ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org

Archives of Physical Medicine and Rehabilitation 2015;96:2027-32

ORIGINAL RESEARCH

Prolotherapy for Refractory Rotator Cuff Disease: Retrospective Case-Control Study of 1-Year Follow-Up

Doo-Hyung Lee, MD, PhD,[a] Kyu-Sung Kwack, MD, PhD,[b] Ueon Woo Rah, MD, PhD,[c] Seung-Hyun Yoon, MD, PhD[c]

From the [a]Department of Orthopedic Surgery, [b]Department of Radiology, and [c]Department of Physical Medicine and Rehabilitation, Ajou University School of Medicine and Ajou University Hospital, Suwon, Republic of Korea.

Abstract

Objective: To determine the efficacy of prolotherapy for refractory rotator cuff disease.

Design: Retrospective case-control study.

Setting: University-affiliated tertiary care hospital.

Participants: Patients with nontraumatic refractory rotator cuff disease (N = 151) who were unresponsive to 3 months of aggressive conservative treatment. Of the patients, 63 received prolotherapies with 16.5% dextrose 10-ml solution (treatment group), and 63 continued conservative treatment (control group).

Interventions: Not applicable.

Main Outcome Measures: Visual analog scale (VAS) score of the average shoulder pain level for the past 1 week, Shoulder Pain and Disability Index (SPADI) score, isometric strength of the shoulder abductor, active range of motion (AROM) of the shoulder, maximal tear size on ultrasonography, and number of analgesic ingestions per day.

Results: Over 1-year follow-up, 57 patients in the treatment group and 53 in the control group were analyzed. There was no significant difference between the 2 groups in age, sex, shoulder dominance, duration of symptoms, and ultrasonographic findings at pretreatment. The average number of injections in the treatment group is 4.8±1.3. Compared with the control group, VAS score, SPADI score, isometric strength of shoulder abductor, and shoulder AROM of flexion, abduction, and external rotation showed significant improvement in the treatment group. There were no adverse events.

Conclusions: To our knowledge, this is the first study to assess the efficacy of prolotherapy in rotator cuff disease. Prolotherapy showed improvement in pain, disability, isometric strength, and shoulder AROM in patients with refractory chronic rotator cuff disease. The results suggest positive outcomes, but one should still take caution in directly interpreting it as an effective treatment option, considering the limitations of this nonrandomized retrospective study. To show the efficacy of prolotherapy, further studies on prospective randomized controlled trials will be required.

Archives of Physical Medicine and Rehabilitation 2015;96:2027-32

Prolotherapy is an injection therapy for chronic painful musculoskeletal conditions. It involves the injection of small volumes of an irritant agent, most commonly a hyperosmolar dextrose solution, at multiple painful tendon and ligament insertions where they connect to bone, over several treatment sessions.[1] The injection of an irritant solution initiates an inflammatory cascade at the site of injection, which causes fibroblast proliferation and subsequent collagen synthesis, resulting in a stronger tendon or ligament.[2] Although many different solutions have been used throughout the last 100 years that prolotherapy has been in practice,[1] the most commonly studied and reported agents are hyperosmolar dextrose, phenol-glycerine-glucose, and morrhuate sodium.[3] Phenol-glycerine-glucose is no longer used, but it was included in most earlier published trials. Hyperosmolar dextrose appears to be the most commonly used agent today, with morrhuate sodium used slightly less often.[4] There is promising recent evidence for prolotherapy, with hyperosmolar dextrose in treating painful

Disclosures: none.

0003-9993/15/$36 - see front matter © 2015 by the American Congress of Rehabilitation Medicine
http://dx.doi.org/10.1016/j.apmr.2015.07.011

tendinopathies. It has been used clinically for multiple tendinopathies and has been studied for the treatment of lateral epicondylitis,[5,6] Achilles tendinopathy,[7,8] plantar fasciitis,[9] and hip adductor tendinopathy.[10] However, there are few studies that report the efficacy of prolotherapy for rotator cuff disease. The aim of this study is to evaluate the efficacy of prolotherapy as a therapeutic option for nontraumatic chronic refractory rotator cuff disease.

