI may be non-responsive to even dramatic clinical change in LE reported in the current study, it is difficult to assign a valid post-treatment role for MRI follow-up compared to monitoring of pain and functional responses alone.

MRI may have a role in the research setting as an outcome measure with which to follow treatment response. The underlying pathophysiology of LE, including the etiology of pain and disability, remains unclear. Given that LE appears abnormal on MRI at baseline, it is reasonable to suppose that complete resolution of pain and full return to function would be associated with improvement in tissue morphology on MRI over time. Three aspects of the MRI methods used in the current and other studies may have resulted in an incomplete assessment of the ability of MRI to detect tissue change. 1) The MRI examination in our study was performed on a 0.2T scanner using T2-weighted sequences without fat-suppression. The use of currently available 1.5T and 3.0T scanners can produce T2-weighted images of the common extensor tendon with much higher spatial resolution and with suppression of the signal intensity of fat within tissue. These factors improve the ability of MRI to distinguish between normal and diseased tendon and allow better grading of the overall severity of tissue degeneration. 2) The follow-up time of 16 weeks may have been too short to detect tissue remodeling on MRI though MRI proven ligament healing in response to prolotherapy has been reported at 15 weeks post treatment initiation. 3) The small size of this study and natural variation in the degree of tissue pathology may have prevented the detection of physiological trends.

These findings have several implications for research. Normalization of tissue on MRI in the context of pain and function improvement would demonstrate disease modification. More powerful MRI with greater than 16 week follow-up therefore remains a potentially important outcome measure in assessments of therapies for LE. Ultrasound may also have a role in LE

assessment. Grey-scale and power Doppler US studies indicate an association between clinical LE symptoms and US-based structural changes of the common extensor tendon, however the degree and nature of the association is not clear.³⁵⁻³⁷

There are several limitations of this pilot study. The primary limitation is the lack of a standardized scale. We attempted address this through the use of 3 distinct scales assessing slightly different aspects of LE. The result of each is consistent (no change at 16 weeks), suggesting that the overall negative finding of the study is real. Limitations also include a small sample size, using a dated MRI protocol and technology and short follow-up time of 16 weeks.

Conclusions

In this pilot study of 20 subjects with severe LE and baseline MRI abnormalities we report the lack of association between MRI-based severity and clinical severity at baseline, and at 8-week and 16-week follow-up despite dramatic clinical improvement in response to PrT compared to control injections. This suggests a limited role for MRI in routine non-surgical follow-up of therapeutic intervention for LE. The role of MRI in the research setting is less clear and further studies using MRI scanners stronger than 0.2 Tesla and protocols over time periods greater than 16 weeks are warranted.

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Conflict of Interest: None

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Figure and Table Legends

Figure 1 Flow diagram of trial recruitment processes and participants

Table 1. Methods and Clinical Results of Parent Randomized Controlled Trial

Table 2. Primary and Secondary MRI Outcome Measures

Table 3. MRI grade and change in pain scores (on 0-10 visual analog scale) by subject from baseline to 16 weeks in PrT and Control groups

Table 4: T2-MRI area of pathology in the common extensor tendon in square millimeters'

No significant relationship regarding T2-based area of pathology at any time point was detected between or within groups

