Oral Ialoral® Forte *versus* ultrasound-guided intra-articular cortisone infiltration: results of a retrospective single-center study

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Abstract

Osteoarthritis (OA) is a common cause of pain and functional limitation. We compared the analgesic and functional outcomes of Ialoral® Forte, a nutraceutical formulation, with those of ultrasound-guided intra-articular triamcinolone in patients with hip or knee OA and baseline Numeric Rating Scale (NRS) ≤5.

This retrospective single-center study included 60 patients (NRS≤5, Kellgren-Lawrence grade I-II) treated between June 2022 and January 2023. Group A received oral Ialoral® Forte (two tablets daily for 40 days); Group B underwent two ultrasound-guided intra-articular corticosteroid injections 20 days apart. Pain intensity (NRS) and joint function (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]) were evaluated at baseline and at 20, 40, 60, and 90 days.

Both treatments significantly reduced pain and improved joint function over time. No statistically significant differences were observed between groups ($p>0.05$). Oral Ialoral® Forte achieved comparable analgesic and functional outcomes to intra-articular corticosteroids, without injection-related risks or contraindications.

Oral Ialoral® Forte represents a safe, effective, and non-invasive alternative to intra-articular corticosteroid injections for the management of mild to moderate osteoarthritis, providing similar short-term pain relief and functional recovery with excellent tolerability.

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Introduction

Osteoarthritis (OA) is the most prevalent form of arthritis, affecting more than 240 million people worldwide.[1,2] It is a chronic, progressive, and degenerative joint disorder that represents the leading cause of functional limitation in adults. OA can affect individuals across different age groups, though its prevalence rises with advancing age. Clinical manifestations range from mild discomfort to severe disability, depending on the joints involved, the extent of lesions, and the frequency of symptomatic exacerbations.

OA develops gradually and often begins asymptomatically. Its progression is influenced by genetic predisposition and several risk factors, including age, female sex, sedentary lifestyle, obesity, previous joint trauma (*e.g.*, cruciate ligament rupture),[3] occupational overload, and participation in high-risk sports. Congenital or acquired joint abnormalities also contribute to disease onset. The hips and knees are the joints most commonly affected.[4]

Pathological changes progressively involve articular cartilage, subchondral bone, synovium, ligaments, periarticular fat, and muscles, ultimately resulting in pain, stiffness, and functional impairment. Diagnosis is primarily clinical, based on patient history and physical examination, whereas imaging studies are used to assess structural damage. Notably, pathological features and symptoms may precede radiographic evidence of disease. Hip and knee radiographs are commonly graded using the Kellgren-Lawrence system, ranging from early osteophyte formation (grade I) to severe joint space narrowing with deformity (grade IV).[5-7]

Conservative management includes non-pharmacological interventions such as weight reduction and muscle-strengthening

exercises, which significantly improve pain and functional outcomes.

Pharmacological treatments – acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, and intra-articular corticosteroids – may provide temporary symptom relief but do not modify disease progression. Moreover, NSAID therapy is associated with gastrointestinal and cardiovascular risks, while repeated corticosteroid injections may accelerate cartilage degeneration.[8-10]

Intra-articular hyaluronic acid has shown inconsistent and controversial efficacy in randomized controlled trials.[11-13]

International guidelines, such as the European League Against Rheumatism (EULAR) recommendations, also emphasize non-pharmacological strategies and multimodal management.[14]

These findings are consistent with previous evidence on intra-articular corticosteroid formulations, including newer microsphere preparations of triamcinolone acetonide.[15-17]

Given the limitations of conventional therapies, interest has increasingly focused on nutraceutical compounds. Hydrolyzed collagen has demonstrated the capacity to stimulate chondrocytes to produce type II collagen and proteoglycans, suggesting a potential reparative effect. A bioactive compound derived from chicken sternum cartilage, consisting of hydrolyzed type II collagen, chondroitin sulfate, and hyaluronic acid, has been shown to significantly improve pain and functional disability in patients with OA.[18,19] Additional natural agents with anti-inflammatory and analgesic properties include bromelain (from pineapple), ginger, and β-caryophyllene, the latter also exhibiting beneficial metabolic and cardiovascular effects.[20]

On this basis, we evaluated a novel nutraceutical formulation, Ialoral® Forte, which combines these bioactive components. This retrospective study investigates its efficacy in patients with Kellgren-Lawrence grade I-II hip and knee OA, comparing oral supplementation with intra-articular triamcinolone acetonide in terms of symptom relief and functional improvement.

