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## **Extracorporeal shockwaves therapy versus hyaluronic acid injection for the treatment of painful non-calcific rotator cuff tendinopathies: preliminary results**

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## ABSTRACT

**BACKGROUND:** Rotator cuff tendinopathy is the most common cause of painful shoulder. The treatment is mainly conservative and several therapeutic approaches have been proposed, including NSAIDs, physiotherapy, injections and physical therapies. The aim of the current study is to compare the clinical effectiveness of low molecular weight hyaluronic acid (LMW-HA) injection versus low-energy Extracorporeal Shock-Wave Therapy (ESWT) until 3 months of follow-up for the management of painful non-calcific rotator cuff tendinopathies, evaluating also the trend over time between the groups.

**METHODS:** A total of 34 patients affected by painful rotator cuff tendinopathy were randomly divided into 2 groups of 17 individuals. The first group (Group A; mean age 58.2 years) underwent 3 injections of LMW-HA (Hyalgan ®, 500-730 kDa), while in the second group (Group B; mean age 58.5 years) the treatment protocol consisted of 4 sessions of low-energy ESWT. Pain level and function were assessed with the DASH and Constant-Murley questionnaires. Parameters were evaluated at baseline (V0), at the end of the treatment (V1) and after 3 months of follow-up (V2).

**RESULTS:** Patients of both groups achieved statistically significant improve in pain and function ( $p < 0.0001$ ). Clinical outcome shows a different trend in time between Group A and Group B for DASH and Constant-Murley questionnaires.

**CONCLUSION:** LMW-HA and low-energy ESWT are effective and safe in patients suffering from non-calcific rotator cuff tendinopathy until 3 months of follow-up. Intra-articular injections of LMW-HA provide prompt clinical improvement compared to ESWT, which results in more gradual improvement over time.

### Keywords:

Hyaluronic Acid, Injections, Rotator Cuff/therapy, Tendinopathy, Low-Energy Shock Waves/therapeutic use



## Introduction

About 3% of the population suffer from shoulder pain [1]. Rotator cuff pathology is the most common cause of shoulder pain, including a combination of different diseases that vary from tendinopathy to rotator cuff tear [2]; the incidence of rotator cuff lesions reported in literature varies from 5 to 40%, with supraspinatus tendon most commonly affected [3].

Rotator cuff tendinopathy is mostly related to functional overload but there is also a growing interest about the possible correlation to metabolic and endocrine pathologies [4-6]. The pathogenesis is multifactorial with a combination of intrinsic and extrinsic factors [7,8].

The diagnosis is mainly clinical, being based on medical history and accurate physical examination [9,10]. The most important symptom is pain, which gradually compromises activities of daily living [11]. Ultrasound (US) and MRI are widely used to support the clinical findings [12,13].

Despite the frequent use of the term "tendinitis", the condition is characterized histologically by absence of classical inflammation features, while dominant lesions exhibit features of a failed healing response [14,15]; tendon pathology may be associated with the presence of calcifications [16,17].

Treatment goals are to decrease pain, to regain muscle strength and to improve life quality and function. Treatment is mainly conservative, while surgery is indicated only in refractory patients [18,19]. Several therapeutic approaches have been proposed, including NSAIDs [20], physiotherapy [21], injections [22] and physical therapies [23]. Intra-articular injections of hyaluronic acid (HA) and extracorporeal shock wave therapy (ESWT) represent two of these therapeutic options.

Strong evidences have proved as hyaluronic acid (HA) injection represent a valuable option for different musculoskeletal diseases [24].

HA is a non-sulfated glycosaminoglycan without a core protein and it is a main component of connective tissues. It suppresses the inflammatory process, lubricates joints, stimulates cell

proliferation, promotes the release of prostaglandins and tissue inhibitors of metalloproteinases and promotes the synthesis of endogenous HA [25,26].

Clinical studies in patients with rotator cuff disease ranging from tendinopathy to rotator cuff tears found a positive influence on the reduction of pain and improved function with no consistent side-effects recorded [27,28]. HA provided equal effectiveness but fewer side effects than corticosteroids, and it is well-tolerated by patients without serious adverse effects [29]. However, the characteristics of the preparation, particularly in terms of molecular weight, that ensure greater effectiveness are still not clear [30].

Shock waves are acoustic waves characterized by high peak pressure (> 500 bar), rapid increase in pressure (<10 ns) and short duration (<10  $\mu$ s). Shock waves stimulate the activation of mediators responsible for specific biological reactions (mechanotransduction) [31], particularly nitric oxide (NO) [32]. ESWT is widely used in several tendon conditions [33,34]. The mechanisms of action determines anti-inflammatory, anti-edema, angiogenetic, reparative and analgesic effects [35,36]. Level I studies have shown that ESWT is effective in calcific rotator cuff tendinopathy, while for the non-calcific form the results are discordant and less satisfying [37,38].

