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Evaluation Study

CLINICAL EFFICACY AND SAFETY OF NEOIAL HC (HYALURONIC ACID + COLLAGEN) FOR INTRA-ARTICULAR USE IN THE TREATMENT OF SEVERE KNEE OSTEOARTHRITIS

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ABSTRACT

Osteoarthritis (OA) is a common cause of pain and disability in adults, with at least 40% of individuals over 65 experiencing symptomatic OA of the hip or knee, according to the Osteoarthritis Research Society International (OARSI). Knee OA is the eleventh leading cause of years lived with disability, as reported by the World Health Organization. Current guidelines recommend using intra-articular injections of hyaluronic acid (HA) to treat OA, which can provide slow and prolonged pain relief for up to six months after the first injection. However, there is limited literature regarding the intra-articular use of isolated collagen or its combination with HA for treating knee OA. The present study (pre-market clinical trial) reports a clinically safe profile. It provides evidence of the efficacy of a viscosupplementation solution containing collagen type I, and HA obtained via bacterial fermentation (NEOIAL HC) in treating symptomatic knee OA. The primary endpoint was the safety and efficacy parameters of NEOIAL HC in intra-articular infiltration to treat severe knee osteoarthritis. The evaluation was conducted through subjective and objective clinical scores and reporting of adverse events. The secondary endpoint will be knee function 6 months after treatment. The preliminary findings suggest sustained benefits in pain and physical function from the cycle of collagen Type I and HA injections.

KEYWORDS: *hyaluronic acid, knee osteoarthritis, viscosupplementation, collagen*

INTRODUCTION

Osteoarthritis (OA) is a degenerative, chronic, and progressive joint disease with a multifactorial etiology and is most common in weight-bearing joints, such as knees (1). Currently, no treatment is available to stop OA progression, and joint replacement surgery is the only solution for severe cases. Non-operative treatment options include intra-articular drug injections into affected joints, which increase local bioavailability and reduce systemic exposure, adverse events (AEs), and costs compared with traditional pharmacologic therapies (2-4). Intra-articular injections of corticosteroids

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having anti-inflammatory properties (5) and of hyaluronic acid (HA), a viscosupplement with analgesic, anti-inflammatory, and potential disease-modifying properties (6, 7), have been widely used (2, 3).

In this context, a viscosupplementation solution containing collagen type I and HA obtained via bacterial fermentation (NEOIAL HC) was applied intraarticularly. Thanks to the interaction between collagen and HA, the local administration of the product into the joint space of patients with osteoarthritis is intended to restore articular cartilage homeostasis.

The medical device referred to in this work, called "Neoial HC (40 mg; HA sodium salt at 2% with two molecular weights 20% with pm at 400 kD and 80% between 1200 and 1500 kD t + collagen) contains HA, one of the most important structural polymers in the body. It is found as molecules on the cell surface and in the extracellular matrix of the skin, the vitreous body of the eye, joints, and muscles. HA is one of the body's most important structural and biological components and plays a fundamental role in viscosupplementation in cases of arthritic conditions. Hyaluronic acid is a biological polysaccharide (glycosaminoglycan) distributed in the extracellular matrix of most tissues; it is strongly hydrophilic and forms a viscous hydrated gel even at low concentrations. HA is a molecule that plays a key role in the joint; it is synthesized by the synovial cells and is responsible for the viscoelastic properties of the synovial fluid. It is one of the main components of the extracellular matrix. It also contributes to the lubrication mechanisms under load conditions and tries to protect the tissue from the penetration of inflammatory cells or lytic enzymes. In joints suffering from severe arthrosis, the inflammatory fluid is poor in elasticity and viscosity. Therefore, the intra-articular injection of HA, called viscosupplementation, restores the viscoelastic properties of the synovial fluid. The action of HA is anti-inflammatory and analgesic (8, 9).

