CLINICAL EFFECTS OF PROLOTHERAPY FOR CHRONIC FOOT AND ANKLE PAIN

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INTRODUCTION

Prolotherapy or proliferative therapy is an injection-based treatment for chronic ligamentous injury, tendinopathy, or joint pain. Animal models suggest prolotherapy may enlarge and strengthen ligament and tendon insertions, although the mechanism is unclear (1-7). Prolotherapy injection protocols were pioneered in the 1950s by George Hackett, MD, a general surgeon in the US (8).

Although there are multiple theories on the mechanism of prolotherapy, the dominant theory suggests dextrose acts as a biologically inactive inflammatory substance, which stimulates tissue repair. The injection of an inflammatory solution briefly stimulates the inflammatory cascade to simulate an acute injury without deforming tissue (9) (Figure 1). The inflammatory cascade at the site of injection induces fibroblast proliferation and subsequent collagen synthesis, resulting in a tighter and stronger ligament or tendon (4).

Prolotherapy has multiple applications in ligamentous and joint pain in the human body. It has been described in the treatment of osteoarthritic joints (10-13), musculoskeletal pain (14-19), low back pain (20-22), lateral epicondylosis (23-25), and ligamentous laxity (26). More specifically, it has been described for treatment of tendons and ligaments in the foot and ankle (27-30), Achilles tendonitis (3-37) as well as chronic recalcitrant plantar fasciitis (38, 39).

It has been shown that eccentric exercises play a key role in the treatment of tendonopathy (40). Physical therapy in combination with prolotherapy was evaluated in a randomized trial by Yelland et al. The study examined chronic Achilles tendinopathy in 40 patients. The study showed greater improvement in subjective scores at 12 months with prolotherapy plus eccentric exercise compared to eccentric exercise alone (36).

Another study by Maxwell et al examined 30 patients with Achilles tendinopathy after prolotherapy treatment using ultrasound imaging to evaluate the Achilles tendon. The study showed pain severity had decreased by 88% during rest, and decreased 84% with usual activity after 12 months. Additionally, tendon thickness was noted to be decreased significantly (37).

The overall aim of this study is to study the clinical effects of prolotherapy on foot and ankle pain. Our objectives were to provide information on the medium term outcomes of prolotherapy injections, as well as study the side effects associated with treatment.

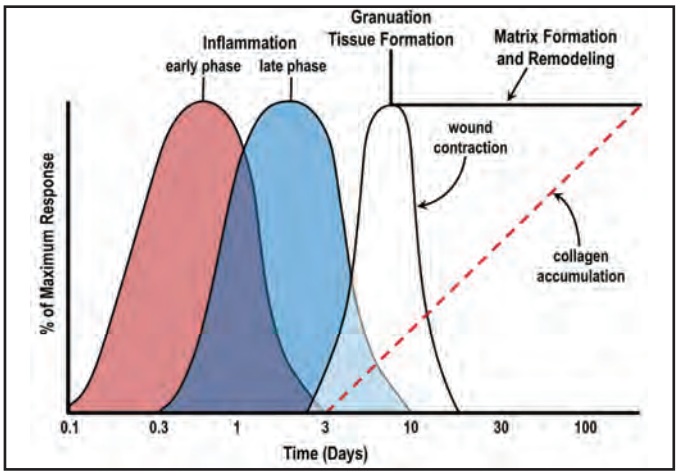

Figure 1. Early and late inflammation (days) leads to fibroblast proliferation creating granulation tissue (weeks), and eventually collagen maturation and healing or scar formation (months to years) (adapted from ref. 7).

MATERIALS AND METHODS

Following Sharp Healthcare Institutional Review Board approval, electronic medical records were retrospectively reviewed. Initially, a query was made to serially isolate all patients who had the treatment code J3490, "unclassified drugs." Records were searched from 2009 to 2013. This query yielded 171 patients. For each patient, the medical progress notes were reviewed to determine if prolotherapy had been used for this patient.

A total of 34 patients matched the treatment code J3490 but did not receive prolotherapy and were excluded from the study. The 14 patients who did not meet the criteria of a minimum of 6 months follow-up were also excluded. The 123 patients who met inclusion criteria were sent a questionnaire by postal mail. Patients not responding to surface mail were phoned for follow-up. Patients participating provided written consent. The survey included questions with subtopics of pain, disability, activity, and global satisfaction questions (Appendix 1). The custom subjective survey is similar to the one used by Hauser et al (28) for chronic ankle pain.

