Article

Intra-articular hybrid hyaluronic acidinjection treatment inknee osteoarthritis in overweight individuals:a single-center, open-label, prospective trial.

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Abstract: (1) Background:A BMI > 25 is the most decisive, albeit modifiable,risk factors for knee osteoarthritis (OA). This study aimed at assessing the efficacy of intra-articular injections of hybrid hyaluronic acid (HA) complexes (Synovial® H-L)for the treatment of kneeOA in overweight patientsin terms ofdisease severity, cardiocirculatory capacity, and quality of life. (2) Materials: In this single-site, open-label, prospective trial, 37 patients with symptomatic knee OA were assessed at baseline and 3 months after ultrasound-guided intra-articular injection of hybrid HA complexes (Synovial® H-L). (3) Results: Primary variables displaying a statistically significant improvement after treatment were pain (NRS), disease severity (WOMAC), and cardiopulmonary capacity a(6-Minute Walk Test). Among secondary variables, quality of life (SF-12) improved significantly, as did analgesic intake for pain control. No statistically significant difference was observed in body fat and muscle mass percentage measured by bioelectrical impedance analysis. (4) Conclusions:Intra-articular hybrid HA injections are significantly effective in improving OA-related disease severity, cardiopulmonary function, and analgesic intake. This supports the role of hybrid HA viscosupplementation as a non-pharmacological treatment to relieve pain, reduce disability and improve quality of life, and limit the risk of polypharmacy in overweight patients with knee OA.

Keywords: Knee osteoarthritis; hybrid hyaluronic acid; viscosupplementation; obesity; overweight.

1. Introduction

Knee osteoarthritis (OA) is a highly prevalent clinical syndrome of joint pain accompanied by a varying degree of functional limitation and decreased quality of life. Among adults aged 60 and older, this chronic musculoskeletal illness is present in 10% of men and 13% of women, or in an estimated 250 million persons worldwide.[1]In terms of pathophysiology, kneeOA is associated with increased levels of inflammation, and is

characterized by loss of articular cartilage and by subchondral bone changes in terms of turnover, mineralization and volume.[2]Notwithstanding, structural changes can be also observed in Hoffa's fat pad, synovia, ligaments and muscles, proof that knee OA is indeed a whole-joint disease.[3]

Age and sex are two of the main risk factors associated with knee OA, with women more likely to develop OA than men due to differences in knee anatomy and kinematics.[4] Previous knee injuries, joint malalignment and instability resulting in increased mechanical stress, repetitive actions such as kneeling and heavy lifting, and professional sports activities such as long-distance running are all strong risk factors for knee OA.[1, 3, 4]However, among the risk factors of KOA, overweight and obesity are the most determinant, albeit considered modifiable. A 2015 meta-analysis show that being overweight and obeseare significantly associated with higher knee OA risks of 2.45 and 4.55, respectively; and that the risk of knee OA increases by 35% with a 5 point increase in BMI.[5]Excess weight correlates with a higher risk of knee OA both by increasing the load on weight-bearing joints, and by collating with the inflammatory milieu caused by metabolic syndrome.[6] Lastly, physical inactivity is also a contributor to the increasing prevalence of OA, with weakness of the knee extensor muscles predisposing to knee damage due to less stable and weaker joints.[7]

Treatment objectives for kneeOA are paincontrol, reducing stiffness, improving mobility and quality of life, with avoidance of toxic pharmacological side effects.[8]The Osteoarthritis Research Society International (OARSI) periodically updates its guidelines for the nonsurgical management of OA.[9] In its 2019 update, OARSI recommended arthritis education and structured land-based exercise programs, with or without dietary weight management, as core treatment for knee OA. Recommended pharmacological treatment options include topical non-steroidal anti-inflammatory drugs (NSAID), cyclo-oxygenase 2 (COX-2) inhibitors, and oral NSAIDs with proton pump inhibitors. Notwithstanding, such drugsstill bear well-known cardiovascular, gastrointestinal and renal toxicities, thus an initial conservative, nonpharmacological approach is to be preferred especially in the elderly population due to its high risk of polypharmacy. Where conservative measures have failed, total knee replacement is indicated in patients with severe OA with extensive pain and deformity.[10]Importantly, some studies suggest obese patients report worse outcomes and quality of life after surgery, making the need for successful conservative measures all the more pressing.[11]