Methods

Participants

This is a retrospective case-control study. After institutional review board approval, a retrospective review of the medical records of patients who were diagnosed with nontraumatic chronic rotator cuff disease (tendinosis, partial and full thickness tears) between January 2009 and August 2014 were reviewed. They were outpatients at rehabilitation and orthopedic clinics of the university hospital. All patients underwent a standardized history, physical examination, and ultrasonographic evaluation. We also carried out active and passive range of motion, painful arc/impingement test, resisted test, strength of muscles, and checked for tenderness and/or swelling of the lesion in the affected shoulder. Inclusion criteria included the following: (1) duration of symptoms >3 months; (2) >40 years of age; (3) having a painful arc, positive impingement test, or resisted test; and (4) correlation between physical examination and ultrasonography or magnetic resonance imaging. Exclusion criteria included the following: (1) presence of other obvious shoulder pathology (eg, fracture, rheumatic diseases, adhesive capsulitis); (2) referred pain from the neck suggestive of cervical radiculopathy; (3) prior surgery to either the shoulder or neck region; (4) active inflammation on ultrasonography, fluid in biceps tendon sheath, and/or subacromial bursa; (5) calcific tendinitis; and (6) recent history of trauma at shoulder.

Ultrasonography was performed by a board certified physiatrist (S.-H.Y.) with >9 years of experience in musculoskeletal rehabilitation and ultrasound-guided injections and a musculoskeletal radiologist (K.-S.K.) with ultrasound equipment (HD 11XE[a]; Logiq P6[b]) using a 10- to 13-MHz linear array transducer. Rotator cuff tendon pathologies were described as follows: tendinosis, partial thickness tear, or full thickness tear. When a rotator cuff tear was detected on ultrasonographic examination, its type (full or partial thickness), location, and size were recorded. Decisions regarding imaging interpretation were based on the findings of previously published studies.[11] Long- and short-axis scans from the rotator cuff, subacromial bursa, and biceps tendon were obtained.

There were 1816 patients who were diagnosed to have rotator cuff disease and underwent conservative treatment for at least 3 months before the prolotherapy (fig 1). We prescribed analgesics, including nonsteroidal anti-inflammatory drugs, acetaminophen/tramadol, opioids, tricyclic antidepressants, and fentanyl patch. They also did institutional flexibility and strengthening exercises of the shoulder girdle and rotator cuff with physical therapists 1 or 2 times a week for 4 to 8 weeks and were educated to do the same exercises at home.[12,13] Patients who could not accommodate regular exercise at the hospital were given education by physical therapists at each outpatient follow-up and educational leaflets. Also, for oral analgesics, if the visual analog scale (VAS) score was ≥5, ultrasonography-guided suprascapular nerve block with triamcinolone acetonide 10mg and 1% lidocaine 9cc was given.

In case of periarticular inflammation (eg, increased fluid in subacromial bursa or biceps tendon sheath, definite impingement on dynamic ultrasound examination), ultrasonography-guided subacromial corticosteroid injection with triamcinolone acetonide 20mg and 1% lidocaine 3cc was administered at up to a maximum of 2 injections. Because corticosteroid injection may lead to temporary weakening of the tendon,[14] patients refrained from rotator cuff strengthening exercises for 3 weeks and allowed only flexibility exercises. After 4 weeks, they started the rotator cuff progressive strengthening exercises.

Despite conservative treatments, if the patients still complained of continued shoulder pain with scores ≥5 on a VAS of the average shoulder pain level for the past 1 week, we recommended prolotherapy and explained its indications and complications. Patients were free to choose either the prolotherapy or other treatment options. Among 151 patients with refractory rotator cuff disease, 63 opted for prolotherapy (treatment group), and 88 opted for some other treatment. Reasons for opting other treatment included needle phobia (n=43, 48.9%), cumbersome visits and number of injections (n=18, 20.5%), not enough clinical results to guarantee efficacy (n=11, 12.5%), concerns about having more pain after prolotherapy (n=5, 5.7%), financial burden (n=2, 2.3%), and no response or uncharted/unknown (n=9, 10.2%).

Sixty-three patients were willing to take conservative treatment without prolotherapy were selected as control group matching demographic characteristics. The 2 groups were then compared in terms of treatment efficacy.

