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ORIGINAL STUDY

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Hyaluronic acid as an alternative treatment option for degenerative rotator cuff tears

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Rotator cuff tears have a high prevalence in older people. This research examines the clinical outcome of the non-operative treatment of symptomatic degenerative rotator cuff tears with hyaluronic acid (HA) injections.

72 patients (43 females/29 males), with an average age of 66 years with symptomatic degenerative full-thickness rotator cuff tear, confirmed with arthro-CT, were treated with three intra-articular hyaluronic acid injections and followed on multiple observational moments during a 5-year follow-up using the SF-36 (Short-Form Health Survey), DASH (Disabilities of the Arm, Shoulder, and Hand), CMS (Constant Murley Score), and OSS (Oxford Shoulder Scale.

54 patients completed the 5-year follow-up questionnaire. 77% of the patients did not require additional treatment for their shoulder pathology, and 89% were treated conservatively. Only 11% of the patients included in this study needed surgery. Between subjects, the analysis revealed a significant difference in response in the DASH (p=0.015) and CMS (p=0.033) when the subscapularis muscle was involved.

Intra-articular infiltrations with hyaluronic acid improve pain and shoulder function, especially if the subscapularis muscle is not involved.

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INTRODUCTION

Although some rotator cuff tears result from a traumatic event, most tears in patients older than 60 are due to age-related degeneration of the tendon. Family history, smoking habits, and poor posture are linked to increased prevalence and severity of rotator cuff tears. At the same time, sex does not seem to influence the prevalence of rotator cuff tears *(1,2)*. Although not necessarily symptomatic, 26% to 40% of people aged 60 or more show rotator cuff tears on MRI *(3,4)*.

As degenerative rotator cuff tears happen slowly over time, they are frequently asymptomatic. How-

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ever, rotator cuff tears can increase shoulder rigidity, instability, and pain and reduce strength, mainly during abduction, endorotation, and forward elevation *(5,6)*. When symptomatic, rotator cuff tears can vary from mild to intense pain located lateral, anterior, or superior on the shoulder, causing sleep disruptions impacting daily activities and life *(6,7)*. Different coping strategies are used by patients, varying from neglecting the condition to self-medication, in order to handle the both mentally and physically heavy condition. The yearly tear progression in asymptomatic shoulders ranges from 10 to 50%. Therefore, increased symptoms are suspected to be due to tear enlargement *(2)*.

Degenerative rotator cuff tears can be treated in different non-operative or operative ways. An optimal solution is found depending on the severity of the tear, age, and activity-state of the patient *(2)*. Besides relative rest and ice, surgery, physiotherapy, oral analgesics, and corticosteroid injections are currently the first treatment options for the condition and can show great results with up to 82% success rates and long-term, satisfying results *(6,8-10)*. Although the tear itself will not restore itself, inflammation and pain will be handled, allowing the patient to perform normal daily activities. The difference in activity levels and expectations between younger and older patients results in somewhat less satisfying outcomes for non-operative procedures in younger patients *(9,11)*.

This study evaluated the use of intra-articular hyaluronic acid (HA) infiltrations. Hyaluronic acid is a glycosaminoglycan synthesized in the plasma membrane found in all tissue of vertebrates, with abundance in skin, skeleton, and joints *(12)*. Within joints, HA is prevalent in the synovial fluid, tendon sheaths, and bursae, where it forms a thin viscous film and acts as a solid biological lubricant *(12)*. Hyaluronic acid has a short half-life, but benefits exceed the lubricant properties through specific TSG-6/ IαI complex interactions. It enhances a negative feedback loop moderating inflammation and stabilizing the granulation tissue during healing *(13)*. It acts anti-inflammatory and anti-nociceptive over a more extended period, comparable to corticoids but with fewer adverse effects *(14-16)*. Furthermore, hyaluronic acid amplifies growth factors and provides a matrix promoting cell proliferation and remodeling *(17)*.

Previous studies show promising results for HA in treating degenerative partial rotator cuff tears *(5,10,18,19)*. The study aims to analyze hyaluronic acid as an alternative treatment option for rotator cuff tears.

