LETTER TO THE EDITOR

Glenohumeral osteoarthritis treatment with a single hyaluronic acid administration: clinical outcomes

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Received July 17, 2020 – Accepted February 16, 2021

To the Editor,

Glenohumeral osteoarthritis (OA) is a very common joint disease characterized by pain and functional limitation, which, particularly in the elderly, may compromise overall health and quality of life. The treatment of this pathology generally includes the use of oral analgesics, physical therapy and intra-articular injections with corticosteroids or hyaluronic acid (HA) aimed at reducing the pain and restoring the range of motion (ROM) of the shoulder, but no standardized protocol is available in clinical practice and literature data are contrasting (1-3). Analgesics and non-steroidal anti-inflammatory drugs are not always effective and may be associated with substantial side effects, particularly in elderly patients (4), whereas intra-articular injections of HA have gained consensus in the treatment of OA thanks to their outcomes in pain reduction and joint function improvement, without relevant side effects (5-7). HA therapeutic activity has been attributed to its high viscosity, which has a shielding effect on the articular surface (visco-supplementation), whereas the long-term efficacy is better explained by normalization of endogenous HA synthesis and chondroprotection (visco-induction) (8). The aim of this randomized, prospective, open-label clinical study was to assess the efficacy in terms of improvement in functional status, daily activities and pain, and safety of a single administration of high molecular weight (HMW) HA (HyalOne® 60mg/4ml) combined with a physical exercise program (PEP) in patients suffering from mild to moderate glenohumeral OA (degree II and III according to the Kellgren-Lawrence classification), and to compare these results with a control group of patients treated with the only PEP.

MATERIALS AND METHODS

In this open-label study, 60 consecutive patients with glenohumeral OA degree II or III were prospectively enrolled in our clinic from September 2018 to March 2019. The study was approved by the Ethics Committee of the Concordia Hospital for Special Surgery Rome (approval n° 4/2018) and performed according to ISO and the Declaration of Helsinki. Informed written consent was obtained from each patients prior to the inclusion in the study. All patients were carefully evaluated and selected based on inclusion and exclusion criteria. As per inclusion criteria patients with good general conditions and glenohumeral OA (KL degree II or III) quantified through the standard X-ray views were included, while patients with concomitant rotator cuff lesions evaluated through MRI, previous shoulder surgery, previous humeral head fracture or shoulder trauma, metabolic diseases, poor general conditions and OA degree IV with surgical indications (shoulder arthroplasty) were excluded from the study.

Key words: hyaluronic acid; glenohumeral osteoarthritis; shoulder

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0393-974X (2021)

DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

The "Constant score" functional scoring systems and ROM were calculated for all 60 patients before treatment. Patients were then randomly allocated to two different homogeneous groups, 30 patients in the treatment group and 30 patients in the control group. Of the 30 patients allocated to the treatment group 21 were male and 9 female. The mean age of the patients was 67.1 years (range 55 to 83 years). The dominant side was treated in 22 patients (73.3%). All patients referred to have had shoulder pain for many months (average 10.3 months); they all had moderate-to-severe pain (17 patients [56.7%] had moderate pain and 13 [43.3%] severe pain). All the patients had a reduced ROM: mean active forward elevation was 136.2°±12.3°, mean external rotation with the arm at the side was 21.5°±5.7°. The mean Constant Score was 69.3±4.2.

Of the 30 patients allocated to the control group 18 were male and 12 female. The mean age of the patients was 64.2 years (range 52 to 81 years). The dominant side was treated in 23 patients (76.7%). All patients had shoulder pain for several months (average 11.2 months); 2 of the patients (6.7%) had mild pain, 18 (60%) had moderate pain and 10 (33.3%) severe pain. All the patients had a reduced ROM: mean active forward elevation was 138.8°±12.2°, mean external rotation with the arm at the side was 22°±3.6°. The mean Constant Score was 69.9±4.4.

Patients in the treatment group received a single intra-articular injection with a HMW HA (HyalOne® 60mg/4ml 1.500-2.000.000 Da) in combination with PEP. Patients in the control group were treated with PEP only. PEP program for both groups was performed with a professional therapist for a 3months duration with a frequency of 3 days every week. The PEP program consisted of passive capsular stretching for recovery of ROM, isometric exercises for deltoid, rotator cuff and scapulo-thoracic muscles, isotonic exercises for scapulo-thoracic muscles (closed kinetic chain), and hydrokinesis therapy. Study follow-up examination was performed after 3 months and 6 months from the beginning of the therapy for both groups.

At the study follow-up visits the Constant Score was analyzed to recorder functional status, daily activities and pain of the treated shoulder and the ROM values of elevation and external rotation of the shoulder were collected. A safety evaluation of intra-articular injection with HyalOne® 60mg/4ml was further performed collecting the adverse events (AEs) that had occurred during the entire duration of the study.

