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Lyftogt perineural injection therapy® as a primary treatment for plantar fasciitis: a randomized, controlled pilot with crossover

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Abstract:

Background: Plantar fasciitis is a common condition that interferes with patient function and activity level. This study compared usual care to Lyftogt perineural injection therapy® as a primary treatment for plantar fasciitis.

Methods: Subjects with foot pain associated with plantar fasciitis were recruited in to the study. They were randomized into the usual care protocol or treatment with Lyftogt perineural injection therapy®. Subjects in the injection group were injected weekly for 8 weeks. Five milliliters of 5% dextrose in water were injected perineural to the saphenous nerve at the adductor canal and the deep tibial nerve at the bifurcation of the gastrocnemius muscles of the affected side. Subjects who completed the 8 week usual care protocol, crossed over into the injection therapy arm. Subject assessed Roles and Maudsley Scores on a 1-4 scale, physician assessed pain with palpation on a 1-4 scale, and MSKUS measured plantar fasciitis thickness were tracked.

Results: Complete information for 9 control and 9 intervention subjects was compiled. MSKUS measured plantar fasciitis thickness was significantly reduced in the intervention group ($p = 0.019$). Physician assessed pain with palpation was also significantly reduced for the compiled intervention group ($p = 0.006$).

Conclusion: Lyftogt perineural injection therapy® may be a viable treatment option for plantar fasciitis.

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Introduction:

Plantar fasciitis occurs at a rate of approximately 11-15% in the adult US population.[1] Although it is often self-limiting, many patients seek treatment due to pain when weight bearing that interferes with their activities. Recommended therapy is step-wise and includes the following Grade B recommendations: Achilles and plantar fascia stretching, padding or strapping the foot, orthotic insoles, oral anti-inflammatories, and corticosteroid injection.[1]

Lyftogt perineural injection therapy® was developed by John Lyftogt, MD, as a treatment for chronic neuropathic pain. It involves a series of subcutaneous injections with 5% dextrose in sterile water (D5W) near painful nerves. The initial research he published focused on using the therapy as a treatment for Achilles tendonitis.[2,3] The proposed mechanism of pain relief is agonism of the TRPV1 receptor, also known as the capsaicin or vanilloid receptor.[4] The TRPV1 receptor is a ligand-gated nonselective cation channel involved in the pain response of multiple stimuli including: endogenous lipids, capsaicin, heat, and low pH.[5] Studies show that activation of this receptor results in the release of calcitonin gene related peptide (CGRP) and substance P (SP), both products of neurogenic inflammation.[5]

Given the success of Lyftogt's trials with Achilles tendonitis, this pilot study sought to determine if perineural injection therapy® could be used as a primary treatment for plantar fasciitis.

Methods:

The study was IRB approved by Florida Hospital IRB #716933. Subjects were recruited from the investigators' practice, local physical

therapy offices, and community organizations such as running clubs.

Inclusion Criteria
1. Adult age 18 to 85
2. Capable of giving informed consent
3. Pain at one or more of the three locations described in "physician assessment of pain" below[1]
4. Roles and Maudsley Score[6] of 3 or 4
5. Available for the study duration

