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## **TREATMENT OF CONSECUTIVE SEVERE FIBROMYALGIA PATIENTS WITH PROLOTHERAPY**

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### **ABSTRACT**

The potential of tendon and ligament triggers as primary nociceptors in fibromyalgia led to treatment of primary fibromyalgia patients with tendon and ligament strengthening injection. Trigger injection of ligament and tendon with proliferant (TILT therapy or prolotherapy) offers the advantage of creating increased strength of the connective tissue in the region of injection as well as affecting the pain cycle. Reduction in pain levels and increased functional abilities were seen in excess of 75 % of patients with severe fibromyalgia in this study. The implications of this for further study are considered.

### **INTRODUCTION**

The search for 'central factors' in the cause of fibromyalgia has revealed evidence of possible alteration of pain modulation in the body such as a decrease in circulating serotonin and possibly antibodies that block serotonin receptors. <sup>27,39</sup> Evidence has also been found for central factors affecting soft tissue homeostasis. (Possible glucocorticoid deficiency or deficient production of growth hormone related factors. <sup>3,14,24</sup>) Search continues for the primary nociceptor in fibromyalgia. It is notable that the classical tender points in fibromyalgia are over tendon and ligament insertions. Semi-elastic tissues are generally recognized to be the sites of acute damage in sprain and strain. <sup>35</sup> Tendon and Ligament attachments to periosteum have the lowest pain threshold of any deep somatic structure. <sup>4</sup> Inman and Saunders reported stimulating periosteum in a variety of ways including pressure, and elicited severe referred pain to muscles or bony prominences in the referral zone in reproducible patterns. <sup>23</sup> De Valera, Gorrell, Hackett, Kelgren, Kraus, Leriche and Travell have all described referral pain from tendinoligamentous structures, with patterns of referral most meticulously set out by Hackett. <sup>8,12,15-22,25,29,40,41,42</sup> Tendon or ligament laxity or weakness has been proposed to cause chronic nociception via

inadequate skeletal support, intermittent stretch of fixed-length sensory fibers, or development of myofascial trigger points. <sup>19,35</sup> The premise of this study is that weak or lax tendons or ligaments are potential nociceptors in fibromyalgia and that this is potentially a correctable nociceptor source.

Prolotherapy involves injecting an area of ligament or tendon laxity or weakness with a solution that stimulates fibroblast proliferation. The goal of proliferation therapy is to restore normal connective tissue length and strength in the affected area, and in so doing to restore adequate skeletal support and eliminate sources of myofascial trigger perpetuation. <sup>2</sup> Borden demonstrated the ability of a simple dextrose solution in 12.5% concentration or more to create a prompt inflammatory reaction. <sup>6</sup> The simple dextrose solution is thought to create irritation by an osmotic gradient. Cells in the area lose water, and desiccate to the point of an injury response. Animal studies have shown a 40% increase in diameter and strength of injected tendons compared to contralateral tendons. <sup>17,32</sup> Changes persisted more than 12 months post injection and were not dependent on any difference in exercise levels of the animals. Human studies have demonstrated collagen fiber diameter increases and increased cellularity on biopsy of injected areas. Disability, range of motion, and pain levels all improved significantly in patients injected after 5 or more years of chronic pain. <sup>26</sup> In human knees with reproducible ligament laxity as measured by a computerized knee analysis device, a statistically significant reduction in ligament laxity was demonstrated with a P value less than 0.05. <sup>37</sup> Randomized double-blind control studies with saline injected controls have demonstrated statistically significant improvements in low back pain and disability rating in treated patients compared to controls. <sup>28,36</sup>

