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Dual intra-articular injections of corticosteroid and hyaluronic acid versus single corticosteroid injection for ankle osteoarthritis: a randomized comparative trial

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Abstract

Background Intra-articular corticosteroid injection is commonly used for pain relief in ankle osteoarthritis (OA). The effects of corticosteroids (CS) are short-lived, whereas hyaluronic acid (HA) have longer-lasting effects. The objective was to compare the efficacy of dual injections of CS and HA to CS alone. We hypothesized that intra-articular injections of dual agents would be more effective than CS alone.

Methods A single-blind, randomized, controlled trial was designed to investigate this hypothesis. 135 patients with ankle OA were enrolled into an intra-articular CS injection group (CS group, $n=61$) or dual HA plus CS injection group (CS + HA group, $n=74$). The CS group received 1 mL of corticosteroid and 1 mL of 0.5% bupivacaine and 1 mL of normal saline once, and the CS + HA group received 3 mL of a total of 5 mL mixtures containing 2 mL of HA, or 1 mL of corticosteroid, 0.5% bupivacaine, and normal saline in the first week, followed by 2 mL of HA in the second and third weeks. Clinical evaluations were performed before injection, 6 and 12 weeks after the first injections. The Ankle Osteoarthritis Scale (AOS) was used as the primary outcome measure, and the Visual Analogue Scale (VAS), Short Form Health Survey (SF-36), and complications were used as secondary outcomes.

Results The mean AOS change from baseline was significantly greater in the CS + HA group than in the CS group at 6 ($p \leq 0.01$) and 12 weeks ($p \leq 0.01$). The mean VAS change from baseline was significantly greater in the CS group than in the CS + HA group at 6 weeks ($p=0.023$), but not at 12 weeks ($p=0.731$). The mean SF-36 change from baseline was not significant between the CS and CS + HA groups at 6 ($p=0.416$) and 12 weeks ($p=0.215$).

Conclusions The combination of corticosteroid and HA injection is more effective than corticosteroid alone in relieving pain in ankle OA.

Trial registration Clinical Research Information Service in South Korea, KCT0008690 // Registration Date (First Posted): July 21th, 2023 (http://cris.nih.go.kr).

Keywords Ankle, Osteoarthritis, Injection, Steroid, Hyaluronic acid

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Background

Introduction

Ankle osteoarthritis (OA) can have a devastating impact on quality of life due to pain and functional limitations [1–4]. In addition, unlike hip or knee OA, ankle OA affects a large proportion of younger age groups due to its high relevance of post-traumatic etiology [1]. Owing to its onset at a relatively young age, appropriate nonoperative treatments including lifestyle modification, analgesics, orthotics, and intra-articular injections are critical to delay operative treatment [4]. Based on the findings of Tejero et al. [1] intra-articular injections demonstrated relatively better outcomes compared to other conservative treatments like other orthotics or braces for ankle OA. This supports the rationale for focusing on injection therapies in this study.

One of these options, intra-articular corticosteroid injection was first introduced as a treatment for OA in 1951 and performed worldwide [5]. Although there is a paucity of published data regarding the influence of an intra-articular corticosteroid (CS) injection for ankle OA, some studies have shown its improvements of clinical symptoms for ankle OA [5–7]. Its mechanism of action is to decrease inflammation in synovial tissues and inflammatory cell numbers in affected joints [8]. Currently, intra-articular CS injection is a widely adopted non-surgical treatment for managing OA in many joints due to rapid action and cost-effectiveness [9]. However, intra-articular injection of CS is effective for only up to 4 weeks, and long-term corticosteroid treatment can cause joint destruction and tissue atrophy [10, 11].