This study compared the clinical effectiveness until 3 months of follow-up of low molecular weight hyaluronic acid (LMW-HA) injection versus low-energy Extracorporeal Shock-Wave Therapy (ESWT) in the management of painful non-calcific rotator cuff tendinopathies, evaluating also the trend over time between the groups.



## Materials and methods

### SUBJECTS AND STUDY DESIGN

This was a prospective, randomized, single centre, single blind comparative pilot-study, in 34 outpatients at the Department of Physical Medicine and Rehabilitation of the University of Padua. All patients gave their written consent to participate in the study. Patients were divided into 2 treatment groups, each consisting of 17 patients randomized by ABAB model; Group A underwent sub-acromial injections of LMW-HA (500-730 kDa, HYALGAN<sup>®</sup> 20mg/2 ml), while Group B received low-energy ESWT.

The clinical course of patients was assessed using the validate cross-cultural adaptation into Italian of the DASH (Disability of the Arm, Shoulder and Hand) and Constant-Murley scales [39,40].

In a single-blind fashion, in each of the two groups, the treatment (injection or ESWT) was administered by a physician, while questionnaires were administered to the patients by another physician, unaware to the delivered treatment. Patients were asked not to reveal which treatment group they had been allocated to. For both groups, clinical and questionnaire evaluations were carried out before treatment (V0), at the end of the treatment (V1), and 3 months after the end of the treatment (V2).

Inclusion and exclusion criteria are listed in Table I.

### INJECTION PROCEDURE

The patients allocated to receive HA received 1 injection weekly for 3 weeks of LMW-HA (HYALGAN<sup>®</sup> 20mg/2 ml).

All the injections were performed by the same fully trained physician under ultrasound guidance to identify the sub-acromial space in a standard sterile fashion using a 21G needle, following the principles of safety and sterility in a sequential procedure [41,42].

### ESWT PROTOCOL



Patients were weekly undergone to a session of low-energy extracorporeal shockwave therapy (MODULITH® SLK, Storz Medical, Tägerwilten, Switzerland) for 4 weeks; each session consisted of 1600 shots at a frequency of 4 Hz. The applied energy was adjusted on the basis of the patient's tolerance, until a maximum level not exceeding 0.15 mJ/mm<sup>2</sup>.

After reading and signing the informed consent, patients were asked to lie supine on the couch in the supine position. After applying to the skin surface a transparent and odorless gel, which facilitates the propagation of waves to biological tissues, the head of the generator was positioned under ultrasound guidance so as to focus shock waves on the target area. At that point, we began to deliver ESWT, starting from a minimum level and gradually increasing it to values compatible with the tolerance of the patient to the discomfort or pain caused by the treatment, without ever exceeding an energy density of 0.15 mJ/mm<sup>2</sup>. Overall, each session of ESWT had a mean duration of about 10 minutes.

## STATISTICAL METHODS

The demographic characteristics of patients and ratings pre-treatment have been reported for each treatment group as number and percentage of patients in each category for categorical variables. Quantitative variables have been reported as mean, deviation or standard error. The comparison of patients' characteristics between treatment groups was performed using Fisher exact test for sex and Wilcoxon rank sum test for age. The trend over time between the groups was analyzed by a general linear model considering the effects of treatment group, time and group×time interaction with a first order autoregressive matrix of variance and covariance. The results relating to the difference between groups at the times considered were reported as mean of this difference accompanied by an interval of confidence at 95%. Significance was set at  $p < 0.05$ . Statistical analysis was conducted with SAS program 9.2 (SAS Institute Inc, Cary, NC, USA) for Windows.

## Results

Both groups consisted in 13 females (76.48%, 26 patients) and 4 males (23.52%, 8 patients) (Fisher exact test  $p = 1.0000$ ) and were comparable for age, since the difference were very slight (58.5 years for Group B and 58.2 years for Group A, Wilcoxon rank sum test  $p = 1.0000$ ) and therefore it is not able to compromise the statistical comparison between the two groups as regards either DASH scores either Constant-Murley scores.

With regard of Constant-Murley and DASH scores before treatment (V0), the groups had the values shown in Table II and Table III. Patients in Group A had a mean score on the Constant-Murley scale lower than Group B. Therefore the two groups started from slightly different situations, as at time 0 the articular condition of Group A was slightly more compromised. However this difference did not result to be statistically significant (Constant Wilcoxon rank sum test  $p = 0.7446$ , DASH Wilcoxon rank sum test  $p = 0.8497$ ), whereby the two groups could be considered comparable to their starting condition.