MATERIALS AND METHOD

The study sample consisted of patients with chronic shoulder pain with a confirmed degenerative rotator cuff tear on arthro-CT that consulted the Ghent University Hospital between September 2014 and June 2016. All patients had a history of chronic pain with a normal passive range of motion, a painful active range of motion, and a positive Jobe test. The suspected diagnose of degenerative rotator cuff tear was objectified by arthro-CT on all patients. Patients were excluded from the study if they had prior treatment for their shoulder pathology, except oral analgesics. No age limits were set. Patients received information about the various treatment options and could decide to treat with hyaluronic acid or an alternative option. When patients opted for treatment with hyaluronic acid, they were asked to participate in the study. The study consists of five evaluation moments with questionnaires. Patients had to fill in a questionnaire before their first injection and at 3 months, 6 months, 1 year, and 5 years after the start of the treatment. Questionnaires were sent to the patients by mail. Detailed information allowed them to fill in the questionnaires without help from medically skilled people. If needed, patients could call or e-mail PT or SV for more detailed information or instructions. No financial benefit was included.

3 injections of Hylan G-F 20 (Synvisc – Sanofi, Paris-France) were given with an interval of 2 weeks. Injections were given through an anterior approach by a skilled physician, AVT or LDW. First 5-10 cc lidocaine 2% were injected into the joint and afterward HA was injected. After injection, pain relief due to the analgetic was checked as an extra confirmation of the correct injection localization into the joint.

The Constant-Murley Score (CMS), Oxford Shoulder Score (OSS) and Disabilities of the Arm, Shoulder, and Hand (DASH) have proven to be good estimators for rotator cuff pathology and are reported in many shoulder-pathology related papers. As they all have been validated in Dutch, they have been found ideal for evaluation. The DASH has the extra benefit of partially evaluating the general health condition of the patients, making the use of general health assessment tools less of a need. Even though the DASH could potentially serve as an alternative, we included the Short Form Health Survey (SF-36) to score general health.

Although all questionnaires used in this study had been translated and validated in Dutch, the newly introduced Patient-based CMS had not been adapted to Dutch. We made the slight adaptation by using the Dutch CMS and adding the pictures and (translated) explanations used in the original paper by Levy et al. *(20)*.

All questionnaires but the DASH attribute a high score to better health. To make the evaluations of different scoring questionnaires less confusing, we adopted the inversed scoring found on a Dutch shoulder specialist website 'http://www.schoudernetwerk.nl/.'The DASH will thus be scored as '1-the original DASH score'.

To raise participation rates, the standard structure of black and white paper questionnaires was replaced by a full-color brochure containing both the questionnaires, their purpose, and some explanations about the condition. We used this questionnaire before the treatment. To limit costs, questionnaires at 3, 6, and 12 months were sent by mail on standard white A4 sheets. Patients received a paid envelope with a printed return address to send the completed questionnaire back. An additional phone call stimulated non-respondents. Questionnaires at 60 months were collected by telephone.

At last, 3 authors separately scored the artho-CT images of the respondents. Affected muscles, general retraction of the tendon, fatty degeneration and atrophy of the supraspinatus, infraspinatus and subscapularis were evaluated. General consensus was obtained by discussion in case of inconsistency. An informed consent was obtained prior to enrollment.

All statistics were analyzed with SPSS 26 ® (IBM Co.). Descriptive statistics were used to describe the population. Analyses were performed using (2-way)-repeated measure Anova's or the non-parametric Friedman's test. The assumption of normal distribution was tested with the Skewness-Kurtosis-test and the Shapiro-Wilk-test, in addition to visually checking the descriptive statistics, boxplot, and QQ-plot. Post-hoc analysis of the parametric data was performed using t-tests on the estimated marginal means with Bonferonni correction. Post-hoc analysis of the non-parametric data was done using the Wilcoxon Signed-Ranks test to evaluate within-subject differences and Mann-Withney's test to assess between-subject differences.

