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Review Article

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Combined Intra-Articular Peptide and Hyaluronic Acid: treating hip Osteoarthritis

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Abstract

Objectives: To evaluate the nine-month clinical effect and tolerability of a single intra-articular HA+peptide injection in patients with symptomatic hip osteoarthritis.

Methods: Forty-five consecutive adult patients (53 hips treated) received one 3 mL intra-articular injection of the proprietary HA+peptide device and were assessed at baseline and at 3, 6 and 9 months. Repeated-measures analyses compared score trajectories over time. Safety and global clinical impressions by both investigators and patients were recorded.

Results: The cohort (mean age 66.1 years) showed clinically meaningful and statistically significant reductions in disability and pain. Mean Lequesne index decreased from 10.9 at baseline to values representing a 40.2%, 53.4% and 49.4% improvement at 3, 6 and 9 months, respectively. Mean NPRS fell from 6.6 at baseline by 44.9%, 50.7% and 54.3% at the same time points. Mean total WOMAC improved by 39.6% at 3 months, 44.8% at 6 months and 53.6% at 9 months. Independent global assessments judged the outcome "optimal" in 32.8% of investigator ratings and 15.6% of patient self-assessments; no treatment-related adverse events were reported.

Conclusions: In this uncontrolled real-world sample a single HA+peptide intra-articular injection was associated with sustained improvements in pain and function for up to nine months and was well tolerated. The findings support further controlled evaluation to confirm efficacy and explore mechanisms.

Keywords: hip osteoarthritis; hyaluronic acid; peptides; Lequesne index; Numeric Pain Rating Scale; WOMAC.

Introduction

Hip osteoarthritis is a prevalent and disabling disease in the elderly population. Its incidence increases with age and body mass index (BMI), and its consequent functional impairments provoke an increase in healthcare expenditures. With increasing life-expectancy, there is a growing interest in treatment approaches which are symptom-relieving and which may delay or even make surgical intervention unnecessary. The stepwise clinical guideline for non-surgical management is as follows: first, non-pharmacological treatment including exercise, weight loss and patient education; second, use of drugs as an analgesic if the need arises; and third, consideration of intra-articular therapies—corticosteroids, hyaluronic acid or biologic agents, for a small subset of patients [1–5].

Hyaluronic acid (HA) is largely exploited as a viscosupplement to enhance the viscoelasticity of synovial fluid and to relieve pain and discomfort in a number of patients. However, its lubricating efficacy may diminish in joints with advanced cartilage fibrillation or structural damage [6]. Conversely, short peptides and peptide-based hydrogels can have biological activities by direct interaction with chondrocytes and synoviocytes, promoting lubrication of the joint surface and, possibly, by diminishing local inflammation and by modulating tissue repair processes, as previously demonstrated in cartilage tissue engineering applications [7]. A combination of HA and peptides within a single intra-articular formulation may therefore provide both immediate mechanical support and longer-term biological benefits, reducing friction and modulating inflammation within the joint environment [10].

With this aim in mind, a prospective, open-label, multicenter, real-life study was designed to evaluate whether a single injection of a patented hyaluronic acid–peptide formulation could produce long-lasting and clinically relevant improvement in pain and functional status in ambulatory adults with painful hip osteoarthritis.

Materials and Methods

An open-label, real-world observational study was conducted involving adults receiving outpatient treatment for symptomatic unilateral or bilateral hip osteoarthritis, regardless of gender. Participants were admitted at the investigators' discretion if they had experienced hip-related symptoms for at least three months—most commonly pain, muscle weakness, brief morning stiffness, crepitus, and limitations in activity. Recruitment was designed to reflect routine orthopedic outpatient practice, deliberately avoiding rigid inclusion and exclusion criteria to maximize generalizability. A prior history of allergy was not treated as an absolute exclusion, since previous knee-osteoarthritis studies suggest the hyaluronic acid+peptide formulation Chondroplus carries a very low risk of hypersensitivity.

Following a baseline assessment, all participants received a single, unilateral or bilateral (3 mL per joint) intra-articular injection of the proprietary HA + peptide formulation (Chondroplus™ medical device, Reganemed, Frankfurt, Germany). The safety and efficacy of the treatment were evaluated at baseline (pre-injection, T0) and at follow-up visits after three (T1), six (T2), and nine (T3) months. Assessments included the Lequesne index, the Numeric Pain Rating Scale (NPRS) for pain intensity, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and monitoring for any treatment-emergent adverse events.