Hyaluronic acid (HA) which was first approved by the Food and Drug Administration (FDA) in 1997 for knee OA, has been administered in various joints, and shown to be effective in OA as a visco-supplementation [12, 13], which refers to synovial fluid replacement by intra-articular injection [14, 15]. HA, which consists of normal joint fluid, is a high-molecular polysaccharide composed of N-acetylglucosamine and glucuronic acid [16, 17]. Intra-articular injection of HA replenishes joint fluid loss, protects damaged articular cartilage, and eventually diminishes pain by relieving OA-related inflammatory changes [18]. Previous randomized controlled trials showed that intra-articular HA injection has long-term effects similar to those of intra-articular corticosteroid injection and fewer side effects [17, 19–21].

Generally, the combined use of CS with various agents, including local anesthetics, has been well-documented in numerous studies. The design of this present study was significantly affected by such prior research [22–25]. However, to our knowledge, no report has been issued on the effect of dual injection of CS and HA for ankle OA. Thus, the purpose of this study is to prospectively show that dual therapy offers a superior alternative for both short- and long-term management. Given the cost-effectiveness and the insurance regulations of various nations including South Korea, CS injection is widely used clinically. We hypothesized that dual intra-articular injections of HA and CS would provide faster, longer-term pain relief than corticosteroid alone in patients with ankle OA.

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Adult patients (> 18 years) who failed to respond to ≥ 3 months of other conservative treatments
Primary ankle osteoarthritis
Varus ankle osteoarthritis
Patients with a follow-up period of > 12 weeks
Exclusion criteria
Rheumatoid arthritis or osteonecrosis caused by another illness (hemophilia or Charcot arthropathy)
Valgus ankle osteoarthritis
Traumatic ankle osteoarthritis
History of intra-articular injection or surgery related to ankle osteoarthritis
Suspicion of pyogenic or inflammatory arthritis
Recent infection history or current cellulitis
Other confounding conditions, such as severe vascular insufficiency and recent sciatica

Materials and methods

Study design

This study was approved by the institutional review board and was conducted following approval of the health authority by Clinical Research Information Service (CRIS) of Korea Disease Control and Prevention Agency (KDCA). The trial has been registered in the CRIS.nih.go.kr database. This also adheres to the CONSORT 2010 guidelines and was performed in accordance with the described procedures in the approved study protocol. Informed consent was obtained from each patient. There have been no changes in the trial protocol after the trial commencement. The detailed protocol was provided in Supplementary Information.

Participants

The study was conducted on patients that met the inclusion and exclusion criteria in full as described in Table 1. This study was conducted to evaluate the effect of adding HA injection to CS injection. Therefore, the control group was set as CS injection alone, and the experimental group was set as dual injection of CS and HA. The injection method of each agent was determined based on the method implemented in previous studies [23, 26, 27]. The CS injection was performed once, and the HA injection was performed three times at one-week intervals [22]. This study is not a fully single-blinded because of the different number of injections between the two groups, however, participants were not informed about

the number of injections to eliminate bias that might be introduced by the different number of injections.

Patients were randomized to receive an intra-articular CS injection (CS group) or intra-articular injections of CS and HA (CS + HA group). Patients were followed-up for 6 and 12 weeks after first injections. Only unilateral injections with more severe side were performed and counted in this study. In this study, we defined traumatic arthritis as having a fracture around the ankle, surgery for severe ankle instability, or three or more repetitive sprains, and excluded these cases from the study.

Randomization

All the study was designed parallelly. From November 2015 to July 2022, patients who were decided to receive the intra-articular injection due to ankle OA via our tertiary orthopedic hospital were recruited and randomly assigned to the CS or CS + HA group by using a permuted block design of two. Randomization was conducted using a computer-generated allocation program (nQquery Advisor PPS 6.01, Saugus, MA, USA) that assigned numbers in strict chronologic. Randomization was stratified by age and OA stage, as defined by the modified Takakura classification [28]. The randomization was conducted by an independent researcher. Each study participant was allocated a unique randomized number.

