Accepted Manuscript

Dextrose Prolotherapy versus Control Injections in Painful Rotator Cuff Tendinopathy

Helene Bertrand, M.D., CCFP, Kenneth Dean Reeves, M.D.,FAAPM&R, Mr. Cameron J. Bennett, Simon Bicknell, M.D., FRCPC, An-Lin Cheng, Ph.D. (Statistics)

PII: S0003-9993(15)01091-6

DOI: 10.1016/j.apmr.2015.08.412

Reference: YAPMR 56287

To appear in: *ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION*

Received Date: 1 August 2015

Accepted Date: 3 August 2015

Please cite this article as: Bertrand H, Reeves KD, Bennett CJ, Bicknell S, Cheng A-L, Dextrose Prolotherapy versus Control Injections in Painful Rotator Cuff Tendinopathy, *ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION* (2015), doi: 10.1016/j.apmr.2015.08.412.

Running Head:

Dextrose Prolotherapy in Rotator Cuff Tendinopathy

Title:

Dextrose Prolotherapy versus Control Injections in Painful Rotator Cuff Tendinopathy

Authors and Affiliations

Helene Bertrand, M.D., CCFP, clinical instructor, Department of Family Practice, School of Medicine, University of British Columbia.

Kenneth Dean Reeves, M.D.,FAAPM&R. Clinical Assistant/Associate Professor, Department of Physical Medicine and Rehabilitation 1986-2015, University of Kansas.

Mr. Cameron J Bennett, Musculoskeletal Physiotherapist, MPhty (MSK), BSc.Private Practice, British Columbia.

Simon Bicknell, M.D., FRCPC, Clinical Associate Professor, Department of Radiology, University of British Columbia.

An-Lin Cheng, Ph.D. (Statistics), Associate Professor, University of Missouri- Kansas City. School of Nursing and Health Studies.

Location of Study

Dr. Bertrand's Private Office: 1940 Lonsdale Avenue, Suite 220, North Vancouver, British Columbia, Canada, V7M 2K2.

Acknowledgment of Any Presentation of This Material

Abstract submitted as a poster in the annual meeting of American Congress of Rehabilitation Medicine and presented as a poster at the Annual meeting of the Canadian Pain Association May 21-22, 2015

Acknowledgment of Financial Support

This research was supported with funds from WorkSafe BC (Worker's Compensation Board of British Columbia, RS2010-OG07). The funding source has no involvement in conduct of the research or preparation of the article.

Other Acknowledgments

Janusz Kaczorowski, Ph.D., Professor & Research Director at Université de Montréal, Adjunct Professor, Department of Family Medicine, McGill University. (Early project development)

Brad Fullerton, M.D, FAAPM&R, Austin, Texas (Assistance with implementation of the Ultrasound Shoulder Pathology Rating Scale)

Audrey Scherbler, Pharm. D. (Preparation, randomization and numbering of the solutions used in the study)

David Rabago, M.D. Assistant Professor, Associate Research Director, University of Wisconsin School of Medicine and Public Health, Department of Family Medicine. (Editorial review)

Corresponding Author Information

K. Dean Reeves M.D., FAAPM&R, 4740 El Monte, Roeland Park, Kansas, 66205.

Office Phone: (913) 362-1600 Mobile Phone: (913) 963-7750

Email: DeanReevesMD@gmail.com

University of British Columbia Human Subject Committee Protocol ID: H09-00911

Clinicaltrials.gov ID: NCT01402011

Dextrose Prolotherapy versus Control Injections in Painful Rotator Cuff Tendinopathy

ABSTRACT

Objective: To compare the effect of dextrose prolotherapy on pain levels and degenerative changes in painful rotator cuff tendinopathy against two potentially active control injection procedures.

Design: Randomized controlled trial, blinded to participants and evaluators.

Setting: Outpatient pain medicine practice.

Participants: Chronic shoulder pain, examination findings of rotator cuff tendinopathy, and ultrasound-confirmed supraspinatus tendinosis/tear.

Interventions: Three monthly injections either onto painful entheses with dextrose (Enth-Dex), onto entheses with saline (Enth-Sal), or above entheses with saline. (Superfic-Sal). All solutions included 0.1% lidocaine. All participants received concurrent programmed physical therapy.

Main Outcome Measures: Primary: Participants achieving an improvement in maximal current shoulder pain ≥ 2.8 or not. (Twice the minimal clinically important difference for (Visual Analog Scale) VAS pain. Secondary: Improvement in the Ultrasound Pathology Rating Scale (USPRS) and a 0-10 satisfaction score (10 = completely satisfied).

Results: The 73 participants had moderate to severe shoulder pain (7.0±2.0) for 7.6±9.6 years. There were no baseline differences between groups. Blinding was effective. At 9 month follow-up 59 percent of Enth-Dex participants maintained ≥ 2.8 improvement in pain compared to Enth-Saline (37%;p=.088) and Superfic-Saline

(27%;p=.017). Enth-Dex participants' satisfaction was 6.7±3.2 compared to Enth-Saline (4.7±4.1;p=.079) and Superfic-Saline (3.9±3.1;p=.003). USPRS findings were not different between groups (p = .734).

Conclusions: In participants with painful rotator cuff tendinopathy who receive physical therapy, injection of hypertonic dextrose on painful entheses resulted in superior long term pain improvement and patient satisfaction compared with blinded saline injection over painful entheses, with intermediate results for entheses injection with saline. These differences could not be attributed to a regenerative effect. Dextrose prolotherapy may improve upon standard care of painful rotator cuff tendinopathy for certain patients.

Key words: Dextrose; prolotherapy; rotator cuff; tendinopathy; tendinitis.