## **METHOD**

### **Patient Population**

Consecutive patients with severe fibromyalgia were treated with tendon/ligament strengthening injection. The fibromyalgia was sufficiently severe in each case that all the patients desired intervention trial. All patients had experienced continuous upper body, back, and lower body pain for more than 6 months, with average duration 7 years and 10 months. Tender points were present in at least 7/9 classic regions on both sides of the body. Functional questionnaires indicated that 37% had regular narcotic intake, sexual function was limited in 48%, arm numbness made handling small objects difficult in 55%, 70% of patients had to lay down during the day due to pain, lifting arms overhead increased pain in 70% of patients and bending, twisting and squatting frequently was intolerable to more than 80% of the patients. Awakening from pain averaged 3.1 times per night. Sitting tolerance was 33 minutes; standing tolerance 27 minutes; light work tolerance 45 minutes; heavy work tolerance 19 minutes; and writing tolerance 17 minutes.

### **Solution used**

The solution used was made by combining 3cc of 50% dextrose with 2cc of 1 % xylocaine (lignocaine) and 7cc of benzyl alcohol type bacteriostatic water, making a dextrose concentration of was 12.5%.

### **Typical first session**

There are several 'methods' of prolotherapy, and two representative texts can be referenced for

details. <sup>9,22</sup> Because of the very diffuse number of painful entheses, the method of injection was the meticulous one of Hackett. <sup>22,38</sup> A typical comprehensive first injection session for upper and lower body included the following numbers and sites of injections, with 0.5 cc to 0.75cc injected at each site, assuming both sides of the body treatment in almost all potential injection sites. Semi-spinalis, splenius and rectus capitus insertions on base of skull (24); cervical facet ligaments (14) ; cervical intertransversarii (28); posterior superior trapezius insertions on back of clavicle (8); lateral costotransverse ligament attachment to ribs (14); infraspinatus, teres major and minor attachments to scapulae posteriorly (28); scalene attachments ant and post tubercles (16); subscapularis, biceps and pectoralis insertions on anterior portion of humerus (16); common extensor attachments at elbow(6); lumbar intertransversarii (10) ; lumbar facets (10); lumbosacral junction (6 with several needle redirections) ; Crest of ilium (6); iliolumbar ligament (4 with several needle redirections); SI ligament (6 with several needle redirections); gluteus maximus, medius and minimus insertions on iliac bone (30); deep articular ligaments of hip (6 with several needle re-directions); external rotator and gluteii attachments posterior trochanter (24); distal adductor attachments knee (2); hamstring attachments in anserine bursa (16). It can immediately be seen that this is a time consuming and exacting procedure when done comprehensively. The volume of solution used can be as much as 200cc with treatment, but the concentration of Xylocaine in the solution of less than .2%, coupled with the length of the procedure causes no problems in terms of anesthetic toxicity.

### **Sedation**

Oral vistaril (hydroxyzine) was used for nausea prophylaxis to avoid rare anaphylaxis with compazine. An anesthetic gun was used to numb the skin in all patients who preferred it to the needle insertion sensation. Intravenous demerol (pethidine) was used as the exclusive sedation except for those with demerol allergy or with prolonged nausea after demerol use. Valium (diazepam) was added or used exclusively when demerol was not feasible as a sole agent. Continuous oximetry was used with an office attendant present to ensure oximetry values above 87% and regular breathing patterns. Narcan (naloxone) was immediately available. It is important to note that demerol should be titrated in 25-50mg increments for first one to two sessions. Careful record keeping should allow determination of ideal amounts for sedation by session. <sup>3</sup> Oximetry or close observation of breathing patterns was considered particularly critical with use of 40mg of demerol or more in the elderly or 75mg or more in the young. Demerol was titrated with first the first one to two sessions to determine the patients' reaction and careful records kept as to ideal amounts for future reference. Note that the reason for significant amounts of demerol was the substantial time period required for comprehensive injection.

### **Injection follow-up**

Because of healing cascade length of 8 weeks, follow-ups were scheduled at that interval in general, though other pain areas may have been treated in the interim. At follow-up, pain areas and palpation determined areas of injection. All sore areas to palpation were not reinjected, but rather potential trigger areas for current pain were addressed. Patients received an average of 3.5 injection sessions to any particular pain region.