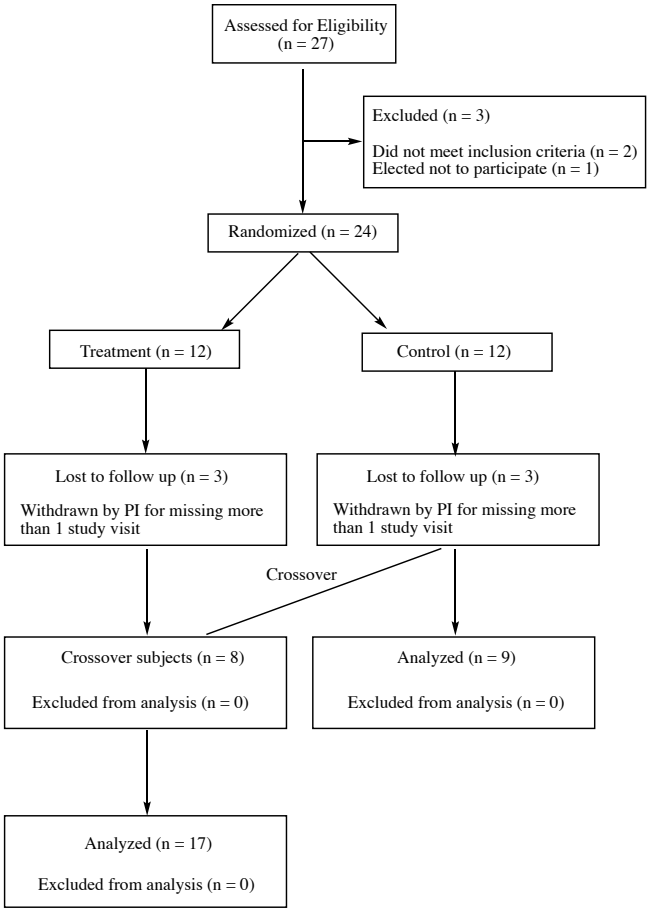
Exclusion Criteria
1. Allergy to corn
3. Any other injection for plantar fasciitis within the duration of the study
4. Treatment for plantar fasciitis by an outside provider within the duration of the study
5. Children 0-18
6. Prisoners
7. Pregnant women – urine pregnancy test at screening visit

Twenty-seven subjects were recruited into the study and signed informed consent. No data was collected on 3 subjects other than randomization assignment and they were therefore discarded prior to analysis. The average subject age was 51 years old (standard deviation 12 years). 18 subjects were female (75%) and 6 subjects were male (25%). The average body mass index (BMI) of the subjects was 30 (standard deviation 6.5). Twelve subjects randomized to the experimental group and 12 randomized to the control with crossover group. Subject recruitment, treatment, and follow up took place from August 2015 through December 2017.

Randomization

Subjects were randomized to either the experimental group or the control with crossover group. The randomization was done with equal treatment allocation of 5 blocks with 20 subjects per block by a statistician using sealedenvelope.com website. Paper slips containing treatment group and study information were placed in sealed envelopes and delivered to the principal investigator. Study personnel were blinded to the treatment allocation until after informed consent was completed. Records of the randomization assignment were retained by the statistician.

Figure 1: Flow of Subjects



Flow of subjects from screening through analysis.
PI = Principle Investigator

Measures: Subject Assessed Roles and Maudsley Score[6]

Subjects were asked to give a numerical rating from 1-4 based on the scale below. They were instructed that their rating should reflect the maximum pain they had experienced in the preceding week.

Table 1: Subject assessed Roles and Maudsley score

	Point	Interpretation
Excellent	1	No pain, full movement and activity
Good	2	Occasional discomfort, full movement and activity
Fair	3	Some discomfort after prolonged activity
Poor	4	Pain-limiting activities

Roles and Maudsley score 1 -4

Physician Assessment of Pain

Tenderness with palpation at each of three locations: centrally along the plantar fascia, at the plantar medial tuberosity, and the plantar calcaneal tuberosity[1] was assessed by the physician on the affected foot or feet. A numerical rating from 1 to 4 was assigned based on the scale below. The area of maximum tenderness was considered for data analysis.

Table 2: Physician assessment of pain

	Point	Assessed Subject Reaction
Excellent	1	No pain
Good	2	Painful
Fair	3	Painful and winces
Poor	4	Painful, winces and withdraws

Pain assessment scale 1 – 4

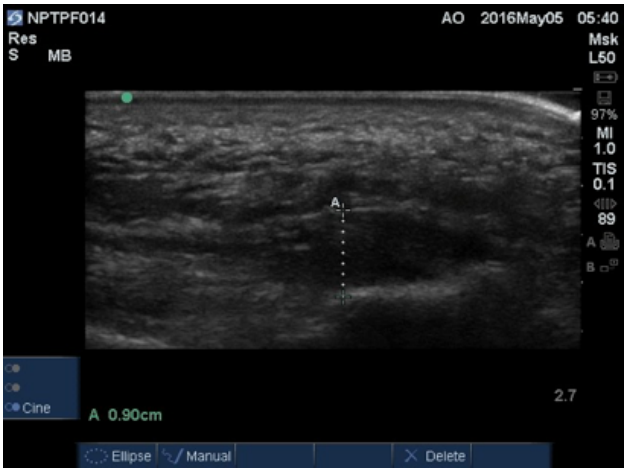
Plantar fascia thickness via musculoskeletal ultrasound (MSKUS)

