Available online at www.sciencedirect.com

ScienceDirect

Journal of the Chinese Medical Association 78 (2015) 127–132

www.jcma-online.com

Original Article

Comparison of the analgesic effect of xylocaine only with xylocaine and corticosteroid injection after ultrasonographically-guided percutaneous treatment for rotator cuff calcific tendonosis

Yen-Huai Lin [a,b,c], Hong-Jen Chiou [a,b,d,*], Hsin-Kai Wang [a,b], Yi-Chen Lai [a,b], Yi-Hong Chou [a,b], Cheng-Yen Chang [a,b]

[a] *Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[b] *School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*
[c] *Kin-Men Hospital, Ministry of Health and Welfare, Kinmen, Taiwan, ROC*
[d] *National Defense Medical Center, Taipei, Taiwan, ROC*

Received January 9, 2014; accepted May 17, 2014

Abstract

Background: The analgesic effect of xylocaine alone versus xylocaine with corticosteroid injection after ultrasonographically (US)-guided treatment of rotator cuff calcific tendonosis has not been described in English literature. The aim of this study was to compare the analgesic effect of xylocaine only with xylocaine and corticosteroid following US-guided percutaneous treatment of rotator cuff calcific tendonosis.
Methods: This prospective study enrolled 88 patients who were given different analgesic treatments [xylocaine only, $n = 23$; xylocaine with corticosteroid, $n = 44$; control (no xylocaine or corticosteroid), $n = 21$]. The assessment of a patient's painful symptoms was recorded before treatment, and 1 day, 1 week, 1 month and 3 months after treatment using the visual analogue scale (VAS).
Results: There were no significant differences in age, sex, calcification size before and after treatment, and amount of calcification decrease after treatment, but there was a significant difference in calcification morphology among the groups ($p = 0.010$). General linear model analysis indicated that the three groups had no difference in pain prior to treatment. After treatment, the xylocaine only and the xylocaine with corticosteroid groups had less pain than the control group at 1 day, 1 week, and 1 month after treatment. At 3 months after treatment, the xylocaine only group had less pain than the control group ($p = 0.039$), and the xylocaine with corticosteroid and control groups had similar levels of pain.
Conclusion: Injection of xylocaine alone after US-guided treatment of rotator cuff calcific tendonosis provided a longer pain relief period than that of a mixture of xylocaine with corticosteroid.

Keywords: analgesic; calcific tendonosis; rotator cuff; ultrasonography; US-guided fine-needle repeated puncture treatment

1. Introduction

Calcific tendonosis of the rotator cuff is a common disorder, especially in the supraspinatus tendon,[1] and usually causes inflammation and pain in the shoulder region. The pathogenesis of rotator cuff calcification is uncertain, but it may be due to ischemia[2] or degeneration[3] leading to fibrocartilaginous metaplasia and ultimately calcification.[4,5] Previous research reported that chronic and acute calcific tendonosis were mostly caused by the deposition of hydroxyapatite (HAP) in the periarticular tendon.[6]

Diverse methods can be used to manage rotator cuff calcific tendonosis. Conservative treatments include physical therapy with a short course of an oral nonsteroidal antiinflammatory

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Hong-Jen Chiou, Department of Radiology, Taipei Veterans General Hospital, 201, Section, 2, Shih-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: hjchiou@gmail.com (H.-J. Chiou).

http://dx.doi.org/10.1016/j.jcma.2014.09.006

drug (NSAID),[1] lithotripsy by arthroscopy,[7,8] an image-guided fluoroscopic procedure,[9,10] extracorporeal shock wave therapy,[1−12] or single or two-needle ultrasonographically (US)-guided techniques.[13−19] Although there is no proven advantage of single or two-needle US-guided techniques, there is potential for tendon damage from use of multiple needles or a large needle. Previous studies indicated that US-guided fine-needle repeated puncture was an effective method for treatment of rotator cuff calcific tendonosis.[17,19]