Intra-articular (IA) corticosteroids and IA hyaluronic acid (HA) were recommended as Level 1B/Level 2 treatments for knee OA, dependent upon comorbidity status, according to the 2019 OARSI guidelines.[9]Viscosupplementation is a nonpharmacological, minimally invasive treatment option for OA. Intra-articular administration of HA-based products was approved in 1997 by the Food Drug Administration (FDA), its aim being to supplement synovial fluid in the affected joint.[12] Intraarticular HAeffectively increases viscosity and reduces friction, thus achieving satisfactory pain reduction and improvement in function in OA.[13] HA is furthermore known to mitigate the activity of proinflammatory mediators and to stimulate fibroblast metabolism, with an analgesic, anti-inflammatory and chondroprotective effect at the joint level.[14]IBSA Pharmaceutical's Sinovial® H-L Hybrid is a formulation of stable, cooperative hybrid HA complexes produced via a patented thermal process from a combination of high (1100-1400 kDa) and low (80-100 kDa) molecular weight (MW)hyaluronans, without the need for 1,4-Butanediol diglycidyl ether (BDDE) or other chemical agents. Sinovial® H-L's unique characteristics include high HA concentration (64 mg in 2 ml), low viscosity with optimal tissue diffusion, and a duration comparable to weakly cross-linked gel.

Previous clinical experiences employing injectable hybrid HA in knee OA showed a statistically significant improvement in pain and function lasting more than six months,

with no serious adverse events.[15–17] These results were also observed in obese patients suffering from knee OA, with improvement in indices such as the International Knee Documentation Committee(IKDC) form, Knee injury and Osteoarthritis Outcome Score (KOOS) and pain.[18] Such study protocols generally involved 2 intra-articular injections administered 2 weeks apart. As a rule, the authors advocate for the use of a personalized, patient-guided approach, to minimize the number of invasive interventions each patient requires to obtain a comparable analgesic result.

In this study, overweight patients referred to our outpatient rehabilitation clinic for knee OA underwent a double-sitting intra-articular HA injection with hybrid HA complexes (Sinovial® H-L). The aim of the study was to assess whether viscosupplementation positively influenced pain, functionality and cardiocirculatory capacity in overweight and obese patients, and the impact of treatment on quality of life, body mass composition, and need for analgesic treatment.

2. Materials and Methods

This single-site, open-label, prospective trial included 37 individuals, selected between December 2020 and June 2021 among patients treated for symptomatic knee OA at the outpatient rehabilitation clinic of the Paolo Giaccone University Polyclinic in Palermo.

Inclusion criteria were: age> 45 years; BMI> 25; radiographic evidence of grade I and II knee OA according to the Kellgren-Lawrence classification; no previous infiltrative treatment in the previous 6 months; and written consent for participation in the study.

The study was conducted according to the ethical guidelines of the Helsinki declaration; information and data were handled in accordance with the Good Clinical Practice (GCP) guidelines. All participants signed an informed consent form at the time of the enrollment in order to collect clinical data.

Patients were assessed at two time points: at baseline (T0) and at the end of treatment (T1). As part of the initial assessment (T0), demographic informationand clinical data regarding disease state were collected. Of the 37 patients, 23 were female (62.2%) and 14were male (37.8%); patients were aged 45 to 75, with an average age of 63. With regard to clinical data, pain was assessed via the Numeric Pain Rating Scale (NRS), quality of life was self-reported via the 12-Item Short Form Survey (SF-12), while disease severity was evaluated via the Western Ontario and McMaster Universities Arthritis Index (WOMAC).[19] WOMAC is a 24-itemself-administered questionnaire developed for hip and knee OA, assessing the three sub-fields of pain, stiffness and physical function related activities of daily living. Patients were furthermore asked to report analgesic intake, expressed as the number of days a week analgesics were required to achieve pain control. Lastly, patient's cardiocirculatory capacity was assessed via a 6 Minute Walk Test (6MWT) in terms of distance traveled, and bioelectrical impedance analysis was performed to measure body fat and muscle mass percentages.

