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Comparison of Two Hyaluronic Acid Preparations for the Treatment of Rizoarthrosis

Marcello Sallì[1]*, Giovanni Grasso[2], Salvatore Sallì[1] and Calogero Foti[3]

[1]Sallì Rheumatological and Rehabilitation Center, Palermo Italy

[2]Neurosurgical Unit, Department of Biomedicine, Neurosciences and Advanced Diagnostics (BiND), University of Palermo, Palermo, Italy

[3]Physical and Rehabilitation Medicine, University of Rome "Tor Vergata", Rome, Italy

ABSTRACT

Osteoarthritis of the trapeziometacarpal joint (TOA) or rizoarthrosis is a pathology particularly prevalent in post-menopausal women. It can be symptomatic, with associated pain, or asymptomatic, and in this latter case it is diagnosed by radiographical examination. TOA, when symptomatic, strongly affects quality of life. The treatment of TOA involves both pharmacological and non-pharmacological treatment (including local application of heat, ultrasound and splints). The major treatments, recommended by the European League Against Rheumatism consists of corticosteroids for pain control and hyaluronic acid (HA) for amelioration of functional capacity. The present study aimed at comparing the efficacy and tolerance of intra articular injections of two HA preparations, high-low molecular weight HA (HL) (Sinovial® HL) and high molecular weight HA (HMW) (Sinovial® Mini), in patients with TOA. The observational and retrospective study involved overall 125 subjects, ageing from 45 to 85 years, who had clinical symptoms of TOA lasting at least 6 months. The patients received HL (66 subjects) or HMW (59 subjects) in two injections at baseline and after 15 days. The subjects were followed for 6 months, and the outcome measurements included pain control (through VAS scale) functional hand capacity, using the Duruoz Hand Index (DHI) and the change of the duration of morning stiffness, using the Italian version of the Health Assessment Questionnaire (HAQ). HL was found superior to HMW in all the three parameters examined, with a quicker and stronger pain relief, recovery of hand function as well as in self-assessment by the subjects. Both treatments were associated with very modest side effects.

In conclusion, our data show the efficacy of HL and HMW for the treatment of TOA and the superiority of HL to HMW. Although these data are observational and retrospective, they pose the basis for future prospective studies focused on the use of HL and HMW in TOA.

***Corresponding author**

Marcello Salli, Sallì Rheumatological and Rehabilitation Center, Palermo Italy. E-mail: sallimarcello@gmail.com

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Introduction

Rizoarthrosis or osteoarthritis of the trapeziometacarpal joint (TOA), is a disease affecting prevalently woman in post-menopausal status; it is estimated that the prevalence of TOA is around 30% for woman above 65 years of age and tends to increase with age [1, 2]. There is a substantial difference between radiographic prevalence and symptomatic prevalence with the former much higher, due to the fact that TOA can or cannot be associated with pain and swelling [2-4]. When symptomatic, TOA strongly impacts on quality of life [5]. Major symptoms of TOA are pain in the trapeziometacarpal joint, reduced mobility of the thumb and consequently decreased hand strength [6-8]. Considering that thumb is necessary for roughly half of the overall hand functions, symptomatic TOA can result in disability of hand function [9, 10].

According to the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), the optimal management of TOA consists of a combination of pharmacological and non-pharmacological (such as local application of heat, ultrasound and splints) treatment [8-11]. It is not completely clear how efficacious is the intra articular (i.a.) therapy. Different metanalysis together with EULAR experts recommend hyaluronic acid (HA) as useful to increase functional capacity and corticosteroids for pain control [11-14].

HA, is the main component of the cartilage matrix in normal joints and it has master functions in maintaining lubrification, in shock absorption and viscoelastic properties of synovial fluid (SF). HA is largely used for the treatment of knee OA as well as for other joints including hip, ankle, shoulder and temporomandibular joint [15-17]. Its high presence in normal human tissues and low immunogenicity, make treatment with HA safe and well tolerated.