List of abbreviations:

AROM	**active range of motion**
SPADI	**Shoulder Pain and Disability Index**
VAS	**visual analog scale**

Prolotherapy injection

Participants sat in an upright position, and the arms were positioned behind their backs with internal rotation and hyperextension of shoulder and the elbow bent for longitudinal supraspinatus view. Ultrasonography was used to locate and mark the pressure pain site that overlaps with the rotator cuff disease. Next, an indirect injection technique was applied; ultrasonography was used to establish the puncture site and depth of the target but not to guide the advancement of the needle.[11] The physiatrist (S.-H.Y.) injected 16.5% dextrose 10ml solution (mixture of 20% dextrose 8cc and 1% lidocaine 2ml) with a 25-gauge 3.5-cm needle into 8 to 12 points of the supraspinatus (and subscapularis) tendon(s). After prolotherapy, the patients were asked to avoid nonsteroidal anti-inflammatory drugs so that it would not interfere with the healing process. The injections were administered at weeks 0, 2, and 5 and then every 4 weeks thereafter. Injection was dropped when (1) the level of pain reduced at least to half compared with preinjection, (2) patients reached the maximum 8 rounds of injections, or (3) patients wanted to withdraw from the treatment.

Outcome measurements

The VAS score, Shoulder Pain and Disability Index (SPADI) score, isometric strength of the shoulder abductor, shoulder active range of motion (AROM), maximum tear size on ultrasonography, and number of analgesic ingestions per day were compared for preinjection and 1 year postinjection. All outcome measurements were evaluated by the board certified physiatrist (S.-H.Y.).

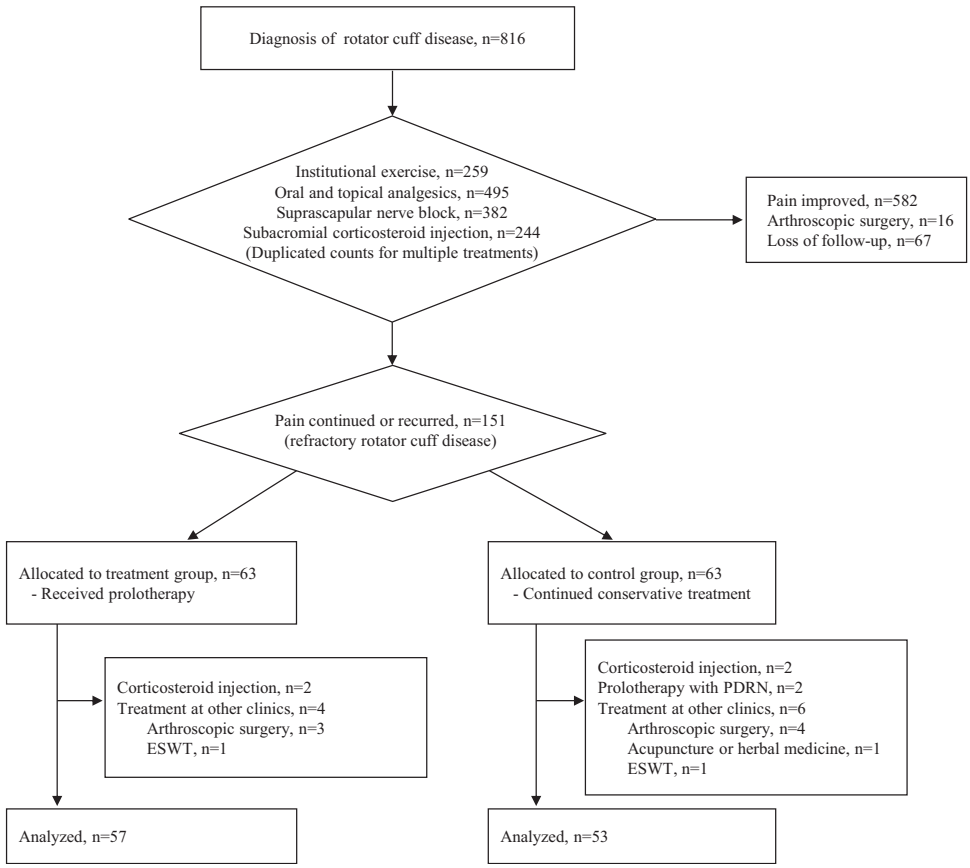

Fig 1 Flow diagram indicating progress of subjects through the study. Abbreviations: ESWT, extracorporeal shock wave therapy; PDRN, polydeoxyribonucleotide.

