Hyaluronic acid injection in patients with knee osteoarthritis

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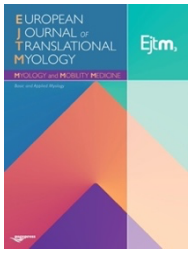

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Clinical efficacy of 4.4 mL single-dose intra-articular cross-linked hyaluronic acid injection in patients with knee osteoarthritis

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Abstract

Osteoarthritis (OA) is a degenerative joint disease with increasing prevalence due to population aging. Conservative management of knee OA has traditionally focused on pain control, with intra-articular injections widely used for targeted local therapy. This study evaluated the clinical efficacy of a single 4.4 mL intra-articular injection of cross-linked hyaluronic acid compared with hylastan SGL-80 (4 mL) in patients with knee OA. In this interventional cohort study, 120 patients with grade III knee OA (Outerbridge) were allocated to two groups: Group 1 (UP; n=60) received 4.4 mL cross-linked hyaluronic acid, and Group 2 (Normal; n=60) received hylastan SGL-80/4 mL. All patients followed a 15-day NSAID protocol before injection and had no prior knee injections within 6 months. Outcomes were assessed using VAS, KOOS, and SF-12 at baseline and up to 6 months. Analgesic use, complications, and VAS–KOOS correlations were evaluated. Both groups showed a low complication rate (5%). Pain reduction over 6 months was significantly greater in Group 1 (VAS 6.93 to 2.32) than in Group 2 (6.44 to 3.52; p=0.030). Group 1 demonstrated superior KOOS (p=0.017), SF-12 scores (p=0.021), and reduced anti-inflammatory drug use (p=0.026). VAS–KOOS correlation confirmed greater clinical improvement in Group 1 at 180 days (p=0.031). A single 4.4 mL intra-articular injection of cross-linked hyaluronic acid provides significant and sustained improvement in pain, function, and quality of life in patients with knee OA.

Key words: pain; knee; osteoarthritis; outcomes; cross-linked; hyaluronic acid; NSAIDs.

Osteoarthritis (OA) is the most prevalent form of arthritis. While it may also affect younger adults, its incidence rises markedly after the age of 45.[1] More than 32 million people in the United States are affected by OA, with the knee being one of the most commonly involved joints. Women are more frequently affected than men.[2] Although age is a predominant risk factor for knee OA, the condition can also occur in younger individuals. OA may have a genetic predisposition in some cases, while in others it arises from joint trauma, infection, or excess body weight.[1,3]

According to current OA treatment guidelines, topical NSAIDs should be used as first-line therapy, with oral NSAIDs and COX-2 inhibitors (COXIBs) considered thereafter, provided that comorbidities and contraindications allow.[3,4] Intra-articular injections with glucocorticoids, Platelet-Rich Plasma (PRP), and Hyaluronic Acid (HA) are also included among recommended treatment options; nevertheless, glucocorticoid use should be restricted to two or three injections annually due to the potential for joint damage.[5,6] According to Busse *et al.* (2019), the toxicity observed with intra-articular injections is mainly attributable to anesthetic agents, with the extent of toxicity varying according to their concentration.[7]

However, intra-articular injections for targeted local treatment have been widely used in clinical practice for many years.[5,6]

Our study evaluated the clinical efficacy of a single 4.4 mL intra-articular injection of cross-linked hyaluronic acid for knee OA in comparison with hylastan SGL-80 (4 mL).

Materials and Methods

This was an interventional, non-randomized cohort study including 120 patients with grade III knee osteoarthritis according to the Outerbridge classification.[8] Patient allocation was based on individual preference, clinical suitability, and relative or absolute contraindications to the proposed treatments; therefore, no randomization procedure was performed.

Inclusion criteria were as follows: male and female patients over 18 years of age diagnosed with knee OA, grade III according to the Outerbridge classification.[8] None of the patients had received any intra-articular knee injection in the previous six months. All patients were non-responders to intra-articular Hyaluronic Acid (HA) and, either by personal preference or because of cardiovascular comorbidities, declined prosthetic surgery.

Exclusion criteria included psychiatric or neoplastic disorders, rheumatic diseases other than OA, alcohol or substance abuse, and pregnancy or breastfeeding.

The sample consisted of 120 patients, divided into two groups. Allocation was based on the patients' free choice, according to relative or absolute contraindications and the type of therapy selected.

The first group (n=60) was treated with a single 4.4 mL single-dose intra-articular cross-linked hyaluronic acid injection (UP).

The second group (n=60) received hylastan SGL-80/4 mL (Normal).

Both groups underwent a pre-infiltration protocol consisting of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for fifteen days (see protocol design).