There are different formulations of HA depending on the molecular weight (MW), its concentration and the presence of additional molecules in the formulation [16, 18, 19]. Recently a new hybrid HA formulation, Sinovial® HL (HL) received CE

authorization for the treatment of OA. This formulation has the unique characteristic of a bimodal MW profile distribution with a combination of both high and low MW fractions. Thanks to this combination, HL maintains unique rheological properties [13, 20]. HL injected i.a. has reported to be more effective than the corticosteroid triamcinolone in improving joint function and reducing pain in TOA [21]. In the present observational, retrospective, comparative study, the efficacy and tolerability of i.a. injections of HL were compared to i.a injections of high MW HA (HMW) (Sinovial® Mini) in patients with TOA.

Materials and Methods

Patients Population

This observational study is based on a retrospective analysis of medical records. The records were collected from clinic outpatients archives for patients affected by TOA, according to ACR criteria, who were treated with intra-articular (i.a.) Sinovial® HL (HL) or Sinovial® Mini (HMW) in a period ranging from December 1st, 2018 to December 1st 2020 [20, 22]. TOA could be either monolateral or bilateral and, in case of bilateral TOA, the target hand was considered the most symptomatic one or, when both hands were equally affected, the patient's dominant one. We included in our analysis the records of 220 patients of both sexes, aged between 45 and 85 years, who had clinical symptoms of TOA lasting for at least 6 months.

Subjects received a diagnosis of first carpometacarpal joint OA on the basis of a thorough history, a physical examination, and a radiographic evaluation. Clinical examination included the presence of thumb or wrist pain at rest, tenderness of the trapeziometacarpal joint, joint stiffness, decreased mobility, deformity, instability, and decreased manual function.

Inclusion criteria were, a history of pain at the base of the thumb for at least 6 months, a minimum score of 4 cm on the 0-10 cm visual analogue scale (VAS), age of 45 years or more, and a stage II or III Kellgren and Lawrence radiological classification of OA [3]. Patients were excluded from the analysis if, in the previous 6 months, had received treatments with steroids, glucosamine, chondroitin sulfate or if they received i.a. injections of HA (or corticosteroids) in any joint. Severe comorbidities, or history of joint disease, hand surgery, or septic arthritis, were additional exclusion criteria. All the subjects signed an informed consent relative to the data collection and were informed on the nature of the study.

Patients treated received one cycle of two injections (at baseline following the first visit and after 15 days) of Sinovial® HL (3.2% - 16 mg + 16 mg/1ml, IBSA), while the others received with the same scheme of treatment (at baseline and after 15 days) Sinovial® Mini (0,8% - 16mg/1ml, IBSA). Sinovial® HL is a hybrid form of HA obtained through thermo-chemical processes of both high (1100–1400 kDa) and low (80–100 kDa) MW fractions. Treatments were performed with a 22G needle according to routine procedures of our center. The hand to be injected was set on a semi prone position and the injection point was determined after palpation of the trapeziometacarpal joint, within the anatomic snuffbox. Treatment of patients followed the EULAR recommendations for the management of hand OA [12].

The follow-up period of at least 6 months has been established on the base of the Schumacher et al. previous experience, in which it was shown that HA MW 500-730 KDa has a long-lasting pain relief up to six months [23]. If needed, and only to relieve TOA associated pain, all patients received the same co-treatments during the study as rescue.

Outcome Measures

Evaluations were carried out at the beginning of treatment (T0), at the end of treatment (T1), and after 1-month (T2), 3-months (T3) and 6-months (T4) of follow-up. All the efficacy and safety parameters were assessed by the same blinded investigator.

One of the primary outcomes was the overall reduction of trapeziometacarpal pain, as assessed by a change in mean VAS score from baseline. This scale consists of a 10 cm horizontal line (with 0 cm referring to 'no pain' and 10 cm to the 'the worst pain ever'); patients were asked to rate the intensity of their pain by making a mark on the line. The test–retest reliability is quite good in general, but is higher among literate ($r=0.94$, $p<0.001$) than illiterate patients ($r=0.71$, $p<0.001$), who were seen before and after attending a rheumatology out-patient clinic [24].

