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Effect of a Single Diclofenac-Ethylhyaluronate Injection on Pain and Function in Patients with Severe Knee Osteoarthritis

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ABSTRACT

Purpose: *This study evaluated the efficacy of diclofenac-etalhyaluronate (DF-HA), a novel conjugate drug composed of diclofenac covalently linked to sodium hyaluronate, in patients with advanced knee osteoarthritis.*

Methods: *Seventy-two outpatients (86 knees) with Kellgren-Lawrence grade III and IV osteoarthritis who have not achieved satisfactory pain control with conventional treatment were recruited. Clinical and functional assessments were performed immediately before and after a single intra-articular injection of DF-HA. The efficacy of DF-HA injections in improving pain using visual analogue scale score (VAS), range of motion (ROM), quadriceps strength (QS: N/kg), single-leg-stance time (SLS), and Japanese Orthopaedic Association Score (JOAS). Values presented as medians (interquartile range).*

Results: *Both VAS and JOAS improved significantly (p< 0.001): VAS from 6 (5, 8) to 3 (2, 5) and JOAS from 65 (59, 75) to 70 (65, 85). ROM also improved from 110° (100°, 120°) to 115° (104°, 125°) (p< 0.001). Additionally, QS increased from 4.1 (2.7) to 4.9 (3.6, 6.1) (p< 0.001) and SLS 12 (5, 52) to 21 (8, 60) (p= 0.002). Improvement rates exceeded 50% for all items. VAS had a significantly higher rate compared to all other indicators (vs. JOAS: p= 0.003, vs. ROM: p<0 .001, vs. QS: p= 0.006, vs. SLS: p= 0.001).*

Conclusions: *DF-HA demonstrated a rapid and significant reduction in pain, improved knee joint function, and led to significant improvements in JOAS in over half of patients with advanced osteoarthritis. However, further longitudinal studies are needed to identify appropriate patient subgroups and optimize the use of repeated injections.*

Keywords
Diclofenac-etalhyaluronate, Knee Osteoarthritis, Pain Management, Clinical assessment.

Introduction
Pain is a primary symptom of osteoarthritis and a critical factor in managing this condition. The pathophysiology of osteoarthritis is complex, involving lesions in multiple joint tissues that contribute to clinical manifestations. Pain management in knee osteoarthritis involves multiple treatment strategies, including lifestyle modifications, exercise therapy, pharmacotherapy, and injections of various substances [1]. The goal of treatment is to alleviate symptoms and improve functional status. Intra-articular injection therapy is widely accepted as a conservative treatment, especially for early to moderate knee osteoarthritis [2]. Among the available options, corticosteroids (CS), hyaluronic acid (HA), and platelet-rich plasma (PRP) are the most commonly used injectables, and various comparative studies have reported their effects on pain [2-

6]. However, the most effective drug for intra-articular treatment of knee osteoarthritis remains a subject of ongoing debate [7,8]. Consequently, current major international society guidelines lack consensus on recommendations, and the discussion regarding the most appropriate intra-articular treatment option for knee OA continues [9-11].

Diclofenac-etalhyaluronate (DF-HA) (JOYCLU®, Ono Pharmaceutical Co., Ltd. Osaka, Japan), a newly developed drug in Japan, represents a significant advancement in the treatment of osteoarthritis. Administered via intra-articular injection, DF-HA uniquely combines the anti-inflammatory and analgesic properties of diclofenac with the joint function-improving effects of HA. Through a chemical bond between diclofenac and HA, Joycul ensures a sustained release of diclofenac while the HA remains in the joint for an extended period, synergistically enhancing their therapeutic benefits. Upon intra-articular injection, DF-HA distributes and resides within the joint cavity, including the synovium and cartilage. Over time, diclofenac is gradually released via hydrolysis. The drug's mechanism of action is threefold [12-15]:

1. **Synovial cells:** Joycul stimulates the production of high-molecular-weight HA, promoting the normalization of pathological synovial fluid.
2. **Chondrocytes:** By inhibiting the production of matrix metalloproteinases, Joycul helps to prevent cartilage degeneration.
3. **Periosteal tissue:** Joycul inhibits cyclooxygenase-2, suppressing the production of prostaglandin E2 and thus exerting anti-inflammatory and analgesic effects.

These multifaceted actions not only alleviate inflammation and pain but also improve joint function by enhancing the lubricating properties of synovial fluid. Previous studies on DF-HA, such as the Phase 2 and 3 clinical trials reported by Nishida et al. [13,14], primarily relied on the Western Ontario and McMaster Universities Arthritis Index [16] to assess pain, range of motion (ROM), and functional limitations. However, these studies lacked within-patient comparisons of pain improvement rates between the DF-HA and placebo groups and lacked quantitative assessments of lower limb function, including the knee joint. In contrast, our study incorporated a visual analogue scale (VAS) score for pain assessment, allowing for a more granular analysis of pain intensity changes over time. Additionally, we conducted knee extensor strength and single-leg stance (SLS) time tests to quantitatively assess lower limb function, providing a more comprehensive evaluation of treatment effects. These additional assessments enable us to provide a more robust analysis of DF-HA's efficacy in improving pain, ROM, and overall lower limb function.