Injection methods

Before first injections, radiographic evaluations were performed using weight-bearing ankle anteroposterior (AP) and lateral radiographs and hindfoot alignment radiographs [29, 30]. All radiographs were obtained digitally, and radiographic parameters were measured using a Picture Archiving Communication System (PACS; Infinity, Seoul, Korea). Ankle OA was classified using the modified Takakura classification. An orthopaedic attending professor and an orthopaedic resident independently determined classifications twice at four-week intervals independently. When disagreement arose, the patient's radiograph was replaced with another considered more representative until consensus was achieved.

A standard sterile skin preparation technique was performed around the ankle joint, and an intra-articular injection was performed medial to the tibialis anterior tendon in the same location used for the anteromedial portal during ankle joint arthroscopy. Since this study was undertaken to investigate the effects of HA plus CS versus CS alone, we decided to add HA to the conventional intra-articular corticosteroid injection regimen [31]. In the CS group, 3 mL of mixture including 1 mL of corticosteroid (2.5 mg/mL, Triam®, ShinPoong Pharmaceuticals, Seoul, Korea), 1 mL of 0.5% bupivacaine (bupivacaine HCl®, Hana Pharm, Seoul, Korea), and 1 mL of normal saline were injected slowly [32]. In the CS + HA group, 2 mL of HA (sodium HA, molecular weight, 3000 kDa; 2 mL, Hyruan Plus®; LG Life Sciences, Iksan, Korea) and 3 mL of mixture including 1 mL of corticosteroid, 1 mL of 0.5% bupivacaine, and 1 mL of normal saline were mixed and 3 mL of total 5 mL was injected on the first week, followed by single injections of 2 mL of HA on the second and third weeks [26, 27]. Patients taking analgesics or NSAIDs stopped at least 7 days before the pre-injection assessment. All oral analgesics were prohibited during the study, and patients who required additional analgesics for uncontrolled pain were excluded from the study.

Outcome assessments

The clinical evaluation was performed by an experienced nurse blinded to group-allocation. Clinical evaluations were performed prior to injections (baseline) and at 6 and 12 weeks after first injections. Clinical evaluations were performed using the Ankle Osteoarthritis Scale (AOS), the 36-item Short Form health survey (SF-36), the visual analogue scale (VAS), and complications after injection [33, 34].

AOS is a patient-rated, validated measurement that contains pain and disability subscales (9 items each). Each item ranges from a score of 0 representing no pain or disability to a score of 10 indicating worst pain or disability [33, 35]. VAS for pain is commonly used, and a score of 0 represents 'no pain' and a score of 10 'worst pain imaginable'. SF-36 is one of the most widely used generic scales and has been tested for validity and reliability. It includes eight scaled scores, which are the weighted sums of the questions in their respective sections. These eight scales are further aggregated into two summary measures: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). PCS score ranges from 0 to 100, standardized with a mean of 50 and a standard deviation of 10 in the general US population [36, 37].

AOS was used as the primary outcome assessment tool due to its reliability and specificity for evaluating ankle OA [33, 34]. Secondary outcomes included VAS, SF-36, and complications after injection. All the parameters before and after injection were evaluated within the CS and CS + HA groups, and between these groups. Given the significant baseline differences in VAS and SF-36 scores, median changes from baseline to 6 and 12 weeks after injection were compared, along the occurrence of complications.

In addition, subgroup analysis was performed to analyze clinical outcomes according to staging of ankle OA in the CS and CS + HA groups. AOS, SF-36, and VAS before and after injection were analyzed in each stage of ankle OA by modified Takakura classification [28, 29] in the CS and CS + HA groups.

Patients were sufficiently informed of possible complications. For assessment purposes, complications were dichotomized as major or minor. Minor complications included injection site pain and superficial swelling manageable without special procedures, and major complications included neurovascular injury and deep ankle joint infection requiring additional treatment. Complications were assessed and recorded at each follow-up visit. The discontinuation of the study protocol was set as the occurrence of major complications or voluntary subject's desire.