Although the US-guided technique is effective for management of calcific tendonosis, most patients complain of severe pain for 1 week or more after this procedure. Fortunately, this pain can often be resolved by use of analgesic drugs and corticosteroid injection into the subdeltoid bursa.[13−19] Nevertheless, the analgesic effect of xylocaine alone versus xylocaine and corticosteroid injection has not been described in English literature. The US-guided fine-needle repeated puncture treatment creates an iatrogenic inflammatory process, which is necessary for effective resorption of calcium HAP following treatment of calcific tendonosis. The additional corticosteroid could potentially compromise the inflammatory process.

The purpose of this study is to compare the analgesic effect of xylocaine alone with xylocaine and corticosteroid injection of the subdeltoid bursa after a US-guided procedure for management of calcific tendonosis.

2. Methods

2.1. Participants

This was a prospective study that enrolled consecutive outpatients at the department of orthopedics or patients in rehabilitation due to chronic shoulder pain for >6 months. The primary inclusion criterion was the presence of calcifications within the rotator cuff with confirmation by gray-scale US. All patients who had previous invasive treatment for calcifications within the rotator cuff, including lithotripsy, arthroscopy or other imaging-guided procedures, and extracorporeal shock wave therapy were excluded. In addition, patients who had corticosteroid injections in the previous 6 months or concomitant rotator cuff tear were excluded. A total of 88 participants (29 men and 59 women; mean age: 57.9 years; age range: 32−83 years) who received US-guided repeated puncture for calcifications were enrolled from October 2009 to December 2011. All participants provided written informed consent for US-guided treatment of rotator cuff calcific tendonosis. Investigative and interventional procedures were performed according to the guidelines of the Helsinki Declaration and were approved by an institutional review board in Taipei Veterans General Hospital.

2.2. Pain assessment

The clinical assessment employed a visual analogue scale (VAS), in which each patient graded his/her own symptoms from 0 (painless) to 10 (the most painful sensation). Pain assessment was performed before treatment, and 1 day, 1 week, 1 month and 3 months after treatment by telephone query from a clinical assistant who was blinded to the treatments of all patients.

2.3. US-guided technique for treatment of rotator cuff calcific tendonosis

The morphology of the calcification, based on high-resolution US (HRUS), was classified as an arc, fragmented, nodular, or cystic[16,17] and the longest diameter of the calcification was recorded. Prior to use of the US-guided technique, each patient was given the opportunity to receive treatment with xylocaine alone, or treatment with xylocaine and corticosteroid, or no analgesic drug (control group). Patients in the xylocaine group were given 2 mL of 2% xylocaine (Recipharm Monts, Monts, France) and patients in the xylocaine with corticosteroid group were given 1 mL of 2% xylocaine mixed with 1 mL of corticosteroid (10 mg triamcinolone acetonide, Shincort, Yung Shin Pharmaceutical Industrial Company, Taichung, Taiwan). All injections were into the subdeltoid bursa with US guidance. If a patient did not want to choose or did not know how to choose a treatment group, a coin toss was used to determine group assignment.

The puncture procedure was performed with a US-monitored free-hand method. The needle tip was placed in the calcification, which was then punctured by moving the needle back and forth. There was no large-needle lavage in this study. The puncture needle was a 3.8 cm 21 gauge needle attached on a 10 mL syringe. Prior to the procedure, the skin of the puncture site was sterilized with beta iodine, and the transducer was covered with a sterilized plastic bag. Less than 2 mL of 2% xylocaine was injected in the subcutaneous and muscle layer. The US-guided repeated punctures were performed by moving the needle back-and-forth 20−40 times, according to the size and other characteristics of the calcifications, without removing the needle from the initial puncture site. The needle tract was monitored by HRUS to ensure that it had penetrated the calcification. After this procedure, analgesia (xylocaine or xylocaine with corticosteroid) was injected into the subdeltoid bursa. The puncture site was bandaged with self-administered hand compression for 15 minutes. All patients were sent home and encouraged to actively exercise the affected shoulder starting the next day.[16,17] All US examinations and US-guided treatments were performed by one of the authors (H.J.C.) who has >20 years of experience in US and 15 years of experience in musculoskeletal US.

