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ORIGINAL RESEARCH

Dextrose Prolotherapy Versus Control Injections in Painful Rotator Cuff Tendinopathy

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Abstract

Objective: To compare the effect of dextrose prolotherapy on pain levels and degenerative changes in painful rotator cuff tendinopathy against 2 potentially active control injection procedures.

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

Setting: Outpatient pain medicine practice.

Participants: Persons (N=73) with chronic shoulder pain, examination findings of rotator cuff tendinopathy, and ultrasound-confirmed supraspinatus tendinosis/tear.

Interventions: Three monthly injections either (1) onto painful entheses with dextrose (Enthesis-Dextrose), (2) onto entheses with saline (Enthesis-Saline), or (3) above entheses with saline (Superficial-Saline). 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 (twice the minimal clinically important difference for visual analog scale pain) or not. Secondary: improvement in the Ultrasound Shoulder Pathology Rating Scale (USPRS) and a 0-to-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% of Enthesis-Dextrose participants maintained ≥2.8 improvement in pain compared with Enthesis-Saline (37%; $P=.088$) and Superficial-Saline (27%; $P=.017$). Enthesis-Dextrose participants' satisfaction was 6.7±3.2 compared with Enthesis-Saline (4.7±4.1; $P=.079$) and Superficial-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 on the standard care of painful rotator cuff tendinopathy for certain patients.

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Rotator cuff tendinopathy is common, affecting 1 in 5 shoulders,[1] and very costly. The Workers' Compensation Board of British Columbia (WorkSafeBC) statistics for 2004 to 2008 show 464 to 653 cases of rotator cuff injury per year, with each case costing an average of $24,300.[2] This tendinopathy impacts the lives of manual workers, athletes, and the elderly, who are more often affected. Shoulder pain and weakness interfere with work tolerance, sports participation, sleep, and everyday self-care.[3]

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Treatments to reduce pain and improve function have included rest, pain medication, physiotherapy, corticosteroid injections, and surgery.[4,5] Unfortunately, after 3 years, 54% of all patients with rotator cuff tendinopathy are still symptomatic.[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 rotator cuff tendinopathy. The purpose of this study was to compare the effect of dextrose prolotherapy against 2 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 because of the 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 1 of 2 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 aged 19 to 75 years from the greater Vancouver area with shoulder pain for more than 3 months were examined using the Physical Examination of Shoulder Scale, which has been used to monitor interval changes in rotator cuff status in wheelchair athletes.[15] Physical examination qualifiers included a positive Neer sign, a positive Hawkins-Kennedy test, or positive painful arc testing. Supraspinatus pathology was required in the form of either noncalcific 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 $<100^\circ$ or external rotation $<25^\circ$, a rotator cuff calcification diameter >0.8cm on plain film or ultrasound, grade II to IV (Kellgren-Lawrence classification) osteoarthritis, type III acromion, supraspinatus tear width >1.2cm, or comorbidity severe enough to affect full participation.

Randomization to 1 of 3 active treatment groups

After the first ultrasound examination, if potential treatment participants met all eligibility criteria, they were randomly assigned by the pharmacist to 1 of 3 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 group; described to participants as dextrose prolotherapy); (2) injection onto painful entheses with 0.1% lidocaine/saline (Enth-Saline group; described to participants as modified prolotherapy); and (3) injection superficial to painful entheses at 0.5- to 1-cm depth with 0.1% lidocaine/saline (Superfic-Saline group; described to participants as sham prolotherapy).

List of abbreviations:

ANCOVA analysis of covariance
NRS numeric rating scale
USPRS Ultrasound Shoulder Pathology Rating Scale
VAS visual analog scale

Table 1 Physical therapy protocol

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:* Correct 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 3 times a week.

* The first session of therapy was conducted before initiation of injection treatment.
† After each injection session, 2 physical therapy sessions were received.