A VAS from 0 (no pain) to 10 (worst imaginable pain) was used to assess pain. The patient answered the question, "With respect to the worst pain you have experienced in your life, what was the average level of your shoulder pain in the last 1 week?" by placing a mark somewhere along the line. The SPADI is a self-reporting questionnaire for patients with shoulder pain, which consists of 13 questions that are divided into 2 domains: pain (5 items) and disability (8 items).[15] Each domain score is equally weighted and added to obtain a total percentage score between the range of 0 (best) and 100 (worst). Shoulder AROM was measured using a goniometer for forward flexion, internal rotation, external rotation, and abduction of the shoulder in a standing position. Patients were asked to move their shoulders slowly, and the angle at onset of pain was measured 3 times to record the median value. Forward flexion and abduction were measured with the palm down. External and internal rotations were measured in 90° abduction of the shoulder and 90° flexion of the elbow position. Isometric strength of the shoulder abductor was measured using a digital handheld dynamometer (MicroFet2).[c] The patient was tested at 90° of abduction in the scapula plane with the thumb down. Then the transducer pad was put on top of the patient's elbow, and the patient was asked to raise his or her arm with as much force as possible. The force was measured 3 times to record the median value. In case of partial and full thickness tear on ultrasonography, we measured the maximal tear size on longitudinal and transverse views. A straight line was used to visualize the distance between the margins of the cuff tear on the transverse and longitudinal view.[16]

The number of analgesic ingestions per day was measured based on the average number of analgesics the patients had taken per day during the last 1 week.

Statistical analysis

After a normality test, within- and between-group comparisons were conducted at baseline and 1-year follow-up using paired and independent *t* tests. Significance was accepted for $P<.05$. Statistical analyses were performed using SPSS version 22.[d]

Results

The average number of injections was 4.8±1.3 at final analysis of 57 patients with refractory rotator cuff disease (treatment group); injections occurred 3 times in 7 patients, 4 times in 21 patients, 5 times in 14 patients, 6 times in 8 patients, 7 times in 5 patients, and 8 times in 2 patients. Prolotherapy was applied at different sites, including the supraspinatus tendon only in 48 patients; supraspinatus and subscapularis tendons in 5 patients; supraspinatus and biceps tendons in 2 patients; and supraspinatus, subscapularis, and biceps tendons in 2 patients. Initial ultrasonography found rotator cuff tendinosis, partial thickness tear, and full thickness tear in 31, 17, and 9 patients, respectively (table 1). The control group included 53 patients who could continue conservative treatment without prolotherapy and had baseline characteristics similar to that of the treatment group. There were no

Table 1 Baseline characteristics of patients

Characteristic	Treatment Group (n=57)	Control Group (n=53)	P
Age (y)	54.1±7.8	55.8±6.6	.23*
Sex, men:women	23:34	17:36	.90*
Shoulder affected, dominant: nondominant	35:22	28:25	.36†
Duration of symptoms (mo)	13.2±3.1	14.0±2.5	.17*
No. of injections	4.8±1.3		
Prolotherapy injection location			
Supraspinatus tendon only	48		
Supraspinatus and subscapularis tendons	5		
Supraspinatus and biceps tendons	2		
Supraspinatus, subscapularis, and biceps tendons	2		
Ultrasonographic finding of rotator cuff lesion			.33†
Tendinosis	31	36	
Partial thickness tear	17	12	
Full thickness tear	9	5	

NOTE. Values are expressed as n, mean ± SD, or as otherwise indicated.
* Independent *t* test for between-group comparison ($P<.05$).
† Chi-square test for between-group comparison ($P<.05$).

Table 2 Changes of outcome measurements after prolotherapy

Outcome Measurement	Treatment Group (n=57)	Control Group (n=53)	P*
VAS score			
Month 0	6.3±1.0	6.1±1.2	.32
Month 12	2.7±1.0	4.6±1.4	<.001
SPADI score			
Month 0	69.4±9.2	67.6±9.4	.30
Month 12	43.8±11.6	51.1±14.4	.004
Isometric strength of abductor, kgf			
Month 0	9.1±4.0	10.4±3.6	.09
Month 12	14.1±3.9	11.8±4.0	.003
Flexion			
Month 0	158.5±13.5	153.0±15.9	.05
Month 12	169.1±11.7	163.1±16.9	.03
Abduction			
Month 0	140.1±24.2	142.5±23.8	.60
Month 12	165.5±16.7	153.1±27.1	.005
Internal rotation			
Month 0	42.1±18.4	41.8±17.1	.93
Month 12	58.3±19.8	54.9±19.6	.36
External rotation			
Month 0	77.4±13.5	74.0±16.5	.25
Month 12	86.8±13.9	81.0±14.1	.03
Maximal tear size, mm			
Month 0	3.4±1.5	2.8±0.9	.06
Month 12	3.1±1.3	3.0±0.9	.77
No. of analgesic ingestions per day			
Month 0	2.8±0.9	2.8±1.0	.86
Month 12	0.6±0.8	0.8±1.0	.22

NOTE. Values are expressed as mean ± SD or as otherwise indicated.
* Independent *t* test for between-group comparison ($P<.05$).

statistical differences between the 2 groups in baseline characteristics, including age, sex, dominancy of shoulder, duration of symptoms, and ultrasonographic findings of rotator cuff lesion.