The trend of the Constant-Murley scale (Figure 1) revealed that in both groups there was an increase of scores after treatment. Furthermore, there was no statistically significant difference ( $p = 0.5065$ ) between the two types of treatment, whereas for both groups the scores change over time significantly ( $p < 0.0001$ ). A different time distribution of the scores in relation to the treatment group was shown ( $p = 0.0063$ ). As regards the DASH scale (Figure 2), in both groups the score decreased as a result of therapy. Also in this case there are no significant differences between groups ( $p = 0.4808$ ), while the scores varied in time significantly in both groups ( $p < 0.0001$ ). Unlike the Constant-Murley, the DASH did not reveal a different pattern of scores over time between the two groups ( $p = 0.1334$ ).

Table II shows the scores obtained in the Constant-Murley scale at the different times of evaluation and makes a comparison between the two groups in terms of difference between means.

In both groups the difference with respect to V0 was statistically significant ( $p < 0.001$ ) for all the two subsequent evaluations (V1 and V2).



In Group A the improvement was greater at V1 and remains almost constant at V2, while in Group B the improvement was less marked (but still significant) at V1, but there was a further increase in the score, although not statistically significant ( $p = 0.066$ ), at the 3 months evaluation.

The last column shows that these differences between means in the two groups were not statistically significant in all evaluations (confidence level set at 95%), while including the confidence interval some relevant differences. Despite this lack of statistical significance, the major difference between means is in the post-treatment evaluation, while pre-treatment and 3 months values are much more similar. The Group A, even starting from a score lower than the Group B, in subsequent evaluations showed higher scores.

Table III shows the scores obtained in the DASH scale at the different times of evaluation and makes a comparison between the two groups.

It was observed a significant decrease of scores in both evaluations after treatment compared to baseline (pre-treatment) in both groups ( $p \leq 0.0001$ ).

Similarly to the Constant-Murley scores, Group A had a statistically significant at V1 which remained constant at 3 months, while in the Group B at the end of the therapeutic cycle the improvement was less clear (though significant) but later the score decreased further, also if not in a statistically significant way ( $p = 0.244$ ), at the 3 months evaluation.

Considering a confidence level of 95%, the differences between means in the two groups were not statistically significant in all evaluations and the most important difference was recorded at the end of the treatment cycle with more similar scores at pre-treatment and 3 months evaluations. Conversely to Constant-Murley, Group A, there was a starting DASH score higher than the Group B, in subsequent evaluations showed lower scores.



## Discussion

We compared the effects of sub-acromial injection of LMW-HA and ESWT in patients with chronic non-calcific rotator cuff tendinopathy. Regardless of the treatment implemented, there was a significant improvement in pain and function, and a significant reduction in shoulder disability following either the HA injections or ESWT.

Merolla et al. showed that sub-acromial injections of sodium hyaluronate determined pain reduction and improve joint function 2, 4 and 12 weeks after treatment [41]. Similarly, HA reduced pain in 56 patients with supraspinatus tendinopathy up to 4 months after the injection [42].

Our study confirms these findings, showing a marked clinical improvement after injections with LMW-HA. This improvement was maintained even 3 months after the end of the treatment (V2). Comparing the outcomes on the basis of Constant-Murley and DASH scores at V1 and V2, it emerges that by the third injection of HA there was a clear and statistically significant benefit which remains almost constant at the 3 month follow-up.

It is conceivable that the use of musculo-skeletal ultrasound to guide the intra-articular injections improves the accuracy of the treatment, helping to achieve better outcomes. Recent studies are suggested as the ultrasound guidance leads to a more effective treatment with respect to blind injections [43], also for less approachable locations [44].

Several authors demonstrated the effectiveness of ESWT in patients with calcific rotator cuff tendinopathies until 6 months of follow-up; both the low-energy and the high-energy ESWT have been successful, although some studies report statistically better results for high-energy shock waves [45]. For non-calcific rotator cuff tendinopathy, clinical studies reported conflicting and less satisfactory results; this fact may be related, at least in part, to the different treatment protocols chosen, since currently there is still no consensus on the protocol of ESWT to be used in the different pathological conditions of the shoulder and at the various stages of condition.

Nevertheless, Galasso et al. found that low energy ESWT, compared to placebo, produced a clinical improvement in 20 patients suffering from non-calcific tendinopathy of the supraspinatus. This

improvement remained significant compared to baseline pre-treatment condition at a follow-up of 3 months [46].