RESULTS

72 patients started the study. 29 (40.2%) participants are men, 43 (59.7%)re women with an average age of 66 years across both genders. 53 (73.6%) patients have injured their dominant shoulder. 54 patients were evaluated at the final evaluation at 60 months.

8 patients were lost for follow-up. Three patients died during the evaluation, 1 patient did not continue to fill in the questionnaires due to language difficulties, 2 patients did not further respond as they found the questionnaires to long, 2 patients found the results of hyaluronic acid insufficient and did not see the purpose in continuing to respond to the questionnaire.

Of the 64 patients that were not lost in follow-up, 10 patients engaged another treatment for their shoulder pathology (8 operation, 2 corticoid infiltration). 84% (54/64) of the surviving did not require additional treatment for their shoulder pathology, and 87,5% (56/64) could be treated conservatively. Table I shows the descriptive analyses for all participants at baseline (month 0).

57 patients filled in the 3-month evaluation, 51 the 6-month evaluation, 47 at 12 months. At the final review, 38 participants completed all SF-36, OSS, and DASH questionnaires, and 36 participants had results for all CMS questionnaires.

CT images of 36 patients were analyzed to identify prognostic success factors. Muscle involvement, retraction and degeneration were put into account.

Table I. — Descriptive analysis month 0

Variable	M (SD.)	N (%)
Average age month 0	66.30 (8.704)	72
Sex		
Men		29 (40.2 %)
Woman		43 (59.7 %)
Injured the dominant shoulder		53 (73.6%)

With M (mean), SD (standard deviation), N (number) and % (percentage).

Table II shows the mean scores of each questionnaire for months 0, 3, 6, and 12 with the number of participants who completed all 4 questionnaires.

The SF-36 PCS, SF-36 MCS, and Oxford scores were evaluated using the non-parametric Friedman's test. Within-subject analysis was performed using Wilcoxson's test. Post-hoc analyses were carried out using Mann-Withney's tests to find between factor differences.

The SF-36 PCS shows a significant increase after treatment. Significant differences within factors were found between all moments except between 3 and 6 months, 3 and 12 months, and 6 and 12 months. Men scored significantly (p=0.038) higher at 12 months than a woman.

The involvement of the subscapularis resulted in a significantly worse result at 60 months (p=0.041). No other significant differences were found. It must be noted that the involvement of the dominant shoulder resulted in a clinical but not statistically significant disadvantage at 6 and 12 months.

The SF-36 MCS shows a significant increase in results at the 60 months evaluation (p<0.001). The MCS did not show a significant difference between observations. No other factor was found to have a significant effect on the SF-36 MCS.

Table III. — Involvement of the muscles resulting from the arthro-CT analysis

Total N=36	Not involved	Involved
Subscapularis involvement	24	12
Supraspinatus involvement	1	35
Infraspinatus involvement	22	14
Bicheps tendon present	5	30

The Oxford Shoulder Score resulted in a significant increase in shoulder function after treatment (p=0.001). A significant increase can already be observed on the 3 monthly evaluations (p=0.001). Both the dominant shoulder and subscapularis being affected showed a non-significant trend to scoring worse than if affected. This non-significance was mainly due to the high variance.

The (1-) DASH score was evaluated using the parametric repeated measures ANOVA.

A significant difference (p<0.001) was found between the observations. Between subject, analysis exposed a significant (p<0.05) difference between baseline and 6, 12, and 60 months. No significant difference was found between baseline and 3 months evaluation. (p=0.211). Gender (p=0.001) showed a significant trend, with men scoring higher than a woman. Age (p=0.988) or the dominant shoulder being affected (p=0.183) did not result in significantly different effects on the treatment. On CT-based findings, only the involvement of the subscapularis resulted in significantly (p=0.015) inferior results. At baseline, the patients with no involvement of the subscapularis had an