Abbreviations:

ANOVA: Analysis of Variance

DASH: Disability of Arm, Shoulder and Hand

NRS: Numerical Rating Scale (0-10)

USPRS: Ultrasound Shoulder Pathology Rating Scale

VAS: Visual Analog Scale (0-10)

PESS: Physical Examination of Shoulder Scale

Rotator cuff tendinopathy (RoCT) is common, affecting one in five shoulders,[1] and very costly: Work Safe BC statistics for 2004 to 2008 show 464 to 653 cases of rotator cuff injury per year, each case costing an average of $24,300.[2] It impacts the lives of manual workers, athletes and the elderly, who are more often affected, because shoulder pain and weakness interfere with work tolerance, sport, sleep and everyday self-care.[3]

Treatments to reduce pain and improve function have included rest, pain medication, physiotherapy, corticosteroid injections, and surgery.[4,5] Unfortunately, after three years, 54% of all RoCT patients are still suffering.[6,7] Injection of painful entheses with hypertonic dextrose (dextrose prolotherapy) has demonstrated clinical benefit[8-11] and improvement in ultrasound-based tendinopathy findings in several tendinopathies,[12-14] but has not been studied in RoCT. The purpose of this study was to compare the effect of dextrose prolotherapy against two potentially active control injection procedures in subjects who were receiving physical therapy. We hypothesized that dextrose prolotherapy would reduce pain significantly more than superficial injection over entheses and improve degenerative findings on ultrasound. Enthesis injection with saline was expected to have intermediate benefit due to potential therapeutic effects from microbleeding or cell membrane rupture with initiation of the inflammatory cascade.

METHODS

This randomized controlled trial compared dextrose prolotherapy (entheses dextrose injection) to one of two control injections, entheses saline injection without dextrose or

superficial saline injection. This study was conducted in an outpatient pain practice and was approved by the Human Subject Committee of the University of British Columbia. Adults 19 to 75 years old from the greater Vancouver area with shoulder pain more than 3 months were examined using the Physical Examination of Shoulder Scale (PESS), which has been utilized to monitor interval changes in rotator cuff status in wheelchair athletes.[15] Physical examination qualifiers included either a positive Neer, positive Hawkins-Kennedy or positive painful arc testing. Supraspinatus pathology was required in the form of either non-calcific or calcific tendinosis, partial tear or full thickness tear as noted on high resolution ultrasound scanning. Exclusion criteria included allergy to local anesthetic, unwillingness to avoid anti-inflammatories for 3 days before and 2 weeks after treatments, corticosteroid injection within the last 8 weeks, passive shoulder abduction less than 100 degrees or external rotation less than 25 degrees, a rotator cuff calcification diameter greater than 0.8 cm on plain film or ultrasound, grade II-IV (Kellgren-Lawrence Classification) osteoarthritis, type III acromion, supraspinatus tear width > 1.2 cm, or comorbidity severe enough to affect full participation.

Randomization to one of three active treatment groups

Following the first ultrasound examination, if potential treatment participants met all eligibility criteria, they were randomly assigned by the pharmacist to one of three injection groups using a random number generator in blocks of 3.

1. Injection onto painful entheses with 25%dextrose/0.1% lidocaine/saline (Enth-Dex; described to participants as dextrose prolotherapy).

2. Injection onto painful enthesis with 0.1% lidocaine/saline (Enth-Saline; described to participants as modified prolotherapy)

3. Injection superficial to painful entheses at ½ to 1 cm depth with 0.1% lidocaine/saline (Superfic-Saline; described to participants as sham prolotherapy).

Physical Therapy:

Each participant was evaluated prior to receiving their first injection and received two physical therapy sessions after each injection session. Treatments are outlined in table one. The emphasis in teaching included helping each participant identify the correct working pressure for their resistance exercises, understand the importance of correct exercise posture, pacing, rest intervals and appropriate progressions, and give attention to proper scapular position (Table 1). Each participant was encouraged to maintain their exercise program three times a week through the point of 3 month follow-up. Physical therapy adherence was assessed by attendance record.

Blinded preparation of solutions and injection:

Solutions were prepared off-site by the unblinded pharmacist. Solutions were identical in appearance and viscosity and masking of the numbered bottles was not performed. The evaluator, ultrasonographer and participants were blinded to both group assignment and solution type. The injector was blinded to solution type for enthesis injection groups, but was alerted to which group was to be injected superficially by a letter placed on the labels of the bottles prepared by the pharmacist. To improve the

blinding of participants between superficial technique and deep technique, anesthetic blebs were not placed over injection sites, and when superficial injections were given, the injector applied firm pressure with a finger 1 cm to each side of the injection point without pressing in the injection site and needle entries were vertical to skin surface and limited to 0.5 to 1.0 cm depth to avoid enthesis contact.

Injection interval and locations

Injections were performed at 0, 1 and 2 months after initiation of active treatment. The needle used was 27 gauge (G) 37 mm, with exception of the long head of the biceps origin and the anterior and posterior inferior glenohumeral ligament, or unless the participant was muscular or obese, in which case a 27G, 51 mm needle was used in selected areas. The supraspinatus, infraspinatus and teres minor insertions, as well as insertions on the coracoid process, were injected with the shoulder in neutral rotation (Figure 1). Biceps long head, subscapularis insertion and inferior glenohumeral ligament were injected with the shoulder in various degrees of external rotation and abduction/adduction (Figure 2). Origins of the teres minor, teres major and the posterior inferior glenohumeral ligament were injected posteriorly (Figure 3). Participants received injections of 1 mL of solution at each primary injection site. Other tender areas along the enthesis and adjacent to the primary site were injected at 1 cm intervals, each with 0.5 mL of solution.

Post Injection Precautions:

Pre-and Post-injection participants were advised to use acetaminophen, tramadol, or

acetaminophen with codeine for discomfort. Participants were discouraged from using non-steroidal anti-inflammatory drugs and from starting new therapies for rotator cuff tendinopathy during the study period. They were advised not to do activities that were painful and to wait for 10 days before resuming physical therapy sessions.

Outcome measures

Baseline demographics, previous treatment methods, examination findings, ultrasound findings, USPRS ratings and number of physical therapy sessions received were tabulated by group to characterize the sample and to evaluate as covariates for statistical analysis. (Table 2).

The primary outcome measure was achieving an improvement in maximal current shoulder pain ≥ 2.8 or not, which is twice the minimal clinically important difference (MCID) for VAS change in rotator cuff tendinopathy.[16] Participants marked shoulder pain at 0 and 3 months on a form provided by a blinded evaluator prior to being seen by the injector. At 9 months a final 0-10 shoulder pain rating was obtained by phone by a blinded evaluator with the same directions (given verbally) as used for the 0-10 VAS. Because this value was obtained verbally without an opportunity to choose values other than whole numbers it would be a 0-10 numerical rating scale (NRS).

Two secondary long term outcome measures were obtained. One was a satisfaction measure obtained at 9 months from all participants by phone ("On a 0-10 scale rate how satisfied you are with your treatment outcome with 0 = Not satisfied at all and 10 =

Completely satisfied").The second was the Ultrasound Shoulder Pathology Rating Scale (USPRS; Figure 4).[15] This rating scale for interval evaluation of rotator cuff tendinopathy was developed for use with wheelchair athletes, and was performed prior to treatment, and at least 6 months after the last injection session, depending on availability of the patient and ultrasonographer. The evaluator was blinded to group assignment.