The criteria used to evaluate the two groups during clinical and radiological follow-up included therapy adherence, daily consumption of pain medication, and health-related quality of life assessed using the Short Form-12 (SF-12) Health Survey.[9]

Clinical assessment was performed using the Visual Analog Scale (VAS)[10,11] and the Knee Injury and OA Outcome Score (KOOS).[12,13] Complications and the correlation between VAS and KOOS were also analyzed.

Endpoints were assessed at baseline (day 0), 1 week, 1 month, 3 months, and 6 months after the injection.

Therapeutic protocol

Patients were allocated into two treatment groups according to patient preference and clinical suitability. The UP group (n=60) received a single 4.4 mL intra-articular injection of cross-linked hyaluronic acid in a single-dose formulation.[14,16] The Normal group (n=60) received a single 4 mL intra-articular injection of Hylastan SGL-80. In both groups, injections were performed using the superolateral approach.[16,19] Both groups followed the same peri-infiltrative protocol, consisting of Aceclofenac 100 mg oral suspension once daily after lunch for 15 days before injection. After the injection, patients were allowed to take up to two doses per day of Aceclofenac 100 mg oral suspension, continuously or as needed, according to pain intensity. Local ice application[16] and a personalized aerobic and proprioceptive rehabilitation program[20] were recommended in both groups.

Statistical analysis

The data was imported into an electronic spreadsheet (Excel, Microsoft Office) for processing and statistical analysis.

The primary endpoint of the study was functional recovery, defined in terms of pain reduction, knee function, and quality of life at six months following the intra-articular injection.

Descriptive statistics were used to summarize the characteristics of the study population and subgroups, including means and standard deviations for all continuous variables.

The *t-test* was applied to compare continuous outcomes, whereas the *Chi-square* test or *Fisher's exact* test (for subgroups with fewer than 10 patients) was used to compare categorical variables. Statistical significance was set at $p<0.05$.

The Pearson correlation coefficient (r) was used to assess the relationship between predictive scores. Average patient ages (and their ranges) were rounded to the nearest year. Predictive outcome scores were rounded to one decimal place, while the Pearson correlation coefficient (r) was reported to two decimal places.

Cohen's kappa coefficient (κ) was used to measure inter-rater agreement for categorical variables and was applied to evaluate concordance between the qualitative values of the VAS and KOOS scores.

Results

Baseline characteristics of the study population are presented in Table 1.

In both groups, the majority of patients were male: 33 (55%) in the UP group and 34 (56.67%) in the Normal group ($p=0.88$). The male-to-female ratio was comparable between groups (1.22 *vs*. 1.30; $p=0.82$).

The mean age was 68.9 years (±26.3; range 33–99) in the UP group and 66.8 years (±24.9; range 31–97) in the Normal group ($p=0.51$). All patients were classified according to the Outerbridge grade.

In both groups, the left knee was the most frequently affected side: 39 patients (65%) in the UP group and 38 patients (63.33%) in the Normal group ($p=0.88$).

The mean BMI was 33.8 (±8.7; range 17–46) in the UP group and 32.6 (±7.9; range 17–46) in the Normal group ($p=0.81$). The most represented BMI categories in both groups were "normal weight" and "obesity." Regarding comorbidities and lifestyle factors, diabetes was present in 12 patients (20%) in the UP group and 10 patients (16.67%) in the Normal group ($p=0.39$). Smokers accounted for 18 patients (30%) in the UP group and 16 patients (26.67%) in the Normal group ($p=0.42$). Alcohol consumption was reported in 26 patients (43.33%) in the UP group and 24 patients (40%) in the Normal group ($p=0.37$).

Pain assessed by VAS during follow-up

VAS scores showed progressive improvement in both groups over time, with a more pronounced reduction in the UP group (Figure 1): i) before injection: UP 6.93 (±0.86; range 1–10); Normal 6.44 (±0.79; range 1–10); p=0.72; ii) immediately after injection: UP 6.93 (±0.86; range 1–10); Normal 6.22 (±2.3; range 1–8); p=0.69; iii) 1 month: UP 4.29 (±2.2; range 0–8); Normal 4.34 (±2.3; range 0–8); p=0.94; iv) 3 months: UP 3.43 (±1.3; range 0–5); Normal 4.01 (±1.6; range 0–7); p=0.066; v) 6 months: UP 2.32 (±0.7; range 0–4); Normal 3.52 (±2.4; range 1–6); p=0.030.