Table II. — Mean score for each questionnaire

Questionnaire Time (months)	M(SD), N 0	M(SD), N 3	M(SD), N 6	M(SD), N 12	M(SD), N 60
SF-36 PCS*	35.19 (13.4), 70	41.82 (15.5), 57	42.68 (17.9), 51	48.68 (18.7), 47	67.72 (24.1), 54
SF-36 MCS*	58.62 (16.1), 70	60.92 (16.9), 57	61.07 (18.3), 51	64.39 (17.9), 47	87.14 (17.7), 54
OSS*	48.16 (15.7), 71	59.66 (15.9), 57	63.94 (19.3), 51	71.36 (16.2), 47	73.34 (18.9), 53
DASH	62.33 (15.5), 70	68.04 (16.1), 57	69.80 (18.7), 51	74.50 (17.4), 47	76.60 (20.9), 53
CMS	52.14 (15.6), 66	53.52 (13.8), 56	55.47 (16.9), 51	58.51 (14.0), 47	76.60 (20.9), 53

With M (mean score), SD (standard deviation), and N (number)

Table IV. — P-Values of within-subject effects

Questionnaires	0 - 3m	0 -6m	0-12m	0- 60m	3-6m	3-12m	3-60m	6-12	6-60	12-60
PCS*	0.001*	0.001*	0.001*	0.001*	0.995	0.031	0.001*	0.046	0.001*	0.001*
MCS*	0.555	0.203	0.091	0.001*	0.695	0.188	0.001*	0.443	0.001*	0.001*
OSS*	0.001*	0.001*	0.001*	0.001*	0.045	0.003*	0.001*	0.092	0.015	0.367
DASH	0.211	0.009*	0.012*	0.001*	1.000	0.297	0.015	1.000	0.149	0.645
CMS	1.000	1.000	0.500	0.762	1.000	0.376	1.000	1.000	1.000	1.000

With * being pairs tested post-hoc by use of a Wilcoxon Signed-Ranks Test.

average score of 60.32, patients with an affected subscapularis had an average score of 60.40. At the final evaluation, these scores were respectively 80.53 and 43.65. Other CT-based findings did not significantly influence the outcome.

The Constant Murley Score was evaluated using the parametric repeated measures ANOVA.

The pairwise comparison did not show significant differences. Similar to the DASH, CMS of female respondents are significantly (p=0.002) lower than those of male respondents, and the involvement of a subscapularis tear results in a significantly lower (p=0.047) CMS. The involvement of the subscapularis resulted in a decrease of 19.5 points over the entire follow-up, compared to a 14-points increase if the subscapularis was not affected.

Table IV describes the p-values of within-subject effects.

Of all the patients included in this study, 8 underwent surgery on average 11 months after the first hyaluronic acid infiltrations. Fifty-six patients did not need additional treatment until 5 years after the first hyaluronic acid treatment. Eight patients opted for an additional infiltration, 2 patients chose for a cortisone infiltration on average 1 month after the hyaluronic acid treatment ended, and 6 patients repeated the hyaluronic acid infiltrations on average 30 months after the previous treatment. Figure 1 shows the survival curve for surgery being failure of treatment and for any intervention being considered a failure of treatment.

