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ORIGINAL

Eficacia de la inyección intrarticular única de ácido hialurónico con una alta concentración para la osteoartritis de rodilla. 12 meses de seguimiento

Efficiency of single intraarticular injection with highly concentrated hyaluronic acid for knee osteoarthritis. 12 months follow-up

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RESUMEN:

Introducción: La osteoartritis (OA) es una enfermedad articular degenerativa que afecta con frecuencia a las rodillas. En España afecta a una parte importante de la población, siendo especialmente frecuente entre los adultos mayores de 40 años. Las inyecciones intrarticulares de ácido hialurónico pretenden complementar el ácido hialurónico natural del líquido articular, que puede estar disminuido en la osteoartritis, mejorando así la lubricación, reduciendo el dolor y mejorando potencialmente la movilidad articular.

Pacientes y método: El objeto del estudio ha sido comprobar la eficacia terapéutica de la infiltración única de ácido hialurónico (Biolevox™ HA ONE, 2,5 %, 4,8 ml) en OA de rodilla. Este estudio abierto, multicéntrico, no comparativo y de práctica clínica real se enfocó en medir la reducción del dolor y la mejora en la función física de los pacientes tras la administración del tratamiento.

Resultados: Se incluyeron 148 pacientes (85 mujeres y 63 hombres) de entre 32 y 82 años, de los cuales 140 acabaron el seguimiento de 1 año de forma ambulatoria, todos ellos afectados de OA de rodilla con una intensidad de dolor al inicio > 4 en una escala analógica visual (VAS) de 10. La medida de resultados del objetivo primario fue un cambio en la intensidad del dolor evaluado mediante VAS a los 3, 6 y 12 meses después del tratamiento. Las medidas secundarias de resultados fueron el resultado de subescalas de test Western Ontario McMaster Universities Osteoarthritis Index (WOMAC): Womac rigidez (0-8) y Womac capacidad funcional (0-68). Se observó una

reducción estadísticamente significativa del dolor y una mejora significativa de la función física en cada visita de seguimiento posterior al tratamiento, que comenzó a los 3 meses y se mantuvo hasta los 12 meses en comparación con los niveles iniciales.

Discusión: Nuestros resultados indican que una única inyección intraarticular de ácido hialurónico ofrece una mejora clínica significativa en pacientes con OA de rodilla sin efectos secundarios relevantes. El beneficio fue significativamente estable durante los 12 meses de seguimiento.

ABSTRACT:

Introduction: Osteoarthritis (OA) is a degenerative joint disease that frequently affects the knees. In Spain, OA impacts a significant portion of the population, with knee osteoarthritis being particularly common among adults over 40. Intra-articular hyaluronic acid injections aim to supplement the natural hyaluronic acid in joint fluid, which may be depleted in OA, thereby enhancing lubrication, reducing pain, and potentially improving joint mobility.

Patients and method: The aim of this study open, multi-center, non-comparative and clinical real practice was to check the therapeutic efficacy of hyaluronic acid (Biolevox™ HA ONE, 2.5 %, 4.8 mL) in knee OA.

Results: A total number of 148 patients (85 women and 63 men) aged between 32 and 82 years were included, of whom 140 completed the 1-year follow-up. All suffered from knee OA with an intensity of pain at baseline > 4 on a visual analogue scale (VAS). The primary endpoint outcome measure was a change in pain intensity assessed by VAS at 3, 6, and 12months after treatment. Secondary outcome measures were Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) subscores: WOMAC stiffness (0-8) and WOMAC functional capacity (0-68). Statistically significant pain reduction and significant improvement in physical function were observed at each follow-up visit post-treatment, beginning at 3 months and sustained through 12 months after treatment compared to baseline levels.

Discussion: Our results indicate that intra-articular injection of highly concentrated hyaluronic acid offers a significant clinical improvement in patients with knee OA without relevant side effects. The improvement remained consistently stable throughout the 12-month follow-up period.

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Palabras clave: *Ácido hialurónico, Biolevox™ HA ONE, osteoartritis, rodilla, inyección intrarticular.*

Key words: *Hyaluronic acid, Biolevox™, osteoarthritis, knee, intra-articular injection.*

Introduction

Osteoarthritis (OA) is a degenerative joint disease that frequently affects the knees, as they are joints that must fully bear the body's weight (1). In Spain, it is estimated that nearly 5 million adults have been diagnosed with this condition (2). OA is one of the main causes of functional disability (3). Patients experience not only persistent pain, stiffness, and limited mobility, but also a significant decline in quality of life (3). Moreover, OA poses a substantial economic burden, with an estimated cost of 0.5% of the country's gross domestic product (4).