In addition to HA, the alpha 1 R polypeptide chain of collagen reinforces the joint by providing structural strength to the cartilage matrix, deteriorated by the pathological processes in progress, whose scaffolding is formed by a dense interweaving of collagen fibers, thus acting as direct reinforcement of weakened and/or deteriorated collagen structures, improving mobility and helping to reduce painful symptoms affecting the joint. In the peri-articular route, collagen acts as a direct reinforcement to the damaged collagen framework of the peri-articular structures, such as tendons and / or ligaments, contributing to a reduction of pain and a faster functional recovery. Based on the preceding, it is possible to conclude that the main components of the medical device, hyaluronic acid with alpha 1 R polypeptide chain of collagen, exercise the expected mechanisms of action and that the medical device allows for the activities described. This gel presents a mechanical and rheological behavior close to the synovial fluid with both lubrication and shock damping effect, offering protection of the patient's cartilage. The first objective of this study was to determine the safety and efficacy parameters of NEOIAL HC (Hyaluronic acid (HA) + collagen) in the intra-articular infiltration for the treatment of severe knee osteoarthritis, which was evaluated through subjective and objective clinical evaluations while reporting the adverse events. The secondary endpoint is knee function at 6 and 12 months after treatment.

MATERIAL AND METHODS

This prospective monocentre, with open design, PMCF phase study, was conducted from November 2021 to March 2022. It was an open study where the patients were enrolled sequentially.

The study included 15 participants aged 50–80 who had been diagnosed with primary knee OA and met the inclusion criteria. Inclusion criteria required a diagnosis of knee OA with pain persisting for more than 3 months, BMI < 30, a VAS score greater than three based on the American College of Rheumatology Criteria, and Radiographic stage III and IV according to the Kellgren-Lawrence system as evidenced by recent x-ray, taken within the last six months (5). The exclusion criteria were: knee surgery, recent knee trauma, lower limb length discrepancy, BMI, intra-articular injection with steroids or HA, and/or current/regular treatments with steroids or non-steroidal anti-inflammatory drugs (NSAIDs) within the previous 3 months (acetaminophen was allowed), rheumatic pathologies (rheumatoid, psoriatic and reactive arthritis, arthritis associated with inflammatory bowel diseases, and spondylarthritis) endocrinopathies, malignancies and systemic diseases (renal, hepatic, cardiac, etc.).

Patients with severe knee osteoarthritis were enrolled in the clinical study and treated with 3 injections of 40 mg NEOIAL HC (HA sodium salt at 2% with two molecular weights 20% with pm at 400 kD and 80% between 1200 and 1500 kD t + collagen) at 1 week from each other, followed by a fourth infiltration of the same product at a distance of 1 month from the third. Patients underwent a baseline clinical evaluation and were monitored for adverse events after each single infiltration: follow-up evaluations were conducted at the end of treatment, 3- and 6-month post-treatment. Efficacy and safety were evaluated on the injection day and approximately 1 week, 1 month, and 3 and 6 months after follow-up. At each follow-up visit, a well-validated VAS score was used on which patients had to mark points on horizontal lines to represent their symptoms' perceptions (from no symptoms (0 mm) to extreme symptoms (100 mm)). The minimal

clinically significant difference (MCID) was defined as 20% or 10 mm of the baseline (10). The primary objective of the study was to evaluate the mean changes from baseline at Month 3 in the VAS Pain Subscale Score.

Moreover, the Knee Injury and Osteoarthritis Outcome Score (KOOS) will be used, and the changes in the functional index of Lequesne and the Womac score will be evaluated. (Timepoint: baseline, 3 months, 6 months). The KOOS is self-administered and assesses 5 domains: pain, symptoms, activities of daily living (ADL), sport and recreation function, and knee-related quality of life. This scale is used to evaluate knee function in terms of activities of daily living (ADL). The Lequesne index measures the severity of osteoarthritis for the knee (ISK). This can be used to assess the effectiveness of therapeutic interventions. Sections for index: (1) Pain or discomfort (2) Maximum distance walked (3) Activities of daily living. The index evaluates the overall assessment of the condition over the last four weeks.