In within-group comparison, the control group showed an improvement in VAS score, SPADI score, isometric strength, and shoulder AROM; decrease in the number of analgesic ingestions; and increase in the maximal tear size, whereas the treatment group showed an improvement in VAS score, SPADI score, isometric strength, shoulder AROM; decrease in the number of analgesic ingestions; and no change in the maximal tear size. In between-group comparison, the treatment group showed improvement in VAS score, SPADI score, isometric strength, and shoulder AROM of flexion, abduction, and external rotation compared with the control group. There were no differences in the number of analgesics taken and maximal tear size (table 2). There were no adverse events reported (eg, bleeding, infection, cellulitis, septic joint).

Discussion

To our knowledge, this is the first study to evaluate the efficacy of prolotherapy in rotator cuff disease. In this retrospective study of a minimum 1-year follow-up, prolotherapy was used (4.8 times on average) to treat patients who had chronic refractory rotator cuff disease but failed conservative treatments. The treatment group showed improvement in VAS score, SPADI score, isometric strength of shoulder abductor, and shoulder AROM of flexion, abduction, and external rotation compared with the control group. The result showed improvement not only in subjective outcome measurements but also objective functional outcomes (eg, isometric strength, shoulder AROM). In the treatment group, the tendon tear size reduced; however, it was not statistically significant in posttreatment compared with pretreatment.

The treatment of rotator cuff disease revolves around controlling pain because pain is the limiting factor for activity. If the rotator cuff disease is chronic or degenerative, nonoperative and conservative management, including exercise, physical modalities (therapeutic ultrasound, low-intensity laser, transcutaneous electrical nerve stimulation), oral analgesics, and corticosteroid injection, were performed as primary treatment.[17] Despite the developments made in conservative management, overuse rotator cuff disease often remains difficult to manage successfully in the longer term. Through long-term follow-up, this study has shown the potential usefulness of prolotherapy—despite it being a conservative therapy—in some patients with chronic pain.

Despite its long history and broad use as a form of complementary treatment, the mode of action for hyperosmolar dextrose is unclear. Although there are controversies over its optimal indications, many studies have reported the use and efficacy of prolotherapy for various musculoskeletal conditions, particularly in the treatment of chronic low back pain. Recent studies have also

examined its use in the treatment of refractory tendinopathies, particularly for lateral epicondylitis[5,6] and Achilles tendinopathy.[7,8] Two systematic reviews concluded that moderate evidence exists to support the use of prolotherapy injections in the management of pain in lateral epicondylitis.[18,19] Given the similar pathologic findings of tendinopathies in different anatomic locations, the researchers believe that it is reasonable to try prolotherapy for other, less studied tendinopathies when first-line treatments fail.[20]

This study showed the efficacy of prolotherapy over the year by enrolling a large number of patients with chronic rotator cuff disease with no progress in pain despite 3 months of aggressive conservative treatments.

Study limitations

The greatest limitation of this study lies in the fact that it is a retrospective study and that the group allocation was not randomized. Patients chose to take the therapy according to their own will, and no randomization process was involved. Therefore, the study has low validity of the statistical tests used to demonstrate significance and fails to minimize confounding and potential biases.

Conclusions

This study looked into the option of prolotherapy as an alternative treatment for rotator cuff disease. Although the authors believe prolotherapy can be an option for patients with refractory chronic rotator cuff disease who showed no response to other treatments, one must take cautionary steps in interpreting the result, considering the limitations of this study. Even though the study suggests positive outcomes after prolotherapy, more evidence is required before applying it directly in clinical practices. To show the efficacy of prolotherapy, further studies on prospective randomized controlled trials will be required to overcome the limitations mentioned in the discussion.