Data collected retrospectively for each patient included

Table 1. Descriptive characteristics of patients included in study

Measurement	Mean (Min-Max)
Age	54.6 (27-83)
Male/Female	13/29
Body Mass index	31.7 (18.9-49.7)
Months after treatment	30.5 (6-65)
Pts with history of PVD	2
Pts with history of diabetes mellitus	3

Table 2. Detailed view of subject distribution by diagnosis, average number of injections by diagnosis

Patient Diagnosis	Number of patients	Average Number of Injections for Diagnosis
Achilles tendonitis	13	5.5
Peroneal tendonitis	5	5
ATFL ligament pain	8	5.7
Plantar fasciitis	2	2.6
Midfoot arthritis	3	1.6
Ankle joint pain	1	11.7
Posterior tibial tendonits	3	12.6
Metatarsalgia	1	2.2
5th met frx pain	1	3.7
Subtalar joint pain	2	20

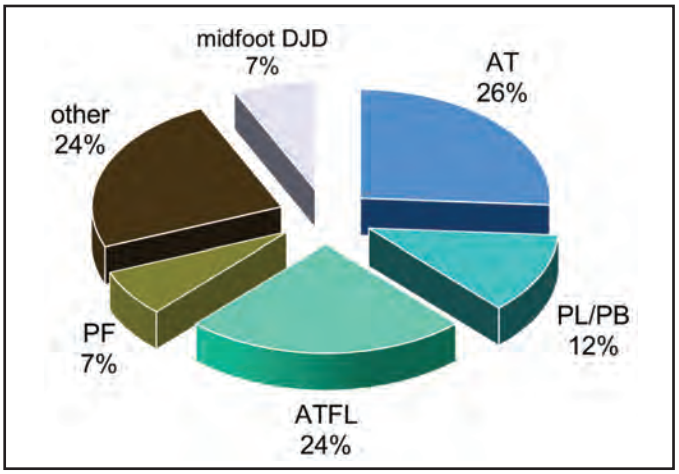

Figure 2. Patient distribution by diagnosis. Midfoot DJD= midfoot degenerative arthritis.

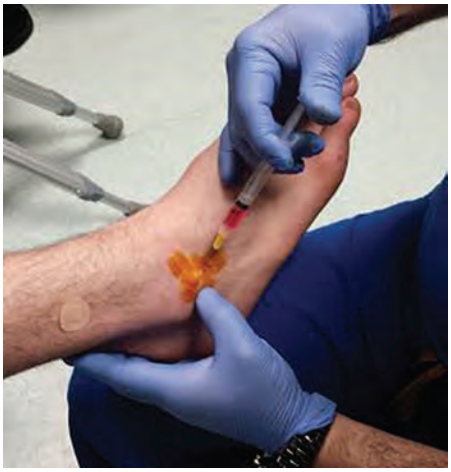

Figure 3. A 20-year-old male receiving a prolotherapy injection at the anterior talofibular ligament.

age, sex, and body mass index. Additionally, the patient records were reviewed for the presence of diabetes mellitus and vascular disease. Patient progress notes were reviewed for any side effects or complications associated with prolotherapy.

A total of 42 patients responded to the study, with a mean age of 54.6 years (range 27-83 years). The patients were followed for a mean of 30.5 months (range 6 to 65 months). The patient baseline characteristics are provided in Table 1. Patient diagnosis and the corresponding number of injections are shown in Table 2. The patient distribution by diagnosis is shown in Figure 2.

PROLOTHERAPY TECHNIQUE

Although injection protocols were pioneered by George Hackett, no formal practice guidelines have been established (41). Patients included had already completed a trial of steroid injection or immobilization. Patients received a single injection once per week in the area of maximal tenderness (Figure 3). Injections were followed by a period of immobilization, then physical therapy. Treatment was administered until pain relief was achieved. If the patient failed to notice significant improvement after several injections, prolotherapy was discontinued.

The prolotherapy injections were a mixture of hyperosmolar dextrose, sarapin, and an amide local anesthetic. Sarapin was selected because of its known inflammatory properties as a sclerosing agent, as well as its reported ability to provide nerve blockade through a different chemical pathway than amide local anesthetic (42). The prolotherapy mixture that was used in our study is described in Table 3. Mixing different prolotherapy agents, and variable dextrose concentration has been described in the literature, however to our knowledge, no clinical trials have compared solutions against one another.