Statistical analysis was performed by STATISTICA 10 software (StatSoft Inc, 1984-2011). Database was constituted of 60 patients with glenohumeral OA defined by the ROM (forward elevation and external rotation) and by the Constant score functional scoring systems (scale 0-100). The distribution of subjects along the three variables (forward elevation, external rotation and Constant score) before the treatment, verged on normality ($p>0.05$; Shapiro-Wilk = 0.974, 0.985 and 0.964, respectively). Therefore, patients were divided into two different groups of treatment and were evaluated before and after the two different kinds of treatments. Sample size was calculated setting the p value at <0.05 and the minimum power of the study at 80%. Considering a mean difference of 5.5 points on Constant score and a standard deviation of 7.5 between the treatment group and the control group, it was estimated that 30 patients per arm had to be recruited. Variables were considered as continuous and a oneway ANOVA for repeated measures was performed. Post-hoc tests (Tukey's test; $p<0.05$) were scheduled between the two groups and within the same group.

RESULTS

Patients were randomized in two different groups and were evaluated before and after the treatment. Means and standard deviations of the outcome measures are reported in Table I. At the three month follow-up, the mean active forward elevation was 159.6°±8.9° (gain of 23.8°), and the mean external rotation with the arm at the side was 28.5°±3.0° (gain of 7°) for patients belonging to the treatment group. The patients also showed a relevant reduction in level of pain and a significant improvement in daily activities ($p<0.05$). The mean Constant score after the treatment with HyalOne® 60mg/4ml increased by 15.8 points to a mean value (±SD) of 85.1±3.4 points (Table I). For patients belonging to the control group the mean active forward elevation was 149.5°±9.7 (gain of 10.7°), and the mean external rotation with the arm at the side was 27°±2.2 (gain of 5°). The patients also showed a lower level of pain and moderate improvement in the daily activities. The mean Constant score after the only PEP was

81.5±3.5 points, 11.6 points more than the initial score (Table I).

At the six month follow-up, the mean active forward elevation was 156.6°±8.8° (gain of 20.4° from baseline), and the mean external rotation with the arm at the side was 26.9°±3.1° (gain of 5.4° from baseline) for patients belonging to the treatment group. The patients also showed a long-lasting pain relief (p<0.05). The mean Constant score after the treatment with HyalOne® 60mg/4ml was 82.7±4.5 points, 13.4 points more than the initial score (Table I). In the control group the mean active forward elevation was 143.8°±10.5° (gain of 5°), and the mean external rotation with the arm at the side was 22.9°±2.8° (gain of 0.9°). This group also had no long-lasting reduction in level of pain. The mean Constant score after PEP alone was 78.8±3.1 points, 8.9 points more than the initial score (Table I).

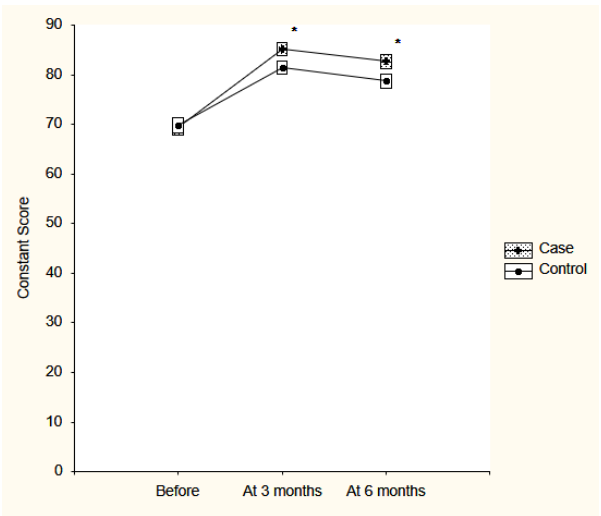

Fig. 1. *Constant score means for treatment and control group at baseline and after 3 and 6 months. Boxes indicate the confidence interval (95%). *p<0.05 (Post Hoc Tukey's Test).*

The ANOVA for repeated measures for the Constant score revealed a significant effect of the treatment ($F_{1,58}$= 7.080; p<0.05) and as function of the length of this ($F_{2,116}$= 19.310; p<0.05). As shown in Fig. 1, there was no difference between groups at baseline in the Constant score (69.3±4.2 and 69.9±4.4 for the treatment group and control group, respectively), while there was a significant effect at three months (85.1±3.4 and 81.5±3.5 for the treatment group and control group, respectively) and at six months after the treatment (82.7±4.5 and 78.8±3.1 for treatment and control group, respectively).