OA is a complex disease involving multiple biological factors, including genetic, hormonal, and age-related alterations (5). The term 'chondrosenescence' is used to describe the age-related deterioration of chondrocyte function. Therapeutic approaches are limited due to this complex pathophysiology. According to the guidelines from the Osteoarthritis Research Society International (OARSI), a core set of evidence-based therapies has been established to reduce the number of patients requiring knee arthroplasty(6). These include non-pharmacological approaches such as patient education, exercise, and rehabilitation. Pharmacological approaches range from mild analgesics to opioids. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed agents for OA (7), although their long-term use is associated with serious side effects. Intra-articular injections of hyaluronic acid (HA) are clinically used to mitigate the reduced function of depolymerized endogenous HA in OA patients (8). Although exogenous HA does not fully restore all functions of endogenous HA in synovial fluid, it can provide satisfactory pain relief through several mechanisms, including stimulation of proteoglycan and/or glucosamine synthesis, anti-inflammatory effects, and maintenance of viscoelasticity (9). Some studies report an overall beneficial effect, while others report only modest improvements (10).

Hyaluronic Acid for OA Treatment

HA can be administered to OA patients either orally or via intra-articular injection. There are various formulations of injectable HA. This variability is one of the main sources of bias in many studies and is a reason why even well-designed research articles may lack conclusive evidence.

For this study, we used a sterile, non-pyrogenic hydrogel made from highly purified sodium hyaluronate obtained via bacterial fermentation. It is indicated for the treatment of arthritic joint pain, conservative treatment of meniscal injuries in the knee, and for improving joint mobility by increasing synovial fluid viscoelasticity. The product's commercial name is Biolevox™ HA ONE (Biovico sp. z o.o., Poland).

When HA is injected locally—as opposed to oral treatment—the full HA molecule is introduced directly into the intra-synovial joint cavity, offering various mechanisms for symptom relief. These include improved synthesis of extracellular matrix proteins, modulation of inflammatory mediators to reduce degradation, reduced lymphocyte motility, and maintenance of cartilage thickness, area, and surface smoothness. Intra-articular HA treatment is effective in OA based on its effects on pain, function, and overall patient assessment. In terms of safety, it has also been shown to be free from negative side effects. A meta-analysis of 26 clinical trials concluded that HA injection should be considered the best conservative treatment option for hip OA, offering substantial pain relief and functional improvement.

Objective

To evaluate the therapeutic efficacy of hyaluronic acid in knee osteoarthritis (OA) under real clinical conditions.

Study Design

Multicenter, open-label, non-comparative clinical trial conducted under real clinical practice conditions between January 2019 and March 2024.

Materials and Methods

Patients who met the inclusion criteria and agreed to participate in the study were included.

Inclusion criteria: patients diagnosed with knee OA by clinical and radiological methods with a pain intensity >4 on a 10-point visual analogue scale (VAS).

Exclusion criteria: prior surgery, excessive deformities, inflammatory knee arthritis, coagulation disorders, infectious, cardiovascular, immune or oncological disorders, and pregnancy.

A total of 148 patients (85 women and 63 men), aged between 32 and 82, were included from participating hospitals, of whom 140 completed the 1-year follow-up as outpatients. All received a single intra-articular injection (IA) of 4.8 mL of a viscoelastic solution containing 120 mg of native HA.

Unlike products designed for multiple injections (usually 3 to 5 injections at 1-week intervals), single-injection products are favored for their specific advantages, such as fewer doctor visits and less invasive interventions, thereby reducing associated risks.

Injections were always administered under ultrasound guidance with the probe placed transversely over the femur. The needle was inserted from lateral to medial, ensuring continuous visualization of the needle's advancement and its intra-articular placement at the suprapatellar recess (Figure 1.).

The primary outcome measure was the change in pain intensity assessed via VAS at 3, 6, and 12 months post-treatment. Secondary outcomes included the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC): stiffness (0–8, 2 items) and physical function (0–68, 17 items) using a 5-level Likert scale.