KOOS trend during follow-up

KOOS scores improved in both groups, with greater functional recovery observed in the UP group at later follow-up points (Figure 2): i) before injection: UP 61.8 (±10.7; range 19–96); Normal 64.4 (±13.7; range 51–96); p=0.42; ii) immediately after injection: UP 61.8 (±10.7; range 19–96); Normal 64.4 (±13.7; range 51–96); p=0.42; iii) 1 month: UP 67.4 (±20.9; range 48–96); Normal 66.2 (±20.3; range 48–92); p=0.91; iv) 3 months: UP 69.2 (±22.6; range 48–92); Normal 66.3 (±20.3; range 48–92); p=0.056; v) 6 months: UP 76.2 (±15.1; range 59–96); Normal 66.2 (±15.4; range 51–92); p=0.017.

Monthly use of painkillers

Analgesic consumption decreased in both groups, with significantly lower use in the UP group from three months onward (Figure 3): i) before injection: UP 17.8 (±6.7; range 10–31); Normal 15.6 (±4.7; range 8–26); p=0.31; ii) immediately after injection: UP 12.7 (±5.7; range 10–31); Normal 13.5 (±2.3; range 8–16); p=0.29; iii) 1 month: UP 9.2 (±1.8; range 1–12); Normal 10.6 (±1.4; range 9–14); p=0.81; iv) 3 months: UP 7.7 (±2.1; range 1–11); Normal 10.4 (±1.4; range 9–14); p=0.038; v) 6 months: UP 4.7 (±0.9; range 1–8); Normal 7.4 (±3.7; range 3–12); p=0.026.

SF-12 trend during follow-up

Quality-of-life scores showed sustained improvement in both groups, with the UP group demonstrating significantly higher scores at 6 months (Figure 4); i) before injection: UP 70.9 (±20.3; range 52–96); Normal 74.1 (±22.7; range 50–96); p=0.26; ii) immediately after injection:

UP 70.9 (±20.3; range 52–96); Normal 76.1 (±22.7; range 50–96); p=0.053; iii) 1 month: UP 75.2 (±20.7; range 56–100); Normal 76.3 (±21.4; range 54–100); p=0.83; iv) 3 months: UP 77.9 (±20.6; range 56–100); Normal 76.3 (±21.4; range 54–100); p=0.86; v) 6 months: UP 85.2 (±12.6; range 68–100); Normal 76.3 (±21.4; range 54–100); p=0.021.

Correlation between VAS and KOOS

At baseline (time zero), the Cohen's κ inter-correlation between VAS and KOOS was 0.75 (±0.23; range 0.51–1.00) in the UP group and 0.76 (±0.15; range 0.61–1.00) in the Normal group (p=0.91). At 6 months, Cohen's κ increased to 0.91 (±0.09; range 0.81–1.00) in the UP group, while remaining 0.76 (±0.15; range 0.61–1.00) in the Normal group (p=0.031), indicating a significant improvement in favour of the UP group**.**

Discussion

Viscosupplementation with intra-articular HA injections is a widely used therapeutic strategy for the management of Knee OA (KOA).[21] HA exerts its clinical benefits through multiple mechanisms, including mechanical effects (joint lubrication, functional support, and shock absorption), anabolic activity (regulation of nutrient diffusion and stimulation of proteoglycan synthesis), analgesic action (desensitization of nociceptive receptors), and anti-inflammatory effects (pain reduction via leukocyte phagocytosis and inhibition of prostaglandin E2 and nitric oxide production). In addition, HA promotes viscoinduction and chondroprotection by stimulating endogenous HA synthesis and reducing apoptosis in arthritic cartilage.[22]

Notably, highly crosslinked HA formulations, characterized by a higher degree of modification (MoD ↑), have been shown to provide superior pain relief and a longer duration of effect while requiring fewer intra-articular injections compared with HA solutions or mildly crosslinked HA (MoD ↓), which are more prone to rapid biodegradation in Synovial Fluid (SF).[23,24]

In this context, a crosslinked sodium hyaluronate formulation, obtained by biofermentation and highly purified, dissolved in a physiological and isotonic buffer (TrHCROSS®) exhibited the highest elasticity, reflecting a highly elastic three-dimensional polymeric network. Its elevated viscosity values indicate a superior ability to resist permanent deformation under prolonged mechanical loading. Furthermore, this formulation demonstrated the capacity to enhance the viscoelastic properties of SF at increasing shear frequencies, such as those occurring during the transition from walking to running.[25]

Basic scientific evidence suggests that cross-linked HA formulations may be associated with an increased inflammatory response; however, this phenomenon has not been conclusively demonstrated in clinical studies. Cross-linked HA has been associated with a higher incidence of acute local inflammatory reactions, although other reviews have attributed these events to the avian origin of most cross-linked products.[11,16-19] While preclinical data support the potential of both HA cross-linking and HA itself to trigger enhanced local inflammation, no review has clearly differentiated which factor is primarily responsible for these reactions.[16-19]

Knee arthroscopic surgery—most commonly partial meniscectomy or diagnostic arthroscopy—combined with exercise therapy in middle-aged patients presenting with meniscal symptoms did not increase the risk of radiographic or symptomatic OA. Long-term findings showed comparable Patient-Reported Outcome Measures (PROMs) at 10-year follow-up between patients undergoing surgery plus exercise therapy and those treated with exercise therapy alone. Considering the short-term benefits and the absence of long-term harm, knee arthroscopic surgery may be considered in patients with persistent symptoms despite first-line treatments, including at least three months of structured exercise therapy.[12] In the present study, infiltrative therapy in both groups did not lead to any patient requiring arthroscopy or knee replacement surgery.