Plantar fascia thickness was measured via SonoSite Edge® with a 6-15 MHz HFL50 linear transducer. All physicians taking the measurements were experienced in MSKUS had been formally trained in MSKUS training courses. Subjects were placed in a prone position with the foot hanging freely off the end of an examination table. Measurements of the vertical thickness of the plantar fascia were made from the anterior aspect of the inferior border of the calcaneus (figure 2).[7] The built-in ultrasound caliper tool was used to make the measurements. The plantar fascia was measured at the initial visit, the final visit, and at the cross-over visit for subjects in the control group.

Injection Technique

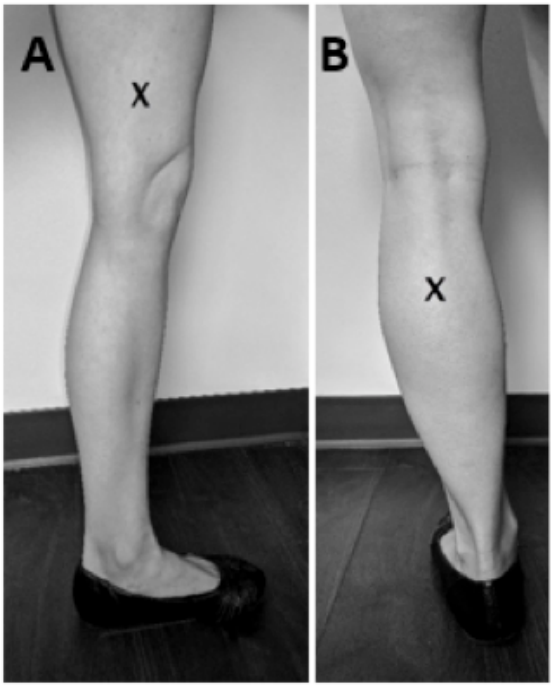
Five mLs of D5W were injected targeting perineural to the saphenous nerve at the adductor canal (figure 3, A) and perineural to the deep tibial nerve between the bifurcation of the gastrocnemius muscles (figure 3, B) on the affected leg(s). Injections were performed every 7 days (+/-2 days) for 8 consecutive weeks. These injections are near nerve injections and based on palpatory landmarks as described. Dr. Lyftogt does not describe specifically how close to the nerve the injection must be given. As a half inch needle is used for all Lyftogt perineural injection therapy® injections, certainly for deeper nerves the injection could be quite a distance away.

Figure 2: Ultrasound Measurement



Ultrasound measurement of the vertical thickness of the plantar fascia from the anterior aspect of the inferior border of the calcaneus

Figure 3: Injection Sites



A: target perineural saphenous nerve at adductor canal (left); B: target perineural deep tibial nerve between the bifurcation of the gastrocnemius muscles (right)

Usual Care Protocol, based on ACFAS Clinical Practice Guidelines: The Diagnosis and Treatment of Heel Pain.[1]

1. Stretching exercises[8]
2. Home cryotherapy: water bottle distributed to subject to fill with water and freeze. The

subject was instructed to apply ice to their affect foot/feet at least once daily.
3. Tuli's classic heel cups™ (bilateral) to be worn in shoes were distributed to subject. The subject was instructed to wear at all times.
4. Avoid barefoot walking and flat shoes.
5. Limit physical activity.
6. Oral anti-inflammatory at appropriate therapeutic dose. Agent based on patient preference and insurance coverage included: diclofenac, flurbiprofen, ibuprofen, ketoprofen, meloxicam, nabumetone, and naproxen.

Cross Over

After 8 weeks, subjects who were enrolled in the control group crossed over into the treatment protocol if they continue to meet inclusion and exclusion criteria. Once they crossed over, they also received the full series of perineural injections every seven days (+/- 2 days) for 8 consecutive weeks. All subjects from the control group, except one who was lost to follow up, crossed over to the treatment portion of the protocol.