### **Questionnaire use**

Questionnaires were sent out to all patients who had received one or more treatments, with the first treatment occurring at least 6 months before questionnaire mailing. This questionnaire asked

about pain levels pre- and post- treatment by body region. Other questions requested assessment of overall frequency and intensity of pain, and tolerance of sitting, standing, walking, sleeping, light work, and heavy work. Patients were also asked to compare tendon/ligament strengthening injection to other treatments they had received in the past, and asked about complications. If questionnaires were not returned, follow-up 'phone contact confirmed if one was received, and the patient was encouraged to return the questionnaire. 'Phone interviews were decided against to avoid leading the answers. 31 of 40 consecutive fibromyalgia patients returned follow-up questionnaires, or 78% of the patients so treated.

## RESULTS

Table 1 depicts the average pain levels of the 31 patients by area, using a 10 point scale with '10' the worst pain imaginable and '0' being no pain at all ever. The 16 regions chosen were rated at 4.86 out of 10 pre-injection and 3.30 post-injection for a reduction of 32.1 %. All regions of the body were noted to have less average pain after injection.

Region	Average Pain before RX	Average Pain after RX
Head	5.81	3.77
Neck	7.00	4.45
Front of Shoulder	4.52	3.03
Top of Shoulder	5.68	3.55
Back of Shoulder	7.03	4.26
Elbow/Forearm	3.52	2.26
Wrist/Hand	3.00	2.00
Upper Back	6.23	4.03
Front of Chest	4.10	2.81
Mid Back	6.71	4.77
Low Back	6.77	4.90
Buttock/Hip	5.42	4.26
Thigh	3.94	2.81
Knee/Calf	3.10	2.42
Ankle	2.19	1.81
Foot	2.68	1.7
<b>Whole Body (average of above)</b>	<b>4.86</b>	<b>3.30</b>

*Table 1*  
*Pain before and after tendon/ligament strengthening injection (prolotherapy)*

Table 2 depicts the functional outcome of injection. 21/31 patients indicated their pain frequency was better, much better or gone, and 18/31 indicated their pain intensity was better, much better, or none. The questionnaire asked for an explanation of 'worse' or 'much worse' responses, with reasons given of stress in 3/5, work in 2/5, needing to follow-up with no insurance in 2/5, and don't know in 1/5. Two of these patients had only one treatment. Improvement in sitting, standing, walking and sleeping ability in minutes was noted to be about the same for each. Of particular interest from a functional point of view was that of the 30 patients indicating problems with tolerating light work, 18 indicated they were better or much better at tolerating light work, and 2 indicated they tolerated light work less. The results were not so favorable for heavy work, with 9 indicating they tolerated heavy work better and 6 less. The 6 indicating they were worse again gave "stress", "work", "had to stop treatment", or "don't know" as the reason.

		Levels of Pain/Ability						
		A: never a problem	B: back to normal	C: much better	D: better	E: same	F: worse	G: much worse
		A	B	C	D	E	F	G
Frequency of Pain		0	1	8	12	5	3	2
Intensity of Pain		0	1	6	11	8	2	3
Sitting Ability		0	2	5	10	10	4	0
Standing Ability		0	2	3	13	6	6	1
Walking Ability		1	3	2	12	6	6	1
Sleeping Ability		1	2	4	6	13	4	1
Light Work Ability		1	1	5	12	10	1	1
Heavy Work Ability		0	1	1	7	16	4	2

*Table 2*  
*Functional results of tendon/ligament strengthening injection; changes post injection*

Table 3 provides results when patients were asked to compare the outcome of tendon-ligament strengthening injection with any previous treatments they had received. They were given a series of statements to choose from, and asked to pick the one that described their opinion. Note that all patients (other than those unable to take time off work for therapy) were offered 6-9 sessions of physical therapy for postural exercise, stretching and massage instruction, instruction in proper

heat use, encouragement to walk, and amitriptyline or flexeril. 22/31 had previously received physical therapy; 14/31 had previously received manipulation; 6/31 acupuncture; and 17/31 massage. Of the 31 patients, 12 indicated that it was the only really effective treatment they had received, and 23 of 31 indicated it was more helpful than any past treatment. Patients were asked to indicate their status with respect to future treatment, and were given several responses to choose from.