The purpose of this study is to evaluate the efficacy of diclofenac-hyaluronate (DF-HA) injections in improving pain and lower limb function in patients with Kellgren-Lawrence (KL) grade III and IV knee osteoarthritis who have not achieved satisfactory pain control with HA injections or oral nonsteroidal anti-inflammatory drugs (NSAIDs).

Materials and Methods

This prospective study included 72 outpatients (86 knees) with KL grade III or IV knee osteoarthritis who received DF-HA injections between May 2021 and October 2024 (Table 1). Patients were included if they had not experienced adequate pain relief from previous treatment with HA injections or oral NSAIDs. Those with a history of adverse reactions to HA or NSAIDs were excluded. The study was approved by the Institutional Review Board of our institution. All patients provided written informed consent. Clinical and functional assessments were performed immediately before and 3-7 days after the initial injection. No additional treatments for pain relief were administered until the primary outcome assessment.

Table 1: Patients' characteristics.

N=86	Median (percentile)
Male (knee) : Female (knee)	24 (30) : 48 (56)
Age	71 (63, 77) {49-87}
BL (cm)	155 (149, 163) {143- 180}
BW (kg)	61 (55, 70) {43- 117}
BMI (kg/m^2)	26 (22, 29) {19- 45}
Kellgren-Lawrence Grade [17]	III 46, IV 40

Values presented as medians (interquartile range) {range}.

BL, body length; BW, body weight; BMI, body mass index

Clinical Assessment

Pain: Our study incorporated a VAS scores for pain assessment, allowing for a more granular analysis of pain intensity changes over time.

KL Grade: All participants had X-rays taken of their knees while standing [18]. We used the KL grading system to assess the severity of their osteoarthritis based on these X-rays [17]. The KL grades range from I to IV, with higher grades indicating more severe osteoarthritis.

The specific criteria for each grade are as follows:

- **Grade I:** Slight narrowing of the joint space with possible bone spurs.
- **Grade II:** Moderate narrowing of the joint space with definite bone spurs.
- **Grade III:** Significant narrowing of the joint space, moderate bone spurs, some hardening of the bone, and possible misshapen bone ends.
- **Grade IV:** Large bone spurs, severe narrowing of the joint space with significant hardening of the bone, and misshapen bone ends.

To ensure the accuracy of our KL grading, we had the same person (Y.I.) review 100 randomly selected X-rays more than 1 month after the first reading. We found that their ratings were consistent (kappa coefficient = 0.894).

Physical Performance Measures

All evaluations were conducted by a senior physical therapist.

ROM

A senior physical therapist measured the ROM of all patients using a standard hand-held goniometer with 38-cm arms. The patient rested supine on the table while the physical therapist passively extended and flexed the knee under non-weight-bearing conditions. The lateral femoral condyle was used as a reference point to align the goniometer. The proximal end of the goniometer was directed toward the greater trochanter, and the distal end was directed toward the lateral malleolus. The physical therapist then measured and recorded the angle to the nearest 5 degrees. The ROM was calculated as the difference between the extension and flexion angles.

Muscle Strength

Lower Extremity: Quadriceps Strength (QS)

To assess QS, isometric knee extension muscle strength was measured in Newtons (N) using a Locomo Scan dynamometer (Alcare Corp., Tokyo, Japan). The knee was positioned at approximately 20 degrees of flexion, following a standard protocol [19]. Three measurements of QS were taken, and the highest value on each side was used in the analysis.

These values were divided by body weight (BW) to adjust for differences in body size. The resulting ratio of QS to BW (QS/BW ratio; N/kg) was used in the analysis.

Body Balance

Static Balance Ability with Eyes Open

SLS with eyes open was assessed using the participant's affected leg. Participants were instructed to place their hands on their waists, stare at a mark on the wall, raise single leg, and maintain balance for as long as possible. They were timed until they lost their balance or reached the maximum time of 60 seconds. Two trials were performed, and the longer time (to the nearest 0.1 second) was used in the analysis.

Japanese Orthopaedic Association Score for Osteoarthritic Knees (JOAS)

The JOAS is a reliable and valid observer-based scoring tool for evaluating functional status in patients with knee osteoarthritis [20]. It consists of four domains, each with a maximum of 100 points: pain while walking (30 points), pain when climbing or descending stairs (25 points), ROM (35 points), and joint swelling (10 points). The total score for these domains is calculated, with a maximum score of 100 points. Higher scores indicate better knee joint function.