Hand function was measured by changes in the Duruoz Hand Index (DHI) from baseline to the different follow up visits [25]. The index is a self-reported questionnaire that measures hand functional ability by detecting a patient's difficulty in performing eighteen tasks in daily life. Each item is scored from 0 (performed without difficulty) to 5 (impossible to do). A total score is obtained by adding the scores on all questions (range, 0-90). The DHI is reliable and valid for people with rheumatoid arthritis and osteoarthritis [25, 26]. We chose as secondary outcome: the change of the duration of morning stiffness, using the Italian version of the Health Assessment Questionnaire (HAQ). HAQ is a self-administered questionnaire developed to measure disability, consists of 8 sections: dressing, arising, eating, walking, hygiene, reach, grip, and activities and the final score ranges from 0 to 3, with a higher score corresponding to worse disability [27, 28].

All adverse events and their severity, spontaneously reported by the patients or observed by the physician, were recorded.

Statistical Analysis

The samples size of the present study was sufficient to demonstrate a difference in changes in VAS scale with an 80% power and an alpha error of 5%. The data, reported as mean ± SD or percentage relative to baseline, were compared using one-way Anova followed by Mann-Whitney-Wilcoxon test (GraphPad PRISM v7 software).

Results

In this study, 220 patients with mono or bilateral TOA who had indication for an i.a. therapy between December 2018 and December 2020) were considered (Figure 1). Of these 220, 40 were excluded from the analysis because they received other formulations of HA or steroid. Additional 55 patients were excluded because they did not meet inclusion criteria (35) or because some visits at follow up were missing (20). The final analysis could be performed in 125 subjects, 66 treated with HL and 59 with HMW. The main characteristics of the patients are reported in Table 1. The two groups were well balanced for the major characteristics, including severity of the pathology and initial VAS and DHI values. Roughly 80% of the patients were female (in both groups), in agreement with the prevalence of TOA. All patients but one in the group of HMW had the dominant hand affected. The presence of comorbidities (hypertension, hypercholesterolemia, osteoporosis, diabetes) was also similar in the two groups (Table 1).