Blinding of participants was assessed at 3 months by asking participants the following written question: "Do you think the treatment you received was true prolotherapy?" They then selected either "Yes", "No, modified prolotherapy", "No, sham prolotherapy", or "I don't know".

Statistical analysis:

Using an estimated effect size of 0.81, a sample size of 25 in each group was determined to provide 80% power to detect a difference in mean pain scores at a significance level of .05.

In order to identify significant covariants for the pain measure, a Repeated Measures ANCOVA for pain scale, followed by post hoc Bonferroni correction for three groups, was applied to compare the groups for magnitude of change in 0-10 pain score between 0 to 3 months and 0 to 9 months. A Pearson Chi-Square Analysis was utilized to determine significant differences between groups in the number of participants who achieved a ≥ 2.8 improvement in pain and to evaluate the effectiveness of the participant blinding procedure while accounting for any significant covariates in the analysis.

A repeated measures ANCOVA was applied for magnitude of change in ultrasound ratings between entry and follow-up ultrasound and an ANCOVA for 0-10 satisfaction levels at 9 months. The statistical program utilized was PASW 18 (Predictive Analytics Software 18.0.0, IBM).

RESULTS

Enrollment and Baseline Characteristics: Patient recruitment began in October 2010, and data collection was completed in July of 2013. Two hundred and thirty-seven people were screened for eligibility (Figure 5). Of these, 135 were ineligible by history, examination or radiographic findings and 25 by ultrasound findings. Seventy seven were randomized. Seventy three tolerated the first injection and seventy two completed all treatments and provided 9 month follow-up data. Baseline demographic, prior shoulder treatments received, examination findings, and ultrasound pathology were similar, as was the number of physical therapy sessions received during the study (Table 2). There were no significant covariates in the repeated measures ANCOVA. Overall, most of the participants (63%) were men, with a mean age of 51, minimum pain duration of 5 months, and mean pain duration of more than 7 years.

Success of Injection Group Blinding:

Three months after starting injection treatment, when participants were asked if they knew which group they were in, only 21 of 73 participants were confident enough of their injection group to make a guess (Table 3) and only 7 of these were correct. There

was no significant difference between groups for number of correct guesses (p = .551), suggesting that participant blinding was effective.

Follow-up Pain, Ultrasound and Satisfaction Data:

At nine months, the Enth-Dex group maintained a 2.9 point improvement in pain in comparison with 1.8 points for the Enth-Saline group and 1.3 points for the Superfic-Saline group (Table 4). The percent of participants reaching and maintaining a clinically significant improvement of 2.8 or more in pain was significantly different between groups (Table 4; p= .046). The Enth-Dex group significantly out-performed the Superfic-Saline group (16[59%] vs 7[27%]; p=.017). The difference between the Enth-Dex group and the intermediate-performing Enth-Saline group did not reach clinical significance. (16[59%] vs 7[37%];p=.088).

Satisfaction was significantly different between groups at long term follow-up (p = .017). Levene statistic results ruled out a lack of homogeneity in variance between groups. Group-by-group analysis revealed that the satisfaction of the Enth-Dex group was significantly more than that of the Superfic-Saline group (6.7±3.2 vs 3.9±3.1;p=.003). Satisfaction differences between the Enth-Dex group and Enth-Saline group did not reach significance. (6.7±3.2 vs 4.7±4.1;p=.079).

Three participants did not follow through with repeat ultrasound examination after treatment, leaving 70 out of 73 (96%) for whom both before and after treatment ratings

were available (Table 4). Although each group showed some improvement (a decline) in the USPRS, there was no between-group difference (p = .734).

One subject in the Enth-Saline group developed adhesive capsulitis, with resolution after therapy provision but was removed from the study. No other side effects or adverse events were noted other than discomfort with injection, and minor post-injection soreness.

DISCUSSION

This RCT of participants with symptomatic ultrasound-confirmed rotator cuff tendinopathy receiving physical therapy found that dextrose prolotherapy significantly improved the number of participants who achieved a clinically-important improvement compared to superficial saline injection above painful entheses, with intermediate results for saline injection of entheses, confirming the primary hypothesis. At 9 months 59% of the enth-dex group maintained a 2.8 or more improvement in pain compared to 27% of the superfic-saline group. Participant satisfaction was significantly more in the Enth-Dex group 6.7±3.2 vs 3.9±3.1 than in the Superfic-Saline group. However, there were no differences of significance either within groups or between groups for changes over time in degenerative findings on systemic interval ultrasound grading of rotator cuff tendinopathy. The intermediate performance of enthesis injection with saline is potentially consistent with a therapeutic effect from the direct needling of entheses. .

These results add to the body of randomized and controlled studies indicating a therapeutic benefit of dextrose prolotherapy in tendinopathy. In Osgood Schlatter Disease, where patellar tendinopathy is the most common finding on ultrasound, injection of 12.5% dextrose and was an effective treatment, outperforming injection of saline and usual care exercise.[8] Dextrose injection was significantly more effective than a randomized "wait and see" control group in the treatment of lateral epicondylosis.[9] In Achilles tendinopathy, peritendinous dextrose injection plus eccentric lengthening exercises was more effective than eccentric lengthening exercises alone.[17] Also notable, albeit not blinded, was a moderately large study of 72 consecutive elite-level soccer and rugby athletes with chronic career-altering tendinopathy-associated pubalgia in which hypertonic dextrose injection resulted in a 90% rate of pain-free sport within a mean of 3 months.[11] Despite these favorable results, the large number of tendinopathies and their potential for variable responsiveness to treatments need to be kept in mind. Two recent reviews of injection techniques for tendinopathy, including steroid injection, sclerosing agents, aprotinin, prolotherapy, and platelet rich plasma noted that injection treatments other than steroid injection may be of benefit for long-term treatment, but the quantity and quality of literature is insufficient for definitive recommendations.[18,19]