RESULTS

When comparing the pain level on a visual analog scale (VAS) before and after prolotherapy, the mean difference between pain scores was decreased by 4.86 points after the prolotherapy intervention (Figure 4). Reviewing medical records of those patients who received prolotherapy, side effects were reported in 9 of the 123 patients (7.3%). Pain at the injection site was the most common side effect (5%), with swelling being the second most common (1.6%). It is unclear whether the single case of a minor plantar fascia partial tear may have been related to steroid injections prior to prolotherapy (Table 4).

SURVEY ANALYSIS

Patients had an average of 15.6 months of pain (range 1-48 months) prior to prolotherapy treatment. When comparing the pain level on a scale before and after prolotherapy, the mean difference between pain scores was 4.86 points less after the prolotherapy intervention. A total of 81.0% of patients felt the prolotherapy was effective. The remainder of the survey results are described in Table 5. There seemed to be no correlation with the presence of diabetes mellitus or vascular disease with outcomes.

Table 3. A 1:1:1:1 mixture of hyperosmolar dextrose, sarapin, a sclerosing agent, and marcaine and lidocaine without epinephrine, was used for the study

Agent	Amount
Dextrose 50%	1 ml (25%)
Sarapin	1 ml (25%)
0.5% marcaine without epinephrine	1 ml (25%)
1.0% lidocaine without epinephrine	1 ml (25%)

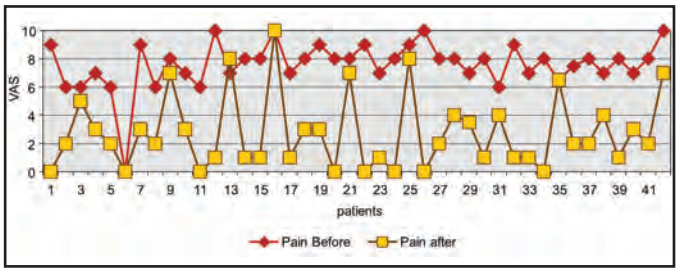

Figure 4. Pain before and after. The x axis represents each individual patient, Y axis is visual analog scale (range 0-10).

Table 4. Side effects evaluated in 123 patients. A majority of the side effects were pain at the injection site

Diagnosis	Side effect	Description
Midfoot arthritis pain	Pain at injection site	Had 2-3 days of pain after prolo x 1 injection.
Anterior talo fibular ligament pain	Pain at injection site	Pain on 2nd prolotherapy injection, resolved in 72 hours.
Achilles tendonitis	Pain at injection site	Pain on 2nd prolotherapy injection, resolved in 72 hours.
Achilles tendonitis	Pain at injection site	Experiencing calf pain, proximal to injection. Negative work up for tendon rupture
Peroneal tendonitis	Pain at injection site	Pain at the injection site after 1st prolotherapy treatment for one week
5th met frx pain	Pain at injection site	Pain and swelling after the 4th injection for one week
Anterior talo fibular ligament pain	Swelling	Swelling for two days possibly due to prolotherapy.
Peroneal tendonitis	Swelling.	Had swelling. Had hot and cold sensation. Related to pre-existing RSD
Plantar fasciitis	Plantar fascia tear	Minor plantar fascial tear diagnosed by MRI after injection treatemtn. Questionable if this was due to multiple cortisone injections prior to prolotherapy.

DISCUSSION

This uncontrolled study showed significant improvement in foot and ankle pain and function, with an average of 2.5 years follow-up after prolotherapy treatment. Overall, the survey results suggest that prolotherapy may play an important role in the treatment of chronic Achilles tendinosis, as well as other areas of chronic ligamentous pain such as the peroneal tendons and anterior talo-fibular ligament, given that patients included in this study did not respond well to other conservative treatments. These outcomes are consistent with another prolotherapy study for the Achilles tendon, though comparison is difficult to make because of different treatment protocols (36), different outcome measures.

In a recent study, the safety and efficacy of steroid injections were compared to alternative injection therapies such as prolotherapy (20,25). The only recorded side effect of prolotherapy in controlled trials was pain. The side effects associated with steroid injections at the Achilles tendon were atrophy (9%), pain (8%), depigmentation (<1%), and rupture (<1%) (43). In our study, the side effect rate was less than 1%, discounting pain at the injection site lasting less than 72 hours.