Western Ontario McMaster Universities (WOMAC®) VA3.1 Osteoarthritis Scores allowed for a thorough evaluation of pain, stiffness, and knee function (24 questions through three subscales). The safety endpoints included the assessment of the occurrence of AEs and serious adverse events (SAEs) reported by patients' open questionnaires, related or not to the product or procedures, abnormal laboratory results in terms of hematology, serum chemistry, coagulation parameters, and clinically relevant findings at physical examination (including vital signs) during the entire study. All investigators assessed safety and efficacy data. The sample of patients was calculated considering both the investigators' clinical experiences and the statistical projection calculated on a clinical improvement in pain after administration of the product, which was estimated at 30%.

The statistical analysis examined the differences in mean changes from baseline in the VAS Pain Scale Score between the baseline and 3 and 6 months after the end of the treatment. Friedman's nonparametric test for paired samples determined differences, which were calculated using the exact method for small samples (a nonparametric test was preferred because the scores do not have a Gaussian distribution). In the case of significant results, a post hoc analysis for paired data with the correction for multiple comparisons was carried out.

Based on published data (10-13), the scenario of a mean baseline versus 3 months after treatment the difference of − 21 mm for the change in the VAS Pain scale from baseline at Month 3 with a standard deviation (SD) of 10.5 mm was assumed, which required 12 patients to reach a power of 80% to test the primary endpoint. With an estimated drop-out level of 10%, 15 patients were planned to be included.

The study was performed in accordance with the current version of the Declaration of Helsinki (Fortaleza, Brazil, October 2013) and the International Conference on Harmonization Good Clinical Practice Guideline. The study protocol, its amendments, and the patient information sheet were reviewed and approved by the appropriate independent Ethics Committees.

RESULTS

The participants enrolled were 15. In all 15 patients, and for all 4 administrations per patient performed, no adverse events were found due to the intra-articular infiltration of the product under study. The most often reported study treatment- or procedure-related AEs were mild and transient arthralgia and injection site pain. All the administrations performed had no pain or swelling during the infiltration procedure. The investigators concluded that there was no occurrence of serious AEs indicating safety concerns.

In the analysis, 14 patients were included to evaluate the efficacy. One patient was excluded due to an error in completing the personal data form, as he met an exclusion criterion (BMI >30). The mean age at enrolment was 71±7 years (range 54-80; median 73), and 12 of the patients were women (85.7%) and 2 male (14.3%). The mean BMI was 26.6±3.4 (range 21-30; median 28.5). Half of the patients were affected with knee OA Kellgren-Lawrence (K&L) grade II and half with K&L grade III.

The difference between baseline and control after 3 months and at the end of treatment in mean change from baseline in VAS Pain scale Score adjusted for baseline values was from 6.0±1.6 (6.0) to 4.4±1.7 (4.0) after 3 months and 3.6±1.2 (3.7) after 6 months, varying significantly (Overall p-value^ =0.002; Basal *vs* 3months p-value^ 0.047) (Table I, Fig. 1).

Table I. *Overall result at baseline and after 3 and 6 months.*

		Mean ±SD (Median)			Overall p-value^	Post hoc pairwise p-value*		
		bas	3m	6m		Bas *vs* 3m	Bas *vs* 6m	3m *vs* 6m
VAS		6.0±1.6 (6.0)	4.4±1.7 (4.0)	3.6±1.2 (3.7)	**0.002**	**0.047**	**0.001**	0.469
KOOS	Pain	57±13 (54)	71±23 (72)	76±15 (78)	**0.010**	0.267	**0.014**	0.771
	Symptoms	60±10 (63)	68±21 (68)	71±19 (67)	0.318			
	ADL	51±11 (54)	70±24 (76)	74±19 (83)	**0.011**	0.176	**0.010**	0.896
	Sport. Rec.	18±14 (15)	63±16 (65)	58±18 (58)	**<0.0005**	**<0.0005**	**<0.0005**	0.850
	QOL	31±8 (28)	61±17 (72)	66±16 (66)	**<0.0005**	**<0.0005**	**<0.0005**	0.896
WOMAC	A	9.4±2.3 (9.0)	4.9±4.6 (3.5)	4.6±4.3 (4.0)	**0.003**	**0.032**	**0.005**	0.978
	B	3.8±1.5 (4.0)	2.5±1.8 (2.0)	2.2±1.7 (2.0)	**0.004**	0.150	**0.018**	0.746
	C	34±10 (35)	19±14 (14)	16±13 (10)	**0.008**	0.176	**0.010**	0.851
LEQUESNE	1	4.7±1.6 (5.0)	3.1±2.6 (1.5)	2.1±1.7 (1.5)	**0.007**	0.108	**0.010**	0.558
	2	4.1±1.1 (4.0)	2.8±1.7 (2.5)	1.9±1.4 (2.0)	**<0.0005**	0.089	**0.001**	0.358
	3	5.1±1.1 (5.5)	2.8±2.1 (1.8)	2.1±1.4 (1.5)	**<0.0005**	0.054	**<0.0005**	0.392