The mechanism of action of dextrose in the current study is not clear. A traditional view is that hypertonic dextrose initiates a brief inflammatory cascade stimulating native healing and subsequent tissue growth, and that clinical improvement follows restoration

of tissue integrity.[20] However, elevation of pericellular dextrose levels as little as 0.5 stimulates production of multiple profibroblastic cytokines.[21,22] Even transport of glucose into human cells by GLUT1, the chief glucose transporter protein, is coupled with cytokine elevations.[21] Randomized and controlled animal studies using injection of non-inflammatory 10% dextrose have confirmed an increase in organized connective tissue width, thickening of collagen bundles, and an increase in energy absorption and of load bearing ability before rupture in response to hypertonic dextrose injection.[23,24] Human ultrasound data suggest that hypertonic dextrose injection is followed by regeneration in ligamentous tissue,[13,14] and machine measurement of consecutive cases of ACL laxity has suggested a reduction in measurable laxity with intraarticular dextrose injection. [25] However, the absence of any demonstrable interval changes on USPRS in this present study does not support regeneration as the source of clinical benefit. Dextrose may also have a direct pain-modulating effect. Two recent RCTs, one with a back pain model[26] and one with a capsaicin pain model [27] have suggested that dextrose and a related alcohol (mannitol) have an analgesic effect. Pain relief in a capsaicin-induced pain model may be indicative of either downregulation of the TRPV1 receptor, a key receptor in maintenance of a chronic pain state, or effects on downstream mediators of TRPV1 activation..

Study limitations and strengths

Study limitations include offering physical therapy. Physical therapy is an active treatment and may account for much of the benefit at short term follow-up. However, it is customary and usual to prescribe physical therapy for rotator cuff tendinopathy, all

patients received the same amount of therapy, and significant outcome differences were seen between injection groups. Failure to utilize Disability of Arm Shoulder and Hand scoring in this study resulted in an inability to confirm that improvement in pain was accompanied by a proportional functional improvement. Administrative limitations resulted in the substitution of the NRS 0-10 pain scale for the VAS 0-10 pain scale at 9 months. However, the two scales are comparable,[28] and verbal NRS pain levels are rated higher, which would have erred on the side of underestimating the amount of pain improvement (reduction in pain on a 0-10 scale) from 0 to 9 months.[29] Our pain question asked about the "current worst pain", which differs from our stated reference on MCID determination in rotator cuff tendinopathy, which asked about "current overall pain".[16] The effect of this difference in wording is uncertain, although the same question was asked of all participants.

Strengths of this study include assessment of a difficult, often refractory, musculoskeletal condition with an innovative therapy in a randomized controlled fashion with practical patient-oriented outcomes, complete patient follow-up data, and ultrasound assessment for potential disease modification. These participants typically had long term chronic shoulder pain and had failed multiple previous treatments. Baseline evaluations included tabulation of physical findings and ultrasound findings of tendinopathy to provide high specificity for diagnosis of rotator cuff tendinopathy. The questionnaire utilized for blinding analysis demonstrated that very few subjects were confident of their group assignment and were usually wrong when they chose, indicating

that it is possible to successfully blind superficial and deep injections.

CONCLUSIONS

Among participants with painful rotator cuff tendinopathy, physical therapy plus dextrose prolotherapy performed by a trained operator resulted in safe, significant and sustained improvements in pain and improved patient satisfaction compared to physical therapy plus superficial saline injections. A regenerative effect was not confirmed by internal ultrasonography in this study. Prolotherapy may provide an effective and welcome addition to the management of patients with painful rotator cuff tendinopathy. Definitive determination of the clinical utility of dextrose prolotherapy will require additional, larger clinical trials with more complete functional assessment tools, supplemented by further basic science to determine mechanism of action and baseline characteristics of responders.

REFERENCES

1. Yamamoto A, Takagishi K, Osawa T, et al. Prevalence and risk factors of a rotator cuff tear in the general population. *J Shoulder Elbow Surg.* 2010;19(1):116-120.
2. Work Safe BC Statistical Services Department. www.worksafebc.com. Accessed March 1, 2009.
3. Burbank KM, Stevenson JH, Czarnecki GR, Dorfman J. Chronic shoulder pain: part I. Evaluation and diagnosis. *Am Fam Physician.* 2008;77(4):453-460.

4. Wilson JJ, Best TM. Common overuse tendon problems: a review and recommendations for treatment. *Am Fam Physician.* 2005;72(5):811-818.

5. Bishay V, Gallo RA. The evaluation and treatment of rotator cuff pathology. *Prim Care.* 2013;40(4):889-910, viii.

6. Bokor D, Hawkins R, Gh H, RL A, MS S. Results of non-operative management of full-thickness tears of the rotator cuff. . *Clin Orthop Relat Res* 1993;294:103-110.

7. Hawkins RH, Dunlop R. Nonoperative treatment of rotator cuff tears. *Clinical orthopedic Relat Res* 1995;321:178-188.

8. Topol GA, Podesta LA, Reeves KD, Raya MF, Fullerton BD, Yeh HW. Hyperosmolar dextrose injection for recalcitrant Osgood-Schlatter disease. *Pediatrics.* 2011;128(5):e1121-1128.

9. Rabago D, Lee KS, Ryan M, et al. Hypertonic dextrose and morrhuate sodium injections (prolotherapy) for lateral epicondylosis (tennis elbow): results of a single-blind, pilot-level, randomized controlled trial. *Am J Phys Med Rehabil.* 2013;92(7):587-596.

10. Scarpone M, Rabago DP, Zgierska A, Arbogast G, Snell E. The efficacy of prolotherapy for lateral epicondylosis: a pilot study. *Clin J Sport Med.* 2008;18(3):248-254.

11. Topol GA, Reeves KD. Regenerative injection of elite athletes with career-altering chronic groin pain who fail conservative treatment: a consecutive case series. *Am J Phys Med Rehabil.* 2008;87(11):890-902.

12. Maxwell NJ, Ryan MB, Taunton JE, Gillies JH, Wong AD. Sonographically guided intratendinous injection of hyperosmolar dextrose to treat chronic tendinosis of the Achilles tendon: a pilot study. *Am J Roentgenol.* 2007;189(4):W215-220.

13. Ryan M, Wong A, Taunton J. Favorable outcomes after sonographically guided intratendinous injection of hyperosmolar dextrose for chronic insertional and midportion Achilles tendinosis. *Am J Roentgenol.* 2010;194(4):1047-1053.

14. Ryan M, Wong A, Rabago D, Lee K, Taunton J. Ultrasound-guided injections of hyperosmolar dextrose for overuse patellar tendinopathy: a pilot study. *Br J Sports Med.* 2011;45(12):972-977.