In 2024, Cioroianu *et al.*[3] evaluated the evolution of WOMAC, KOOS-ADL, OKS, and VAS scores in patients with knee OA. The combined use of physical therapy modalities and a NSAID (diclofenac) resulted in significant improvements in pain and function at 24 weeks. In our study, both populations underwent a pre-infiltration NSAID protocol consisting of Aceclofenac 100 mg oral suspension, administered once daily after lunch for fifteen days.[15] These effects were likely attributable to the anti-inflammatory action of the drug within the knee microenvironment, potentially limiting early degradation of the subsequently administered injectable compounds.[3,15-19] Patients subsequently received a single intra-articular dose of high–molecular-weight hyaluronic acid (HMW-IAHA; hylastan SGL-80, 4 mL),[16-18] administered via the superolateral approach.[19]

Evidence also highlights differences in cost-effectiveness among intra-articular HA, polynucleotides, and other injectable products, and between the use of IA-HA in early/moderate *versus* advanced stages of knee OA. These findings underscore the heterogeneity among IA-HA products, demonstrating that their biological effects, clinical outcomes, and cost-effectiveness are not equivalent.

The superolateral approach is the most commonly used entry site for intra-articular knee injections. Sher[18,26] advocates this approach—with the knee extended—for joint aspiration, as it targets the suprapatellar pouch and allows the needle to pass beneath the articular surface of the patella. Hermans *et al.*[19,27] reported that the superolateral approach achieves the highest pooled accuracy

rate (91%; 95% CI, 84%–99%), although a notable proportion of extra-articular needle placements may still occur.

Mild swelling or tenderness at the injection site may occur within the first one to two days. Physicians may recommend the application of ice two or three times daily or the use of over-the-counter analgesics to alleviate pain and reduce swelling.[19] Patients are advised to avoid high-intensity activities involving the knee for approximately 48 hours, while routine activities, including walking, may be safely continued. The most commonly reported side effects following intra-articular therapy include transient pain, swelling, and/or fluid accumulation in the injected knee.[20]

In Group 1, two minutes before the administration of hyaluronic acid, 200 mg of clodronic acid[8] was injected using the same needle and the same superolateral approach.[19]

In 2019, Busse *et al.*[7] investigated the cytotoxic effects of various intra-articular agents on the viability of primary human chondrocytes and tenocytes. Tested compounds included Local Anesthetics (LA), Glucocorticoids (GC), Hyaluronic Acid (HA), Contrast Agents (CA), and Tranexamic Acid (TA). The study demonstrated that cytotoxicity toward chondrocytes and tenocytes was concentration-dependent. LAs such as lidocaine and bupivacaine exhibited the highest levels of toxicity, whereas glucocorticoids also showed deleterious effects, with triamcinolone acetonide proving more cytotoxic than dexamethasone. TA produced only minimal effects on cell viability.

TA is commonly administered intra-articular to prevent postoperative bleeding after arthroplasty. Based on these findings, intra-articular TA can also be considered safe in native joints, as its effects on chondrocytes and tenocytes are comparable to those of iodine-based contrast media, which have been used for decades without clinically significant adverse events. HA did not demonstrate any *in vitro* cytotoxicity.

The WORMS scoring system[13] uses conventional MRI sequences widely available in standard clinical imaging settings. In patients with mild-to-moderate knee OA, pain severity correlates with structural abnormalities that are not detectable on standard radiographs. Consequently, MRI is increasingly recognized as an essential tool for understanding OA pathogenesis and for guiding targeted interventions at the earliest stages of the disease.[13]

To date, no definitive evidence exists regarding the efficacy of alendronate sodium/vitamin D_3 on knee joint stability, OA progression, pain severity, or quality of life in individuals with early-stage knee OA. For this reason, their randomized, placebo-controlled trial was designed to generate high-quality data on the therapeutic value of alendronate in this patient population.[28]

One case of septic arthritis was observed during follow-up. Although the patient reported intense physical activity before symptom onset, the available data do not allow us to establish a direct

causal relationship. This complication was therefore reported descriptively and interpreted with caution.[29]

Our findings indicate that a single-shot intra-articular administration of HA+CA in patients with painful knee OA leads to meaningful reductions in pain and measurable improvements in function. Although some outcomes showed numerical differences between groups, these differences did not reach statistical significance and should therefore be interpreted cautiously. They may represent exploratory signals requiring confirmation in larger, adequately powered randomized studies.