Materials and Methods

Study design and setting

This single-center retrospective pilot study was conducted at the Pain Therapy Clinic (Spoke II level), Unit of Anesthesia, Resuscitation and Pain Therapy, F. Spaziani Hospital, Frosinone (Italy), between June 2022 and January 2023. A total of 60 patients with hip pain (coxalgia) or knee pain (gonalgia) due to OA were included. The study was performed in accordance with the ethical standards of the Declaration of Helsinki for research involving human subjects. Written informed consent was obtained from all participants.

Study population

The inclusion criteria were as follows: written informed consent; age between 18 and 80 years; diagnosis of hip or knee OA grade I-II according to the Kellgren-Lawrence scale; baseline pain intensity ≤5 on the Numeric Rating Scale (NRS); and random enrollment.

The exclusion criteria included: refusal to provide consent; age <18 years; severe obesity (body mass index [BMI]≥40); baseline NRS>5; pregnancy; local skin infections or degenerative lesions at the treatment site; known allergy to corticosteroids, local anesthetics, or study-related compounds; presence of motor or sensory deficits; neuropathy, myopathy, or central nervous system disorders; diabetes mellitus; anticoagulant therapy; indication for surgical intervention.

Intervention participants were randomly assigned into two groups (n=30 each): i) Group A (nutraceutical group): oral administration of Ialoral® Forte, 2 tablets daily (one tablet twice daily after main meals) for 40 days; ii) Group B (corticosteroid group): treatment with triamcinolone acetonide, consisting of two ultrasound-guided intra-articular injections administered 20 days apart.

All patients underwent baseline radiological imaging to confirm diagnosis and to classify OA severity according to the Kellgren-Lawrence grading system.

Study objectives

Primary objective

The primary objective was to evaluate pain relief from comparing the administration of Ialoral® Forte (1 tablet twice daily, Group A) with a cycle of 2 ultrasound-guided triamcinolone acetonide injections (one injection every 20 days, Group B) over a 40-day period. Pain relief was measured using the NRS, where 0 represents no pain and 10 indicates the most intense pain imaginable. Additionally, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) – a PRO (Patient Reported Outcome) questionnaire that aims to assess changes in pain symptoms, joint stiffness, and joint function and activity restrictions in subjects with osteoarthritis of the hip and knee – was used to assess changes in symptoms and functional activity in individuals with hip and knee OA.

Secondary objective

The secondary objective was to assess the degree of functional improvement of the joint by means of the WOMAC questionnaire.

Clinical evaluations and follow-up pain intensity and joint function were assessed according to the following schedule: T0 (baseline): NRS and WOMAC administration; T1 (day 20): NRS assessment; T2 (day 40): NRS and WOMAC assessment; T3 (day 60): NRS assessment; T4 (day 90): NRS and WOMAC assessment.

At baseline (T0), a standardized clinical record was completed for each patient, including demographic data (sex, age, body weight, BMI), medical history, physical examination, current pharmacological therapy, imaging results, NRS and WOMAC scores, Kellgren-Lawrence grade, and signed informed consent. Records were updated at each follow-up visit according to the predefined protocol.

Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQR), and categorical variables as counts and percentages. Baseline characteristics of the two treatment cohorts were compared using the Mann-Whitney U test for continuous variables and the Pearson chi-square test for categorical variables.

Changes in NRS and WOMAC scores over time were analyzed using a linear random-effects regression (LRER) model. The dependent variable was either the NRS or WOMAC score (continuous), while predictors included time (discrete: 0, 1, 2, 3, and 4 for NRS; 0, 2, and 4 for WOMAC), treatment group (discrete: 0=intra-articular corticosteroid [triamcinolone], 1=oral Ialoral® Forte), and the time of treatment interaction. A random effect was assigned at the patient level.