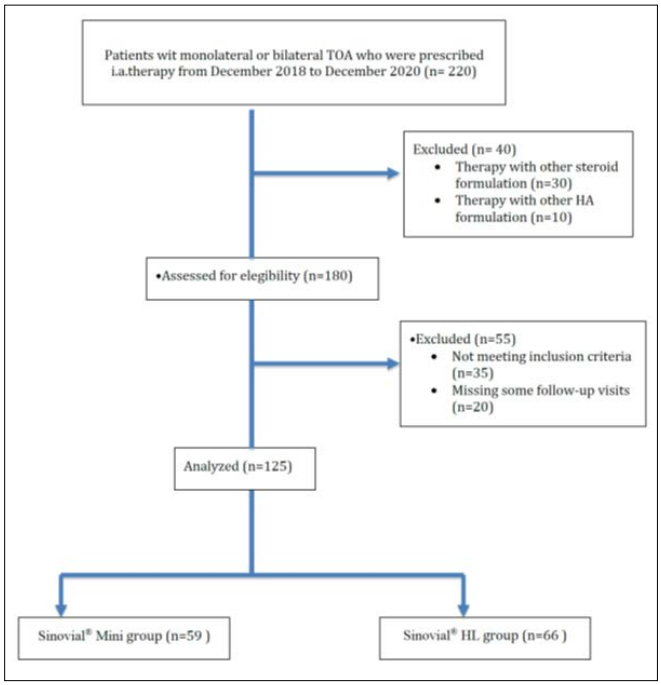


Figure 1: Flow Chart of the Study

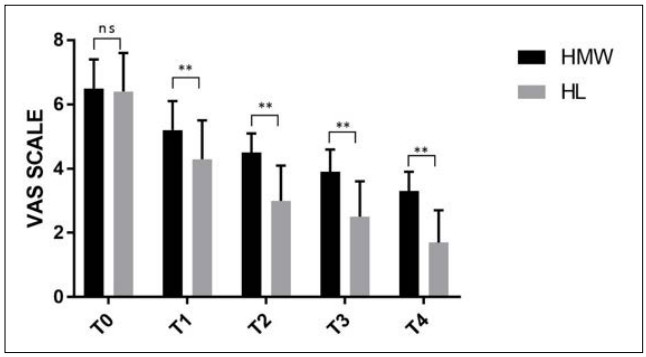
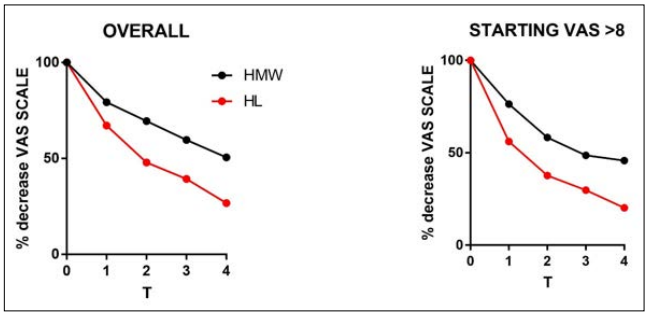


Figure 2: VAS values at baseline (TO) and at the subsequent visits (T1, T2, T3, T4) in HL and HMW groups. Values in columns are reported as mean ± SD ns not statistically significant, ** p< 0.01

Table 1: Main Characteristics of the Patients Analyzed

		HL	HMW
Age (yrs+SD)		69.7±8.6	70.0±7.8
Female/male		53/13	46/13
K-L grade, number (%)			
	II	35 (51)	28 (47)
	III	31 (49)	31 (53)
Bilateral/monolateral		13/53	9/50
VAS pain at baseline (cm)		6.4±1.2	6.5±0.9
DHI at baseline		69.4±4.7	68.6±4.9
Haq at baseline		2.2±0.2	2.2±0.2
Comorbidities number (%)			
	none	5 (7.6)	4 (6.8)
	hypertension	38 (55)	30 (51)
	hypercholesterolemia	10 (15)	6 (10)
	diabetes	4 (6)	6 (10)
	osteoporosis	13 (19)	7 (12)

Considering the response in terms of pain, as it can be seen in Figure 1, the group of patients receiving HL had a quicker and stronger pain relief, with a statistically significant difference (p <0.01) already observed at T1, i.e. immediately after the end of the treatment. This difference, in favor of HL, further increased at the subsequent visits up to the last, in which the highest difference was found. At this time point, there was a decrease in VAS value by 75% and less than 50% in the synovial HL and HMW groups, respectively. Interestingly, considering those patients with initial high VAS values (>8), the difference between the two groups were maintained with 80% reduction in the HL group and 54% reduction in the HMW group (Supplementary Figure S1). These percentages were calculated on the mean values, but the general trend was maintained when single patient changes were considered, as reported in Supplementary Figure S2 panel A.



Supplementary Figure 1

Regarding the hand function, DHI index decreased from baseline to T1 similarly in both groups. HL treated patients performed better than those receiving HMW at the subsequent visits (T2, T3 and T4). At all these time points, the differences were statistically significant (p < 0.01, Figure 3). At T4 there was a 92% and 79% reduction of DHI in HL and HMW groups, respectively. The decrease in DHI was homogenous among all the treated patients, as it can be seen in Supplementary Figure 2 panel B, where the superiority of HL can be better appreciated.

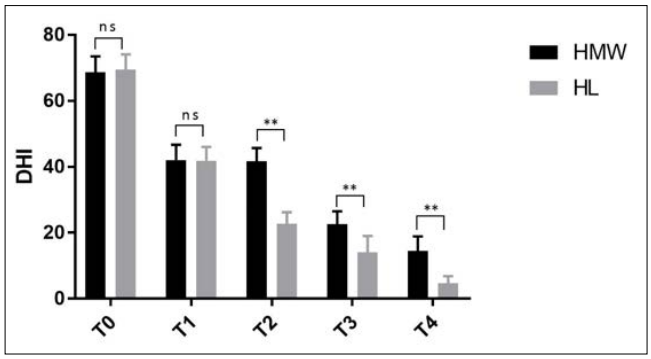


Figure 3: Effect of HL or HMW treatment on DHI. Values in columns are reported as mean ± SD at baseline (TO) and at the subsequent visits (T1, T2, T3, T4) ns not statistically significant, ** p< 0.01