^*Friedman nonparametric test* ***Bonferroni correction for multiple comparisons.***

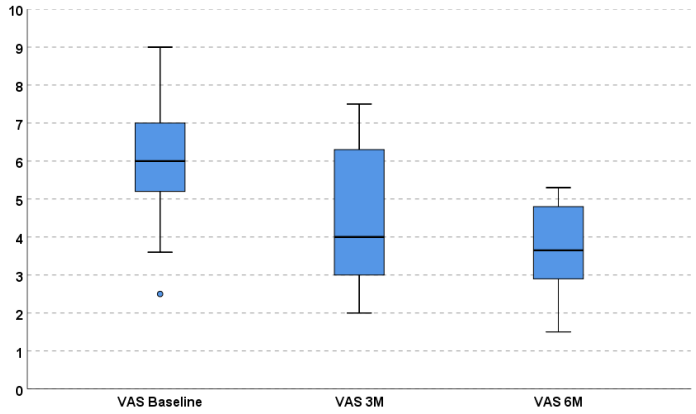

Fig. 1. *VAS score at baseline and after 3 and 6 months.*

The results of the KOOS questionnaire confirmed the data observed on the VAS scale. It is essential to consider that the score of the KOOS questionnaire related to pain (0-100 score) needs to be interpreted inversely to the score on the VAS scale (0-10 score). Indeed, the section's pain and physical function, sport, and free time correlate in a positive manner with VAS score, baseline 57±13 (median 54) *vs.* 3 months (71±23; median 72) and 6 months (76±15; median 78). Interestingly, the baseline values of the VAS scale, as well as the pain scale of the KOOS questionnaire (VAS score: 6.0±1.6 and KOOS pain score: 57±13), significantly correlate after six months of treatment (VAS score: 3.6±1.2 ($p>0.001$) and KOOS pain score: 76±15 ($p>0.014$). All other items of the KOOS questionnaire do not show significant changes after 3 and 6 months (Table I, Fig. 2).