Only really effective treatment was injection	12/31
Injection was much more effective than other treatments I have received	8/31
Injection was helpful but effects did not last	5/31
Injection was more effective than other treatments	3/31
Injection was as helpful as any other treatment	1/31
Injection not as helpful as other treatments	1/31
Injection not helpful	1/31

*Table 3  
Comparison of prolotherapy with other treatments previously received*

Table 4 displays their answers. Particularly notable was that of those not desiring follow-up at the time of the questionnaire mailing, 6 were better or plateau, two did not specify, and only one thought the treatment was too much to go through. Despite the use of sedation and skin anesthesia with a jet gun, there is no way to truly make this treatment pleasant. Patient tolerance of treatment was impressive, however, in that only 1/31 stated they were not continuing treatment because it was too much to go through. Patients did need substantial support not only during the treatment sessions which averaged 1 hour and 30 minutes in length, but also between treatments with questions that arise. The implication is that this treatment at this level of intensity would be impractical for the busy clinician.

Follow-up planned because my original pain needs to get better	21/31
I am enough better and don't need treatment now	3/31
No treatment planned. I am as good as I think I will get	2/31
No follow-up planned because I am	1/31

all better	
Follow-up planned because new pains have developed	1/31
Insurance or workman's compensation does not cover treatment	1/31
Treatment is too much to go through	1/31
I am not better. I don't think treatment will help	0/31
Other (Non specified)	2/31

*Table 4*  
*Follow-up plans post prolotherapy*

When patients were asked if they had any significant complications or side effects from treatment they answered as in Table 5. Note that, of what would truly be considered a complication, one had superficial phlebitis of a vein injected for sedation purposes and one had a spinal headache. It is important to warn patients of temporary new pains, variable pain periods after injection, small marks from anesthetic gun if it is used, nausea, and, if injections are given over posterior rib attachments, pneumothorax. In this practitioner's experience with this particular injection method a symptomatic pneumothorax has occurred approximately once each year when injections over posterior thorax average 100 or more per day - given the large numbers of injections in each session could be significantly high if the clinician is not trained in angles to use, lengths of needles to use, and depths of injection. Injections of arterial structures are rare since injection never occurs unless bone is touched, and aspiration occurs in critical areas such as the neck laterally. The amount of anesthetic injected at any one time is substantially smaller than the smallest amount ever shown to cause a seizure or cessation of respiration, even with direct vertebral artery instillation. <sup>5</sup> Nerve damage has never been reported with use of dextrose instillation and generally thin caliber needles used. If electrical sensation occurs, however, the needle should be repositioned.

New pains for a while	11
Not specified	5
Vein irritated from sedative agents	1
Longer recuperation after some treatments	1
Spinal headache	1
Pain after injection	1
Appearance (Small marks from anesthetic gun)	1
Nausea for several days	1

*Table 5*  
*Side effects/complications of prolotherapy in severe fibromyalgia syndrome*

A complicating factor in follow-up exam of these patients is that the number of tender points diminished as symptoms improved. Note that the 'tender points' were often injected during the course of treatment. (i.e. common extensors elbow, distal adductors knee, cervical paraspinals, costotransverse ligaments, upper trapezius).