Regarding the clinical use of intra-articular cross-linked hyaluronic acid injections in athletic patients, although clinical evidence specifically generated in athletes treated with Hylastan SGL-80 is limited, available data on Hylastan SGL-80 (Jonexa) in osteoarthritis populations, together with robust evidence on intra-articular hyaluronic acid in sport-active individuals, support its use in subjects exposed to high physical and mechanical joint stress, such as athletes and individuals engaged in physically demanding occupations.[21]

IA-HA injections have consistently demonstrated a significant reduction in joint pain, as measured by VAS and validated functional outcome scores, in both OA patients and sport-active populations. This analgesic effect is particularly relevant in athletes, as it is often associated with a reduced need for systemic analgesics and NSAIDs, thereby limiting the risks related to prolonged pharmacological pain management. The sustained pain relief observed after viscosupplementation supports its role as a localized, non-systemic approach to pain control in physically active patients.[30-32]

Clinical and real-world studies on hylastan SGL-80 have reported meaningful improvements in joint function and symptom control in patients with moderate to advanced OA. In this setting, viscosupplementation has been associated with the ability to postpone surgical interventions, including joint replacement, particularly in patients aiming to maintain an active lifestyle.

The ability of conservative treatments such as intra-articular cross-linked hyaluronic acid to delay or potentially reduce the need for arthroplasty has become increasingly relevant in contemporary orthopedic practice. As life expectancy and functional demands continue to rise, preserving the native joint for as long as possible represents an important therapeutic objective, particularly in elderly yet active individuals and in patients who may be exposed to the risks associated with major reconstructive procedures. Recent advances in orthopedic surgery, including the development of robotic-assisted Total Knee Arthroplasty (TKA), patient-specific surgical planning, and digital technologies, have substantially improved the accuracy and reproducibility of knee reconstruction procedures. Bosco et al. demonstrated that imageless robotic-assisted TKA provides high surgical accuracy and supports a precision-medicine approach to knee replacement surgery, highlighting the

ongoing evolution of individualized orthopedic care.[33] Similarly, the growing integration of digital innovations and data-driven technologies into musculoskeletal care pathways, including emerging applications such as blockchain-based systems, reflects the broader trend toward more efficient and personalized orthopedic management strategies.[34] Despite these technological advances, TKA remains a major surgical procedure associated with potential complications and long-term biomechanical considerations. Factors such as posterior tibial slope have been shown to significantly influence postoperative outcomes following TKA, emphasizing the complexity of achieving optimal functional results after joint replacement.[35] Furthermore, complications occurring in fragile populations, including periprosthetic fractures in elderly patients, may require complex revision or reconstructive procedures are associated with substantial morbidity.[36] In this context, effective conservative interventions capable of relieving symptoms, improving function, and postponing prosthetic surgery may provide meaningful clinical benefits. Therefore, the positive outcomes observed with single-dose cross-linked HA injections in the present study may contribute to a broader joint-preservation strategy, bridging the gap between early conservative management and eventual surgical intervention when required.

For athletes and physically active individuals, delaying surgery represents a critical therapeutic objective, enabling continued participation in sport or work activities while preserving joint function and quality of life.[31,32]

Hylastan SGL-80 is characterized by high viscoelastic properties designed to closely mimic those of healthy synovial fluid. These properties confer a mechanical cushioning and shock-absorbing effect, which is particularly beneficial in joints exposed to repetitive loading, impact, and microtrauma. This mechanism is especially relevant for competitive and recreational athletes, as well as for individuals performing physically demanding or strenuous work, where continuous mechanical stress plays a central role in symptom progression.[31,32]

While randomized controlled trials specifically evaluating hylastan SGL-80 in athletes are limited, extrapolation from clinical studies in OA populations treated with hylastan SGL-80 and from evidence obtained in sport-active patients treated with IA-HA supports its use as a safe and effective therapeutic option. The favorable safety profile, combined with its local mechanism of action and mechanical support, makes IA-HA particularly suitable for long-term joint management strategies in athletes and individuals exposed to sustained biomechanical overload.[30-32]

The main limitation of this study is its non-randomized design. Since treatment allocation was based on patient preference and clinical suitability rather than random assignment, a potential selection bias cannot be excluded. Therefore, although the two groups were prospectively followed

using the same clinical and functional endpoints, the comparative findings should be interpreted with caution and should be confirmed by future randomized controlled trials.

