Viscosupplementation with Hyaluronic Acid or Polynucleotides: Results and Hypothesis for Condro-synchronization

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Abstract

In literature the treatment of rotator cuff syndrome is basically conservative using NSAIDs, cortisone infiltrations and cryotherapy to relieve pain, electroanalgesia, kinesiotherapy to restore the impaired mobility of the joint and strengthen the muscles, physical therapies using energy such as ultrasound, laser, hyperthermia and shock waves. In the case of lack of response to conservative treatment, arthroscopic surgery can be proposed. International literature is unanimous in considering the viscosupplementation as an effective treatment for reducing pain associated with the rotator cuff syndrome and improve joint function. The intra-articular treatment should ideally not only ensure the mechanical protection of the articular surface, but also rebalance homeostasis of chondrocytes through the restoration of the microenvironment and nutritional supplements of the joint. The aim of this study was to evaluate the efficacy of viscosupplementation with hyaluronic acid and polynucleotides in the treatment of patients with rotator cuff syndrome for incomplete lesion of the supraspinatus. 80 subjects (43 M - 37 F) aged between 40 and 65 years (average age 54) were evaluated and treated. All they suffered from rotator cuff syndrome with incomplete injury of the tendon of the supraspinatus ascertained clinically and by ultrasound examination and MRI. The subjects were randomly divided into 2 groups (A and B). Group A made 4 sessions of infiltrative treatment with hyaluronic acid, once per week. Group B made 4 sessions of infiltrative treatment with infiltrative polynucleotides, 1 time per week. All subjects performed, during the whole period of treatment, upper limb proprioception and joint ROM functional recovery with Multi Joint System (MJS) at a frequency of 3 weekly sessions each one of 45 minutes. The results are comparable in the two groups in terms of improvement in both short and medium term. In view of these evidences we could hypothesize that the association of supplementation of the 2 elements, given together or temporally delayed could be further significant for an additional maintenance of results in the long term.

Keywords: Chondro-synchronization; Viscosupplementation; Hyluronic acid; Polynucleotides; Shoulder; Pain

Introduction

The upper limbs perform many functions in relation to daily activities and work, which can be done thanks to a considerable range of motion of the shoulder joints, with a cost for their inherent stability [1].

Shoulder pain represents the most common complication. The incidence of shoulder problems between 7 and 25 cases per thousand visits to the primary care physician [2]. The prevalence in adults under 70 ranges between 7 and 27%, while in more than 70 the prevalence is between 13.2 and 26% [3].

In literature there are many definitions to identify this painful and disabling condition, like for example Duplay syndrome and humeroscapularis periarthritis also called (PHS).

The rotator cuff syndrome is classified by our group into four stages:

- The 1st stage is characterized by edema caused by overuse of the arm above shoulder level in sports and work;
- The 2nd stage is characterized by fibrosis and tendinitis: episodes of inflammation and thickening of the bursa;
- The 3rd stage is characterized by a partial tear of the rotator cuff tendons and with the involvement of the biceps brachii;
- The 4th stage is characterized by at least 2 complete tearing of the tendons in the rotator cuff.

In literature the treatment of rotator cuff syndrome is basically conservative using NSAIDs, cortisone infiltrations and cryotherapy to relieve pain, electroanalgesia, kinesiotherapy to restore the impaired mobility of the joint and strengthen the muscles, physical therapies using energy such as ultrasound, laser, hyperthermia and shock waves. In the case of lack of response to conservative treatment, arthroscopic surgery can be proposed [4-7].

International literature is unanimous in considering the viscosupplementation as an effective treatment for reducing pain associated with the rotator cuff syndrome and improve joint function. [8-10].

The viscosupplementation is performed through the intra-articular infiltration of exogenous hyaluronic acid, or its derivatives, in order to restore the rheological properties of the synovial fluid which is also made by lubricina and phospholipids [10]. Hyaluronic acid is able to...
increase the viscoelastic properties of synovial fluid protecting cartilage from mechanical stress and reducing pain.

The literature agrees that viscosupplementation can be considered a safe and effective therapy [11-13].

It is thought that the algiesic effect of treatment with intra-articular hyaluronic acid may be correlated to several mechanisms which include the reduction of nociceptive stimulation through the production of a elasto-viscous barrier, around the nociceptive afferent fibers in the intracellular matrix [14]. The long-term efficacy of this treatment on symptoms (which ends after a certain time in relation to the effective time of permanence of the product in the joint) may be related to the restoration of the endogenous synthesis of high quality collagen [15].

Literature has also demonstrated the effectiveness of polynucleotides in the treatment of osteoarthritis in comparison to the standard treatment of viscosupplementation with hyaluronic acid with encouraging results [16,17].

The aim of this study was to evaluate the efficacy of viscosupplementation with hyaluronic acid or polynucleotides in the treatment of patients with rotator cuff syndrome for incomplete lesion of the supraspinatus.