Physical therapy

Each participant was evaluated before receiving the first injection and received 2 physical therapy sessions after each injection session. Treatments are outlined in table 1. 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 (see table 1). Each participant was encouraged to maintain the exercise program 3 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 1cm to each side of the injection point without pressing in the injection site, and needle entries were vertical to the 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 37mm, with the exceptions 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 27-gauge, 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 (fig 1). The biceps long head, subscapularis insertion, and inferior glenohumeral ligament were injected with the shoulder in various degrees of external rotation and abduction/adduction (fig 2). Origins of the teres minor, teres major, and the posterior inferior glenohumeral ligament were injected posteriorly (fig 3). Participants received injections of 1mL 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 0.5mL of solution.

Postinjection precautions

Pre- and postinjection, participants were advised to use acetaminophen, tramadol, or acetaminophen with codeine for discomfort. Participants were discouraged from using nonsteroidal 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.

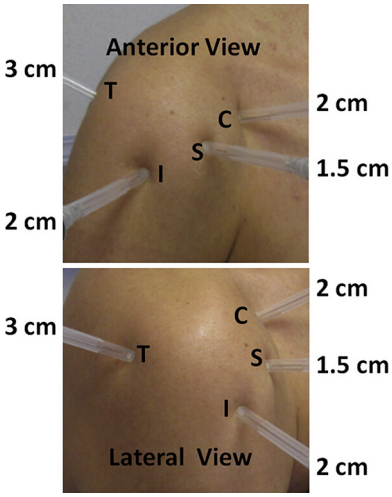

Fig 1 Structures injected in neutral rotation and typical depth of injection. Supraspinatus (S) insertion: 1 to 3mL on the anterior superior part of the greater tuberosity, generally tender to palpation over about 2 to 3cm in height and 0.5cm in width. Infraspinatus (I) insertion: 1 to 3mL immediately posterior to the superior portion of the supraspinatus tendon, in line with the spine of the scapula on the greater tuberosity. Teres minor (T) insertion: 1 to 3mL on the posterior superior surface of the greater tuberosity. Coracoid process (C): 1mL on the bony prominence under the clavicle, medial to the head of the humerus. The coracoid is contacted at its most shallow location.

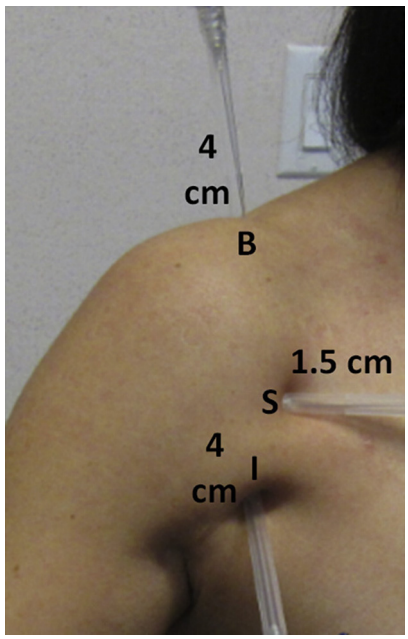

Fig 2 Structures injected in variable external rotation and abduction and typical depth of injection. Biceps long head (B): 1mL immediately medial to the acromioclavicular joint and posterior to the clavicle, with the arm in slight external rotation. Needle insertion is vertical with a 15° anterior tilt until bone is reached. Subscapularis (S) insertion: 1 to 3mL (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 0.5cm lateral to the coracoid process until it reaches the humerus. Inferior glenohumeral ligament (I): 3mL 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.

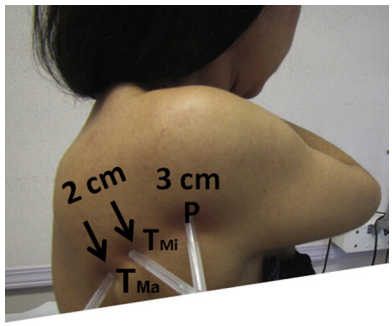

Fig 3 Structures injected posteriorly. Teres major (TMa) and teres minor (TMi): 1 to 3mL (depending on the extent of surface tenderness) with arm fully adducted and hand on opposite shoulder, inject edge of scapula only where tender to avoid risk of pneumothorax. Posterior inferior glenohumeral ligament (P): 1mL with the shoulder fully adducted, the inferior part of the glenohumeral joint is palpated and injected.