When the results of the self-administered questionnaire (HAQ) were considered, a strong improvement in the index was reported by patients receiving HL already at T1, while no changes from baseline were reported by patients treated with HMW (Figure 4). At the end of study (T4) the HL group overall reported an improvement of 85% relative to baseline, while the other group had only 60% improvement (p < 0.01). As was the case for the other two outcomes, when single patients values were considered (Supplementary figure S2, panel C) the difference among the patients treated with HL and HMW was maintained, in favor of

the former. A summary of the mean decrease relative to baseline of the three outcome measurements is reported in Supplementary Figure 3, where it can be appreciated that HL outperformed over HMW in all the tests, with statistically significant differences.

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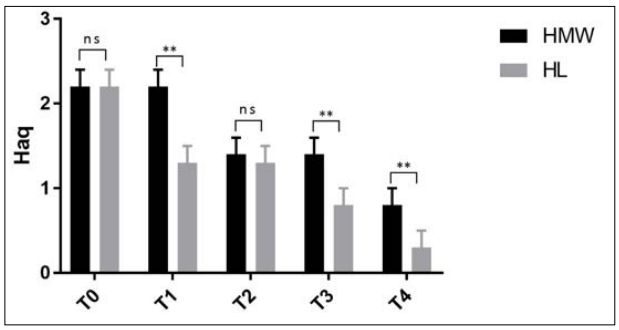
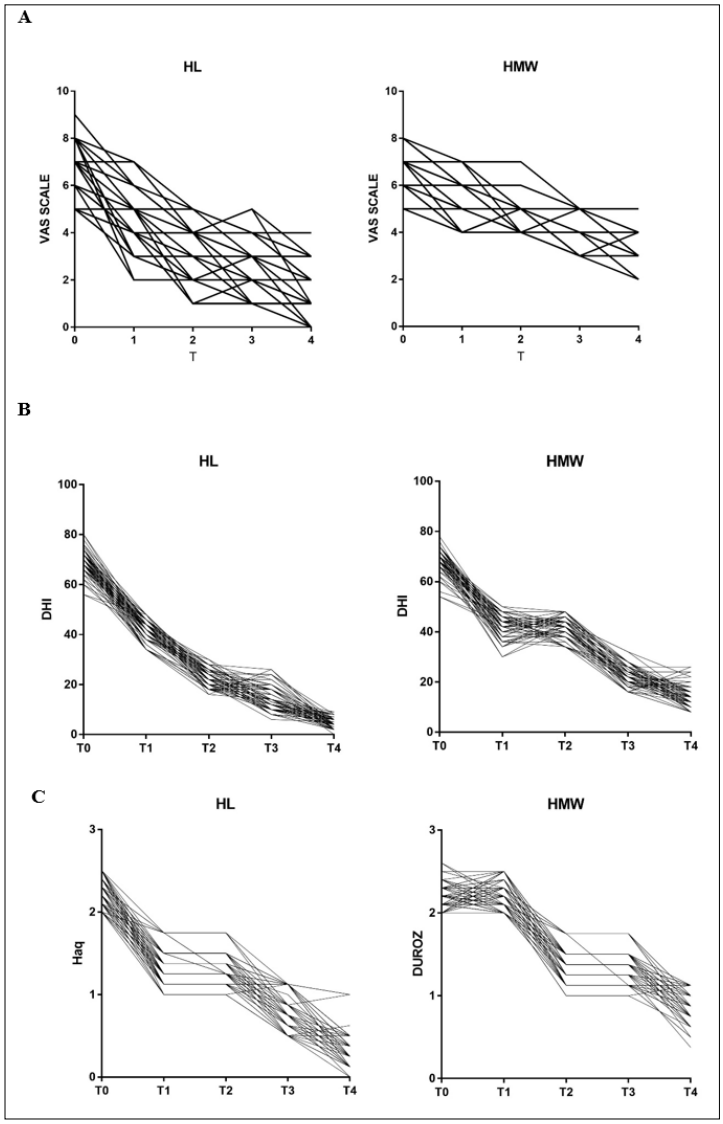
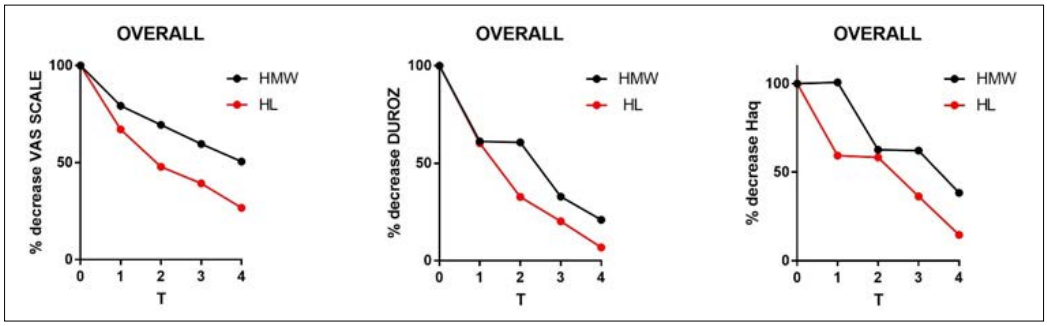