Statistical Analysis

Assumptions of normality were rejected based on the Q-Q plot, Kolmogorov-Smirnov test, and Shapiro-Wilk test. For comparisons of continuous variables, we used Wilcoxon's signed rank test for paired data. Ryan's method was used to evaluate differences in ratios between groups and to correct for multiple comparisons. All statistical analyses were performed using R (version 4.4.1). Values are presented as medians (interquartile range), and a p-value of <0.05 was considered statistically significant.

Results

No serious adverse events related to the injection of the study drug were reported during the study period, and no previously reported serious complications [21,22] were observed.

VAS scores and JOAS improved significantly. VAS scores decreased from 6 (5, 8) to 3 (2, 5) ($p < 0.001$), and JOAS scores increased from 65 (59, 75) to 70 (65, 85) ($p < 0.001$) (Table 2). ROM also improved significantly from 110 (100, 120) to 115 (104, 125) ($p < 0.001$) (Table 2). Furthermore, QF increased from 4.1 (2.7, 5.6) to 4.9 (3.6, 6.1) ($p < 0.001$), and SLS time increased from 12 (5, 52) to 21 (8, 60) ($p = 0.002$) (Table 2).

Table 2: Changes in scores and joint function following diclofenac-etalhyaluronate administration.

N=86	Pre-DH	Post-DH	Differences	P
VAS score	6 (5, 8)	3 (2, 5)	3 (1, 4)	<0.001
JOAS	65 (59, 75)	70 (65, 85)	5 (0, 10)	<0.001
ROM	110 (100, 120)	115 (104, 125)	5 (0, 10)	<0.001
QF (N/kg)	4.1 (2.7, 5.6)	4.9 (3.6, 6.1)	0.5 (-0.2, 1.8)	<0.001
SLS (minutes)	12 (5, 52)	21 (8, 60)	0 (0, 6)	0.002

Values presented as medians (interquartile range).

VAS: visual analogue scale, JOAS: Japanese Orthopaedic Association Score, ROM: range of motion, QF: quadriceps force, SLS: single-legged stance.

The improvement rate exceeded 50% for all items, with the highest improvement rate of 86% observed for VAS scores and the lowest improvement rate of 52% observed for SLS (Table 3). When comparing the improvement rates of the five indicators, the VAS scores showed a significantly higher improvement rate than all other indicators after correction using Ryan's method for multiple comparisons (VAS scores vs. JOAS: $p = 0.003$, VAS scores vs. ROM: $p < 0.001$, VAS scores vs. QF: $p = 0.006$, VAS scores vs. SLS: $p < 0.001$). No significant differences were found in the improvement rates among the indicators other than VAS scores. These are the results of this study.

Discussion

Two significant findings emerged from this study. Firstly, the most notable improvement was observed in VAS scores, indicating that intra-articular injection of this injection may be more effective in alleviating self-reported pain experienced by patients than objective measures. Secondly, we were able to quantitatively evaluate lower limb function, including QS, ROM, and SLS time. These results confirmed the improvement in JOAS, which assesses both pain and knee joint function. Intra-articular injection therapy is widely used as a conservative treatment for early to moderate knee osteoarthritis [2]. The primary options include (CS, HA, and PRP, and their effects on pain have been compared in numerous meta-analyses [3-6]. Hegaze et al. [4] reported improvements in VAS scores of 4.33 for KL III and 3.25 for KL IV after intra-articular injection in patients with moderate to severe osteoarthritis. Our study population consisted of patients with advanced KL III or IV knee osteoarthritis who were resistant to conservative treatment with HA or NSAIDs. The VAS scores improved by 3 points, representing an 86% improvement rate, indicating a highly effective analgesic effect. However, the lack of improvement in some patients suggests that extra-articular lesions should also be considered. In other words, osteoarthritis begins as a subchondral bone lesion and subsequently progresses to articular cartilage destruction [22-28]. To identify cases where these subchondral bone changes play a major role in osteoarthritis progression, we are currently using Magnetic Resonance Imaging to determine whether the lesion is intra-articular or extra-articular and to consider appropriate cases for intra-articular injection of this drug.

Table 3: Rate of improvement in scores and joint function following diclofenac-etalhyaluronate treatment.

N=86	YES (%)	NO	p (VAS scores vs.)
VAS score	74 (86)	12	
JOAS	57 (68)	29	0.003
ROM	47 (55)	39	<0.001
Q force (N/kg)	59 (69)	27	0.006
SLS (minutes)	45 (52)	41	< 0.001

VAS, visual analogue scale; JOAS, Japanese Orthopaedic Association Score; ROM, range of motion; QF, quadriceps force; SLS, single-legged stance.