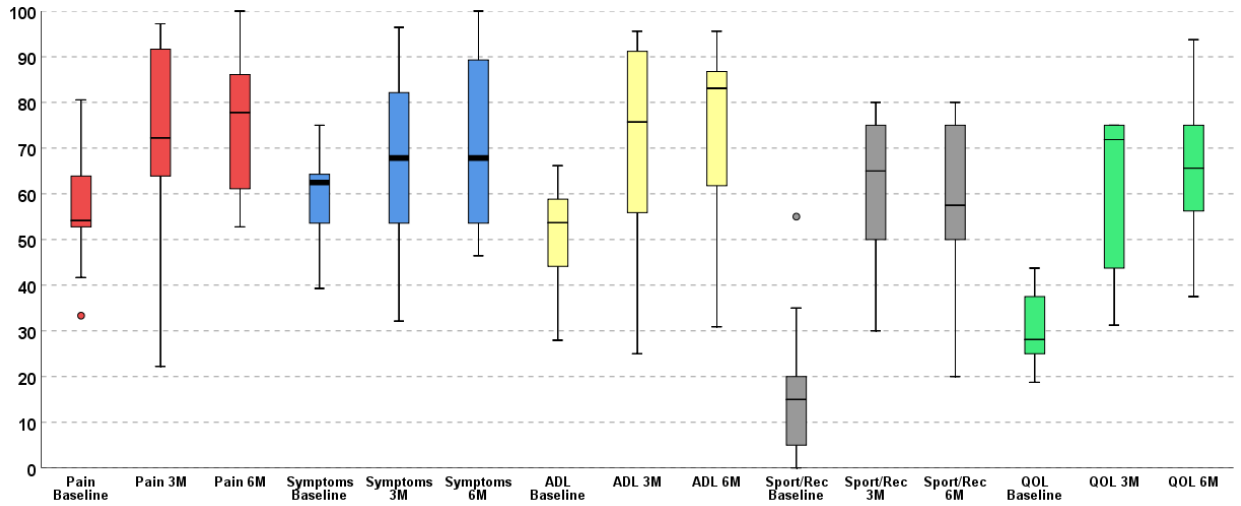

Fig. 2. *KOOS score items at baseline and after 3 and 6 months.*

The decrease in WOMAC pain subscale (A)at month 3 for the treatment group decreased from 9.4±2.3 (9.0) at baseline to 4.9±4.6 (3.5) after 3 months and 4.6±4.3 (4.0) at 6 months (Overall p-value^0.003; Basal *vs.* 3 months p=0.032; 3 months *vs.* 6 months p=0.005) (Tab.I, Fig. 3). The rigidity subscale (B) at months 3 for treatment group decreased from 3.8±1.5 (4.0) at baseline to 2.5±1.8 (2.0) after 3 months and 2.2±1.7 (2,0) at 6 months (Overall p-value^0.004; Basal *vs.* 3 months p=0.150; basal *vs* 6 months p=0.018) (Tab. I, Fig. 4). Daily living activity subscale (C)at months 3 for treatment group decreased from 34±10 (35) at baseline to 19±14 (14) after 3 months and 16±13 (10) at 6 months (Overall p-value^0.008; Basal *vs* 3 months p=0.176; basal *vs* 6 months p=0.010) (Tab. I, Fig. 5).