Primary Endpoints

The primary endpoints were the mean changes from baseline in the Lequesne algofunctional index and the NPRS score at the three, six, and nine-month follow-up visits [13, 14]. The Lequesne index is a composite, investigator-administered, ten-question tool encompassing pain or discomfort, maximum walking distance, and difficulties with activities of daily living, originally developed and validated for hip and knee osteoarthritis assessment [8, 13]. The NPRS is an eleven-point (0 = no pain to 10 = worst possible pain) patient self-assessment scale measuring pain intensity, typically referring to pain experienced in the preceding 24 hours, a widely validated instrument for clinical pain assessment [9, 14].

Secondary Endpoints

The secondary endpoint was the mean change from baseline in the WOMAC index at all follow-up time points [15]. The WOMAC is a validated, three-dimensional, self-administered questionnaire assessing pain (5 questions), stiffness (2 questions), and physical function (17 questions). The Likert version, with each question scored from 0 to 4, was used, providing total subscale scores ranging from 0 to 20 for pain, 0 to 8 for stiffness, and 0 to 68 for physical function.

Additionally, both investigators and patients provided an independent, global assessment of the clinical evolution of the treated hip OA at the final visit. This categorical evaluation used the descriptors: "Worsened," "No change," "Slightly improved," "Improved," and "Optimal results."

Sample Size and Statistical Analysis

The required sample size was determined a priori using G*Power (version 3.1.4), following established methodological guidelines for power analysis [11]. Drawing on published results for similar knee-OA interventions, we conservatively assumed a 35% long-term improvement in the Lequesne index. With a two-tailed alpha of 0.05 and a target power of 0.90 ($\beta = 0.10$), this calculation indicated that at least 48 patients would be needed — yielding an achieved power slightly above 0.91 under these assumptions.

For inferential testing, we used repeated-measures one-way ANOVA to compare mean Lequesne, NPRS, and WOMAC scores across the four assessment points (T0, T1, T2, T3), with time as the within-subject factor. All tests were two-sided and significance was set at $p < 0.05$. Statistical analyses were performed using StatPlus.

Results

Baseline Demographics and Patient Disposition

Forty-five consecutive patients of both genders were included in the study, reflecting an unselected ambulatory treatment cohort. Twelve patients received injections in both hips, for a total of 53 treated hips. Demographic details are shown in Table 1: the mean age was 66.1 years (range 44–75) and 55.5% were female. Investigator-rated baseline severity is illustrated in Figure 1; besides pain, most participants reported meaningful limitations in mobility and daily activities. All 45 patients (53 hips) completed the nine-month follow-up, with only occasional missing assessment data.

Characteristic	Value (Mean (Range))
Age (years)	66.1 (44–75)
Gender, n (%)	
Female	25 (55.5%)
Male	20 (44.5%)
Weight (kg)	74.0 (55–91)
Height (cm)	158.3 (145–182)
Affected Hip, n (%)	
Right Hip	30 (56.6%)
Left Hip	23 (43.4%)
Bilateral Involvement (patients)	12 (26.7%)

Table 1: Baseline Demographics and Clinical Characteristics of the Study Cohort (n=45 patients, 53 hips).

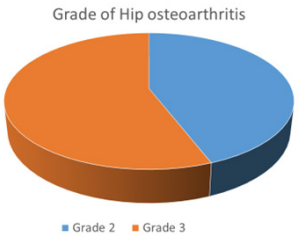

Figure 1: Baseline distribution of clinical severity grades among enrolled hip osteoarthritis patients (n=45 patients, 53 hips).

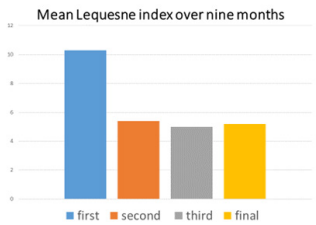

Figure 2: Evolution of mean Lequesne algofunctional index scores over nine months following a single intra-articular HA + peptide injection (n=53 hips; **p < 0.01 vs. baseline).

Primary Endpoint Results

The Lequesne Algofunctional Index score at baseline was 10.9 ± 4.5 in the entire cohort, indicative of severe to very severe symptoms. At each follow-up there was statistically significant improvement in scores ($p < 0.01$). The mean score dropped 40.2% at three months, bringing the group average into the moderate severity range. This improvement reached its maximum at 6 months, a 53.4% reduction, and was still large at 9 months, when the mean was 49.4% lower than the baseline. In general, participants transitioned to lower severity levels and the percentage considered as a high/moderate disability also reduced (Figure 3). NPRS — The mean pain score at baseline was 6.6 ± 1.4, with the sample experiencing pain of moderate/severe intensity. Pain intensity decreased significantly during all follow-ups ($p < 0.01$) by 44.9% at three months, 50.7% at six months and 54.3% at nine months. While 94% of the participants were initially experiencing moderate-to-severe pain, at nine months two-thirds (67%) considered their pain mild (0–3), and felt only occasional pain that hardly interfered with their daily activities (Figure 5).