Conclusions

A single 4.4 mL intra-articular injection of cross-linked hyaluronic acid demonstrated a consistent and clinically meaningful improvement in pain, function, and quality of life in patients with knee OA. Progressive reductions in VAS scores, paralleled by significant gains in KOOS and SF-12 outcomes and a decreased reliance on analgesics, indicate a sustained therapeutic benefit over six months. The strengthening of the VAS–KOOS correlation further supports a coherent clinical response and suggests a potential effect on synovial inflammation and joint homeostasis. The treatment was well tolerated, with no major adverse events or progression to surgical intervention throughout follow-up.

Although these findings reinforce the value of cross-linked hyaluronic acid as a safe and effective conservative option for symptomatic knee OA, the non-blinded design, limited sample size, and short follow-up constrain the generalizability of the results. Future randomized controlled trials with larger cohorts, longer observation periods, and imaging-based assessments of structural progression are warranted to confirm these outcomes and clarify the long-term impact on cartilage integrity and disease modification.

List of abbreviations

OA, Osteoarthritis

NSAIDs, Non-Steroidal Anti-Inflammatory

VAS, Visual Analog Scale

KOOS, Knee Injury and Osteoarthritis Outcome

COXIBs, COX-2 inhibitors

PRP, Platelet-Rich Plasma

HA, Hyaluronic Acid

PROMs, Patient-Reported Outcome Measures

WOMAC, Western Ontario and McMaster University Arthritis Index

KOOS-ADL, Knee Injury and Osteoarthritis Outcome Score - Activities of Daily Living subscale

OKS, Oxford Knee Score

HMW-IAHA, Intra-Articular dose of High–Molecular-Weight Hyaluronic Acid

LA, Local Anesthetics

GC Glucocorticoids

CA, Contrast Agents

TA Tranexamic Acid

WORMS Whole-Organ Magnetic Resonance Imaging Score

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Conflict of interests

The Authors declare no conflict of interest

Contributions

Conceptualization, Luigi Meccariello and Giuseppina Casolaro; methodology, Luigi Meccariello, Clemente Villari and Jacopo Conteduca; validation, Luigi Meccariello, Clemente Villari and Jacopo Conteduca..; formal analysis, Luigi Meccariello and Giuseppe Rovere; investigation, Luigi Meccariello Lawrance Camarda.; software development, Giuseppina Casolaro and Giuseppe Rovere; data curation, Giuseppe Rovere and Luigi Meccariello.; writing—original draft preparation, Luigi Meccariello and Giuseppe rovere; writing—review and editing, Luigi Meccariello and Giuseppe Rovere; visualization, Lawrance Camarda; supervision, Luigi Meccariello; resource management and project administration, Giuseppina Casolaro.

All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

The study was conducted in accordance with the Declaration of Helsinki; informed consent was obtained from each patient prior to the initiation of the study.

Institutional Review Board Statement

Not applicable**;** ethical committee approval was not required, since the study exclusively involved medical devices that are already approved for routine clinical use, have established safety profiles, and are widely validated and described in the current scientific literature.

Data Availability Statement

The datasets generated during the current study are available from the corresponding author on reasonable request.

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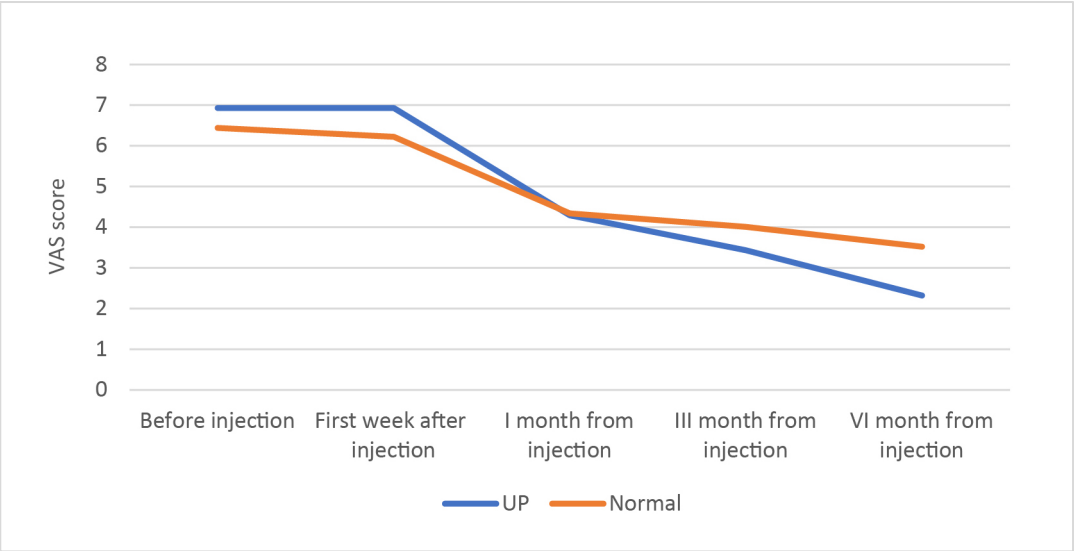

Figure 1. VAS trend in 6 months of follow-up. Up to the 6 months follow-up, there was an improvement in mean ± standard deviation values of VAS score in UP group, p=0.030 for UP group.