Similar results were obtained for the forward elevation movement. In this case, the ANOVA for repeated measure showed a significant effect of the treatment alone ($F_{1,58}$= 7.120; p<0.05) and over time between groups ($F_{2,116}$= 48.870; p<0.05). As shown in Fig. 2, there was no difference at baseline between the two groups (136.2±12.3 and 138.8±12.2 for treatment and control groups, respectively), while

Table I. *Means and standard deviation for treatment and control group, at baseline and after 3 and 6 months of therapy.*

	Baseline	3 months	6 months
Constant score			
Treatment	69.3± 4.2	85.1±3.4	82.7±4.5
Control	69.9±4.4	81.5±3.5	78.8±3.1
Elevation			
Treatment	136.2±12.3	159.6±8.9	156.6±8.8
Control	138.8±12.2	149.5±9.7	143.8±10.5
External Rotation			
Treatment	21.5±5.7	28.5±3.0	26.9±3.1
Control	22.0±3.6	27.0±2.2	22.9±2.8

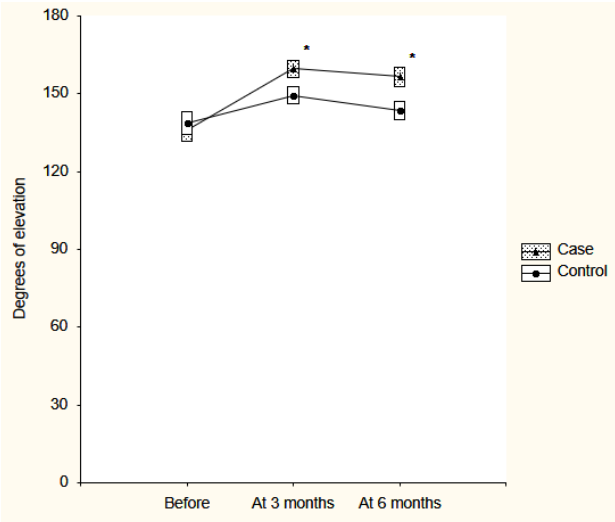

Fig. 2. *Means of the elevation's grades for treatment and control group at baseline and after 3 and 6 months. Boxes indicate the confidence interval (95%). *p<0.05 (Post Hoc Tukey's Test).*

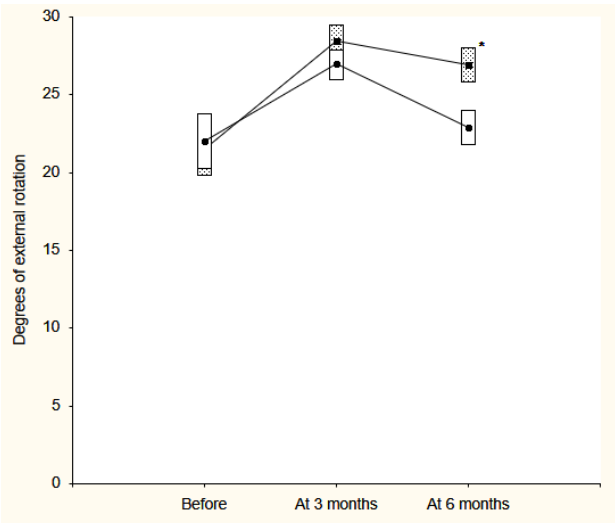

Fig. 3. *Means of the external rotation's grades for treatment and control group at baseline and after 3 and 6 months. Boxes indicate the confidence interval (95%). *p<0.05 (Post Hoc Tukey's Test).*

there was a significant difference between groups at three months (159.6±8.9 for the treatment group and 149.5±9.7 for the control group, respectively) and at six months (156.6±8.8 for the treatment group and 143.8±10.5 for the control group, respectively).

Evaluation of the external rotation movement, also showed a significant effect of the treatment over time ($F_{2,116}$= 28.006; p<0.05). In particular, there was a significant difference at six months after the treatment (26.9±3.1 and 22.9±2.8 for the treatment group and the control group, respectively). The effect is reported in Fig. 3.

No side effects occurred in patients treated with HyalOne® 60mg/4ml intra-articular injection.

DISCUSSION

The aim of this study was to evaluate the effects of the treatment with a single intra-articular injections of HMW HA combined with PEP in patients affected by shoulder OA degree II or III. We evaluated two different kind of therapies: a single intra-articular injection with a HMW HA (HyalOne® 60mg/4ml) associated with PEP *versus* PEP alone. The role of HA in patients affected by shoulder OA is controversial in literature (9-12). Patients treated with a single HyalOne® 60mg/4ml intra-articular injection in addition to PEP demonstrated to have a significantly higher decrease of shoulder pain in comparison to patients of the control group at the 3 and 6 month follow-ups (p<0.05). This result supports the concept that these patients benefit from a greater and long-lasting positive effect compared to patients who underwent PEP alone. Moreover, this study reported a significant long-term improvement in ROM between the two groups (p<0.05) and in daily activities. These results could be probably associated to the large reduction of shoulder pain. This study has some limitations. The first limitation is the possible concomitant inflammation of the long head of the biceps or the rotator cuff, very frequent in patients affected by glenohumeral OA, that could influence the results of the treatment in terms of pain. In addition, the second limitation is that we did not consider the scapular morphology that could partially influence the shoulder ROM. The present study demonstrates that patients affected by mild-to-moderate glenohumeral OA (KL degree II-III) treated with a single injection of HA (HyalOne® 60mg/4ml) combined with a physical exercise program had better results and longer duration, in terms of reduction of shoulder pain and improvement in daily activities, compared to patients treated with physical therapy alone. The great advantage of HyalOne® 60mg/4ml is also represented by the

single administration. Further studies are needed to better assess a standardized conservative protocol of treatment for shoulder OA.

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