In accordance with these results, our study showed a significant clinical relevant improvement in patients with non-calcific rotator cuff tendinopathy treated with low-energy shock waves. Comparing Constant-Murley and DASH scores at V1 and V2, the treatment showed a further positive trend, although not statistically significant at 3 months follow-up. In our knowledge, only one study investigating the effectiveness of low energy ESWT in comparison to high energy ESWT in the long-term follow-up of non-calcific shoulder tendinopathy has been already performed. In both groups the functional and pain scores improve at 1-year follow-up in comparison to pre-treatment and 12 weeks of follow-up values. Furthermore, there were no significant differences between the groups, with low-energy ESWT that appear to be non-inferior to high-energy ESWT in the management of non-calcific shoulder tendinopathy [47].

The baseline values were slightly different between the groups, with Group A starting from a clinical condition slightly worse than Group B. However this difference is not statistically significant so that the two groups can be considered comparable as regards the pre-treatment condition. After treatment both groups show a significant improvement in the outcome of patients and no statistically significant difference in the overall effect of the two treatments was found. However, while in Group A all scores were clinical relevant in V1 and V2, for Group B the values in Constant-Murley scale were not clinical relevant in V1 (<17 points) [48], but still statistically significant.

There appears to be a different time course in clinical outcome in the two groups, but we are unsure whether this will have any clinical relevance. These findings may be relevant in subjects that need to prompt recovery function, as athletes affected by painful shoulder. LMW-HA seemed to be effective by the end of the treatment, with the improvement being maintained by 3 months of follow-up. After 3 months, patients who had received ESWT were still experiencing some improvement, as reported by other authors [47]. Given the different trend of efficacy between the



groups at V1 and V2, it may be useful to perform further studies that include patients treated with a combination therapy (LMW-HA + low-energy ESWT) in comparison to LMW-HA and ESWT groups, that may determine sudden pain and function restoration.

## **Conclusions**

Both LMW-HA and low-energy ESWT are effective in improving joint function and reducing pain in patients with non-calcific rotator cuff tendinopathy until 3 months of follow-up, with no clinically significant difference in outcome.

The main weaknesses of our study are represented by small sample size and short follow-up. Therefore, further studies with larger cohorts of patients are necessary to confirm and compare the efficacy of these approaches in the medium and long term.



## REFERENCES

1. Luime JJ, Koes BW, Hendriksen IJ, Burdorf A, Verhagen AP, Miedema HS, et al. Prevalence and incidence of shoulder pain in the general population; a systematic review. *Scand J Rheumatol* 2004; 33:73-78
2. Harryman DT, Lazarus MD, Rozencwaig R. The stiff shoulder. In: *The shoulder*, 2nd ed, Rockwood CA Jr, Matsen FA III eds, 1998, pp 1064 e 1106
3. Yamamoto A, Takagishi K, Osawa T, Yanagawa T, Nakajima D, Shitara H, et al. Prevalence and risk factors of a rotator cuff tear in the general population. *J Shoulder Elbow Surg* 2010;19:116-20
4. Maffulli N, Khan KM, Puddu G. Overuse tendon conditions: time to change a confusing terminology. *Arthroscopy* 1998; 14: 840-3
5. Lin TT, Lin CH, Chang CL, Chi CH, Chang ST, Sheu WH. The effect of diabetes, hyperlipidemia, and statins on the development of rotator cuff disease: a nationwide, 11-year, longitudinal, population-based follow-up study. *Am J Sports Med* 2015, 43(9):2126-32
6. Oliva F, Osti L, Padulo J, Maffulli N. Epidemiology of rotator cuff tears: a new incidence related to thyroid disease. *Muscles Ligaments Tendons J* 2014;4:309-14
7. Mehta S, Gimbel JA, Soslowky LJ. Etiologic and pathogenetic factors for rotator cuff tendinopathy. *Clin Sports Med* 2003; 22(4):791-812
8. Mc Farland EG, Maffulli N, Del Buono A, Murrell GA, Garzon-Muvdi J, Petersen SA. Impingement is not impingement: the case for calling it "Rotator Cuff Disease", *MLTJ* 2013; 3: 196-200
9. May S, Chance-Larsen K, Littlewood C, Lomas D, Saad M. Reliability of physical examination tests used in the assessment of patients with shoulder problems: a systematic review. *Physiotherapy* 2010; 96:179-90