Figure 4: Self-Administered Questionnaire results. HAQ score values at baseline (TO) and at the subsequent visits (T1, T2, T3, T4) in HL and HMW groups. Values are reported as mean ± SD
ns not statistically significant, ** $p < 0.01$



Supplementary Figure 2



Supplementary Figure 3

Finally, considering the adverse events, these were limited and overall the treatments were well tolerated, but again in favor of HL. In fact, in this group joint pain after injection was reported in 3 out of 66 patients, while 4 out of 59 reported this event in the HMW group. No joint swelling after injections was reported in the HL group, while this event was experienced by two patients in the HMW group.

Discussion

This observational study is the first comparing two different HA-based formulations as i.a. injection in patients with TOA. In agreement with a recent report in which HL was used and found efficacious for the treatment of TOA, we found a strong and lost acting activity of two i.a. injections of this preparation and, when compared to HMW, a superior activity in all the outcomes considered [21]. The results of the data collected through the use of the VAS scale, clearly indicated a superiority of HL over HMW already at the first visit and then throughout the observation period. Although the population studied here was well balanced in terms of baseline parameters, including VAS values, when the effect of the two treatments was compared in the population with high VAS values only (values equal or greater than 8), the higher efficacy of HL was maintained, further supporting its role in very debilitating stage of the illness.

The three different outcomes considered, all converged (although with different kinetic) in sustained efficacy of HL for the treatment of TOA. Furthermore, the data collected here not only show efficacy in terms of mean activity, but also strikingly show that the positive effects could be observed in all the single patients (with the exception of one patient who experienced a worsening between T3 and T4). This means that the presence of different co-morbidities, sex, age or other factors do not influence the activity of the treatment.

Tenti et al., showed maximal effect of HL injected i.a. at 3 months after treatment (corresponding to our T3) with then a low, but detectable, worsening after 6 months (corresponding to our T4) [21]. In the present study, we found a continuous amelioration with time, which was already evident from T1 and reached a peak at T4 (i.e. 6 months after treatment with HL). We do not have at present an explanation for this, but our data could suggest a potential long-lasting effect (longer than 6 months) of the treatment on both pain and joint functionality.

Our study clearly showed that HA per se is effective in increasing functionality of thumb. This is the first study comparing two different HA preparations for the treatment of TOA. The results obtained are in line with other studies comparing HA of different compositions for other purposes (skin ageing, neck wrinkles, ect) and clearly indicate that combining different properties associated with the different HA MWs, is a good strategy for maximizing the positive effects of HA [29-32]. Considering that HL treatment associated with very low adverse event, overall, the results suggest that changes in HA composition can potentially enhance efficacy and reduce toxicity.

In conclusion, our data show the efficacy of HL and HMW for the treatment of TOA and the superiority of HL to HMW. Although these data are observational and retrospective, they pose the basis for future prospective studies focused on the use of HL and HMW in TOA.

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