15. Brose SW, Boninger ML, Fullerton BD, et al. Shoulder ultrasound abnormalities, physical examination findings, and pain in manual wheelchair users with spinal cord injury. *Arch Phys Med Rehabil.* 2008;89(11):2086-2093.

16. Tashjian RZ, Deloach J, Porucznik CA, Powell AP. Minimal clinically important differences (MCID) and patient acceptable symptomatic state (PASS) for visual analog scales (VAS) measuring pain in patients treated for rotator cuff disease. *J Shoulder Elbow Surg.* 2009;18(6):927-932.

17. Yelland MJ, Sweeting KR, Lyftogt JA, Ng SK, Scuffham PA, Evans KA. Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: a randomised trial. *Br J Sports Med.* 2011;45(5):421-428.

18. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. *Lancet.* 2010;20(376(9754)):1751-1767.

19. Skjong CC, Meininger AK, Ho SS. Tendinopathy treatment: where is the evidence? *Clin Sports Med.* 2012;31(2):329-350.

20. Reeves KD, Topol GA, Fullerton BD. Evidence-based regenerative injection therapy (prolotherapy) in sports medicine. In: Seidelberg PH, Beutler PL, eds. *The Sports Medicine Resource Manual*. Philadelphia: Saunders (Elsevier); 2008:611-619.

21. Heilig CW, Deb DK, Abdul A, et al. GLUT1 regulation of the pro-sclerotic mediators of diabetic nephropathy *Am J Nephrol.* 2013;38(1):39-49

22. Pradhan L, Cai X, Wu S, et al. Gene expression of pro-inflammatory cytokines and neuropeptides in diabetic wound healing. *J Surg Res* 2011;167(2):336-342.

23. Yoshii Y, Zhao C, Schmelzer JD, Low PA, An KN, Amadio PC. Effects of multiple injections of hypertonic dextrose in the rabbit carpal tunnel: a potential model of carpal tunnel syndrome development. *Hand (N Y).* 2014;9(1):52-57.

24. Yoshii Y, Zhao C, Schmelzer JD, Low PA, An KN, Amadio PC. The effects of hypertonic dextrose injection on connective tissue and nerve conduction through the rabbit carpal tunnel. *Arch Phys Med Rehabil.* 2009;90(2):333-339.

25. Reeves KD, Hassanein K. Long term effects of dextrose prolotherapy for anterior cruciate ligament laxity: A prospective and consecutive patient study. *Altern Ther Health Med.* 2003;9(3):58-62.

26. Smigel L, Reeves KD, Lyftogt J, Rabago D. Analgesic Effect of Caudal 5% Dextrose in Water in Chronic Low Back Pain (Abs) *Arch Phys Med Rehabil.* 2015;In Press

27. Bertrand H, Kyriazis M, Reeves KD, Lyftogt J, Rabago D. Topical Mannitol Reduces Capsaicin-induced Pain: Results of a Pilot Level, Double-Blind Randomized Controlled Trial. *PM&R.* 2015;In Press PMID 25978942.

28. Hjermstad MJ, Fayers PM, Haugen DF, et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. *J Pain Symptom Manage.* 2011;41(6):1073-1093.

29. Holdgate A, Asha S, Craig J, Thompson J. Comparison of a verbal numeric rating scale with the visual analogue scale for the measurement of acute pain. *Emerg Med.* 2003;15(5-6):441-446.

Figure Titles and Legends

Figure One Title: Structures Injected in Neutral Rotation and Typical Depth of Injection

Figure One Legend:

(S)Supraspinatus insertion: 1 to 3 ml on the anterior superior part of the greater tuberosity, generally tender to palpation over about 2-3 cm in height and .5 cm in width. (I) Infraspinatus insertion: 1 to 3 ml immediately posterior to the superior portion of the supraspinatus tendon, in line with the spine of the scapula on the greater tuberosity. (T) Teres minor insertion: 1 to 3 ml on the posterior superior surface of the greater tuberosity.

(C) Coracoid process: 1 ml on the bony prominence under the clavicle, medial to the head of the humerus. The coracoid is contacted at its most shallow location.

Figure Two Title: Structures Injected in Variable External Rotation and Abduction and Typical Depth of Injection

Figure TwoLegend:

(B)Biceps long head: 1 ml immediately medial to the acromioclavicular joint and posterior to the clavicle, with the arm in slight external rotation. Needle insertion is vertical with a 15 degree anterior tilt until bone is reached.

(S) Subscapularis insertion: 1 to 3 ml (depending on surface of tender area) on the lesser tuberosity of the humerus, posterior to the long tendon of the biceps. With the arm in full external rotation and adduction needle insertion is .5 cm lateral to the coracoid process until it reaches the humerus.

(I) Inferior glenohumeral ligament: 3 ml with the arm externally rotated and abducted 90° as tolerated; the inferior part of the glenohumeral joint is palpated and injected. Solution is injected on the scapular and humeral insertions of the ligament.

Figure Three Title: Structures Injected Posteriorly

Figure Three Legend:

(Tma) Teres major and (Tmi) Teres minor: 1 to 3 ml (depending on surface of tender area with arm fully adducted and hand on opposite shoulder, inject edge of scapula only where tender to avoid risk of pneumothorax. Posterior inferior glenohumeral ligament (P): 1 ml with the shoulder -fully adducted, the inferior part of the glenohumeral joint is palpated and injected.

Figure FourTitle: Ultrasound Pathology Rating Scale (USPRS) (Range 0-20)

Figure Four Legend: Descriptions of intermediate levels of pathology are found in the original source. [15]

Figure Five Title: Enrollment of Participants and Study Conduct

Figure Five Legend: All 73 participants provided long term data for analysis and all participants completed treatment except for one participant in the Enth-Saline group who developed adhesive capsulitis after session one.

Table One Title: Physical Therapy Protocol

Table One Legend:

* The first session of therapy was conducted prior to initiation of injection treatment.

† After each injection session, two physical therapy sessions were received.

Table Two Title: Baseline Comparison of Treatment Groups

Table Two Legend:

* P values obtained from One Way ANOVA for numeric and Pearson chi square for non-numeric variables.

† Retired and not working were not distinguished.

‡ Percentage does not sum to 100 due to participants varied use of individual therapies.

Table Three Title: Success of Blinding the Method of Injection

Table Three Legend:

* The question presented was :Do you think the treatment you received was true prolotherapy? O Yes O No, modified prolotherapy O No, sham treatment O Don't know

† There was no significant difference between groups for number of correct guesses (*P* = .551). The correct responses for each group are indicated in bold.