10. Park HB, Yokota A, Gill HS, El Rassi G, McFarland EG. Diagnostic accuracy of clinical tests for the different degrees of subacromial impingement syndrome. *J Bone Joint Surg*, 2005; 87 (7): 1446-55
11. Roy A, Dahan THM, Belair M, Dahan B. Rotator cuff disease. *Medscape*. 2006
12. de Jesus JO, Parker L, Frangos AJ. Accuracy of MRI, MR arthrography and ultrasound in the diagnosis of rotator cuff tears. *AJR Am J* 2009; 192 (6): 1701-7
13. Ottenheijm RP, Jansen MJ, Staal JB, van den Bruel A, Weijers RE, de Bie RA, et al. Accuracy of diagnostic ultrasound in patients with suspected subacromial disorders: a systematic review and meta-analysis. *Arch Phys Med* 2010, 1616-25
14. Giai Via A, De Cupis M, Spoliti M, Oliva F. Clinical and biological aspects of rotator cuff tears. *Muscles Ligaments Tendons J* 2013; 3(2):70-79
15. Abate M, Silbernagel KG, Siljeholm C, Di Iorio A, De Amicis D, Salini V et al. Pathogenesis of tendinopathies: inflammation or degeneration? *Arthritis Res Ther* 2009; 11: 235
16. Frizziero A, Oliva F, Maffulli N, Tendinopatie: stato dell'arte e prospettive, Pacini Editore, 2011
17. Oliva F, Via AG, Maffulli N. Calcific tendinopathy of the rotator cuff tendons. *Sports Med Arthrosc* 2011, 19:237-243
18. Andrews JR. Diagnosis and treatment of chronic painful shoulder: review of nonsurgical interventions. *Arthroscopy* 2005; 21: 333-47
19. Dorrestijn O, Stevens M, Winters J C, van der Meer K, Diercks RL. Conservative or surgical treatment for subacromial impingement syndrome? A systematic review. *J Shoulder Elbow Surg* 2009; 18: 652-60
20. Petri M, Hufman SL, Waser G, Cui H, Snabes MC, Verburg KM. Celecoxib effectively treats patients with acute shoulder tendinitis/bursitis. *J Rheumatol* 2004; 31 (8): 1614-20
21. Dickens V, Williams JAB. Role of physiotherapy in the treatment of subacromial impingement syndrome: A prospective study. *Physiotherapy* 2005; 91 (3): 159-64



22. Arroll B, Goodyear-Smith F. Corticosteroid injections for painful shoulder: A meta-analysis. *Br J Gen Pract* 2005; 55 (512): 224-8
23. Lee EW, Maffulli N, Li CK, Chan KM. Pulsed magnetic and electromagnetic fields in experimental achilles tendonitis in the rat. *Arch Phys Med* 1997; 399-404
24. Monticone M, Frizziero A, Rovere G, Vittadini F, Uliano D, La Bruna S, Gatto R, Nava C, Leggero V, Masiero S. Hyaluronic acid intra-articular Injection and exercise therapy: effects on pain and disability in subjects affected by lower limb joints osteoarthritis. The Italian Society of Physical and Rehabilitation Medicine (SIMFER) systematic review. *Eur J Phys Rehabil Med*. 2015 Sep 10.
25. Mitsui Y, Gotoh M, Nakama K, Yamada T, Higuchi F, Nagata K. Hyaluronic acid inhibits mRNA expression of proinflammatory cytokines and cyclooxygenase-2/prostaglandin E2 production via CD44 in interleukin-1-stimulated subacromial synovial fibroblasts from patients with rotator cuff disease. *J Orthop Res* 2008, 26:1032-7
26. Salamanna F, Frizziero A, Pagani S, Giavaresi G, Curzi D, Falcieri E, et al, Metabolic and cytoprotective effects of in vivo peri-patellar hyaluronic acid injections in cultured tenocytes, *Connect Tissue Res*, 2015, 56:35-43
27. Costantino C, Olvirri S. Rehabilitative and infiltrative treatment with hyaluronic acid in elderly patients with rotator cuff tears. *Acta Biomed* 2009; 80:225-9
28. Abate M, Schiavone S, Salini V, The use of hyaluronic acid after tendon surgery and in tendinopathies, *BioMed Research International*, 2014
29. Coombes BK, Bisset L, Vicenzino B, Efficacy and safety of steroid injections and other injections for management of tendinopathy, *Lancet* 2010, 1751-67
30. Osti L, Berardocco M, di Giacomo V, Di Bernardo G, Oliva F, Berardi AC. Hyaluronic acid increases tendon derived cell viability and collagen type I expression in vitro: Comparative study of four different Hyaluronic acid preparations by molecular weight. *BMC Musculoskelet Disord*. 2015 Oct 6;16(1):284.