Each participant's symptoms were recorded before treatment, and 1 day, 1 week, 1 month and 3 months after treatment by telephone query from a clinical assistant who was blinded to the treatment. All patients also returned for follow-up US examinations by the same author (H.J.C.) at 6 months after treatment.

The US machines were the GE Voluson E8 system (GE Medical Systems, Milwaukee, WI, USA) with the SP 10-16-D linear transducer, the Philips iU 22 system (Philips-ATL, Bothell, WA, USA) with the L12-5 linear transducer, and the

Siemens S2000 system (Siemens, Mountain View, CA, USA) with the 14L5 linear transducer.

2.4. Statistical analysis

The Chi-square test or Fisher's exact test was used to assess differences in sex and type of calcification, and a one-way analysis of variance was used to assess differences in patient age, calcification size, and VAS scores at different times. A general linear model was used to assess differences in pre- and posttreatment VAS values. A p value <0.05 was considered significant and all statistical analyses were performed with SPSS version 17 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 23 patients received 2 mL of xylocaine only, 44 patients received 1 mL of xylocaine mixed with 1 mL of corticosteroid, and 21 patients received no analgesic. There were no significant differences among these groups in age ($p = 0.696$), sex ($p = 0.698$), calcification size before treatment ($p = 0.245$), calcification size after treatment ($p = 0.970$), and change in calcification size ($p = 0.900$) (Table 1). However, there was a significant difference in calcific morphology among the three groups ($p = 0.020$). Arc type of calcification was most common in the control group, nodular type of calcification was most common in the xylocaine only group, and arc type of calcification was most common in the xylocaine with corticosteroid group.

In the xylocaine-only group, the mean VAS pain declined from 6.35 to 0.65 at 3 months after treatment, and the mean size of the calcification declined from 1.00 cm to 0.3 cm at 6 months after treatment. Fig. 1 shows a representative patient from this group. In the xylocaine with corticosteroid group, the mean VAS pain declined from 6.18 to 1.98 at 3 months after treatment and the mean size of the calcification declined from 0.92 cm to 0.28 cm at 6 months after treatment. Fig. 2 shows a representative patient from this group. In the control group, the mean VAS pain declined from 5.14 to 1.81 at 3 months after treatment and the mean size of the calcification declined from 1.02 cm to 0.29 cm at 6 months after treatment. Among the three groups, there was no significant difference in VAS pain before treatment ($p = 0.194$), but the VAS pain 1 day ($p < 0.001$), 1 week ($p < 0.001$), 1 month ($p = 0.017$) and 3 months ($p = 0.019$) after treatment was significantly lower in the xylocaine-only group and in the xylocaine with corticosteroid group relative to the control group (Table 1). None of the patients experienced complications, such as bleeding, infection, or ligament tear.

Finally, we used general linear model analysis to compare the levels of VAS pain in the three groups at different times after treatment. The results indicate no significant difference in pain before treatment, but significantly less pain in the xylocaine-only and the xylocaine with corticosteroid groups relative to the control group at 1 day, 1 week, and 1 month after treatment (Table 2). At 3 months after treatment, VAS pain in the xylocaine only group was significantly less than that in the control group ($p = 0.039$), but VAS pain in the xylocaine with corticosteroid group was not significantly different from that in the control group ($p = 0.730$). The same results were found after controlling for type of calcification (data not shown).

4. Discussion

The US-guided procedure used to treat calcific tendonosis introduces iatrogenic minor trauma over the calcification, which results in acute inflammation, neovascularization, and

Table 1
Demographic data.