‡ This is the group for which blinding was likely to be more difficult. The combination of pressure around injection site, and not using local anesthetic appears to have been successful with 77% uncertain of which group they were in and only 11.5% correct in their guess.

Table Four Title: Change in VAS for Pain, DASH and PESS during Control and Short Term Active Treatment Periods.

Table Four Legend:

* Defined as equal to or more than twice the MCID (1.4) for a change in 0-10 NRS pain scale.(≥2.8). A Pearson Chi-Square Analysis was utilized for intragroup analysis.

† Enth-Dex significantly out-performed Superfic-Saline (p=.017).The difference between the Enth-Dex group and the intermediate-performing Enth-Saline did not reach clinical significance. (p=.088).)

‡ A decrease in the UPRPS represents an improvement. No significant differences between groups were noted. (p = .734)

Session	Objective
1*	**Survey:** Prior treatment, location and severity of shoulder pain, and provocative maneuvers and activities. **Goals:** Prior treatment and current treatment goals discussed.
2-7†	**Stretching:** Gentle stretches appropriate to range restrictions**.** **General exercise teaching: C**orrect working pressure for resistance exercises, correct posture/scapula position, pacing, rest intervals and appropriate progressions. **Isometric exercises for cuff and deltoid:** (Thera-Band® yellow to blue). Minimal or no pain as only acceptable symptoms. **Active exercise progression with attention to arm position and assessment of simple loading patterns:** Rowing, curling, shrug, shoulder forward press and front raise, neutral cuff exercises, scapular strengthening exercises, former provocative maneuvers, body weight exercises including dips, pushups and plank style exercises. **Ice massage:** Normally used around subacromial region to minimize symptoms after exercise. Review and encouragement: To maintain exercise program three times a week.

*** The first session of therapy was conducted prior to initiation of injection treatment.**

† **After each injection session, two physical therapy sessions were received.**

Characteristic	Enth-Dex #27	Enth-Saline #20	Superfic-Saline #27	P Value*
Demographics				
Female, n (%)	11 (41%)	6 (32%)	10 (38%)	.812
Age years, mean (SD)	53.8±13.5	51.1±9.2	49.0±11.9	.333
Pain Duration months mean (SD)	61±81	131±155	101±115	.125
VAS pain, mean (SD)	7.7±1.7	8.1±1.4	7.6±1.8	.573
Currently Working[†] n, (%)	21(78%)	18(90%)	24(92%)	.479
Dominant Side n, (%)	16(59%)	13(65%)	17(65%)	.878
Current Smoker n, (%)	4(15%)	0(0%)	1(4%)	.758
Prior Shoulder Treatments, n (%)[‡]				
Physical Therapy	18(67%)	15(75%)	15(58%)	.459
Massage Therapy	10(37%)	6(30%)	8(31%)	.844
Steroid Injection	3(11%)	1(5%)	1(4%)	.588
Manipulation	5(19%)	2(10%)	4(15%)	.721
Acupuncture	0(0%)	5(25%)	9(35%)	.004
Examination Findings, n (%)				
Biceps Long Head/Groove Pain	19(70%)	13(68%)	20(77%)	.791
Supraspinatus/Greater Tuberosity Pain	26(96%)	19(100%)	26(100%)	.430
AC Joint Pain	8(30%)	3(16%)	6(23%)	.551
Ext. Rot. Resistance Pain	18(67%)	11(58%)	18(69%)	.719
Int. Rot. Resistance Pain	13(49%)	7(37%)	11(42%)	.744
Supraspinatus Resistance Pain	24(89%)	16(84%)	23(89%)	.879
Painful Arc	22(75%)	18(95%)	25(96%)	.147
Neer Impingement Pain	23(85%)	18(95%)	25(96%)	.301
Hawkins-Kennedy Pain	26(96%)	19(100%)	24(92%)	.438

O'Briens Active Compression-AC	**21(78%)**	**17(89%)**	**22(85%)**	**.564**
O'Briens Active Compression-Labrum	**15(56%)**	**10(53%)**	**13(50%)**	**.921**
Baseline Ultrasound Pathology: Number Yes (%)				
Non-Calcific Tendinosis	**10 (37%)**	**6 (32%)**	**9 (33%)**	**.586**
Calcific Tendinosis	**12 (44%)**	**10 (53%)**	**14 (54%)**	**.763**
Partial Supraspinatus Tear	**12 (44%)**	**11 (58%)**	**13 (50%)**	**.668**
Full Thickness Supraspinatus Tear	**6 (22%)**	**2 (11%)**	**5 (19%)**	**.586**
Baseline Ultrasound Pathology Rating				
USPRS, mean (SD)	**4.0±1.8**	**4.3±1.8**	**4.3±1.8**	**.858**
Physical Therapy During Active Study				
Number of Sessions Received, mean (SD)	**5.1±1.5**	**4.3±1.6**	**5.0±1.8**	**.172**

* P values obtained from One Way ANOVA for numeric and Pearson chi square for non-numeric variables.

† Retired and not working were not distinguished.

‡ Percentage does not sum to 100 due to participants varied use of individual therapies.

Table Three: Success of Blinding the Method of Injection

		Participant's Choice of Group*†			
		"Dextrose Prolotherapy" (Enth-Dex)	"Modified Prolotherapy" (Enth-Saline)	"Sham Prolotherapy" (Superfic-Saline)	"I Don't Know"
Actual Group Assignment	Enth-Dex (n=27)	**2 (7%)**	4(15%)	3 (11%)	18 (67%)
	Enth-Saline (n=20)	2(10%)	**2 (10%)**	2(10%)	14 (70%)
	Superfic-Saline (n=26) ‡	3 (11.5)	0	**3 (11.5%)**	20 (77%)

* The question presented was : Do you think the treatment you received was true prolotherapy? O Yes O No, modified prolotherapy O No, sham treatment O Don't know

† There was no significant difference between groups for number of correct guesses (p = .551). The correct responses for each group are indicated in bold.

‡ This is the group for which blinding was likely to be more difficult. The combination of pressure around injection site, and not using local anesthetic appears to have been successful with 77% uncertain of which group they were in and only 11.5% correct in their guess.