31. Dahl KN, Ribeiro AJ, Lammerding J, Nuclear shape, mechanics and mechanotransduction, *Circ Res*, 2008, 102: 1307-18
32. Ciampa AR, de Prati AC, Amelio E, Cavalieri E, Persichini T, Colasanti M, et al, Nitric oxide mediates anti-inflammatory action of extracorporeal shockwaves, *FEBS Letters*, 2005, 6839-45
33. Moretti B, Amelio E, Notarnicola A, Onde d'urto nella pratica medica, *Wip* 2012
34. Ioppolo F, Rompe D, Furia P, Cacchio A, Clinical application of shock wave therapy (SWT) in musculoskeletal disorders, *Eur J Phys Med*, 2014, 217-30
35. Visco V, Vulpiani M, Torrisi M, Ferretti A, Pavan A, Vetrano M, Experimental studies on the biological effects of extracorporeal shock wave therapy on tendon. *MLTJ* 2014; 357-61
36. Han SH, Lee JW, Guyton GP, Parks BG, Courneya JP, Schon LC. Effect of extracorporeal shock wave therapy on cultured tenocytes. *Foot Ankle Int*. 2009; 30:93-98
37. Rompe JD, Burger R, Hopf C, Eysel P. Shoulder function after extracorporeal shock wave therapy for calcific tendinitis. *J Shoulder Elbow Surg* 1998; 7:505-9
38. Huisstede BMA, Gebremariam L, van der Sande R, Hay EM, Koes BW. Evidence for effectiveness of extracorporeal shock-wave therapy (ESWT) to treat calcific and non-calcific rotator cuff tendinosis. *Man Ther* 2011; 16 (5): 419-33
39. Padua R, Padua L, Ceccarelli E, Romanini E, Zanolli G, Amadio PC, Campi A. Italian version of the Disability of the Arm, Shoulder and Hand (DASH) questionnaire. Cross-cultural adaptation and validation. *J Hand Surg Br*. 2003 Apr;28(2):179-86.
40. Constant C, Murley A. A clinical method of functional assessment of the shoulder. *Clin Orthop* 1987; 214:160-164
41. Merolla G, Bianchi P, Porcellini G. Ultrasound-guided subacromial injections of sodium hyaluronate for the management of rotator cuff tendinopathy: a prospective comparative study with rehabilitation therapy. *Musc Surg* 2013; 49-56

42. Meloni F, Milia F, Cavazzuti M, Doria C, Lisai P, Profili S, et al, Clinical evaluation of sodium hyaluronate in the treatment of patients with supraspinatus tendinosis under echographic guide: experimental study of periarticular injections. *Eur J Radiol* 2008, 68:170–3
43. Bum Park Y, Ah Choi W, Kim YK, Chul Lee S, Hae Lee J. Accuracy of blind versus ultrasound-guided suprapatellar bursal injection. *J Clin Ultrasound* 2012; 40:20-5.
44. Di Gesù M, Fusco A, Vetro A, Iosa M, Mantia F, Iovane A, Mantia R. Clinical effects of image-guided hyaluronate injections for the osteochondral lesions of ankle in sport active population. *J Sports Med Phys Fitness*. 2016 Jan 12.
45. Ioppolo F, Tattoli M, Di Sante L, Attanasi C, Venditto T, Servidio M, et al. Extracorporeal shock-wave therapy for supraspinatus calcifying tendinitis: a randomized clinical trial comparing two different energy levels. *Phys Ther*. 2012; 92:1376-85
46. Galasso O, Amelio E, Riccelli DA, Gasparini G. Short-term outcomes of extracorporeal shock wave therapy for the treatment of chronic non-calcific tendinopathy of the supraspinatus. *BMC Musculoskelet Disord* 2012; 13:86
47. Schofer MD, Hinrichs F, Peterlein CD, Arendt M, Schmitt J. High- versus low-energy extracorporeal shock wave therapy of rotator cuff tendinopathy: a prospective, randomised, controlled study. *Acta Orthop Belg*. 2009 Aug;75(4):452-8.
48. Holmgren T, Oberg B, Adolfsson L, Björnsson Hallgren H, Johansson K. Minimal important changes in the Constant-Murley score in patients with subacromial pain. *J Shoulder Elbow Surg*. 2014 Aug;23(8):1083-90

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Table I: inclusion and exclusion criteria

Table II: comparison between Constant-Murley scores of the two groups at the different evaluations

Table III: comparison between DASH scores of the two groups at the different evaluations

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Figure 1: trend over time of Constant-Murley scale