Materials and Methods

165 subjects (97 M - 68 F) aged between 40 and 65 years (average age 55) were evaluated and treated. All them suffered from shoulder pain due to rotator cuff syndrome with incomplete injury of the tendon of the supraspinatus ascertained clinically and by ultrasound examination and MRI [18]. The multicenter study was conducted at the D’Annunzio University in Chieti and at the conventioned rehabilitation centers in Conegliano Veneto and Florence.

Inclusion criteria were: age between 40 and 65 years, symptoms of rotator cuff syndrome for at least 6 months, partial-thickness tear of supraspinatus, subacromial artropathy.

Exclusion criteria are: pregnancy, known hypersensitivity to products, infiltrative therapy with hyaluronic acid, polynucleotides or corticosteroids in progress, drug abuse or alcohol abuse, total-thickness tear of supraspinatus, concomitant use of antiocoagulants, significant co-morbidities.

During the study period was not allowed corticosteroids or NSAIDs intake.

The subjects were randomly divided into 3 groups (A, B and C).

- Group A made 4 sessions of infiltrative treatment with hyaluronic acid (sodium hyaluronate 40.0 mg - 1100 million Dalton, Synovial One, IBSA), once a week.
- Group B made 4 sessions of infiltrative treatment with polynucleotides (40 mg of a compound made up of polynucleotides, polymeric molecules which can retrieve large amounts of water and reorganize their structure directing and coordinating water molecules to form a three-dimensional gel, Condrotide, BIOFUTURA), once a week;
- Group C made 4 sessions of infiltrative treatment with local anaesthetic (control group) with 0.5 ml of lidocaine 2%, once a week.

Anterior infiltrative approach was used in both groups; the injection site was marked and disinfected with iodine, or with chlorhexidine solution in case of known allergy; all injections were ecugoided [19].

All subjects performed, during the whole period of treatment, upper limb proprioception and joint ROM functional recovery with Multi Joint System (MJS) at a frequency of 3 weekly sessions each one of 45 minutes.

All subjects were evaluated at the beginning of the protocol (T0), at the end of the protocol after 30 days (T1) and at follow-up at 90 (T2) and 120 days (T3) using the VAS scale for measuring the level of subjective pain, specific clinical tests for rotator cuff, Constant Murley Scale (simple standardized method of clinical assessment of shoulder function with a maximum score of 100 points), measurement of shoulder ROM in the movements of flexion and abduction-adduction, Davies isokinetic test to the angular velocity of 90°/sec [20].

Statistical analysis of data was performed using non-parametric t-test for unpaired samples according to Welch. The minimum level for statistical significance was set at P<0.05. The software used for statistical analysis was GraphPad Prism (version 5) (Abacus Concepts GraphPad Software, San Diego, CA).

Results

At time T1 all subjects in both groups had positive Jobe test, a sign of lesion of the supraspinatus; 8 subjects in group A and 5 in group B also showed a positivity to the lift-off test, sign of concomitant involvement of the subscapularis, all subjects showed also positivity to Neer test.

The clinical evaluation performed after 30 days (T2), showed negative Jobe test in 37 subjects in group A and 38 subjects in group B; Neer test was negative in all subjects, the lift-off test resulted positive only in 2 subjects in group A and 3 subjects in group B.

In group A after 30 days was found a significant improvement (P<0.01) in the average final score achieved at the Constant Murley Score: by 49 (T2) to 85 at T1 time.

The overall average score in VAS scale for pain in Group A was reduced from 7.72 to 2.11 (p<0.01) at T1; it was also observed an increase of joint ROM with a final average range 0-123° in flexion (T0: 0-88°) and 0-98° in abduction (0°-85°).

Davis isokinetic test showed at T1: increase in the values of the peak of moment of maximum force (Max MdF), both for external rotators (T2 23.1 - 25.1 T1) and intra-rotators (41.5 T2 - T1 45.6).

In group B, after 30 days it was found a significant improvement (P<0.01) in the average final score achieved at the Constant Murley Score: by 48 (T2) to 87 at T1.

The overall average score in VAS scale for pain in Group A was reduced from 8.03 to 2.07 (p<0.01) at T1; it was also observed an increase of joint ROM with a final average range 0-125° in flexion (T2: 0-89°) and 0-97° in abduction (0°-86°).

Davis isokinetic test showed at T1: increase in the values of the peak of moment of maximum force (Max MdF), both for external rotators (T2 23.7 - T1 25.4) and intra-rotators (T2 41.4 - T1 45.6).

In group C, after 30 days was found: no significant improvement in the average final score achieved at the Constant Murley Score (47 (T2) to 49 at T1); a mild but no significant reduction in pain level assessed by VAS (8.05 T2: 5.5 T1); no increase in strength at Davis isokinetic test.
both in external rotators ($T_0$ 23.5 – $T_1$ 23.6) and in intra-rotators ($T_0$ 40.8 – $T_1$ 41); no significant increase in the joint ROM (flexion 0-85 $T_0$ – 0-88 $T_1$; abduction 0-85 $T_0$ – 0-87 $T_1$).

The ultrasound control after 30 days showed significant reduction of the hypoechoic image which was highlighted in the initial evaluation in groups A and B, sign of edema and inflammatory state reduction.