Table Four: Short Term Change in 0-10 Pain Scale and Long term Change in 0-10 Pain and Ultrasound Pathology Rating Scales

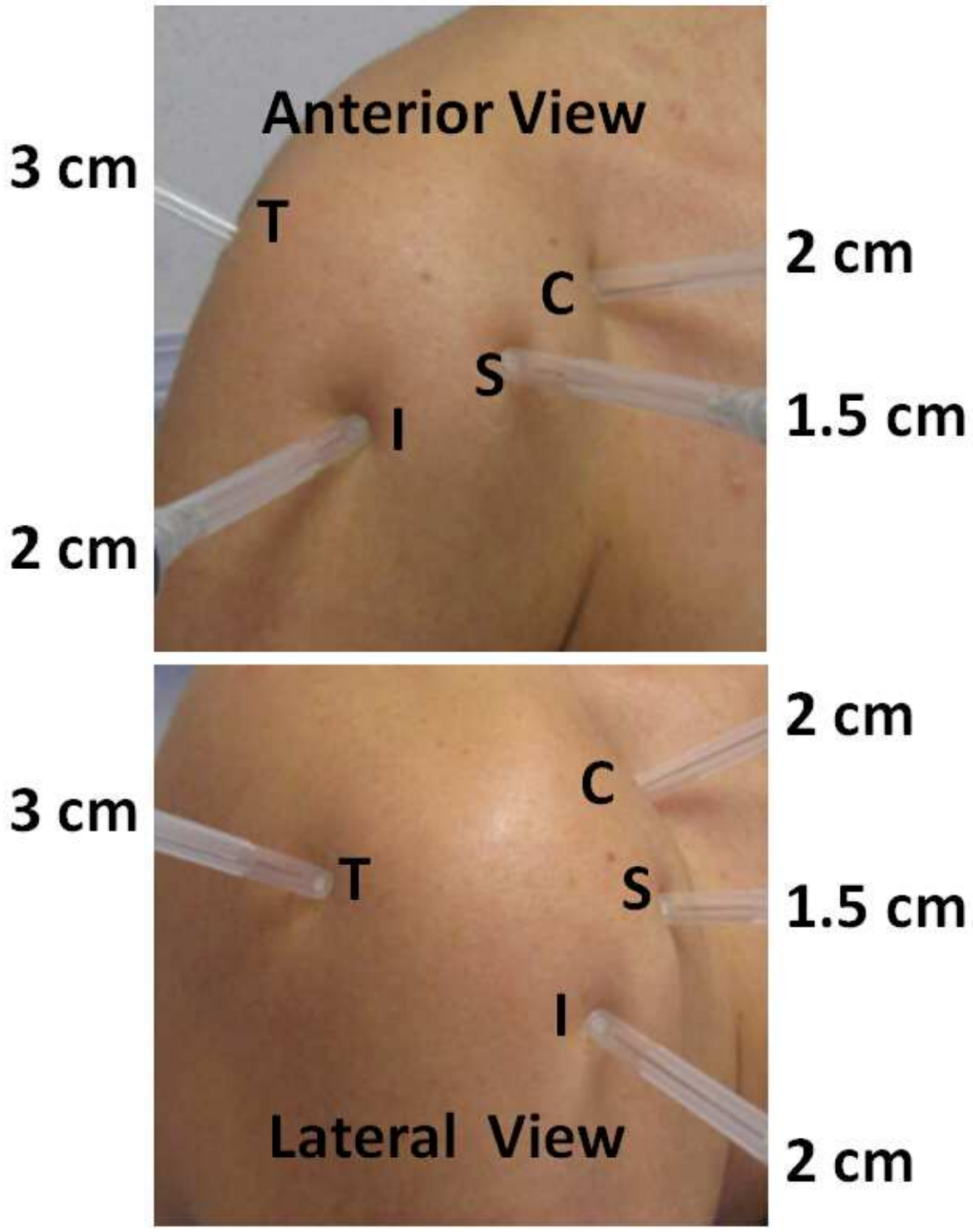
0-10 Pain Level				
	Mean (SD) Baseline	Mean (SD) Reduction (Improvement) 0-3 Months	Mean (SD) Reduction (Improvement) 0-9 Months	Number (%) With Clinically Significant Improvement * at 9 Months
Enth-Dextrose	7.3 (.4)	3.0 (0.5)	2.9 (0.6)	16/27(59%) †
Enth-Saline	6.9 (.5)	2.7 (0.7)	1.8 (0.7)	7/19(37%)
Superfic-Saline	6.9 (.4)	2.7 (.6)	1.3 (0.6)	7/26(27%)