Statistical analysis was performed using SPSS for Windows, version 19.0. The aim was to compare central tendency variables (means and standard deviation) over time and between measurements. Student's t-test and ANOVA were used, considering $p < 0.05$ as statistically significant.

Evaluations were conducted by the physicians who administered the treatment.

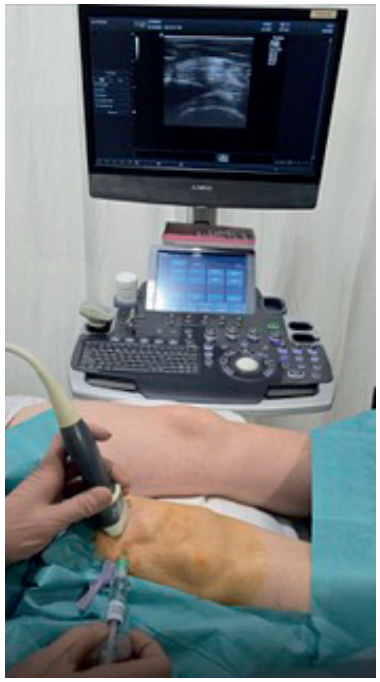

Figure 1. Ultrasound-Guided In-Plane Administration of Hyaluronic Acid in the Knee.

Results

All patients showed significant improvement in VAS, WOMAC stiffness, and WOMAC physical function scores from baseline through the 6- and 12-month follow-ups ($p < 0.05$). At 12 months, the VAS and WOMAC stiffness scores increased slightly but not significantly compared to the 6-month results ($p > 0.05$) (Table 1 and 2, Figure 2).

As shown in Table I, there were statistically significant improvements in pain reduction, quality of life, and functional recovery.

Discussion

The objective of this study is to present retrospective results from our clinical practice in treating knee OA with intra-articular hyaluronic acid (HA) injections. Most of the published literature has focused on HA use in knee OA treatment.

Efficacy and mechanisms of action of hyaluronic acid in knee osteoarthritis

Knee OA treatment with HA has been widely studied due to its viscoelastic and anti-inflammatory properties, which enhance joint function and reduce pain. This article evaluates the effectiveness of HA in preserving articular cartilage and modulating inflammation in the affected joint in real-world clinical practice.

Intra-articular administration of HA aims to preserve cartilage, alleviate pain symptoms, and act as a temporary substitute for synovial fluid. It has proven effective in slowing progressive cartilage deterioration (10).

Cartilage Preservation and Anti-Inflammatory Effects

The HA contributes to the homeostasis of articular cartilage by enhancing the viscoelasticity of synovial fluid, thereby reducing joint friction and wear. Moreover, the chemical structure of HA allows it to persist within the joint for extended periods, providing continuous cushioning effects that absorb impact and minimize cartilage degradation (11). These characteristics are particularly advantageous for patients with osteoarthritis (OA), where cartilage degeneration is a primary concern.

From an anti-inflammatory perspective, HA modulates the inflammatory response by binding to specific receptors on synoviocytes and chondrocytes, such as the CD44 receptor. This interaction triggers intracellular signaling pathways that promote chondrocyte survival and extracellular matrix synthesis, which are essential for cartilage repair and regeneration (12). Additionally, HA has been shown to downregulate the expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), key mediators in OA pathogenesis (13).

Due to its chemical structure, HA remains in the joint for prolonged periods, maintaining its three-dimensional network, which enables sustained impact absorption even under repeated mechanical stress. Furthermore, its high lubricating capacity reduces friction between joint surfaces, promoting cartilage healing through the biological properties of the polymer itself. This results in improved joint function. These attributes make HA particularly suitable for OA patients, as it has been demonstrated to slow cartilage damage progression, enhance joint functionality, and alleviate pain symptoms (14).

The mechanism of action of HA is twofold: first, it exerts a biological anti-inflammatory effect and mitigates cartilage degradation progression through its capacity to bind to specific synoviocyte and chondrocyte receptors, modulating the release of inflammatory mediators. Second, it serves as a potent lubricant and shock absorber due to the viscoelastic properties of the biopolymer, functioning as a three-dimensional protective cushion (15).

Table 1. Descriptive Data (Mean ± SD). Results for Pain (VAS) and Functional Capacity (WOMAC).