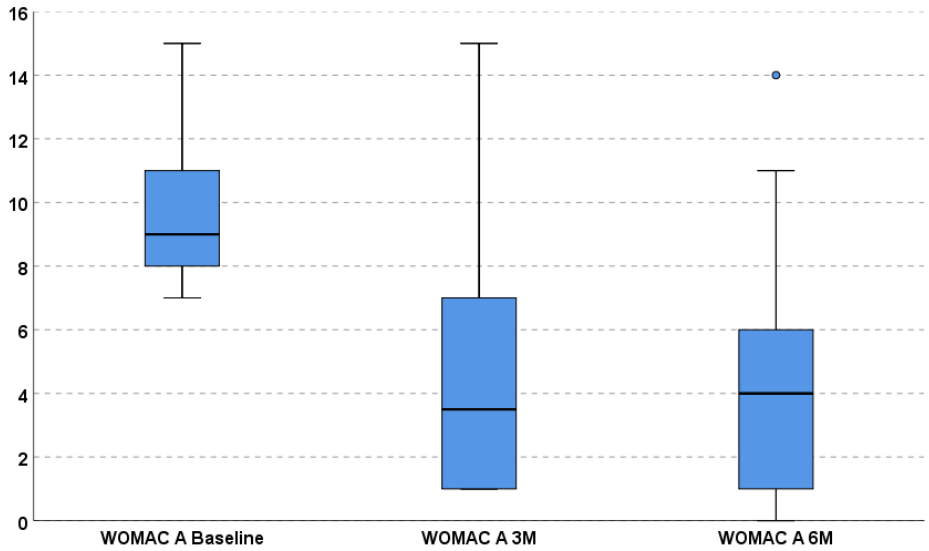

Fig. 3. *WOMAC subscore A items at baseline and after 3 and 6 months.*

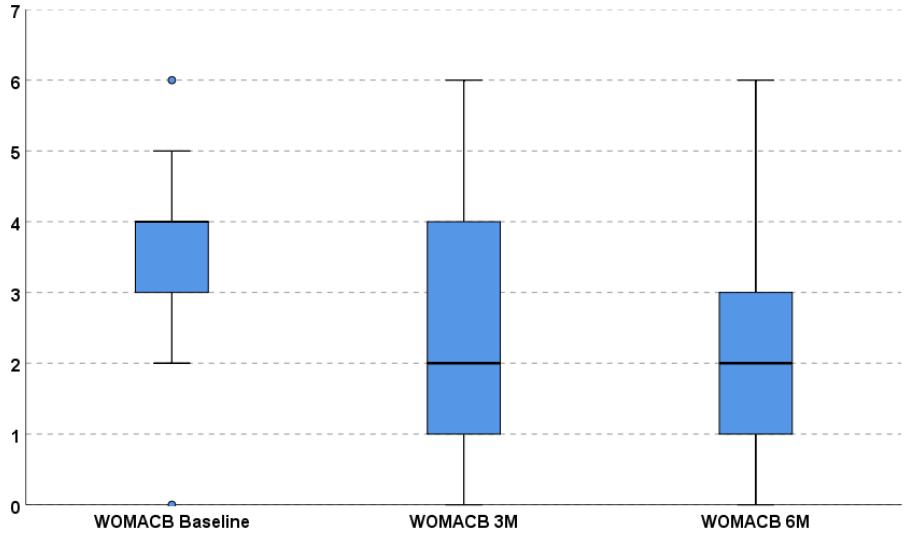

Fig. 4. *WOMAC subscore B items at baseline and after 3 and 6 months.*

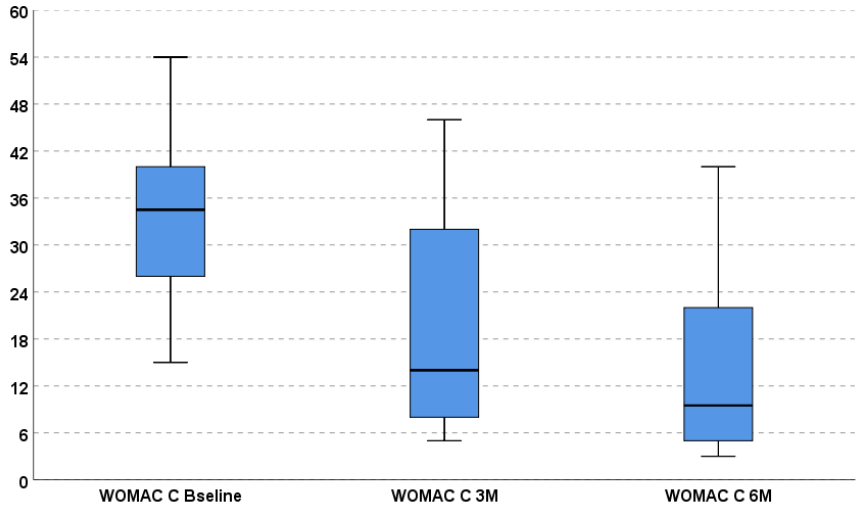

Fig. 5. *WOMAC subscore C items at baseline and after 3 and 6 months.*

The treated group experienced significant improvement over their baseline values in several domains of the Lequesne index (LI), predominantly belonging to physical functioning. LI is an objective tool to assess the study outcome of OA knee. LI contains parameters like Subscales of Pain and discomfort, Maximum Distance Walked Score, and Activity of Daily Life (ADL). This study-based findings of Lequesne parameters regarding subscales of Pain and discomfort, Activity of Daily Life (ADL) outcomes are highly significant. All subscales of LI decreased,

Pain and discomfort (Score 1) decreased from 4.7±1.6 (5.0) at baseline to 3.1±2.6 (1.5) after 3 months and 2.1±1.7 (1.5)at 6 months (Overall p-value^0.007; Basal *vs* 6 months p=0.010) (Tab. I, Fig. 6). Furthermore Maximum Distance Walked Score decreased from 4.1±1.1 (4.0) at baseline to 2.8±1.7 (2.5) after 3 months and 1.9±1.4 (2.0) at 6 months (Overall p-value^ <0.0005; Basal *vs* 6 months p=0.001) (Tab. I, Fig. 7).The Activity of Daily Life subscore (Score 3) decreased from 5.1±1.1 (5.5) at baseline to 2.8±2.1 (1.8) after 3 months and2.1±1.4 (1.5) at 6 months (Overall p-value^ <0.0005; Basal *vs* 6 months p=0.0005) (Tab. I, Fig. 8).