Suppliers

a. HD 11XE; Philips Ultrasound.
b. Logiq P6; GE Healthcare.
c. MicroFet2; Hoggan Health Industries.
d. SPSS version 22; IBM Inc.

Keywords

Injections, intralesional; Rehabilitation; Rotator cuff; Shoulder impingement syndrome; Shoulder pain; Tendinopathy

Corresponding author

Seung-Hyun Yoon, MD, PhD, Department of Physical Medicine and Rehabilitation, Ajou University School of Medicine and Ajou University Hospital, Worldcup-ro 164, Yeongtong-gu, Suwon 443-721, Republic of Korea. *E-mail address:* yoonsh@ajou.ac.kr.

Acknowledgement

We thank Aeree Park, MA, for the English translation of the Korean manuscript.

References

1. Rabago D, Slattengren A, Zgierska A. Prolotherapy in primary care practice. Prim Care 2010;37:65-80.
2. Liu YK, Tipton CM, Matthes RD, Bedford TG, Maynard JA, Walmer HC. An in situ study of the influence of a sclerosing solution in rabbit medial collateral ligaments and its junction strength. Connect Tissue Res 1983;11:95-102.
3. Dagenais S, Ogunseitan O, Haldeman S, Wooley JR, Newcomb RL. Side effects and adverse events related to intraligamentous injection of sclerosing solutions (prolotherapy) for back and neck pain: a survey of practitioners. Arch Phys Med Rehabil 2006;87:909-13.
4. Jensen KT, Rabago DP, Best TM, Patterson JJ, Vanderby R. Response of knee ligaments to prolotherapy in a rat injury model. Am J Sports Med 2008;36:1347-57.
5. 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;18:248-54.
6. Carayannopoulos A, Borg-Stein J, Sokolof J, Meleger A, Rosenberg D. Prolotherapy versus corticosteroid injections for the treatment of lateral epicondylosis: a randomized controlled trial. PM R 2011;3:706-15.
7. 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. AJR Am J Roentgenol 2007;189:W215-20.
8. 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;45:421-8.
9. Ryan MB, Wong A, Gillies J, Wong J, Taunton J. Sonographically guided intratendinous injections of hyperosmolar dextrose/lidocaine: a pilot study for the treatment of chronic plantar fasciitis. Br J Sports Med 2009;43:303-6.
10. Topol GA, Reeves KD, Hassanein KM. Efficacy of dextrose prolotherapy in elite male kicking-sport athletes with chronic groin pain. Arch Phys Med Rehabil 2005;86:697-702.
11. Bianchi S, Martinoli C, Baert A, et al. Ultrasound of the musculoskeletal system. Berlin: Springer Verlag; 2007.
12. Kuhn JE, Dunn WR, Sanders R, et al. Effectiveness of physical therapy in treating atraumatic full-thickness rotator cuff tears: a multicenter prospective cohort study. J Shoulder Elbow Surg 2013;22:1371-9.
13. Krischak G, Gebhard F, Reichel H, et al. A prospective randomized controlled trial comparing occupational therapy with home-based exercises in conservative treatment of rotator cuff tears. J Shoulder Elbow Surg 2013;22:1173-9.
14. Hong JY, Yoon SH, Moon do J, Kwack KS, Joen B, Lee HY. Comparison of high- and low-dose corticosteroid in subacromial injection for periarticular shoulder disorder: a randomized, triple-blind, placebo-controlled trial. Arch Phys Med Rehabil 2011;92:1951-60.
15. Roach KE, Budiman-Mak E, Songsiridej N, Lertratanakul Y. Development of a shoulder pain and disability index. Arthritis Care Res 1991;4:143-9.
16. Moosmayer S, Heir S, Smith HJ. Sonography of the rotator cuff in painful shoulders performed without knowledge of clinical information: results from 58 sonographic examinations with surgical correlation. J Clin Ultrasound 2007;35:20-6.

17. Rees JD, Maffulli N, Cook J. Management of tendinopathy. Am J Sports Med 2009;37:1855-67.
18. Rabago D, Best TM, Zgierska AE, Zeisig E, Ryan M, Crane D. A systematic review of four injection therapies for lateral epicondylosis: prolotherapy, polidocanol, whole blood and platelet-rich plasma. Br J Sports Med 2009;43:471-81.
19. 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;376:1751-67.
20. Distel LM, Best TM. Prolotherapy: a clinical review of its role in treating chronic musculoskeletal pain. PM R 2011;3(6 Suppl 1):S78-81.