	Baseline	3 months	6 months	12 months
VAS	5,66 ± 1,12	3,23 ± 1,37	2,38 ± 1,33	3,12 ± 1,54
WOMAC-stiffness	4,52 ± 1,42	2,84 ± 1,58	2,65 ± 1,15	2,91 ± 1,02
WOMAC-functional capacity	36,54 ± 6,12	24,2 ± 7,81	21,23 ± 7,34	20,31 ± 6,52

Table 2. Mean Differences ± SD. Results for Pain (VAS) and Functional Capacity (WOMAC) in Each Group.

	Baseline-3 months	Baseline-6 months	Baseline-12 months
VAS	2,43 ± 1,95	3,28 ± 1,58	2,54 ± 1,54
***p*-value**	< 0,01	< 0,01	< 0,01
WOMAC-rigidez	1,68 ± 0,96	1,84 ± 0,74	1,61 ± 1,17
***p*-value**	< 0,001	< 0,001	< 0,001
WOMAC-functional capacity	12,34 ± 2,74	15,31 ± 3,85	16,23 ± 4,58
***p*-value**	< 0,01	< 0,01	< 0,01

HA interacts with chondrocyte receptors, particularly CD44, which is located on the surface of these cells. The binding of HA to CD44 triggers a cascade of intracellular signals that enhance chondrocyte proliferation and survival, as well as extracellular matrix synthesis. This process is crucial for maintaining cartilage integrity, as it contributes to the repair and regeneration of the cartilage matrix, thereby slowing the progression of structural damage characteristic of OA (12).

Beyond its structural effects, HA plays a significant role in modulating inflammatory cytokines, which are key factors in OA pathogenesis. Various studies have demonstrated that HA can downregulate the expression of pro-inflammatory cytokines such as TNF-α and IL-1β. These cytokines are involved in cartilage degradation and the amplification of the inflammatory response within the joint. By inhibiting the activity of these molecules, HA contributes to the reduction of synovial inflammation, leading to pain relief and reduced joint deterioration (13).

The viscoelastic properties of HA allow it to function as a natural shock absorber within the joint. This impact-absorbing and friction-reducing capacity is fundamental not only for immediate pain relief but also for long-term cartilage protection. HA increases synovial fluid viscosity, enhancing joint lubrication and minimizing mechanical wear on cartilage. This cushioning effect reduces damage caused by repetitive loading and compressive forces exerted on the joint, fostering a healthier environment for cartilage maintenance (14).

Although the use of HA injections for knee and hip OA treatment is gaining popularity, patient age remains a relevant factor. In our clinical practice, we have observed that this treatment can be effective across a broad age range, suggesting its applicability in diverse patient populations. While HA injections are initially more costly than corticosteroid injections, they may be more cost-effective in the long term (15). Additionally, HA therapy is widely regarded as a cost-efficient intervention.

One of the primary controversies in this field pertains to the optimal timing and duration of HA injections and whether these factors influence treatment efficacy and sustainability. Some studies have compared intra-articular injections of Hylan G-F 20 (a type of HA) with saline solutions in OA patients, observing that optimal pain relief was achieved in the HA-treated group starting from the third week, while functional improvement became evident by the eighth week (16).