Outcome measures

Baseline demographics, previous treatment methods, examination findings, ultrasound findings, Ultrasound Shoulder Pathology Rating Scale (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 for visual analog scale (VAS) change in rotator cuff tendinopathy.[16] Participants marked shoulder pain at 0 and 3 months on a form provided by a blinded evaluator before being seen by the injector. At 9 months, a final 0-to-10 shoulder pain rating was obtained by phone by a blinded evaluator with the same directions (given verbally) as used for the 0-to-10 VAS. Because this value was obtained verbally without an opportunity to choose values other than whole numbers, it would be a 0-to-10 numeric 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 USPRS (fig 4).[15] This rating scale for interval evaluation of rotator cuff tendinopathy was developed for use with wheelchair athletes, and was performed before 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

Table 2 Baseline comparison of treatment groups

Characteristics	Enth-Dex (n=27)	Enth-Saline (n=20)	Superfic-Saline (n=27)	P*
Demographics				
Women	11 (41)	6 (32)	10 (38)	.812
Age (y)	53.8±13.5	51.1±9.2	49.0±11.9	.333
Pain duration (mo)	61±81	131±155	101±115	.125
VAS pain (0−10)	7.7±1.7	8.1±1.4	7.6±1.8	.573
Currently working†	21 (78)	18 (90)	24 (92)	.479
Dominant side	16 (59)	13 (65)	17 (65)	.878
Current smoker	4 (15)	0 (0)	1 (4)	.758
Prior shoulder treatments‡				
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				
Biceps long head/groove pain	19 (70)	13 (68)	20 (77)	.791
Supraspinatus/greater tuberosity pain	26 (96)	19 (100)	26 (100)	.430
Acromioclavicular joint pain	8 (30)	3 (16)	6 (23)	.551
External rotation resistance pain	18 (67)	11 (58)	18 (69)	.719
Internal rotation 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'Brien's active compression—acromioclavicular	21 (78)	17 (89)	22 (85)	.564
O'Brien's active compression—labrum	15 (56)	10 (53)	13 (50)	.921
Baseline ultrasound pathology				
Noncalcific 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	4.0±1.8	4.3±1.8	4.3±1.8	.858
Physical therapy during active study				
No. of sessions received	5.1±1.5	4.3±1.6	5.0±1.8	.172

NOTE. Values are n (%), mean ± SD, or as otherwise indicated.

Abbreviations: Enth-Dex, onto painful entheses with dextrose; Enth-Saline, onto entheses with saline; Superfic-Saline, above entheses with saline.

* *P* values obtained from 1-way analysis of variance for numeric and Pearson chi-square for nonnumeric variables.

† Retired and not working were not distinguished.

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

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

Fig 4 USPRS (range, 0–20). Descriptions of intermediate levels of pathology are found in the original source.[15]

selected either "Yes," "No, modified prolotherapy," "No, sham prolotherapy," or "I don't know."

Statistical analysis

With the use of an estimated effect size of .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 analysis of covariance (ANCOVA) for the pain scale, followed by post hoc Bonferroni correction for 3 groups, was applied to compare the groups for magnitude of change in the 0-to-10 pain score between 0 to 3 months and 0 to 9 months. A Pearson chi-square analysis was used to determine significant differences between groups in the number of participants who achieved a $\geq$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-to-10 satisfaction levels at 9 months. The statistical program used was Predictive Analytics Software (PASW) 18.0.0.[a]

Results

Enrollment and baseline characteristics

Patient recruitment began in October 2010, and data collection was completed in July 2013. A total of 237 people were screened for eligibility (fig 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 72 completed all treatments and provided 9-month follow-up data. Baseline demographics, prior shoulder treatments received, examination findings, and ultrasound pathology were similar, as was the number of physical therapy sessions received during the study (see 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 years, a minimum pain duration of 5 months, and a 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 9 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 percentage of participants reaching and maintaining a clinically significant improvement of $\geq$2.8 in pain was significantly different between groups (P=.046) (see table 4). The Enth-Dex group significantly outperformed 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 a repeat ultrasound examination after treatment, leaving 70 (96%) of 73 persons for whom both before and after treatment ratings were available (see 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 randomized controlled trial 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 with 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