Variables	Xylocaine only ($n = 23$)	Xylocaine/corticosteroid ($n = 44$)	Control ($n = 21$)	p
Sex				
Male	6	16	7	0.698
Female	17	28	14	
Type of calcification				
Arc	8	23	15	0.010
Nodular	12	12	1	
Cystic	3	4	2	
Fragmented	0	5	3	
Age (y)	55.8 ± 7.10	59.6 ± 10.8	56.8 ± 13.1	0.696
Size of calcification (cm)				
Before treatment	1.00 ± 0.52	0.92 ± 0.42	1.02 ± 0.64	0.245
6 mo after treatment	0.30 ± 0.39	0.28 ± 0.29	0.29 ± 0.26	0.970
Decreasing % of calcification	71.5 ± 28.1	67.9 ± 30.6	68.0 ± 16.7	0.900
Visual analogue scale				
Before treatment	6.35 ± 2.62	6.18 ± 2.52	5.14 ± 1.93	0.194
1 d after treatment	3.22 ± 2.35	2.61 ± 2.07	6.67 ± 1.65	<0.001
1 wk after treatment	1.83 ± 1.67	1.68 ± 1.52	6.10 ± 1.76	<0.001
1 mo after treatment	1.52 ± 1.59	2.14 ± 1.95	3.10 ± 1.67	0.017
3 mo after treatment	0.65 ± 1.03	1.98 ± 2.34	1.81 ± 1.12	0.019

Data are presented as mean ± standard deviation.