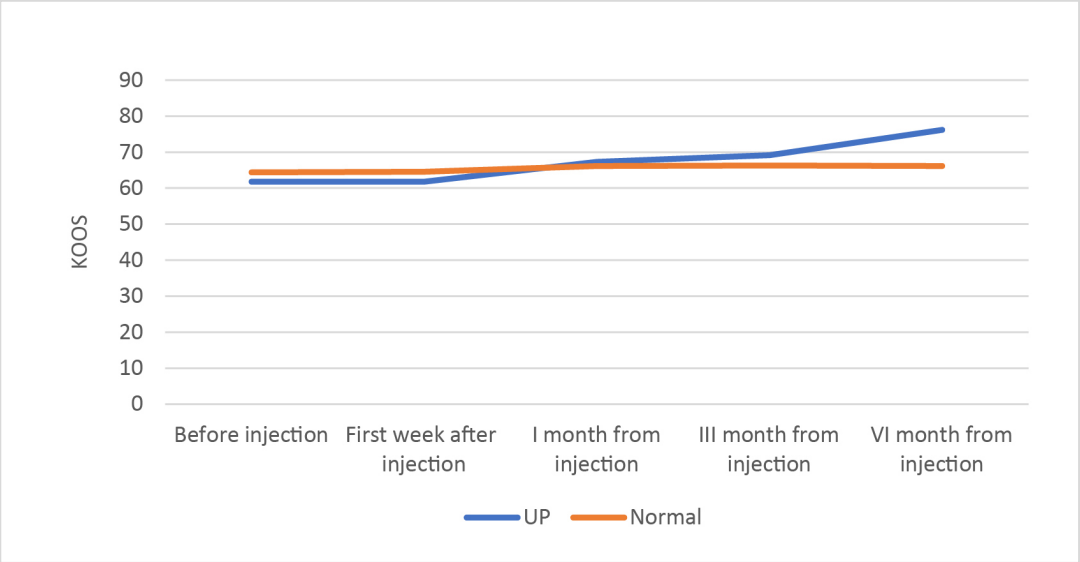

Figure 2. KOOS trend in 6 months of follow-up. Just at the sixth month from the injection, KOOS score was better in the UP, p=0.017.

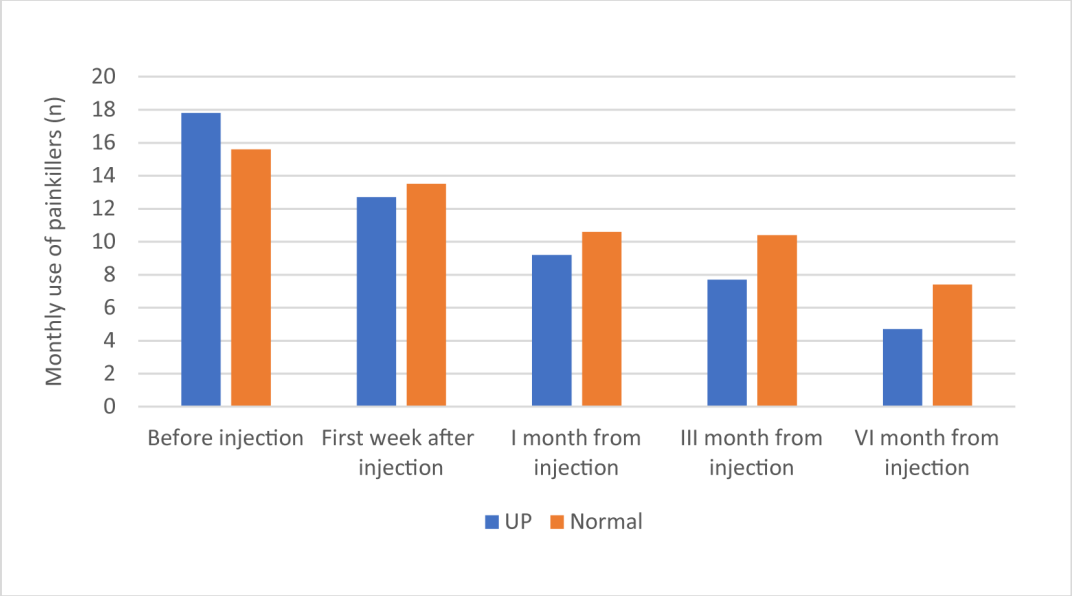

Figure 3. The trend of painkillers used during a month. At the sixth month from the injection, the use in a month of painkiller intake was lesser in UP group, p=0.026.