Figure 2: trend over time of DASH scale



INCLUSION CRITERIA	EXCLUSION CRITERIA
1) shoulder pain that exacerbates in overhead movements	1) complete rupture of cuff tendons diagnosed by US or MRI
2) pain for at least 3 months not responding adequately to conventional therapy with NSAIDs and/or physiotherapy	2) calcifications of diameter greater than 1 cm in rotator cuff tendons at ultrasound evaluation
3) age between 18 and 85 years	3) pregnancy or breast-feeding
4) pain on palpation at the site of insertion of rotator cuff tendons on humeral head and positive clinical test for the pathology of the rotator cuff	4) tumors, coagulation disorders or rheumatic diseases in acute phase
5) instrumental diagnosis (US or MRI) of the rotator cuff tendonitis	5) significant trauma to the target shoulder within 6 months
6) reduced joint movement of the shoulder in flexion, abduction, internal and external rotation	6) history of allergies or hypersensitivity to chicken proteins or hyaluronic acid
	7) steroid therapy in the last three months, steroid therapy in the contralateral shoulder in the last 4 weeks, viscosupplementation in the target shoulder in the last 24 weeks, oral NSAIDs in the past 48 hours

Table II

Comparison between Constant scores of the two groups at the different evaluations

<b>Time</b>	<b>Group A mean</b>	<b>Group B mean</b>	<b>Difference between means A – B (95% CI*)</b>
<b>pre-treatment (V0)</b>	51.8 / 100	56.7 / 100	- 4.9 (-18.4 ; +8.5)
<b>post-treatment (V1)</b>	81.2 / 100	69.8 / 100	+ 11.4 (-2.1 ; +24.9)
<b>3 months (V2)</b>	81.8 / 100	76.5 / 100	+ 5.4 (-8.1 ; +18.8)

\* 95%CI: confidence interval 95%

Table III

Comparison between DASH scores of the two groups at the different evaluations

<b>Time</b>	<b>Group A mean</b>	<b>Group B mean</b>	<b>Difference between means A – B (95% CI*)</b>
<b>pre-treatment (V0)</b>	80.3 / 150	78.2 / 150	+ 2.1 (-11.6 ; +15.8)
<b>post-treatment (V1)</b>	49.6 / 150	59.2 / 150	- 9.6 (-23.3 ; +4.0)
<b>3 months (V2)</b>	49.6 / 150	54.3 / 150	- 4.6 (-18.3 ; +9.0)