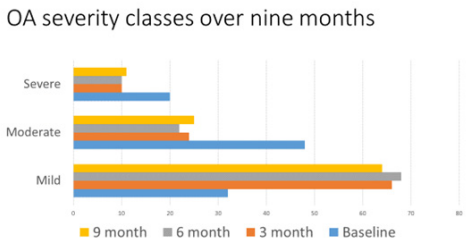

Figure 3: Shift in the distribution of Lequesne index severity categories from baseline to nine months post-injection (n=53 hips).

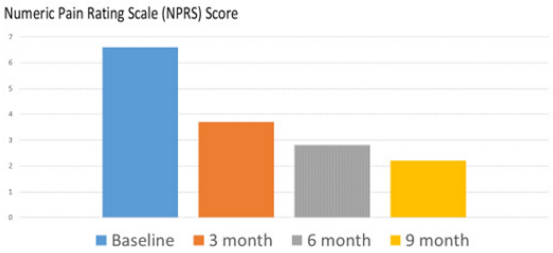

Figure 4. Changes in mean Numeric Pain Rating Scale (NPRS) scores over the nine-month study period after HA + peptide treatment (n=53 hips; **p < 0.01 vs. baseline).

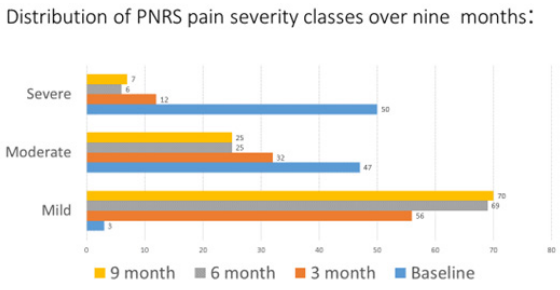

Figure 5: Reclassification of NPRS pain severity categories at baseline, three, six, and nine months following intra-articular injection (n=53 hips).

Secondary Endpoint Results

WOMAC Index: The mean total WOMAC score at baseline was 36.6 ± 18.8. A significant and progressive improvement was observed throughout the study ($p < 0.01$, Figure 6). The mean total score decreased by 39.6% at three months, 44.8% at six months, and 53.6% at the nine-month follow-up. This symptomatic improvement was reflected in the changing distribution of severity classes, as shown in Figure 7. The proportion of patients classified as having severe or moderate symptoms and disability (WOMAC scores >40 and 21–40, respectively) fell progressively from 77% at baseline to 46% at three months and further to 33% by the nine-month visit.

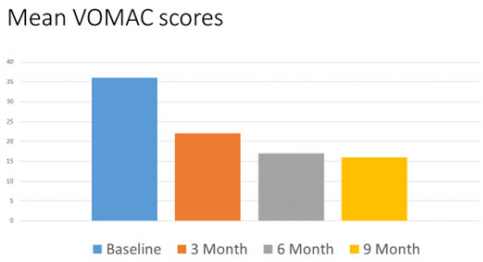

Figure 6: Mean total WOMAC score improvements over nine months after a single HA + peptide injection (n=53 hips; **p < 0.01 vs. baseline).

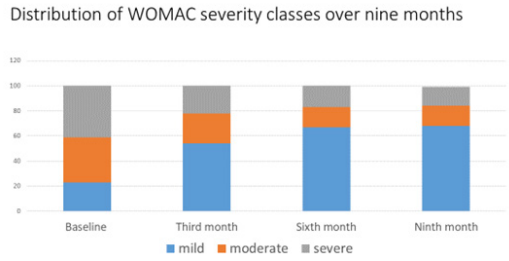

Figure 7: Longitudinal distribution of WOMAC severity classes at baseline and at each follow-up visit post-treatment (n=53 hips).

Global Clinical Assessment and Safety

At the final nine-month visit, both investigators and patients provided an independent, global assessment of the treatment outcome (Table 2). No patients or investigators reported a worsening of the condition. Notably, 32.8% of investigators rated the outcome as "Optimal results," while 15.6% of patients provided the same rating. The majority of both investigators (56.3%) and patients (73.5%) rated the outcome as at least "Improved." Throughout the nine-month study period, no treatment-related side effects or adverse events were reported.

Evaluation	Investigator's Assessment n (%)	Patient's Self-Assessment n (%)
Worsened	0 (0%)	0 (0%)
No change	5 (10.9%)	5 (10.9%)
Slightly improved	13 (28.1%)	18 (39.1%)
Improved	14 (30.5%)	20 (43.5%)
Optimal results	13 (28.3%)	2 (4.3%)
Total Patients	**45 (100%)**	**45 (100%)**

Table 2: Global Assessment of Clinical Outcome at Nine Months Post-Injection.