Power calculation

The proposed study sample size was based on an equivalence trial for two treatment groups using the patient pain score (1 to 4 scale) from baseline to 60-days as the primary outcome measure. The clinical pain difference of 0.6 points was set as the delta or change. Standard deviation was estimated at 1 point for the treatment group and one-half point for the control group. Setting statistical power to 80%, alpha to 0.05 and using a one to one ratio, this study needed 50 subjects per group to be adequately powered.

Statistical Methods

Continuous variables were summarized as either mean and standard deviation for normally distributed values or median and interquartile range due to the non-normal distribution of values. Categorical variables were summarized using counts and percentages. Comparison of treatment and control was tested using Mann-Whitney for continuous variables and Chi-square test of independence for categorical variables. Comparison of initial to final values (2-month time period) within a subject for the intervention period were tested using a paired non-parametric comparison (Wilcoxon-signed rank test). Analysis was based on an intention to treat analysis as there were 3 subjects that did not meet intervention criteria. A 2-tailed p-value less than 0.05 was considered statistically significant.

Results:

The study collected data on 24 subjects. The mean age was 51 (IQR 43 – 58) years with a mean BMI percentile of 30 (IQR 26 – 33) with female subjects composing 75% of the study group.
Complete information for 9 control and 9 intervention subjects was compiled (table 3). Subjects with both feet in the study were examined and only the primary foot was retained due to the correlation of subjective measures.

Table 3: Results Control vs. Intervention

Differences from initial visit to 2-month visit	Intervention (N=9)	Control (N=9)	p-value
Mean Difference in plantar fascia thickness (mm)	2.0 mm (decrease)	0.7 mm (increase)	.019
Standard deviation (mm)	2.1 mm	2.2 mm	
Median difference (decrease)	1.6 mm	0.4 mm (increase)	
A numerical decrease (benefit)	8 (89%)	4 (44%)	
An increase in thickness	1 (11%)	5 (56%)	
Roles & Maudsley Score (scale 1- 4)			.666
A decrease in score (benefit)	4 (44%)	3 (33%)	
No change	5 (56%)	5 (55%)	
An increase in score	0	1 (11%)	
Physician assessed pain (scale 1-4)			.435
A decrease in score (benefit)	4 (44%)	4 (44%)	
No change	5 (56%)	3 (33%)	
An increase in score	0	2 (22%)	

Mann-Whitney test with 95% confidence level

Based on the Mann-Whitney test there is a statistically significant difference in the Plantar Fasciitis thickness (p=.019) when comparing the intervention and control groups with the intervention group having an average decrease of 2 mm as compared to the control with a 0.4 mm increase. There was no statistical difference in the physician assessed pain score or the Roles & Maudsley score when comparing the intervention and control groups.

Assessing intervention results

Seventeen subjects had completed values for the treatment period. These subjects include 8 subjects that were initially in the control group and crossed over to the intervention (table 4). Compared changes during the intervention period was based on Wilcoxon-signed rank test.

Based on the Wilcoxon signed rank test there is a statistically significant average decrease of 1.3 mm in the plantar fascia thickness when comparing the initial visit to the final visit. There was no statistical difference in Roles and Maudsley score (p=.101). Of the 17 subjects, 9 (53%) reported a decrease in score or benefit to the treatment with the remaining 7 patients (47%) having no change in their reported score. There was a significant improvement in general for the physician assessed pain score (p=.006) when comparing the initial and final visits.

Table 4: Intervention + cross over group

Differences from initial visit to the final intervention visit (N=17)	Initial Visit	Final Visit	p-value
Mean Difference in plantar fascia thickness (mm)	8.6 mm	7.3 mm	.019
Standard deviation (mm)	2.4	2.2	
Median thickness	9 mm	6.8 mm	
A numerical decrease (benefit)		14 (82%)	
An increase in thickness		3 (18%)	
Roles & Maudsley Score (scale 1- 4)			.101
A decrease in score (benefit)		7 (41%)	
No change		9 (53%)	
An increase in score		1 (6%)	
Physician assessed pain (scale 1-4)			.006
A decrease in score (benefit)		9 (53%)	
No change		8 (47%)	
An increase in score		0	

Wilcoxon-signed rank test with 95% confidence level

Discussion:

An exhaustive literature review was performed and there are no other studies that have investigated the use of Lyftogt perineural injection therapy® as a treatment for plantar fasciitis. In addition to Achilles tendonitis it has been studied in knee, shoulder, lateral elbow,[9] and low back pain.[10] Although Lyftogt perineural injection therapy® is an injection of dextrose, it is not the same technique as prolotherapy. Prolotherapy injections typically are either intra-articular or at an enthesis. Lyftogt perineural injection therapy® is a soft tissue injection near a peripheral nerve.