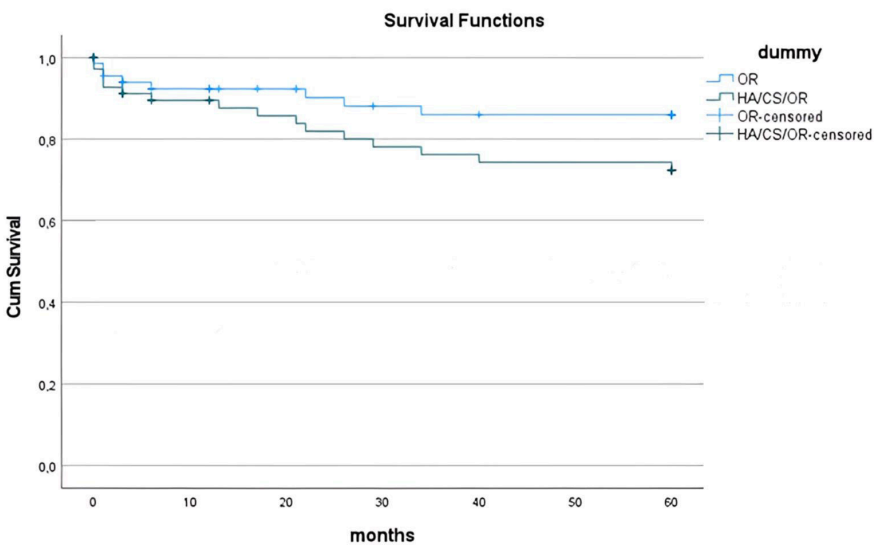

Figure 1. — Kaplan-Meier survival curve. The Kaplan-Meier curve shows the survival curve with failure of treatment being surgery (OR-group) and with failure of treatment being surgery, corticosteroid or additional hyaluronic acid infiltration (HA/CS/OR-group).

DISCUSSION

Hyaluronic acid has a wide range of applications. This study focused on the potential benefit of intra-articular hyaluronic acid injections to treat symptomatic degenerative rotator cuff tears. The treatment did not intend to restore the tear but to restore a pain-free range of motion. To assess the improvement of the patients, multiple questionnaires were scored. Furthermore, demographic and CT-based data were used to find underlying trends that could explain differences in the effect of the treatment.

Overall, all scores increased on the next evaluation moment, meaning a continuous improvement of the shoulder pain or function. Statistically significant increases were recorded in all shoulder-specific scales except for the CMS.

We assessed the SF-36 in separate parts. The overall physical health showed a significant increase compared to the baseline. The MCS is significantly higher at 60 months and differs from all observation moments. As no variable was found to influence the MCS significantly, it can be concluded that patients feel better with age. The high MCS could be explained by a selection bias that selects the people who feel better still have the energy to participate in the study while people with little energy drop out. Another possibility is that as patients get older, they can put things more in perspective and have lower treatment expectations. Younger people are often less satisfied with conservative treatment than older patients due to higher expectations and a difference in daily activities *(9,11)*. The MCS did not show a significant difference between observations. This implies the mental health of the participants was stable during the evaluation period. This finding makes the results of the physical score and shoulder-specific scores more accurate for interpretation.

DASH results were transformed to '1-DASH score' to make it easier to interpret next to other positive scales.

All physical scores improved significantly after the treatment. This result supports the assumption that hyaluronic acid significantly improves shoulder pain and performance.

Both demographic and CT-based data were analyzed and used to find significant predictors of success in the data. Male respondents scored the SF-36 MCS, DASH and CMS significantly higher than women, although the within groups trend was not significantly different and therefore is not relevant as an indicator to decide on treatment with intra-articular hyaluronic acid infiltrations.

Two independent variables were found to be good predictors for success. First, the involvement of the subscapularis muscle had a significant negative effect on the treatment on both the DASH and CMS and showed a non-significant trend on the OSS. Second, the dominant shoulder being affected results in a clinical, but non significant, decreased response to the treatment compared to the non-dominant shoulder. This trend was found in the DASH and OSS.

The CMS (to be consistant) showed a significant trend, but the pairwise comparison did not show significant differences. This is mainly due to the strength component, which has a substantial floor effect when people are incapable of painlessly reaching the measurement position and thus receive 0 points for that part of 25 out of 100 *(21)*.

The Kaplan-Meier curve shows that not everyone with a symptomatic rotator cuff tear needs surgical treatment. Only 8 patients dropped out because they needed surgery. At the latest follow-up, 87,5% (56/64) were treated conservatively and 84,3% (54/64) did not need additional treatment. After interpreting the patient-reported questionnaires, the clinical improvement was mainly noticeable in the first 6 months. Due to the lower costs of treatment with hyaluronic acid (€160) compared to surgery (€1000-€1650) and the avoidance of 6 months of work disability that follows after the surgery, a conservative approach seems appropriate in some cases for at least six months, as the greatest gains are achieved during this period.

Hyaluronic acid has been proven to suppress inflammation and have an analgesic effect by suppressing PGE2 production *(15)*. During a study by Kim et al., hyaluronic acid proved to improve range of motion and pain better than corticosteroids, which have been associated with several significant side effects *(15)*. Several other studies have evaluated

the effectiveness of hyaluronic acid to treat rotator cuff tears. Similar to this study, most of these trials showed a significant improvement in shoulder function and pain.