A limitation of this study was lack of a comparison group. The assessment of participant satisfaction was subject to bias, because the pre- and postintervention pain scores were collected at the same time. Our response rate to the survey was only 35%, which fell short of our goal of 70% (44,45). The study survey that was sent out was not a validated scoring system. Our intention was to include open-ended questions for patients to respond about prolotherapy. Ultrasound analysis of the Achilles tendon was not done due to the heterogeneity of treatment sites in this study.

Strengths include pragmatic assessment using the VAS, as well as a robust analysis of the retrospective data. Although lacking in control and randomization, this is the largest published study of the use of prolotherapy for chronic foot and ankle pain, to our knowledge. Mean follow- up was approximately 2.5 years, a longer follow-up time than the Maxwell (37) and Yelland (36) studies, which were specific to the Achilles tendon alone. Determination of clinical utility of prolotherapy for foot and ankle ligaments will require assessment in a larger randomized multidisciplinary trial.

Prolotherapy resulted in a relatively safe and sustained improvement on pain, function, and stiffness measures in patients presenting with foot and ankle pain. Prolotherapy performed by an experienced clinician may be an appropriate therapy for selected patients with moderate to severe foot and ankle pain who are refractory to conservative care, especially those who are otherwise unable to undergo surgical treatment.

Special thanks to the Sharp Rees Steely Clinical Research Group and to Research Assistant Brenda Lin for her diligent work.

Table 5. Survey Results: Quantitative scaled responses were formatted in an ordinal fashion to better interpret the data

Question	**Good**	**Fair**	**Poor**
Foot and ankle stiffness	76%	17%	7%
Foot and ankle ROM	78%	12%	10%
Exercise ability	60%	23%	18%
Question	**Never**	**Sometimes**	**Always**
Uses crutches, cane, walker outdoors	88%	0	12%
Need to limit physical activities	71%	17%	12%
Question	**Pleased**	**Moderately Pleased**	**Not Pleased**
Overall how pleased with therapy	81%	5%	14%
Question	**Much better**	**Somewhat better**	**Not improved/Worse**
Problems now compared to before	85%	12%	2%

APPENDIX 1

Prolotherapy Injections Survey

SURVEY IDENTIFICATION CODE: _____

This is a research study being performed by Dr. Amir Hajimirsadeghi and Dr. George Rivello.
This study is for the purpose of determining outcomes of prolotherapy injection treatment for the treatment of chronic foot and ankle pain. You are being asked to participate in a survey to understand the long term benefits, complications and outcomes of an injection therapy that you have had in the past.
We ask that you complete the following questions as truthfully as possible. There are no anticipated risks to completing this survey. Your personal information is protected and private. You are under no obligation to participate and choosing not to will in no way affect your medical care.

Please answer the following questions about your pain level by circling one of the numbers, 0 -10.

1. Pain before prolotherapy

No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain imaginable

2. Pain after prolotherapy

No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain imaginable

Answer the following questions about your ability after therapy by circling one of the numbers, 0 -10.

3. Foot and ankle Stiffness

Extremely good 0 1 2 3 4 5 6 7 8 9 10 Extremely limited

4. Range of motion of affected foot and ankle

Extremely good 0 1 2 3 4 5 6 7 8 9 10 Extremely limited

5. Exercise ability

Extremely good 0 1 2 3 4 5 6 7 8 9 10 Extremely limited

Answer all of the following questions related to your activities over the past week by circling one of the numbers, 0 -10. How much of the time did you:

6. Use an assistive device (cane, walker, crutches) indoors?

None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time

7. Use and assistive device (cane, walker, crutches) outdoors?

None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time

8. Limit physical activities?

None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time

Please answer the following.

9. Months of pain prior to prolotherapy treatment: ____

Answer the following questions by circling YES or NO.

10. Have you ever been told by a medical professional that "nothing could be done" or that "surgery is the only option" for your foot/ankle related problem?

YES NO

11. Have you reduced pain medication after therapy?

YES NO

Answer the following question in your own words.

12. Do you feel the therapy was effective? Briefly explain why or why not:

Answer the following question about your overall satisfaction by circling one of the numbers, 0 -10.

13. Overall how pleased have you been with the result of the prolotherapy on your foot/ankle, so far?

Very pleased 0 1 2 3 4 5 6 7 8 9 10 Very disappointed

Answer this question related to your therapy overall by circling one of the numbers, 0 -10.

14. How are the problems related to your foot/ankle now, compared to with before your prolotherapy injections?

Much better 0 1 2 3 4 5 6 7 8 9 10 Much worse

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