Subject compliance with the usual care protocol in the control arm was intentionally not assessed. Patient adherence to medical therapy is a constant challenge in medicine and studies show that human behavior tends to improve when the subject is observed or even thinks they are being observed.[11] As the usual care protocol was given as a part of a clinical trial it is likely that the subjects were more compliant then a general patient population would have been. Additionally, the investigators were unable to identify a method to objectively assess subject compliance with the usual care protocol. Not assessing compliance in the control group is more translatable to actual clinical practice.

The main strength of the study is that of the three endpoints: reduction in Roles and Maudsley score, reduction in physician assessed pain score, and reduction in plantar fascia thickness measured on MSKUS; the sole objective measurement, decrease in plantar fascia thickness remained statistically significant across all analyses.

Normal plantar fascia thickness measured at the calcaneus is 4mm.[12] In patients with plantar fasciitis, the plantar fascia becomes thicker although the mechanism for this process is unknown. Studies show correlation between pain and increased thickness.[13,14] The reduction of 2mm seen in the treatment group is consistent with other studies of effective treatment correlating reduction of thickness with pain relief.[15] There is a lack of consensus regarding the mechanism resulting in the thickening of the plantar fascia in people suffering from plantar fasciitis. As this biological process is unclear, it is difficult to postulate a mechanism by which Lyftogt perineural injection therapy® resulted in decreasing the plantar fascia thickness. The indication for the original study investigating the use of this therapy was Achilles tendinopathy. As with plantar fasciitis, Achilles tendonitis/tendinopathy was originally though to be an inflammatory process but now no longer considered so. Perhaps the underlying mechanism of these non-inflammatory processes are similar given their response to the same therapy.

The postulated mechanism of Lyftogt perineural injection therapy® pain relief is agonism

of the TRPV1, or capsaicin, receptor. The TRPV1 receptor is most heavily concentrated on sensory neurons and is implicated in chronic neuropathic pain.[15,16] The proposed action of dextrose on the TRPV1 receptor is based on its structural similarly to mannitol which has been shown to decrease pain due to capsaicin-induced burning pain.[17] Dextrose has also been shown to improve pain better than lidocaine when compared in trigger point injections.[18] An *in vitro* study to demonstrate glucose agonism of the TRPV1 receptor would be beneficial in confirming this theoretical mechanism.

The Roles and Maudsley score was selected for the subjective patient measurement because it correlated pain with disability and the investigators thought this would lead to more a more meaningful measurement than a traditional 1-10 pain scale. In retrospect the small 1-4 scale made it more difficult to achieve statistical significance due to the minimal numeric change between ratings. Additionally, some subjects commented that although their pain was improved from baseline, they continued to avoid activities that had caused pain previously due to fear that their pain would return. All subjects in the treatment group were encouraged to engage in their regular activities, unless limited by actual pain. Furthermore, the sample size was not achieved therefore statistical tests are underpowered therefore, statistical testing was changed to classical detection of clinical differences.

The injection therapy in this study focused on the peripheral nerves involved in the pain pattern: the deep tibial and the saphenous nerves. Recent pain research suggests that the sensitized spinal segment(s) implicated in a pain pattern must also be addressed for there to be good pain resolution.[18,19] Future studies could include applying this idea to Lyftogt perineural injection therapy® for plantar fasciitis and performing additional perineural injections at relevant dorsal rami of spinal segments L5-S2.

Conclusion:

Lyftogt perineural injection therapy® for the treatment of plantar fasciitis when compared to usual care is non-inferior with regards to subject perceived and physician assessed pain. It may be superior in reduction of plantar fascia thickness. A larger randomized-controlled trial would allow for a higher powered investigation of this treatment protocol.

Author Contributions:

All below authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data.

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Potential Conflicts of Interest Disclosures:

The authors declare no conflict of interest.

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