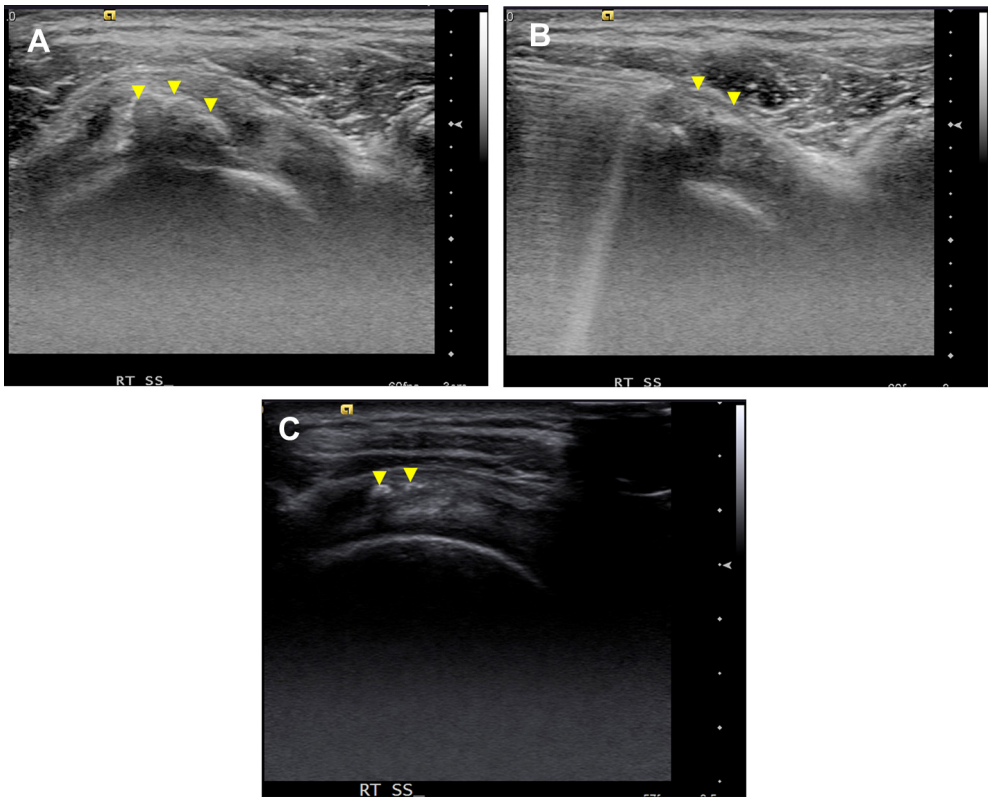

Fig. 1. A 45-year-old female patient complained of right shoulder pain for >1 year. Ultrasonography showed an arc-shaped calcification in the right supraspinatus tendon (arrowheads in A). After ultrasonography (US)-guided repeated puncture, 2 mL of xylocaine was injected into the right subdeltoid bursa (arrowheads in B). Six months later, ultrasonography showed only tiny calcification spots (arrowheads in C), and the patient reported marked reduction of pain.

increased macrophages that remove the calcium.[17] Although the US-guided technique is effective for management of calcific tendonosis,[13–18] most patients complain of severe pain for >1 week after the procedure. Fortunately, this pain can be managed by use of analgesic drugs or corticosteroid injections into the subdeltoid bursa. In this study, we found that the percent decrease in calcifications after surgery was similar for patients in the xylocaine, xylocaine with corticosteroid, and control groups. Thus, these analgesics appeared to have no effect on the resorption of calcifications. However, patients in the xylocaine only group had less pain at 3 months after surgery than those in the xylocaine with corticosteroid group and in the control group.

Corticosteroid injection can relieve the shoulder pain associated with diverse musculoskeletal conditions.[20–26] These drugs have antiinflammatory effects, inhibit the synthesis of glycosaminoglycans, proteins, and collagen,[27] and alter fibroblast proliferation and metabolism.[28] However, these later effects may be classified as antianabolic, so corticosteroids may also have adverse effects on wound and soft tissue healing.[29,30] Thus, the short term use of an analgesic such as xylocaine is often recommended for relief of shoulder pain in order to prevent the adverse effects of corticosteroids in soft tissue.[21,23–26] Xylocaine is generally used as a local analgesic and is injected into subcutaneous, intramuscular, or intrabursal regions. Although xylocaine is also associated with some adverse cardiovascular and neurological effects, these typically only occur following large doses or intravascular injections.

Xylocaine only provides short-term relief from pain, so it may be combined with a corticosteroid in order to provide prolonged pain relief. In particular, xylocaine provides short-term pain relief due to its effect as a local anesthetic (inhibition of neuronal ion fluxes), but corticosteroids provide long-term relief from pain due to their long-term effects on diverse types of cells and endogenous molecules involved in inflammation.[31,32] The US-guided fine-needle repeated puncture treatment creates an iatrogenic inflammatory process, which is necessary for effective resorption of calcium HAP following treatment of calcific tendonosis. Our results indicate that the xylocaine only and the xylocaine with corticosteroid groups had similarly reduced levels of pain relative to the control group for up to 1 month after US-guided treatment for calcific tendonosis. However, the xylocaine only group had less pain than the xylocaine with corticosteroid group at 3 months after treatment. Corticosteroid injections are believed to compromise the inflammatory process and inhibit the resorption of calcifications following percutaneous treatment of rotator cuff calcific tendonosis.

Our study had several limitations. First, participants were not randomized and this could have led to selection bias. Second, all patients were treated by US-guided repeated punctures, and single or double lavage techniques, which are common in some institutions, were not performed. Third, the