Clinically meaningful improvements in ROM were observed, with a median increase of 5° and a response rate of 55%. Improvement in ROM associated with pain relief has been previously reported [4]. Hegaze et al. [4] reported improvements of 0.5° and 5.5° in KL III and KL IV, respectively, following PRP injection. In the case of DF-HA, in addition to pain relief provided by DF, the HA itself is expected to have effects on synovial cells and act as a lubricant within the joint due to its viscosity [29,30]. Therefore, it is considered that the synergistic effects of both drugs, as expected during development, have been demonstrated, and the results are reasonable.

As reported by Muraki et al. [31], there is a significant correlation between quadriceps muscle strength and knee pain. Based on this, it can be inferred that the 69% reduction in pain observed with this injection was accompanied by a quantitative improvement in muscle strength of 0.5 N/kg. Improvements in quadriceps muscle strength contribute not only to increased knee joint stability and pain reduction, but also to improved activities of daily living (ADLs) [32,33]. The observed improvement in muscle strength is considered to be due to improved muscle output associated with pain relief, rather than an improvement in muscle substance itself. By establishing an efficient rehabilitation program during the 28-day period of expected drug efficacy following injection [15], substantial improvements in quadriceps muscle strength can be anticipated.

Balance control in older adults with osteoarthritis is generally influenced by proprioception, ROM, muscle strength, pain, and plantar sensation [34]. SLS balance in medial knee osteoarthritis patients is not affected by KL grade but is related to modifiable factors such as lower limb alignment, knee pain, and quadriceps muscle strength [35,36]. Hunt et al. [36] concluded that interventions targeting these factors are necessary given the decreased balance ability in the osteoarthritis population. Our results suggest that the improvement in pain and associated increase in muscle strength following this injection may have led to improved SLS balance. Sun et al. [37] also reported that pain relief associated with HA intra-articular injection improved SLS. Knee pain, regardless of the presence of radiographic osteoarthritis findings, has been reported to decrease the peak isometric and isokinetic torque of knee extensors and flexors [38]. This decrease may hinder effective and timely motor responses in postural control. Considering these reports, it is thought that pain relief through this injection and HA has suppressed the decrease in muscle output and had a positive effect on postural control. The improvement in SLS observed in more than half of the subjects following this injection is expected to lead not only to improvements in ADL but also to reductions in the risk of falls [39,40], fractures [41] and mortality [41,42].

The Western Ontario and McMaster Universities Osteoarthritis Index 3.1 [16] is commonly used to assess function in patients with osteoarthritis of the knee [2,5-7,13,14,43,44]. However, the JOAS has recently become more widely used to evaluate treatment effects for knee osteoarthritis [43-47]. In this study, the injection of DF-HA led to improvements in pain, ROM, and muscle strength. These improvements contributed to enhanced ADLs and balance ability. Consequently, we believe that the JOAS also improved.

There are several limitations to this study.

1. **Lack of a control group:** Given the ethical concerns of administering a placebo to patients with osteoarthritis experiencing pain refractory to HA injections and NSAIDs, the placebo effect associated with intra-articular injections was not investigated.
2. **Lack of subgroup analysis:** While participants were recorded for age, sex, weight, and body mass index, no subgroup analysis was conducted based on the severity of osteoarthritis. Future studies should recruit patients with mild KL scale grades (I to II) to examine the effects of intra-articular DF-HA injection on pain and knee balance function.
3. **Short-term effects:** This study investigated the short-term effects of the first DF-HA injection in patients with moderate to severe osteoarthritis (KL III and IV). Future studies should identify the patient subgroup that benefits most from this treatment and clarify the role of repeated injection series.
4. **Sample size and duration:** Larger, long-term longitudinal studies are needed to determine whether this injection is effective in relieving pain and improving motor function in knee osteoarthritis patients, including the elderly.
5. **Functional outcomes:** Further research is needed to investigate whether intra-articular replenishment of this injection, which is highly valued for its ability to improve patients' perceived pain, also improves lower limb motor

function, including balance, and consequently significantly reduces the risk of falls.

Conclusions

This study demonstrated that intra-articular injection of DF-HA significantly alleviated self-reported pain in patients with knee osteoarthritis. The most notable improvement was observed in VAS scores, suggesting that pain relief is the primary benefit of this treatment. Furthermore, objective assessments such as QS, ROM, and SLS time, as well as the JOAS, confirmed improvements in knee joint function. These findings suggest that DF-HA is effective in treating both pain and functional impairment in knee osteoarthritis, making it a promising new therapeutic option. Future studies should investigate the long-term effects and the applicability of DF-HA to different patient populations.

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