Following initial assessment, patients underwent ultrasound (US)-guided intra-articular injection of hybrid HA complexes (Sinovial® H-L) in the knee joint every 15 days. A sterile linear probe was employed for US joint inspection. The patient was positioned supine on the bed, knee slightly flexion or fully extended. Using a transverse approach, the joint was scanned with the US. A 21G needle was introduced using a lateral approach, 1-2 cm below the superior lateral margin of the patella, to perform an intra-articular injection. The passage of the needle through the capsule was facilitated by lateral subluxation of the patella. Having positioned the needle in the joint, the presence or absence of inflammatory synovial fluid was verified by aspiration. Excluding this, 2 ml of hybrid HA complexes (Sinovial® H-L) were then injected into the knee joint, verifying intra-articular positioning in real time via US (direct visualization of viscous fluid or air bubbles). Having removed the needle, knee mobilization in flexion-extension was per-

formed. Of the 37 patients, 16 (43.2%) underwent intra-articular HA injection on the left side, while 21 (56.8%) on the right side.

Patients were subsequently reassessed after 3 months (T1), and clinical data on disease state post-treatment was collected.

To evaluate the effect of HA viscosupplementation in overweight knee OA patients, we assessed the following primary variables for statistically significant differences pre- and post-treatment:

- pain severity, as assessed by NRS scale;
- disease severity, as assessed by the WOMAC Index;
- cardio-circulatory capacity, as assessed by distance walked in a 6MWT.

Three secondary variables were furthermore considered:

- quality of life, as assessed by SF-12;
- the percentage of fat and muscle mass, measured by bioelectrical impedance analysis;
- analgesic intake (days per week).

Statistical analyses were performed using R software (R Core Team, 2013). Depending on the type of variable, the following statistical tests were performed: t-test to compare means for quantitative variables, Mood's median test to compare medians for ordinal variables, and the test for two proportions. For NRS, WOMAC, SF-12, and analgesic intake, data is summarized using median values with their interquartile range; for all other variables, mean ± SD is employed. Results were considered statistically significant with a P-value (P)< 0.05.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee ofthe "Paolo Giaccone University Hospital" in Palermo, Italy (approval number: 11/2020 on 18/12/2020).

3. Results

Table 1 and Figure 1 show test results for the three primary variables. A statistically significant (P<0.01) improvement in cardiocirculatory capacity as measured by distance covered in a 6MWT was observed post-treatment, from a mean of 164.3 ± 52.9meters at T0 to a mean of 254.9 ± 52.6meters at T1. A significant reduction (P<0.01) in disease severity assessed by WOMAC was also observed at T1: median WOMAC was 56 before treatment, plummeting to 26 after viscosupplemention. Thirdly, a reduction in pain severity as assessed via NRS was recorded, from a mean of 8 at T1 to a mean of 5 at T1; this too was found to be statistically significant (P<0.01).

Table 1. Analyses on primary variables

	T0	T1	p-value
Distance	164.3 ± 52.9	254.9 ± 52.6	<0.01
WOMAC	56 (16)	26 (12)	<0.01
VAS	8 (1)	5 (1)	<0.01

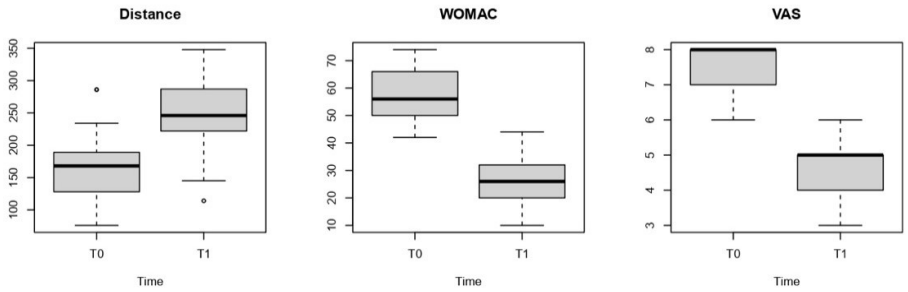

Figure 1. Boxplot analyses of primary variables.