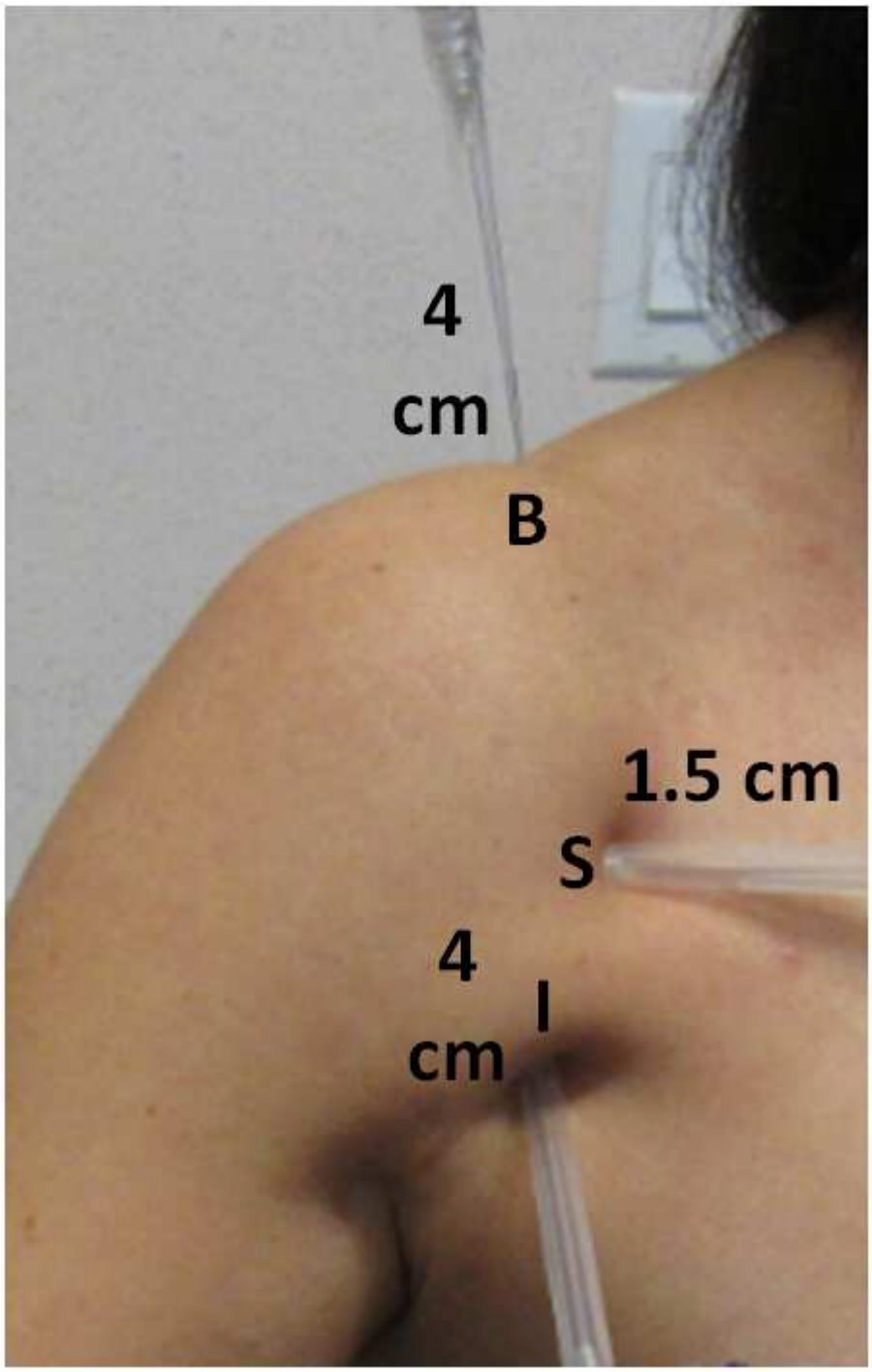
Ultrasound Pathology Rating Scale		
	Mean (SD) Baseline	Mean (SD) change at 9.4± 2.2 Months‡
Enth-Dextrose	4.0(.4)	-.3(.5)
Enth-Saline	4.3 (.5)	-.6(.5)
Superfic-Saline	4.3 (.4)	-6 (.4)

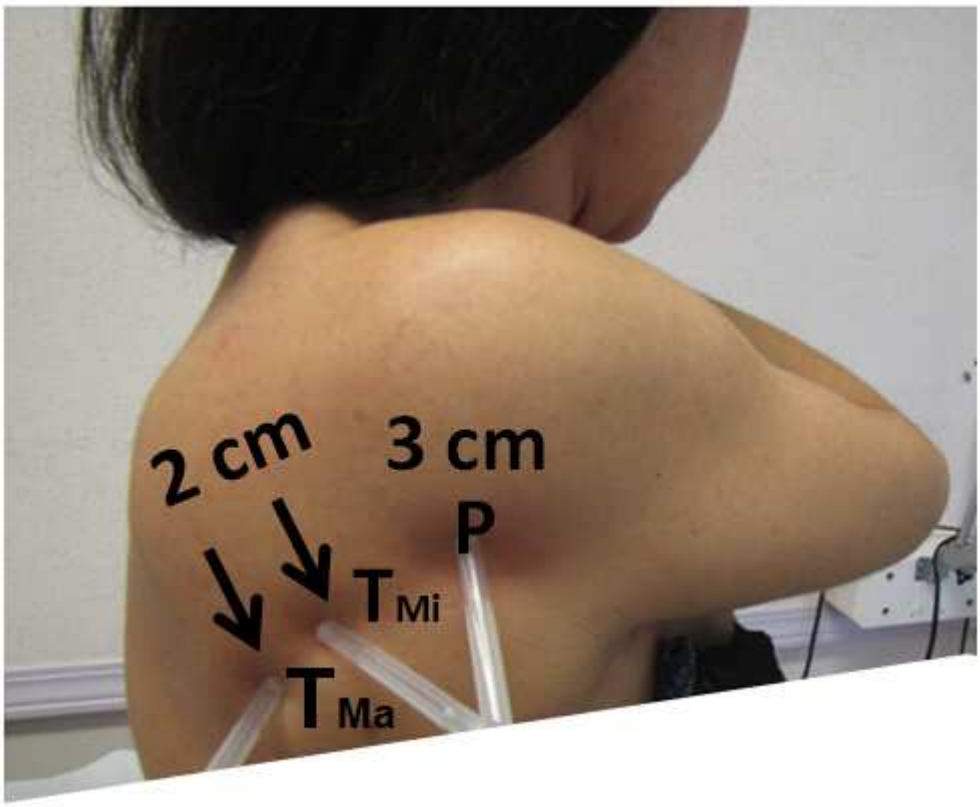
* Defined as equal to or more than twice the MCID (1.4) for a change in 0-10 NRS pain scale.(≥2.8). A Pearson Chi-Square Analysis was utilized for intragroup analysis.

† Enth-Dex significantly out-performed Superfic-Saline (p=.017).The difference between the Enth-Dex group and the intermediate-performing Enth-Saline did not reach clinical significance. (p=.088).)

‡ A decrease in the UPRPS represents an improvement. No significant differences between groups were noted. (p = .734)


Anterior View
3 cm
T
2 cm
C
S
1.5 cm
I
2 cm
3 cm
2 cm
C
T
S
1.5 cm
I
Lateral View
2 cm


4
cm
B
1.5 cm
S
4
cm
I



Biceps Tendinopathy: Graded 0 to 6

0 = Normal fibrillar pattern and echogenicity.

6 = Full rupture/absence of tendon.

Supraspinatus Tendinopathy: Graded 0 to 5

0 = Normal fibrillar pattern and echogenicity.

5 = A clear full thickness tear.

Greater Tuberosity Cortical Surface: Graded 0 to 3

0 = Smooth hyperechoic cortical surface.

3 = Marked irregularity or pitting.

Dynamic Supraspinatus Impingement: Graded 0 to 3

0 = No evidence of impingement; smooth motion without crepitis.

3 = Marked impingement; lack of full range of motion/greater tuberosity contact with acromion.

Dynamic Subscapularis/ Biceps/Coracoid Impingement: Graded 0 to 3

0 = No evidence of impingement; smooth motion without crepitis.

3 = Marked impingement; Lack of full range of motion or clear biceps contact with coracoid process.