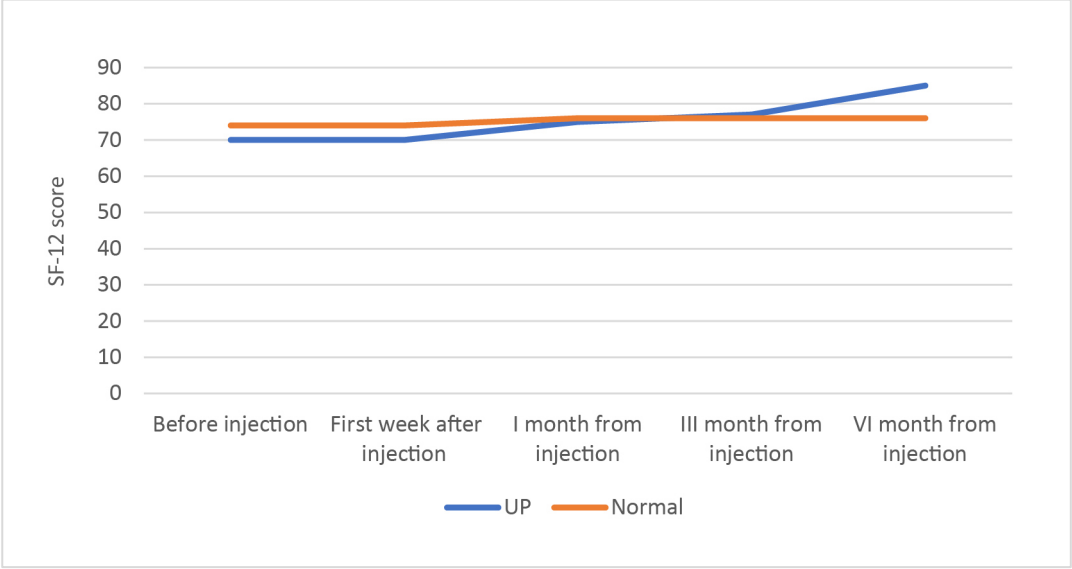

Figure 4. SF-12 trend in 6 months of follow-up. Just at the sixth month from the injection, SF-12 score was better in the UP, p=0.021.

Table 1. Characteristics of the study sample divided into two groups: 4.4 mL single-dose intra-articular cross linked hyaluronic acid (UP); hylastan SGL-80/4mL (Normal). The study population consisted of two homogeneous groups of 60 individuals each.

Characteristics	**UP (n= 60)**	**Normal (n=60)**	**p**
Females [(n) (%)]	**27(45%)**	**26(43.33%)**	**0.88**
Males [(n) (%)]	**33 (55%)**	**34 (56.67%)**	**0.88**
Gender ratio *(m:f)*	**1.22 (33:27)**	**1.30 (34:26)**	**0.82**
Average age in years(SD;range)	**68.9 (±26.3; 33-99)**	**66.8 (±24.9; 31-97)**	**0.51**
Classification according Outerbride criteria[10]	**60(100%)**	**60(100%)**	**1**
Side of Injured Knee [(n) (%)]	Right: **21(35%)** Left: **39(65%)**	Right: **22(36.67%)** Left: **38(63.33%)**	**0.88** **0.88**
BMI average (Kg/m2)	**33.8 (±8.7; 17-46)**	**32.6 (±7.9; 17-46)**	**0.81**
BMI Category (Kg/m2) [(n) (%)]	Under Weight (BMI < 20): **5 (8.33%)** Normal Weight (BMI = 20-29): **25 (41.67%)** Obese (BMI = 30-39): **25 (41.67%)** Morbidly Obese (BMI > 40): **5 (8.33%)**	Under Weight (BMI < 20): **6(10%)** Normal Weight (BMI = 20-29): **25 (41.67%)** Obese (BMI = 30-39): **24 (40%)** Morbidly Obese (BMI > 40): **5 (8.33%)**	**0.93** **1** **0.88** **1**
Diabetes [(n) (%)]	**12(20%)**	**10(16.67%)**	**0.39**
Smoker [(n) (%)]	**18(30%)**	**16(26.67%)**	**0.42**
Driking [(n) (%)]	**26(43.33%)**	**24(40%)**	**0.37**