The 90 and 120 days follow-up showed negativity to specific tests for the rotator cuff syndrome and the maintenance of the obtained results in groups A and B as shown in Table 1- Table 4 and Graph 1- Graph 4.

**Discussion**

A significant reduction in pain and increase in constant score after hyaluronic acid or polynucleotides injection has been described in the results both in the short and medium term (90 and 120 days follow up).

Ideally the intra-articular treatment should not only ensure the mechanical protection of the articular surface, but also rebalance

### Table I: VAS results in the 3 groups.

<table>
<thead>
<tr>
<th></th>
<th>$T_0$</th>
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<th>$T_1$ (90 days)</th>
<th>$T_1$ (120 days)</th>
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<tbody>
<tr>
<td>Gr. A</td>
<td>7.72</td>
<td>2.11</td>
<td>2.23</td>
<td>2</td>
</tr>
<tr>
<td>Gr. B</td>
<td>8.03</td>
<td>2.07</td>
<td>2.05</td>
<td>1.9</td>
</tr>
<tr>
<td>Gr. C</td>
<td>8.05</td>
<td>5.50</td>
<td>7</td>
<td>7.96</td>
</tr>
</tbody>
</table>

### Table II: ROM in flexion.

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<th>$T_1$ (90 days)</th>
<th>$T_1$ (120 days)</th>
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</thead>
<tbody>
<tr>
<td>Gr. A</td>
<td>0-88</td>
<td>0-123</td>
<td>0-125</td>
<td>0-135</td>
</tr>
<tr>
<td>Gr. B</td>
<td>0-89</td>
<td>0-125</td>
<td>0-129</td>
<td>0-137</td>
</tr>
<tr>
<td>Gr. C</td>
<td>0-85</td>
<td>0-88</td>
<td>0-91</td>
<td>0-90</td>
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### Table III: ROM in abduction/adduction.

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<thead>
<tr>
<th></th>
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<th>$T_1$ (90 days)</th>
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<tbody>
<tr>
<td>Gr. A</td>
<td>49</td>
<td>85</td>
<td>88</td>
<td>94</td>
</tr>
<tr>
<td>Gr. B</td>
<td>48</td>
<td>87</td>
<td>89</td>
<td>93</td>
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<td>Gr. C</td>
<td>47</td>
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### Table IV: Constant-Murley score results.

### Graph 1: Trend in the level of subjective pain of VAS scale after the treatment period and at follow-up at 90 and 120 days.

### Graph 2: Trend of Constant Murley Scale after the treatment period and at follow-up at 90 and 120 days.

### Graph 3: Trend of isokinetic test of extra-rotators after the treatment period and at follow-up at 90 and 120 days.

### Graph 4: Trend of isokinetic test of intra-rotators after the treatment period and at follow-up at 90 and 120 days.
homeostasis of chondrocytes through the restoration of the microenvironment and nutritional supplements of the joint.

Polynucleotides are polymeric molecules which can deeply moisturize the articular surface and are subjected to enzymatic cleavage with progressive intra-articular release both of the water molecules and of the small oligonucleotides (nucleosides, nucleotides, nucleobases), thus maintaining for long time the moisturizing, viscoelastic and metabolic effect [21–23].

Sodium hyaluronate is effective in managing acute or chronic ligaments and tendon injuries HA are believed to integrate into the extracellular fibrin matrix to help realignment of fibrils thanks to electrostatic interactions. Thus, stability of form and function is then restored allowing healing to occur in structures (ligaments and tendons) and shortening the rehabilitation process. Recent research findings demonstrated that repeated periarticular injections of the study materials were more effective in pain relief and joint function improvement, compared to placebo or standard conservative treatment Long-term follow-up by investigators confirmed the therapeutic effects persist after 12 and 24 months. Several trials using sodium hyaluronate in the treatment for chronic shoulder pain have been documented, on shoulder osteoarthritis (OA) tears, peri-artthritis, adhesive capsulitis, and chronic shoulder pain of different etiologies. The effectiveness of subacromial injections of HA alone in patients with chronic RC tendinopathy is also reported in the literature. In an open label multicenter study, Itokazu et al., [9] observed a significant pain and range of motion improvement after subacromial high-molecular weight sodium hyaluronate injection for 5 weeks or more, and they conclude that this treatment was effective in patients with periarthritis of the shoulder [10].

From the meta-analysis of the literature and our data it appears that is not so much the molecular weight expressed in million Dalton to influence the evolution of treatment, since the amount of hyaluronic acid introduced into the joint cavity in one solution, thus to unleash an action lubricant and anti-inflammatory. We believe that this can be applied even to polynucleotides in order to determine the significant metabolic action.

Conclusion

The chondro-synchronization, through the recovery of the mixture of articular lubrication is the target to be searched in the local therapy of complex joint damage. In view of these evidences we could hypothesize that the association of supplementation of the 2 elements, given together or temporally delayed could be further significant for an additional maintenance of results in the long term.

It might be conceivable that a better treatment could provide for a cycle of alternating introduction of the two substances, ie hyaluronic acid and polynucleotides.

Further studies with a larger series are needed to further clarify methods of administration of the best therapy.

References