Table 2 shows test results for the four secondary variables. Quality of life as self-reported via SF-12 displayed a statistically significant improvement (P<0.05), from a mean of 25 at T0 to a mean of 28 at T1. Regarding the results of bioelectrical impedance analysis, although a mild increase in the percentage of lean mass and a parallel decrease in fat mass was recorded, it was found not to be statistically significant (P=0.62 and 0.54, respectively). However, a statistically significant difference (P<0.01) was observed in the use of analgesics pre- and post-treatment. Indeed, before treatment almost half of patients took analgesics more than twice a week (48.6%), while after HA viscosupplementation no patients (0%) still required analgesics more than twice a week, and almost half of patients only took analgesics 1-2 times a week (43.2%). Interestingly, before treatment 0% of patients took no analgesics, while this percentage rocketed to 56.8% post-treatment.

Table 2. Analyses on secondaryvariables.

		T0	**T1**	P-value
SF-12		25 (4)	28 (8)	< 0.05
Muscle mass		36.1 ± 4.5	37.0 ± 3.8	0.62
Fat mass		35 ± 3.6	34.5 ± 3.6	0.54
Number of days taking analgesics	0	0 (0)	21 (56.8)	
	1-2	19 (51.4)	16 (43.2)	
	>2	18 (48.6)	0 (0)	

Regarding safety, the treatment was well tolerated, and no serious adverse effects were reported by the patients during the study period.

4. Discussion

The authors conducted a prospective trial to investigate the efficacy of HA viscosupplementation in overweight patients suffering from knee OA. Knee OA is one of the leading causes of disability worldwide, and the most common cause of difficulty in walking. This chronic condition has an inestimable impact on quality of life, especially in terms of pain and functional disability.[2]Overweight and obesity are well known to increase the risk of knee OA by mechanical load on weight-bearing joints and by fueling the proinflammatory milieu associated with metabolic syndrome. The functional limitation resulting from knee OA is a pejorative factor in such patients' already-limited physical activity level.

HA's powerful anti-inflammatory and analgesic potential has proven effective in several disease states including knee OA, in both normal- and overweight patients. In this study, we observed that overweight and obese patients who underwent intra-articular hybrid HA injection experienced a statistically significant 5-point reduction in pain severity on the NRS scale. Additionally, a 30-point reduction in disease severity on the WOMAC scale was observed: such scale includes parameters relative to pain, stiffness, and physi-

cal function as related to the ability to execute activities of daily living. Our results additionally show a statistically significant 3-point increase in quality of life as self-reported via SF-12. Lastly, we observed a reduction in patients' analgesic intake, a particularly crucial endpoint when considering the toxicity burden borne by traditional pharmacological treatment options for knee OA, namely NSAIDs. Such results therefore greatly support the role of hybrid HA viscosupplementation as a nonpharmacological approach to relieve pain, reduce disability and improve quality of life, and limit the risk of polypharmacy in overweight patients.

Individuals affected by OA suffer from more comorbidities and lead a more sedentary lifestyle as compared to healthy peers, and studies have observed a 20% higher age-adjusted mortality in such patients.[20]After viscosupplementation with hybrid HA, we observed a 54.9% improvement in patients' cardiocirculatory capacity as evaluated by 6MWT, supporting a role for such treatment in improving outcomes in overweight and obese patients suffering from knee OA.

Although a non-statistically significant increase in lean mass and a decrease in fat mass was observed post-treatment, significant variations were not to be expected after such a short follow-up period and after only one injection sitting. Furthermore, exercise therapy is a fundamental adjunct in knee OA treatment, and the level of physical activitypracticed by patients was not recorded as a therapeutic variable in this study. The authors however posit that, by combining a patient-oriented number of sittings with exercise therapy and prolonging observation over a longer follow-up period, the promising results in terms of pain reduction and disease severity will permit improvements in physical function in such overweight patients and – long term – in an improvement in lean to fat mass percentage ratios.

In conclusion, the present study is an important addition to the bulk of clinical evidence supporting the analgesic role of hybrid HA in the treatment of knee OA, and supporting its already-known anti-inflammatory and chondrogenic properties. Crucially, it also provides precious new data on the safety and efficacy of this noninvasive, nonpharmacological treatment option in overweight and obese patients. Lastly, the US-guided intra-articular injection technique presented above was found to be safe and well-tolerated by patients.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data used to support the findings of this study is available from the corresponding author upon request.

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Conflicts of Interest: The authors declare no conflict of interest.

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