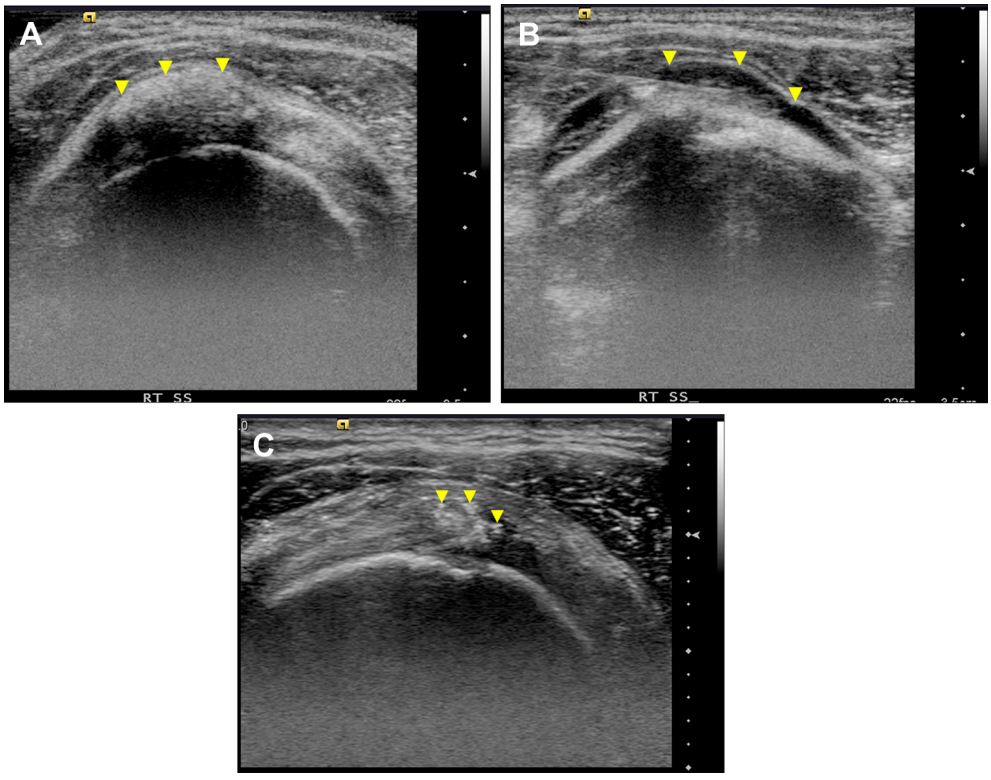

Fig. 2. A 41-year-old female complained of right shoulder pain for 1 year. Ultrasonography showed a nodular calcification in the right supraspinatus tendon (arrowheads in A). After ultrasonography (US)-guided repeated puncture, 1 mL of xylocaine with 1 mL of corticosteroid was injected into the right subdeltoid bursa (arrowheads in B). Six months later, ultrasonography showed a cluster of punctate calcification spots, with >50% reduction in calcification (arrowheads in C), and the patient reported marked reduction of pain.

follow-up time was only 3 months for assessment of pain, but was 6 months for assessment of calcific morphology. It would have been better to perform a final pain assessment at 6 months. In our institute, US-guided treatment of rotator cuff tendonosis is routinely performed 6 months after treatment. Fourth, we only examined the effect of a single corticosteroid dose of 10 mg. However, our results showed a clear difference between the xylocaine only and the xylocaine with corticosteroid groups compared to the control group from 1 day to 1 month after surgery.

Table 2
General linear model analysis for visual analogue scale at different time frames.

Visual analogue scale	Regression coefficient	Standard error	*p*	95% CI
Before treatment				
Xylocaine only	1.21	0.73	0.103	−0.25~2.66
Xylocaine/corticosteroid	1.04	0.64	0.109	−0.24~2.32
Control	Reference			
One day after treatment				
Xylocaine only	−3.45	0.62	<0.001	−4.69~−2.21
Xylocaine/corticosteroid	−4.05	0.55	<0.001	−5.14~−2.97
Control	Reference			
One week after treatment				
Xylocaine only	−4.27	0.49	<0.001	−5.24~−3.30
Xylocaine/corticosteroid	−4.41	0.43	<0.001	−5.27~−3.56
Control	Reference			
One month after treatment				
Xylocaine only	−1.57	0.54	0.005	−2.65~−0.50
Xylocaine/corticosteroid	−0.96	0.48	0.048	−1.91~−0.01
Control	Reference			
Three months after treatment				
Xylocaine only	−1.16	0.55	0.039	−2.25~−0.06
Xylocaine/corticosteroid	0.17	0.48	0.730	−0.80~−1.13
Control	Reference			

CI = confidence interval.