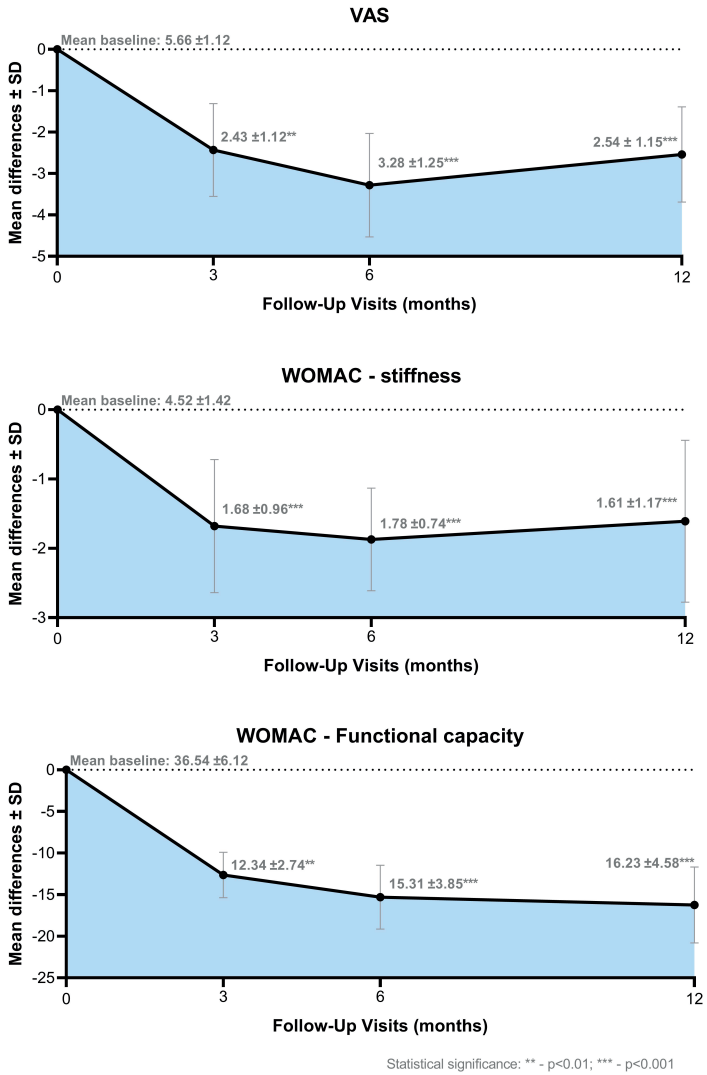

Figure 2. Mean Differences ± SD. Results for Pain (VAS) and Functional Capacity (WOMAC) in Each Group.

A 2003 study (16) demonstrated that three HA injections were safe and effective in providing rapid pain relief for patients with mild to moderate hip OA. Furthermore, HA injections were associated with a 48.2% reduction in nonsteroidal anti-inflammatory drug (NSAID) consumption by the third month compared to baseline values (17-20). Overall, studies conclude that HA injections should be considered among the best conservative treatment options for knee OA, as they provide substantial pain relief and improved joint function (21).

Comparison with other therapies and cost-effectiveness considerations

A comparison of HA with other treatments, such as corticosteroids and platelet-rich plasma (PRP), reveals significant advantages, particularly in terms of side effects and long-term benefits. While corticosteroids can provide faster pain relief, prolonged use is associated with considerable adverse effects, including the potential acceleration of cartilage degeneration (22). In contrast, PRP has shown promise in cartilage regeneration; however, evidence of its efficacy remains variable, and its cost may be prohibitive for some patients. HA is particularly cost-effective in the long term, especially considering its ability to delay more invasive interventions such as arthroplasty. Recent studies suggest that HA not only improves OA symptoms but also represents a cost-effective approach for the long-term management of the disease (23).

Our results align with previous studies documenting the effectiveness of HA injections in reducing pain and improving function in knee OA patients (18). However, the consistent improvements observed over 12 months suggest that the use of concentrated, single-dose formulations could optimize patient adherence and experience by reducing the need for repeated medical interventions. This finding is particularly relevant in real-world clinical settings, where frequent visits may pose logistical challenges for patients (24).

In our study, all patients exhibited improvements in the VAS and WOMAC scores from baseline to 12 months post-treatment. However, it is important to note that a key limitation of our study is the absence of a placebo group and the lack of comparisons with other HA formulations. Nonetheless, these results reflect routine clinical practice, supporting the adopted approach.

Limitations and future research directions

A notable limitation of our study is the lack of a control group or placebo group to directly compare HA with other interventions. Future research should focus on multicenter randomized studies to more effectively validate the efficacy and cost-effectiveness of HA compared to other treatment modalities. Another limitation is that the treatment evaluation was performed by the same physician administering the therapy.

HA remains a valuable conservative treatment for knee OA, offering significant benefits in pain reduction, improved joint function, and potential disease progression delay. Its ability to interact with both the biological and mechanical components of the joint environment positions it favorably in comparison to other available therapies (25).

Conclusion

In conclusion, this study supports the clinical efficacy of a single 4.8 mL intra-articular injection of a viscoelastic solution containing 120 mg of native HA. The results demonstrate that a single HA injection offers significant clinical improvement in knee OA patients without notable side effects. The benefit remained significantly stable over 12 months.

Conflicts of Interest

The authors declare no conflicts of interest.

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