## DISCUSSION

There is an accumulating body of evidence for peripheral soft tissue changes in fibromyalgia. An example would be strong evidence for an increase in tissue compliance and reactive skin hyperemia in fibromyalgia. <sup>3</sup> Searching in skeletal muscle has not yielded consistent findings on biopsy, though changes of degeneration are often seen. <sup>10</sup> Bennett postulated that a defect in repair processes after micro or macrotrauma in fibromyalgia may prevent resolution of such injuries, with development of chronic pathology. <sup>3</sup> Recent evidence has indicated that Somatomedin C (a growth hormone-related factor important in musculoskeletal homeostasis) is deficient in fibromyalgia patients. <sup>3</sup> Note that growth hormone-related factors are secreted primarily during stage IV sleep and that stage IV sleep disturbance by alpha wave intrusion is characteristic of fibromyalgia. <sup>3,33,34</sup> Jacobsen et al's finding of somewhat lower levels of Type III procollagen in serum in fibromyalgia patients is interesting, in that procollagen is a critical precursor in the healing of connective tissue. <sup>24</sup> The healing cascade after semi-elastic tissue damage is critical in making the ligament/tendon sufficiently tight and thick to continue normal function, but is time-limited to 2-3 months after injury, and is dependent on adequacy of fibroblast density, procollagen deposition, maturation to collagen, cross band formation with shortening of the tendon and ligament laxity. <sup>7</sup> Injection of tendon and ligament triggers, since it includes anesthetic, may be considered capable of having acupuncture effects or effects on breaking the pain cycle; but acupuncture points were not specifically treated in this study, and trigger injection with anesthetic alone has not been convincingly demonstrated to be effective in allowing a sustainable improvement in function or pain level in the presence of whole body pain of fibromyalgia.

With respect to the study patients, there can be little doubt that they have severe fibromyalgia - given sitting and standing tolerance less than 30 minutes, having to lay down during the day due to pain in 70%, light work tolerance only 45 minutes, and intolerance of bending, twisting, and squatting. In addition the average duration of whole body pain of 7 years 10 months suggests strongly that spontaneous remissions to marked degree would not be expected in this population and that spontaneous worsening would be at least as likely. This is supported by Ledingham's long term study showing 97% of patients persisting with symptoms, 85% still fulfilling criteria after 4 years post onset, with 60% rating their symptoms as worse and 26% better than at presentation 4 years post onset. <sup>30</sup> His study included fibromyalgia patients without severe functional impairment at onset of study. Results in this study of resuming the healing cascade in areas of proposed ligament laxity indicate 33% pain reduction. This can mean that the treatment is only partially effective, that there are perpetuating factors preventing full resolution, or that the critical ligament laxities were not addressed.

Further studies are under way using various combinations of ligaments. Functional status after treatment indicates improvability of pain frequency and intensity, sitting, standing, walking and sleeping. Since for most fibromyalgia patients a key goal is to keep working with their disease, 18/31 experiencing improvement in light work ability and 2/31 a worsening is of particular functional significance. The rating of this treatment by 22/31 as better than any previously received over the average 7 years of fibromyalgia and less effective in only 2/31 is encouraging for a potential unique role of this treatment in refractory fibromyalgia.

## SUMMARY

The improvements in pain levels and functional ability after injection is supportive of tendon and ligaments being a major source of symptomatology in fibromyalgia. In order to make this treatment more practical further studies to determine the relative importance of various ligament/tendon nociceptors in fibromyalgia will be important. In addition it is hoped that this study will encourage basic science investigators to further research homeostasis of connective tissue in fibromyalgia, as even microtrauma of daily living in the presence of impaired homeostasis may sufficient to explain onset of symptoms. The tendency of ligaments and tendons to refer pain and numbness in non-radicular patterns and to inhibit muscular function to create such symptoms as give-way weakness and a feeling of non-specific fatigue could go a long way in explaining why physicians tend to mis-diagnose these patients as having somatisation disorder. The lack of evidence for primary psychiatric disorders as the cause for fibromyalgia has been set out in the literature in a convincing fashion, but until the symptomatology of ligament and tendon pathology is more widely recognized, the symptoms of fibromyalgia will remain an enigma to most practicing physicians. 1

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