In conclusion, patients who received US-guided percutaneous treatment for rotator cuff calcific tendonosis and were given a xylocaine injection experienced less pain at 3 months than those given a xylocaine and corticosteroid injection. Injection of xylocaine alone appears to provide effective relief from the shoulder pain associated with US-guided repeated punctures for treatment of rotator cuff calcific tendonosis.

Acknowledgments

This work was supported by a grant from the National Science Council, Taipei, Taiwan, Republic of China (NSC-97–2320-B075–054-MY3).

References

1. Bianchi S. Shoulder. In: Bianchi S, Martinoli C, editors. *Ultrasound of the musculoskeletal system*. Berlin: Springer-Verlag; 2007. p. 190–331.
2. Rathbun JB, Macnab I. The microvascular pattern of the rotator cuff. *J Bone Joint Surg Br* 1970;**52**:540–53.
3. Chard MD, Cawston TE, Riley GP, Gresham GA, Hazleman BL. Rotator cuff degeneration and lateral epicondylitis: a comparative histological study. *Ann Rheum Dis* 1994;**53**:30–4.

4. Uhthoff HK, Loehr JW. Calcific Tendinopathy of the rotator cuff: pathogenesis, diagnosis, and management. *J Am Acad Orthop Surg* 1997;**5**:183−91.
5. Uhthoff HK, Sarkar K. Calcifying tendinitis. *Baillieres Clin Rheumatol* 1989;**3**:567−81.
6. Hamada J, Tamai K, Ono W, Saotome K. Does the nature of deposited basic calcium phosphate crystals determine clinical course in calcific periarthritis of the shoulder? *J Rheumatol* 2006;**33**:326−32.
7. Hurt G, Baker Jr CL. Calcific tendinitis of the shoulder. *Orthop Clin North Am* 2003;**34**:567−75.
8. Jerosch J, Strauss JM, Schmiel S. Arthroscopic treatment of calcific tendinitis of the shoulder. *J Shoulder Elbow Surg* 1998;**7**:30−7.
9. Comfort TH, Arafiles RP. Barbotage of the shoulder with image-intensified fluoroscopic control of needle placement for calcific tendinitis. *Clin Orthop Relat Res* 1978;**135**:171−8.
10. Pfister J, Gerber H. Chronic calcifying tendinitis of the shoulder-therapy by percutaneous needle aspiration and lavage: a prospective open study of 62 shoulders. *Clin Rheumatol* 1997;**16**:269−74.
11. Hsu CJ, Wang DY, Tseng KF, Fong YC, Hsu HC, Jim YF. Extracorporeal shock wave therapy for calcifying tendinitis of the shoulder. *J Shoulder Elbow Surg* 2008;**17**:55−9.
12. Pan PJ, Chou CL, Chiou HJ, Ma HL, Lee HC, Chan RC. Extracorporeal shock wave therapy for chronic calcific tendinitis of the shoulders: a functional and sonographic study. *Arch Phys Med Rehabil* 2003;**84**:988−93.
13. Aina R, Cardinal E, Bureau NJ, Aubin B, Brassard P. Calcific shoulder tendinitis: treatment with modified US-guided fine-needle technique. *Radiology* 2001;**221**:455−61.
14. del Cura JL, Torre I, Zabala R, Legorburu A. Sonographically guided percutaneous needle lavage in calcific tendinitis of the shoulder: short- and long-term results. *AJR Am J Roentgenol* 2007;**189**:W128−34.
15. Galletti S, Magnani M, Rotini R, Mignani G, Affinito D, Pelotti P, et al. The echo-guided treatment of calcific tendinitis of the shoulder. *Chir Organi Mov* 2004;**89**:319−23.