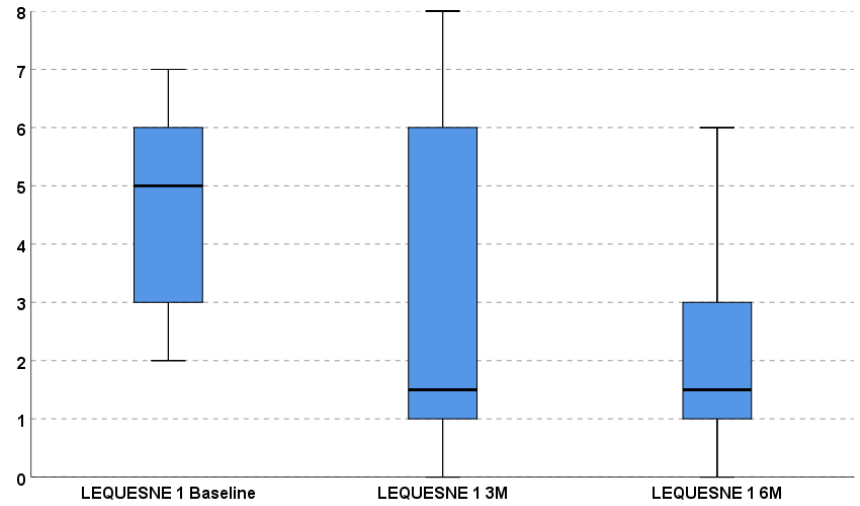

Fig. 6. *LEQUESNE subscore 1 items at baseline and after 3 and 6 months.*

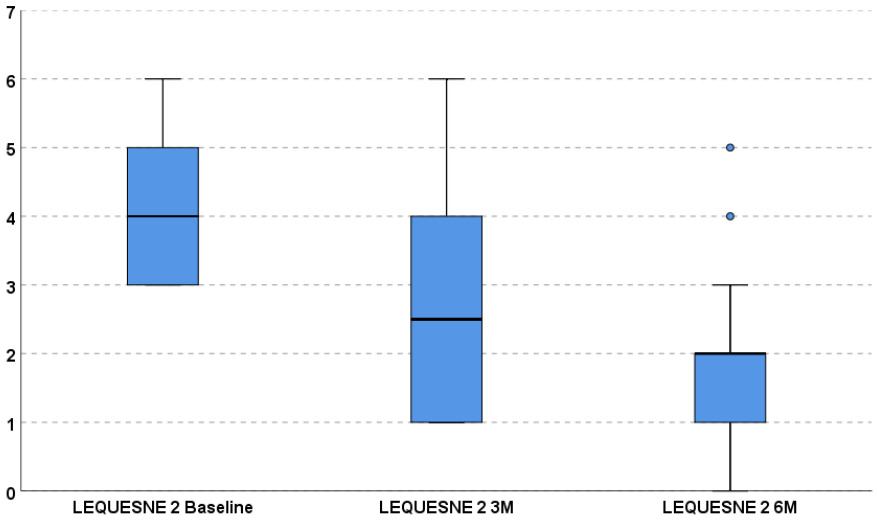

Fig. 7. *LEQUESNE subscore 2 items at baseline and after 3 and 6 months.*

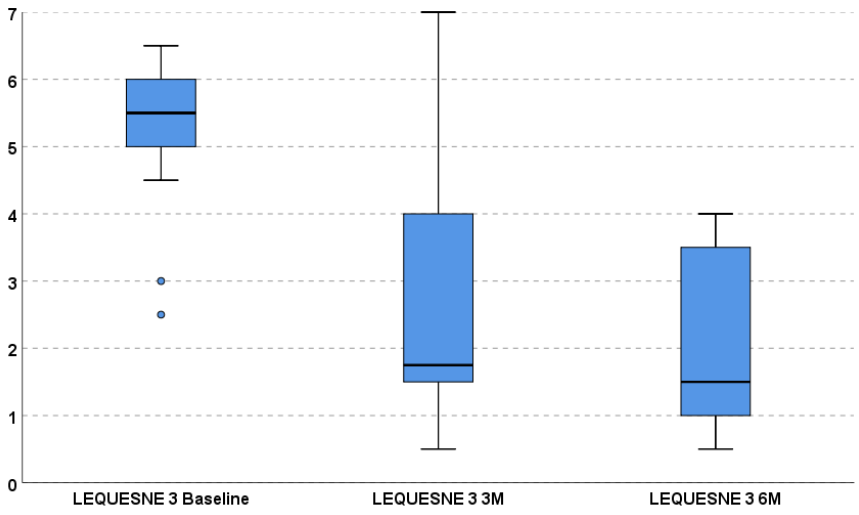

Fig. 8. *LEQUESNE subscore 3 items at baseline and after 3 and 6 months.*

No significant changes were recorded in the comparison data between baseline and 3 and between 3 months and 6 months in the subscores Maximum Distance Walked Score, Activity of Daily Life.

DISCUSSION

This study aimed to assess the safety and efficacy of NEOIAL HC for knee OA treatment over 6 months. Its statistical superiority over the baseline was observed, as demonstrated by the difference in adjusted mean changes in the VAS Pain Scale Score from baseline at 3 and 6 months post-injection, with a clinically relevant difference from baseline (>10mm, the MCID). Furthermore, the KOOS questionnaire showed a significant reduction in pain and physical function, sports, and free time items, which correlated with the VAS score results. Although this medical device induced more significant improvements than the reference in WOMAC Pain Subscale, Physical Function Subscale, and Total Scores at all time points, no differences met the statistical significance criteria.

Improvements in the WOMAC Physical Function Subscale from baseline were statistically more significant in the pooled patients who received the experimental product at 3 months post-injection. More specifically, age was found to directly correlate significantly with pain (Rho=0.808 $p<0.0005$) and inversely with WOMAC B (Rho=-0.582 p=0.029) and C (Rho=-0.558 p=0.038), LEQUESNE1 (Rho= -0.614 p=0.020) only in baseline values tendentially with LEQUESNE3.

BMI inversely correlated significantly with pain symptoms trending with ADL; directly correlated significantly with LEQUESNE1, tendentially with WOMAC A and C and LEQUESNE2, all only in baseline values. The influence of sex was not analyzable due to only 2 men, and there was no significant influence of KL or side on baseline or follow-up scores.