Pairwise comparisons of NRS and WOMAC scores between groups at different time points were performed using contrasts adjusted for multiple testing. Bonferroni correction was applied,

with five comparisons for the NRS scale and three for the WOMAC scale. Results of inferential analyses are reported as means with 95% confidence intervals (CI), derived from the LRER model.

Results

Baseline characteristics

Baseline characteristics of patients in the two treatment groups (intra-articular corticosteroid [triamcinolone] *vs.* oral Ialoral® Forte) are reported in Table 1. The two groups were comparable with respect to sex distribution, age, baseline NRS, and WOMAC scores.

Comparisons were performed using Pearson's chi-square test for categorical variables and the Mann-Whitney U test for continuous variables.

Numeric Rating Scale

The trajectory of NRS scores in the two treatment groups is illustrated in Figure 1 and detailed in Table 2. Mean NRS values (95% CI) at baseline and follow-up were:

- Intra-articular corticosteroid group: 4.3 (4.1-4.6), 2.8 (2.5-3.1), 1.7 (1.4-1.9), 1.2 (0.9-1.4), 1.3 (1.0-1.5) at T0, T1, T2, T3, and T4, respectively.
- Ialoral® Forte group: 4.3 (4.0-4.6), 3.5 (3.2-3.8), 2.4 (2.1-2.7), 1.7 (1.4-2.0), 1.8 (1.5-2.0).

The corresponding mean differences (95% CI with Bonferroni correction) for Ialoral® Forte *vs.* corticosteroid were: 0.0 (−0.5 to 0.5, p=1.000), 0.7 (0.2 to 1.2, p=0.0014), 0.7 (0.2 to 1.2, p=0.0007), 0.5 (0.01 to 1.0, p=0.0280), and 0.5 (0.01 to 1.0, p=0.0471).

Western Ontario and McMaster Universities Osteoarthritis Index

The trajectory of WOMAC scores in the two groups is shown in Figure 2 and reported in Table 3. Mean WOMAC values (95% CI) at baseline, day 40, and day 90 were:

- Intra-articular corticosteroid group: 32 (30-35), 20 (17-22), 19 (16-21).
- Ialoral® Forte group: 33 (31-36), 28 (25-30), 27 (24-29).

The corresponding mean differences (95% CI with Bonferroni correction) for Ialoral® Forte *vs.* corticosteroid were: 1 (−3 to 6, p=1.000), 8 (4 to 13, p<0.0001), and 8 (4 to 13, p<0.0001).

Discussion

OA is the most common form of arthritis, affecting approximately 240 million people worldwide. It is a chronic, progressive, and degenerative joint disease that represents the leading cause of functional limitation in adults.

Currently, no universally accepted treatment protocol exists for OA. Conventional management includes non-pharmacological

Table 1. Baseline characteristics of the two treatment groups. Continuous variables are expressed as median (interquartile range) and categorical variables as number and percentage.

Characteristics	Intra-articular corticosteroid (n=30)	Oral Ialoral® Forte	p-value
Sex (male/female)	14/16	13/17	0.79
Age, years	65 (58-72)	64 (57-71)	0.64
BMI, kg/m^2	28 (25-30)	27 (25-30)	0.71
Baseline NRS	4 (4-5)	4 (4-5)	0.88
Baseline WOMAC	32 (30-35)	33 (31-36)	0.77

BMI, body mass index; NRS, Numeric Rating Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2. Mean NRS scores at baseline and follow-up in the two treatment groups. Reported values include mean differences (95% CI) and Bonferroni-adjusted p-values.