Chou et al. tested the effect of hyaluronic acid injections in partial rotator cuff tears during a randomized, double-blind placebo-controlled trial *(18)*. Like our trial, the CMS was used to evaluate shoulder function. An improvement from 61.6 to 79.2 was recorded 6 weeks after the 5 injections. Both in terms of pain and function, the HA group outperformed the placebo group proving the effectiveness in partial cuff tears. Our study included full cuff tears resulting in a lower CMS at baseline and after 1 year. The increase noted in their study is approximately 20 points compared to 7 points gained in our study. Although not conclusive, this could suggest HA may result in higher benefits for partial tears than full rotator cuff tears. Second, Chou et al. used a different type of hyaluronic acid, which they injected 5 times, while our study only had 3 injections. A study by Blain et al. tested intra articular hyaluronic acid injections in 660 patients with persistent shoulder pain, including patients with rotator cuff ears, during a double-blind placebo-controlled trial *(10)*. In the 3 and 5 injections, significant improvements were noted, slightly favoring the group that received 5 injections. The beneficial effects of the treatment were mainly seen in patients with osteoarthritis, of whom 66% had rotator cuff tears.

Shibata et al. performed a trial similar to ours but included a control group with corticosteroids *(19)*. Both groups showed a similar therapeutic effect. A trial by Constantino and Olvirri treated rotator cuff tears with 3 infiltrations of hyaluronic acid and a rehabilitation program *(5)*. The CMS improved significantly without adverse effects.

A review by Osty et al. demonstrated results in the same range of our study *(22)*. HA proves to be a good alternative for CS or oral drugs. None of the analyzed studies showed severe adverse events.

This study was the first to analyze the use of intra-articular hyaluronic acid injections to treat rotator cuff tears in Belgium. All tears were classified using an arthro-CT. Skilled physicians performed the injections with the use of analgesics to assess the localization of the injection. Although several patients were lost in follow-up, and many did not fill in all questionnaires, a fair sample size was obtained. Detailed analysis of patients experiencing failure of treatment was not performed.

The study has several weaknesses. The study was not a randomized controlled clinical trial, and patients chose this option after discussing the several treatment options with its advantages and disadvantages with the medical doctor. This strongly limited the possibility to compare other treatment options to the hyaluronic acid injections. Furthermore, we did not include smoking habits in our analyses, although studies show smoking habits are linked to increased prevalence and severity of rotator cuff tears and have a negative impact on tear size, progression, and post-operative results *(2)*.

Patients had to assess the evolution of their shoulder and health themselves using the questionnaires. Depending on their mood at that time, the questionnaires might have been subjected to a more positive or negative evaluation. Despite this being possible, the stable results of the MCS of the SF-36 make this very unlikely. As a consequence of the self-assessment, multiple patients did not fill out the questionnaires completely, which inhibited the scoring of that specific questionnaire.

Our research focused mainly on clinical outcomes. The pain was incorporated in several scores we used to analyze the condition, like the CMS and the DASH. Despite the widespread use of pain scores, we did not evaluate pain individually despite pain relief being a key element of hyaluronic acid treatment. Furthermore, patient satisfaction was not measured. Dropouts and non-responders were not analyzed further. Although most cases of treatment failure are known, we cannot determine whether non-responders suffered a failure of treatment or had a successful treatment.

While all patients received an arthro-CT that objectified a full rotator cuff tear on the time of enrollment, some of the CT images were not available anymore at time of its analysis. As the CT report was not deemed sufficient for this detailed analysis it unfortunately resulted in fewer analyzed CTs than patients.

CONCLUSION

Hyaluronic acid has multiple uses. Intra-articular injections with hyaluronic acid proves to be a good nonsurgical treatment for degenerative rotator cuff tears, especially if the subscapularis muscle is not affected. A significant improvement was noted during the first six months of the observational period for the DASH, OSS, CMS, and the continuous physical score of the SF-36. After six months an increasing non-significant trend was still observed. Multi-center randomized controlled trials are warranted to objectify the findings of this study.

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