The more significant pain and function improvements observed with NEOIAL HC from baseline are encouraging since injections of HA-only were shown to result in pain relief, joint function, and quality of life improvements in knee OA patients, leading to the introduction of intra-articular HA injections in international recommendations. In our study, the potentially larger effect observed with NEOIAL HC from baseline may be explained by the fact that besides the natural HA polysaccharide obtained by bacterial fermentation, NEOIAL HC also contains active substances such as collagen type I with jellification and anti-inflammatory properties. This unique formulation has the potential to provide better lubrication and cartilage protection with a prolonged effect. Furthermore, the encouraging results observed in our study suggest that NEOIAL HC could be an effective treatment option for knee OA patients.

CONCLUSIONS

The present study showed a clinically good safety profile and provided preliminary evidence of NEOIAL HC's efficacy in treating symptomatic knee OA. The data analysis obtained at 3 months for the 14 patients enrolled in the study showed a significant improvement in the values in all 4 evaluation scales (VAS, KOOS Knee Survey, Womac Osteoarthritis Index, and Lequesne). This improvement was confirmed at 6 months, with a slight improvement noted for 4 out of 5 parameters on the KOOS evaluation board, 1 parameter of the WOMAC board, and all 3 parameters of the Lequesne index. The only figure that recorded a slight decrease was the "sports and recreational activities" parameter, which is not considered significant for the elderly sarcopenic patient population.

DECLARATIONS

Ethics approval and consent

This study was approved by the Ethics Committee “COMITATO ETICO DELLE PROVINCE DI CHIETI E PESCARA” (approval no. 12 of 06.05.2021). All participants provided written informed consent prior to enrolment in the study.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions

The individual contributions of authors to the manuscript are specified below: R.B. and D.B. collected clinical data, and A. P. and D.D. were major contributors to writing the manuscript. All authors read and approved the final manuscript.

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