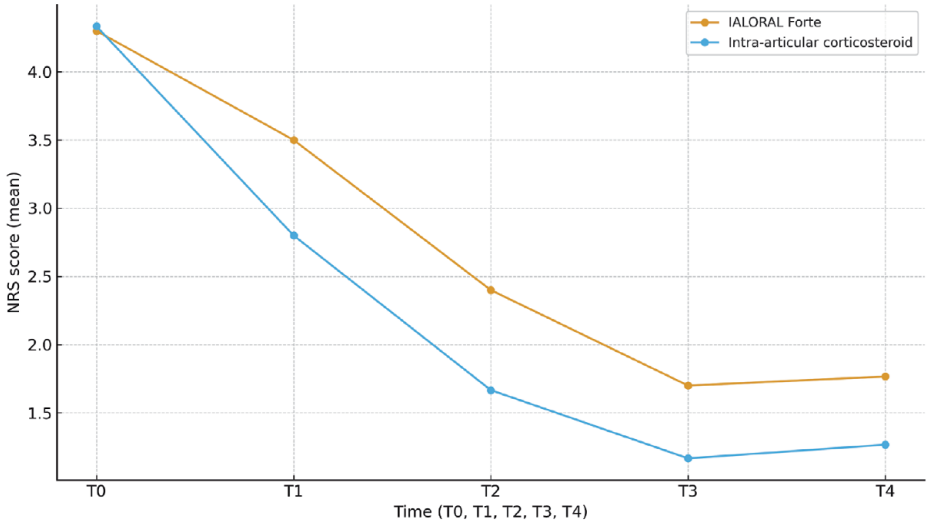
Time point	Intra-articular corticosteroid (mean, 95% CI)	Oral Ialoral® Forte	Mean difference (95% CI), p-value
T0 (baseline)	4.3 (4.1-4.6)	4.3 (4.0-4.6)	0.0 (−0.5 to 0.5), p=1.000
T1 (day 20)	2.8 (2.5-3.1)	3.5 (3.2-3.8)	0.7 (0.2 to 1.2), p=0.0014
T2 (day 40)	1.7 (1.4-1.9)	2.4 (2.1-2.7)	0.7 (0.2 to 1.2), p=0.0007
T3 (day 60)	1.2 (0.9-1.4)	1.7 (1.4-2.0)	0.5 (0.01 to 1.0), p=0.0280
T4 (day 90)	1.3 (1.0-1.5)	1.8 (1.5-2.0)	0.5 (0.01 to 1.0), p=0.0471

CI, confidence interval.

Table 3. Mean WOMAC scores at baseline and follow-up in the two treatment groups. Reported values include mean differences (95% CI) and Bonferroni-adjustedp-values.

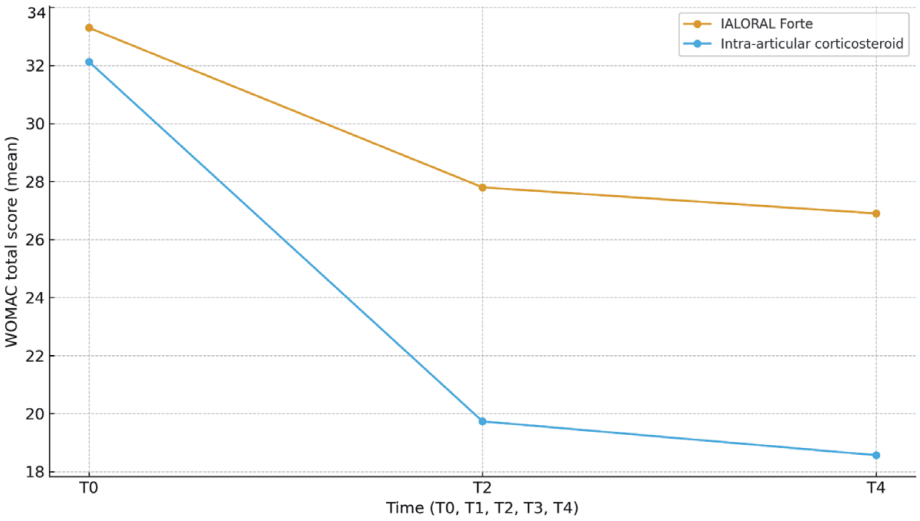
Time point	Intra-articular corticosteroid (mean, 95% CI)	Oral Ialoral® Forte	Mean difference (95% CI), p-value
T0 (baseline)	32 (30-35)	33 (31-36)	1 (−3 to 6), p=1.000
T2 (day 40)	20 (17-22)	28 (25-30)	8 (4 to 13), p<0.0001
T4 (day 90)	19 (16-21)	27 (24-29)	8 (4 to 13), p<0.0001

CI, confidence interval.