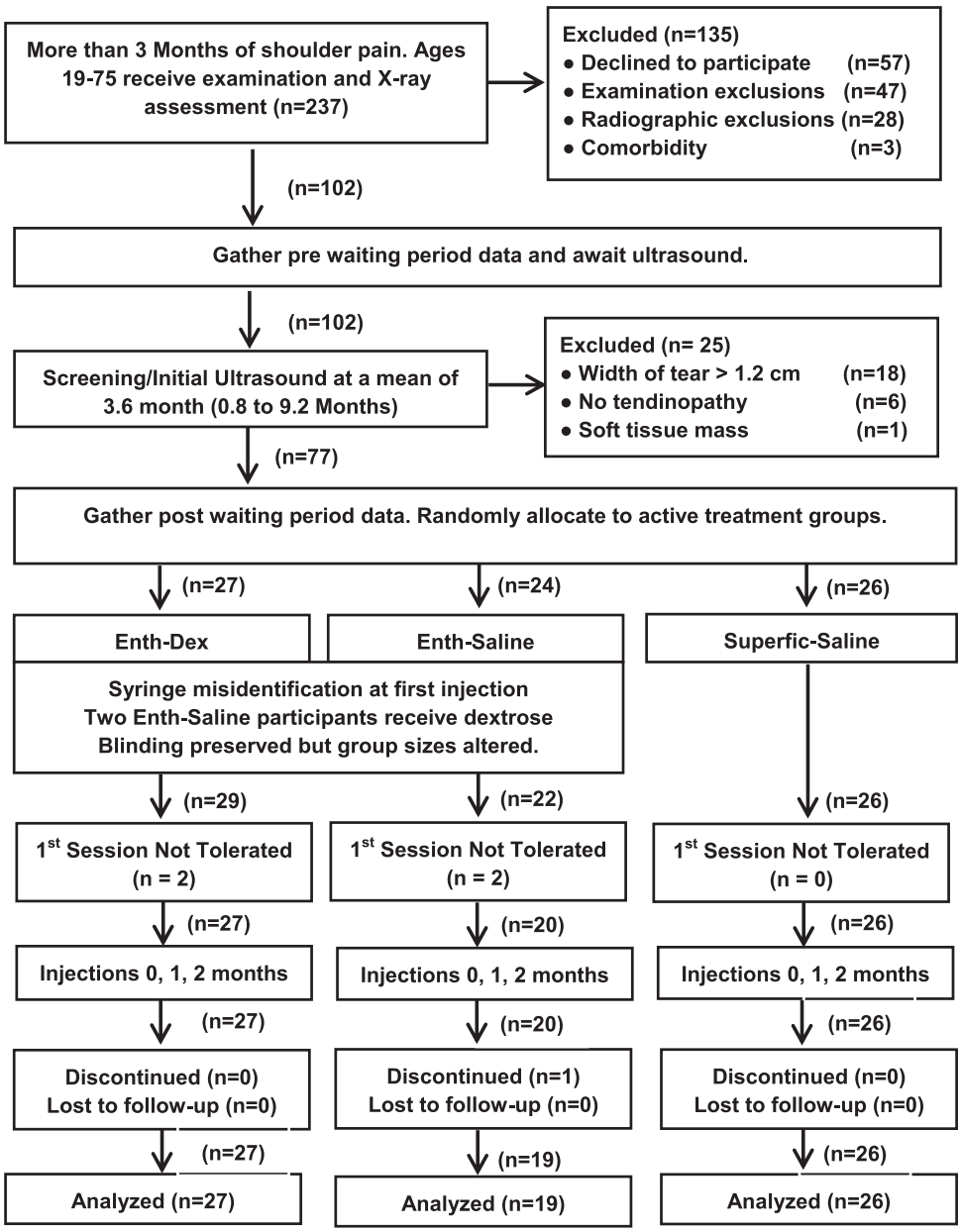

Fig 5 Enrollment of participants and study conduct. All 73 participants provided long-term data for analysis, and all participants completed treatment except 1 participant in the Enth-Saline group who developed adhesive capsulitis after session 1.