Discussion

The findings of this real-world, nine-month observational study lend substantial support to the growing body of evidence suggesting that combining peptides with hyaluronic acid in a single intra-articular injection offers significant therapeutic benefits for patients with hip osteoarthritis [18]. The data demonstrate a rapid, sustained, and clinically meaningful improvement in pain, function, and patient global assessment following a single injection. The magnitude of improvement observed across all three validated outcome measures (Lequesne, NPRS, and WOMAC) consistently exceeded the pre-defined clinically relevant threshold of 35% improvement from baseline, with benefits persisting throughout the nine-month follow-up period.

The basis for the use of these materials in combination is their different but complementary mode of action. Hyaluronic acid (HA) has the ability to restore the viscosity and viscoelasticity of synovial fluid, which may contribute to restoration of shock absorption and lubrication, especially during low-impact activities. However, it may not be as effective in the joints that have a high degree of cartilage fibrillation or damage structurally [3, 19, 20]. Peptides, on the other hand, also play a role in boundary lubrication by interacting with open or damaged cartilage surfaces and interacting with each other forming a relatively thin protective layer. This layer contributes to reduce direct surface contact and friction during the joint loading—also at low velocity motion [3, 10]. Together, HA provides bulk fluid viscosity, peptide protects the articular surface. This dual mode of action may explain the rapid and long-lasting symptom relief in the present investigation as well as the concomitant reduction of secondary inflammation due to friction, a key factor in OA pathogenesis [10, 12, 17].

This level of improvement is remarkable– 54.3% reduction in pain (NPRS) and 53.6% reduction in the total WOMAC score at month 9. These findings compare favorably with reported results of other intra-articular agents and suggest the exciting prospect of a disease modification, as opposed to merely symptomatic relief [5, 19]. The prolonged nine-month salient benefit being achieved in a single injection may reflect a long term therapeutic gain and might be in part attributed to the peptide moiety's ability to form a biomechanical and biochemical environment that shields chondrocytes and synoviocytes from relentless mechano-inflammatory stress [10, 17].

Nevertheless, a few caveats are in order for these encouraging findings. The open-label, single-arm, non-randomized design of the study may introduce bias, regression to the mean and placebo effect. Furthermore, in the absence of a comparator arm, either placebo or HA, it is not possible to dissociate or evaluate the incremental effect of the peptide. In spite of the validated instruments, most of primary endpoints were subjective (patient-reported or investigator-assessed), and they may be insufficient to detect objectively any structural alterations of the joint. Inclusion of a small number of bilaterally treated patients, which might have resulted in data correlation, but it is unlikely to be a substantial effect to the overall findings.

A key objective for this investigation was to obtain safety information under clinical practice conditions. Hence, the efficacy findings, albeit positive, are to be considered as hypothesis-generating and supportive of previous work, rather than as conclusive proof of disease modification. Ultimately, to assess the superiority, long-term effect, and cost-effectiveness of this combined therapeutic strategy, appropriately designed randomized controlled trials, which include an active comparator and a longer period of follow-up, are warranted.

Conclusions

These findings add to the growing body of evidence supporting the real-world benefits of combining peptides and hyaluronic acid in a single intra-articular medical device for hip osteoarthritis. A single injection was associated with clinically meaningful and sustained improvements lasting up to nine months. The rheological and anti-friction properties of the peptide component likely contribute to this durable therapeutic effect.

Institutional Review Board Statement

All procedures performed were in accordance with the approved regulatory indications for the intra-articular use of the peptide/HA combination as detailed in the Patient Information Leaflet and complied with relevant regulations (Article 16 of Malta Legislative Decree 137/2022). These provisions allowed the study to proceed as a post-market clinical follow-up activity without requiring formal, separate Institutional Review Board approval.

Informed Consent Statement

All participating patients, who sought specialist care for hip OA-related symptoms, provided written informed consent. This consent encompassed comprehensive information about the procedure, its anticipated benefits, and potential risks. Patients also explicitly consented to the anonymous publication of their aggregated clinical data and outcomes for research purposes.

Conflict of Interest

The authors declare no conflicts of interest.

Funding Statement

This research received no external funding.

Ethical Approval: All procedures performed were in accordance with the approved regulatory indications for the intra-articular use of the peptide/HA combination as detailed in the Patient Information Leaflet and complied with relevant regulations (Article 16 of Malta Legislative Decree 137/2022).

Informed Consent

Written informed consent was obtained from all participants.

Data Availability Statement

The data supporting this study are available from the corresponding author upon reasonable request.

Author Contributions

M.G.F. and B.A. contributed equally to this work, including study design, data collection, analysis, manuscript writing, and final approval.

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