NRS, Numeric Rating Scale.

Figure 1. Mean NRS scores over time in patients treated with oral Ialoral® Forte compared with intra-articular corticosteroid injections. Both groups showed progressive pain reduction, with corticosteroids providing a more rapid initial improvement (T1-T2), while Ialoral® Forte maintained a more gradual and sustained effect up to T4 (90 days).



WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Figure 2. Mean WOMAC scores over time in patients treated with oral Ialoral® Forte compared with intra-articular corticosteroid injections. Both groups showed significant improvement, with greater sustained benefit observed in the Ialoral® Forte group at later follow-up (day 40 and day 90).

strategies such as weight loss and strengthening exercises, as well as pharmacological therapies such as acetaminophen, NSAIDs, opioids, intra-articular corticosteroids, and hyaluronic acid. These approaches are primarily symptomatic: they can reduce pain but do not modify disease progression. Moreover, each presents limitations, including gastrointestinal and cardiovascular adverse effects with NSAIDs,[21] accelerated cartilage degeneration with repeated corticosteroid injections, and high costs with hyaluronic acid of uncertain efficacy.[11,12,17]

Among pharmacological options, duloxetine has also demonstrated clinically relevant reductions in osteoarthritis-related pain, as supported by randomized trials and meta-analyses.[22,23]

Given these limitations, nutraceuticals have gained increasing attention as potentially safe and cost-effective adjuncts. Hydrolyzed collagen has shown the ability to stimulate chondrocytes to produce type II collagen and proteoglycans, suggesting a possible reparative or protective effect on articular cartilage. Based on this rationale, we investigated a novel formulation, Ialoral® Forte, which combines hydrolyzed collagen with other bioactive components. This aligns with prior reviews supporting the beneficial effects of collagen hydrolysate in osteoarthritis.

In this single-center retrospective pilot study, we compared oral

Ialoral® Forte with intra-articular triamcinolone acetonide in patients with Kellgren-Lawrence grade I-II hip or knee OA and baseline NRS≤5. Both interventions resulted in significant improvements in pain and joint function. However, while corticosteroid injections achieved more rapid pain relief in the early phase, Ialoral® Forte demonstrated sustained benefits on both NRS and WOMAC scores during follow-up, with a favorable safety and cost profile.

Overall, these findings suggest that Ialoral® Forte may represent a promising nutraceutical option for patients with early-stage hip and knee OA, either as an alternative or complementary approach to intra-articular corticosteroids. Larger, prospective, and randomized studies are warranted to confirm these preliminary observations.

Study limitations and future directions

This study has some limitations, primarily the small sample size and its retrospective design, which restrict the generalizability of the findings. Future research should focus on prospective, multicenter randomized controlled trials with larger cohorts and extended follow-up (12-24 months). Additional endpoints, such as quality of life assessed through validated questionnaires and objective range of motion measurements, should also be included to provide a more comprehensive evaluation of treatment efficacy.

Conclusions

Both treatments demonstrated significant analgesic and functional benefits in patients with mild-to-moderate hip and knee osteoarthritis. Intra-articular corticosteroid injections provided more rapid short-term pain relief, but their repeated use is limited by safety concerns. Conversely, Ialoral® Forte, with its favorable safety profile and suitability for continuous administration, appears particularly appropriate for long-term management aimed at preserving joint functionality.

In summary, in patients with Kellgren-Lawrence grade I-II hip and knee OA and baseline NRS≤5, oral Ialoral® Forte was statistically comparable to intra-articular corticosteroid injections in terms of efficacy, while avoiding the risks and contraindications associated with invasive intra-articular procedures.

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