Figure 1 Flow diagram of trial recruitment processes and participants

Table 1. Methods and Clinical Results of Parent Randomized Controlled Trial

Inclusion Criteria	18-65 yrs old LE with elbow pain for ≥ 6 months Failed each of: relative rest, PT, NSAIDS, 2 Corticosteroid injections
Intervention	3 blinded injection sessions at 0, 4, 8 weeks with active or control solution at the supracondylar ridge, lateral epicondyle and the annular ligament (approximately 0.5mL at each site) using a total of 1.5 mL of: <u>Active solution:</u> 1.5 parts 50% dextrose, 0.5 parts 4% lidocaine, 0.5 parts sensorcaine and 3.5 parts normal saline or <u>Control solution:</u> 0.9% saline Both operator and participant were blinded to allocation
Primary Outcome Measure	Resting pain using 0-10 visual analog scale (VAS) at baseline, 8 and 16 weeks
Secondary Outcome Measures	Isometric strength using Baltimore Therapeutic Equipment Primus device at baseline, 8 and 16 weeks Grip strength using hand dynamometer at baseline, 8 and 16 weeks Qualitative assessment of pain, effect on activities of daily living at 52 weeks
Randomization	Balanced randomization of 20 adult participants aged $48.0 \pm SD 8.8$ years old with moderate to severe resting elbow pain ($4.8/10 \pm SD 1.3$ points) for $1.9 \pm SD 2.7$ years.
Primary Outcome Results	Resting pain scores: PrT participants reported absolute effect size of 3.6 points (68%) on the 0-10 VAS pain scale compared to Control at 16 weeks. ($p < 0.001$)
Secondary Outcomes Results	Isometric strength: PrT participants improved compared to Control ($p < 0.01$) Grip strength: PrT participants improved compared to baseline ($p < 0.05$) Qualitative assessment at 52 weeks: Maintenance of clinical improvement among PrT participants compared to control. Safety: No significant side effects or adverse events.

Table 2. Primary and Secondary MRI Outcome Measures	
Primary Outcome: Semi-qualitative Assessment	
0	Normal common extensor tendon of uniform low signal intensity on T1-weighted and T2-weighted images

1	Mild tendinopathy of common extensor tendon; thickened, intermediate signal intensity on T1-weighted and T2-weighted images
2	Moderate tendinopathy of common extensor tendon; thinned, showed focal areas of intense fluid-like signal intensity on T2-weighted images which comprised less than 50% of the total cross sectional diameter of the tendon
3	Severe tendinopathy of common extensor tendon; thinned, showed focal areas of intense fluid like signal intensity on T2-weighted images which comprised more than 50% of the total cross sectional diameter of the tendon
Secondary Outcome Measures	
<p>Quantitative Assessment: Degree of Pathology</p> <p>The radiologist measured the largest anterior-posterior and medial-lateral width of the area of increased signal intensity within the common extensor tendon on the axial T2-weighted spin-echo images using the electronic calipers on the Efilm software.</p> <p>Qualitative Assessment: Change in Global Disease Severity Over Time</p> <p>When reviewing the post-treatment MR examinations, the radiologist documented whether the overall severity of the lateral epicondylitis has increased, decreased, or remained the same when compared to the pre-treatment MR examinations.</p>	

Table 3. MRI grade and change in pain scores (on 0-10 visual analog scale) by subject from baseline to 16 weeks in PrT and Control groups

Participants by group	MRI grading			Reduction in pain severity score (baseline versus 16 weeks)
	Baseline	8 weeks	16 weeks	
Prolotherapy group, subject number:				
1	2	2	2	5
2	3	2	2	6
3	1	2	2	5
4	2	2	2	4
5	2	2	2	5
6	1	1	MD	4
7	1	1	2	4

8	2	2	2	4
9	3	1	MD	3
10	1	1	MD	5
Control group, subject number:				
11	1	1	1	2
12	1	2	MD	1
13	1	1	1	1
14	1	1	1	0
15	2	2	2	1
16	2	2	2	2
17	1	1	1	1
18	2	2	2	0
19	2	2	2	-3 (worsened)
20	2	2	2	3

MD = missing data

Table 4: T2-MRI area of pathology in the common extensor tendon in square millimeters'

No significant relationship regarding T2-based area of pathology at any time point was detected between or within groups

Group assignment	Baseline	8 weeks	16 weeks
Prolotherapy	115.5 ± 166.9	72.4 ± 94.8	81.3 ± 100.6
Control	49.2 ± 110.8	112.6 ± 224.0	158.9 ± 352.047