\* 95%CI: confidence interval 95%



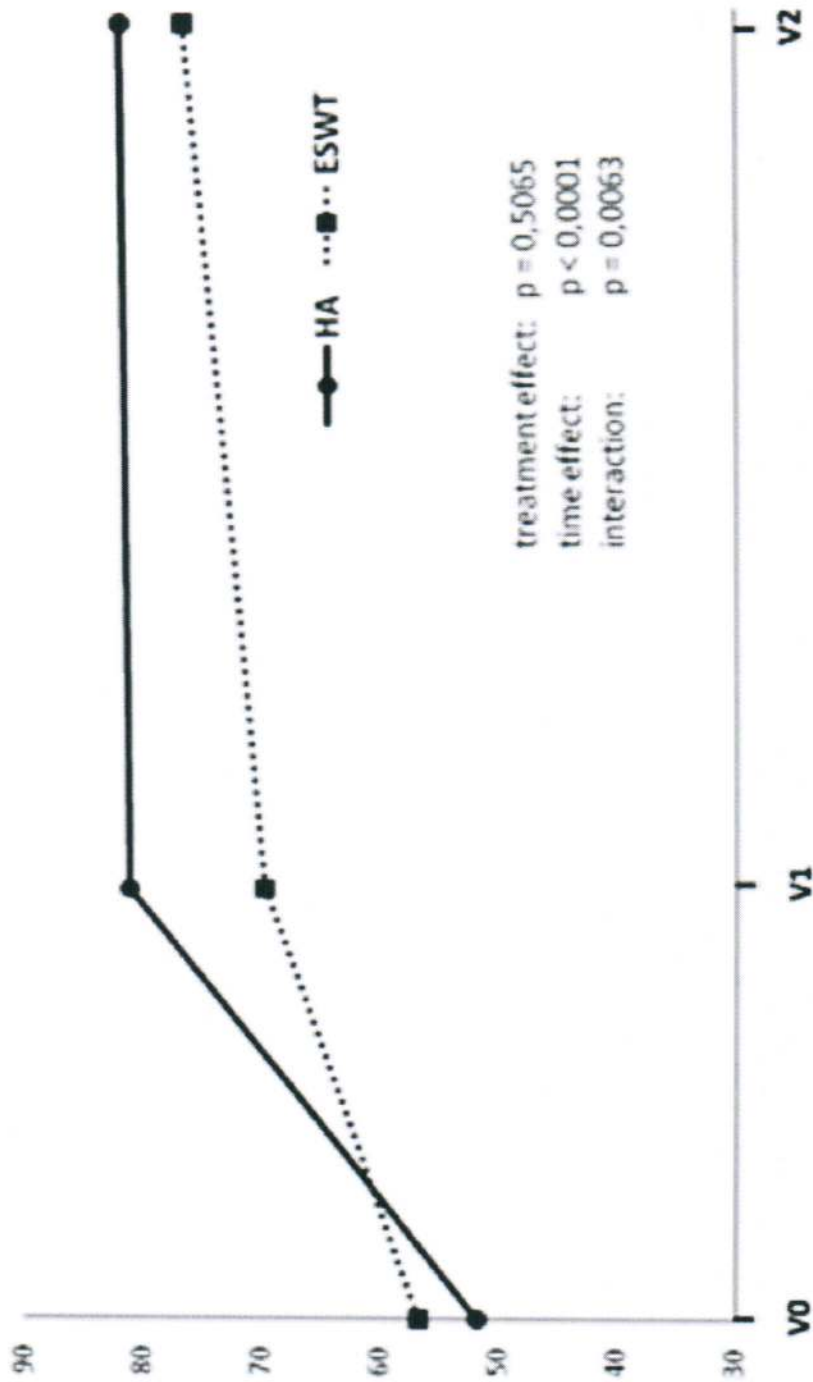


Figure 1  
Trend over time of Constant-Murley scale

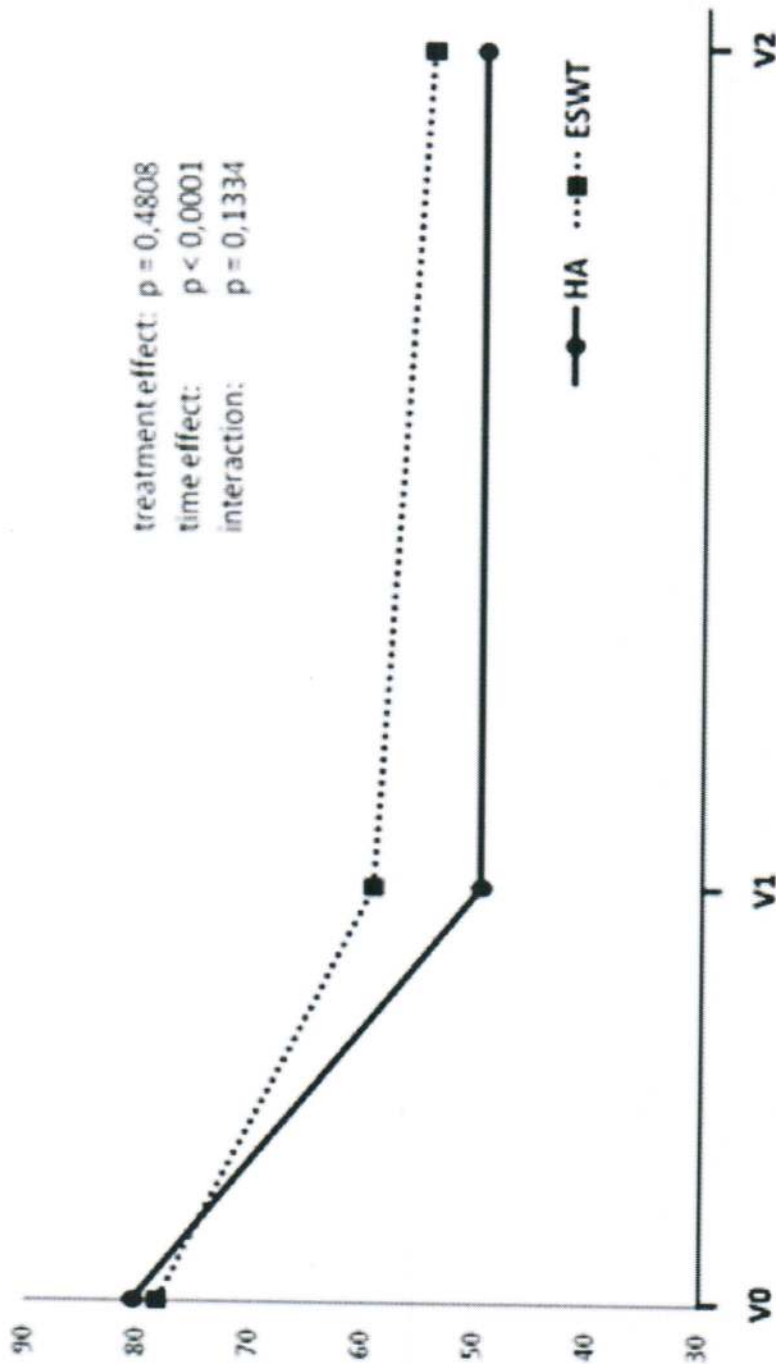


Figure 2  
Trend over time of DASH scale