pain compared with 27% of the Superfic-Saline group. Participant satisfaction was significantly more in the Enth-Dex group than in the Superfic-Saline group (6.7±3.2 vs 3.9±3.1). 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 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[11] 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. 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[18,19] 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

Table 3 Success of blinding the method of injection

	Participant's Choice of Group*,†			
Actual Group Assignment	"Dextrose Prolotherapy" (Enth-Dex)	"Modified Prolotherapy" (Enth-Saline)	"Sham Prolotherapy" (Superfic-Saline)	"I Don't Know"
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)

NOTE. Values are n (%).
Abbreviations: Enth-Dex, onto painful entheses with dextrose; Enth-Saline, onto entheses with saline; Superfic-Saline, above entheses with saline.
* The following question was presented: "Do you think the treatment you received was true prolotherapy?" (Yes), (No, modified prolotherapy), (No, sham prolotherapy), or (Don't know).
† There was no significant difference between groups for number of correct guesses ($P=.551$).
‡ Indicates correct responses for each group.
§ 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.

for long-term treatment, but the quantity and quality of literature are insufficient for definitive recommendations.

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 0.5g per 100 mL (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[23,24] using injection of noninflammatory 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. Human ultrasound data suggest that hypertonic dextrose injection is followed by regeneration in ligamentous tissue,[13,14] and machine measurement of consecutive cases of anterior cruciate ligament laxity has suggested a reduction in measurable laxity with intra-articular dextrose injection.[25] However, the absence of any demonstrable interval changes on USPRS in the present study does not support regeneration as the source of clinical benefit. Dextrose may also have a direct pain-modulating effect. Two recent randomized controlled trials, 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 down-regulation of the TRPV1 receptor, a key receptor in maintenance of a chronic pain state, or the effects on downstream mediators of TRPV1 activation.

Study limitations

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. In this study, all patients received the same amount of therapy, and significant outcome differences were seen between injection groups.

Table 4 Short-term change in 0-to-10 pain scale and long-term change in 0-to-10 pain and ultrasound pathology rating scales

	0–10 Pain Level			
Group	Baseline	Reduction (Improvement) 0–3mo	Reduction (Improvement) 0–9mo	No. (%) With Clinically Significant Improvement* at 9mo
Enth-Dex	7.3±0.4	3.0±0.5	2.9±0.6	16/27 (59)†
Enth-Saline	6.9±0.5	2.7±0.7	1.8±0.7	7/19 (37)
Superfic-Saline	6.9±0.4	2.7±0.6	1.3±0.6	7/26 (27)

	Ultrasound Pathology Rating Scale	
Group	Baseline	Change at 9.4±2.2mo‡
Enth-Dex	4.0±0.4	−0.3±0.5
Enth-Saline	4.3±0.5	−0.6±0.5
Superfic-Saline	4.3±0.4	−0.6±0.4

NOTE. Values are mean ± SD or as otherwise indicated.
Abbreviations: Enth-Dex, onto painful entheses with dextrose; Enth-Saline, onto entheses with saline; Superfic-Saline, above entheses with saline.
* Defined as equal to or more than twice the minimal clinically important difference (1.4) for a change in 0–10 NRS pain scale (≥2.8). A Pearson chi-square analysis was used for intragroup analysis.
† Enth-Dex significantly outperformed 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 USPRS represents an improvement. No significant differences between groups were noted ($P=.734$).

Failure to use the Disabilities of the 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-to-10 pain scale for the VAS 0-to-10 pain scale at 9 months. However, the 2 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 the minimal clinically important difference 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

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 shoulder pain for years and had failed multiple previous treatments. Baseline evaluations included tabulation of physical findings and ultrasound findings of tendinopathy to provide high specificity for the diagnosis of rotator cuff tendinopathy. The questionnaire used 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 with 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 the mechanism of action and baseline characteristics of responders.

Supplier

a. Predictive Analytics Software (PASW) 18.0.0; IBM Corp.

Keywords

Glucose; Regenerative medicine; Rehabilitation; Rotator cuff; Shoulder; Tendinopathy

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