16. Chiou HJ, Chou YH, Wu JJ, Hsu CC, Huang DY, Chang CY. Evaluation of calcific tendonitis of the rotator cuff: role of color Doppler ultrasonography. *J Ultrasound Med* 2002;**21**:289−95.
17. Chiou HJ, Chou YH, Wu JJ, Huang TF, Ma HL, Hsu CC, et al. The role of high-resolution ultrasonography in management of calcific tendonitis of the rotator cuff. *Ultrasound Med Biol* 2001;**27**:735−43.
18. Serafini G, Sconfienza LM, Lacelli F, Silvestri E, Aliprandi A, Sardanelli F. Rotator cuff calcific tendonitis: short-term and 10-year outcomes after two-needle us-guided percutaneous treatment−nonrandomized controlled trial. *Radiology* 2009;**252**:157−64.
19. Zhu J, Jiang Y, Hu Y, Xing C, Hu B. Evaluating the long-term effect of ultrasound-guided needle puncture without aspiration on calcifying supraspinatus tendinitis. *Adv Ther* 2008;**25**:1229−34.
20. 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.
21. Khan JA, Devkota P, Acharya BM, Pradhan NM, Shreshtha SK, Singh M, et al. Manipulation under local anesthesia in idiopathic frozen shoulder−a new effective and simple technique. *Nepal Med Coll J* 2009;**11**:247−53.
22. Arroll B, Goodyear-Smith F. Corticosteroid injections for painful shoulder: a meta-analysis. *Br J Gen Pract* 2005;**55**:224−8.
23. Lee HJ, Lim KB, Kim DY, Lee KT. Randomized controlled trial for efficacy of intra-articular injection for adhesive capsulitis: ultrasonography-guided versus blind technique. *Arch Phys Med Rehabil* 2009;**90**:1997−2002.
24. Chen MJ, Lew HL, Hsu TC, Tsai WC, Lin WC, Tang SF, et al. Ultrasound-guided shoulder injections in the treatment of subacromial bursitis. *Am J Phys Med Rehabil* 2006;**85**:31−5.
25. Yu CM, Chen CH, Liu HT, Dai MH, Wang IC, Wang KC. Subacromial injections of corticosteroids and xylocaine for painful subacromial impingement syndrome. *Chang Gung Med J* 2006;**29**:474−9.
26. Alvarez CM, Litchfield R, Jackowski D, Griffin S, Kirkley A. A prospective, double-blind, randomized clinical trial comparing subacromial injection of betamethasone and xylocaine to xylocaine alone in chronic rotator cuff tendinosis. *Am J Sports Med* 2005;**33**:255−62.
27. Uitto J, Mustakallio KK. Effect of hydrocortisone acetate, fluocinolone acetonide, fluclorolone acetonide, betamethasone-17-valerate and fluprednyliden-21-acetate on collagen biosynthesis. *Biochem Pharmacol* 1971;**20**:2495−503.
28. Harvey W, Grahame R, Panayi GS. Effects of steroid hormones on human fibroblasts in vitro. I. Glucocorticoid action on cell growth and collagen synthesis. *Ann Rheum Dis* 1974;**33**:437−41.
29. Branemark PI, Ekholm R, Goldie I, Lundskog J. The influence of some anti-inflammatory drugs on original and regenerating synovial tissue. *Acta Orthop Scand* 1969;**40**:279−99.
30. Wrenn RN, Goldner JL, Markee JL. An experimental study of the effect of cortisone on the healing process and tensile strength of tendons. *J Bone Joint Surg Am* 1954;**36-A**:588−601.
31. Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. *Ann NY Acad Sci* 2012;**1261**:55−63.
32. Tsai MJ, O'Malley BW. Molecular mechanisms of action of steroid/thyroid receptor superfamily members. *Annu Rev Biochem* 1994;**63**:451−86.