Sample size

To determine the appropriate number of participants, we performed a power analysis. This helps ensure that our study is statistically reliable. We used a two-tailed matched-pairs t-test with the following settings: an effect size of 0.25 for our primary outcome measure, a significance level (alpha) of 0.05, and a power of 0.80. Additionally, we factored in a 10% dropout rate [38, 39]. Based on these criteria, we calculated that we needed a total of 141 patients to achieve reliable results.

Statistical analysis

We analyzed the data using SPSS 17.0 software (SPSS, Chicago, IL). Results are presented as means and standard deviations. First, we checked if the data followed a normal distribution using the Shapiro-Wilk test. For comparisons between groups, we used chi-squared tests for categorical data and independent t-tests for continuous data. Within each group, we compared pre- and post-injection data using paired t-tests. We also used Analysis of Variance (ANOVA) for within-group comparisons over time, applying a Bonferroni post hoc test for pairwise comparisons. (small 0.01; medium 0.06; large 0.14). Effect sizes were reported using partial eta squared values. A significance level of $p < 0.05$ was used, adjusted to 0.016 for repeated measures ANOVA to account for multiple comparisons.

Minimum clinically important difference (MCID)

The MCID represents the smallest change in a treatment outcome that an individual patient would identify as important [40]. To calculate MCID, we used two main approaches: anchor-based and distribution-based methods [41]. The anchor-based method relies on external criteria or 'anchors,' such as patient-reported improvement [42, 43]. The distribution-based method uses statistical calculations, often defining MCID as half of the standard deviation of the change scores between pre- and post-treatment [44]. While there is no universally superior method, these approaches help us understand the clinical significance of our results.

Results

Patient characteristics

From November 2015 to July 2022, 238 patients with ankle OA were screened. After exclusions (Figs. 1), 135 patients met the inclusion criteria and were randomly assigned to either the CS group or the CS + HA group. The demographic details of these groups are summarized in Table 2, showing no significant differences between them.

Primary outcome

For the Ankle Osteoarthritis Scale (AOS), there was no significant improvement in the CS group at 6 ($p = 0.761$) and 12 weeks ($p = 0.893$) after injection compared to baseline. However, the CS + HA group showed significant improvements at both 6 ($p \leq 0.01$) and 12 weeks ($p \leq 0.01$) compared to baseline. Overall, the improvement in AOS scores was significantly greater in the CS + HA group than in the CS group (repeated measures ANOVA $p < 0.001$), with mean changes from baseline being significantly higher in the CS + HA group at both 6 ($p \leq 0.01$) and 12 weeks ($p \leq 0.01$). These results were depicted in Table 3.

Secondary outcomes

Both groups exhibited significant improvements in VAS and SF-36 scores at 6 ($p \leq 0.01$ for both groups) and 12 weeks ($p \leq 0.01$ for both groups) after injection compared to baseline. When comparing the groups, the CS group showed a greater mean VAS improvement at 6 weeks ($p = 0.023$) but not at 12 weeks ($p = 0.731$). Both groups showed significant improvements in PCS scores of the SF-36 at 6 ($p \leq 0.01$ for both groups) and 12 weeks ($p \leq 0.01$ for both groups) after injection compared to baseline, but there were no significant differences between the groups at either 6 ($p = 0.416$) or 12 weeks ($p = 0.215$). No major or minor complications were reported in either group at 6 or 12 weeks after injection. The following results were described in detail in Table 3; Fig. 2a. and 2b.

Correlation with modified Takakura classification

Figure 3 illustrates the changes in AOS, VAS, and SF-36 from baseline to 6 and 12 weeks after injection for two treatment groups across different stages of ankle OA. For AOS, the CS group shows minimal changes over time, whereas the CS + HA group exhibits a significant decrease, especially at stages 2 and 4. In VAS, both groups show a reduction over time, with the CS + HA group experiencing a more significant decline. The SF-36 scores increase for both groups, indicating an improvement. Overall, the CS + HA group demonstrates a tendency to exhibit more significant changes in comparison to the CS group across all parameters.

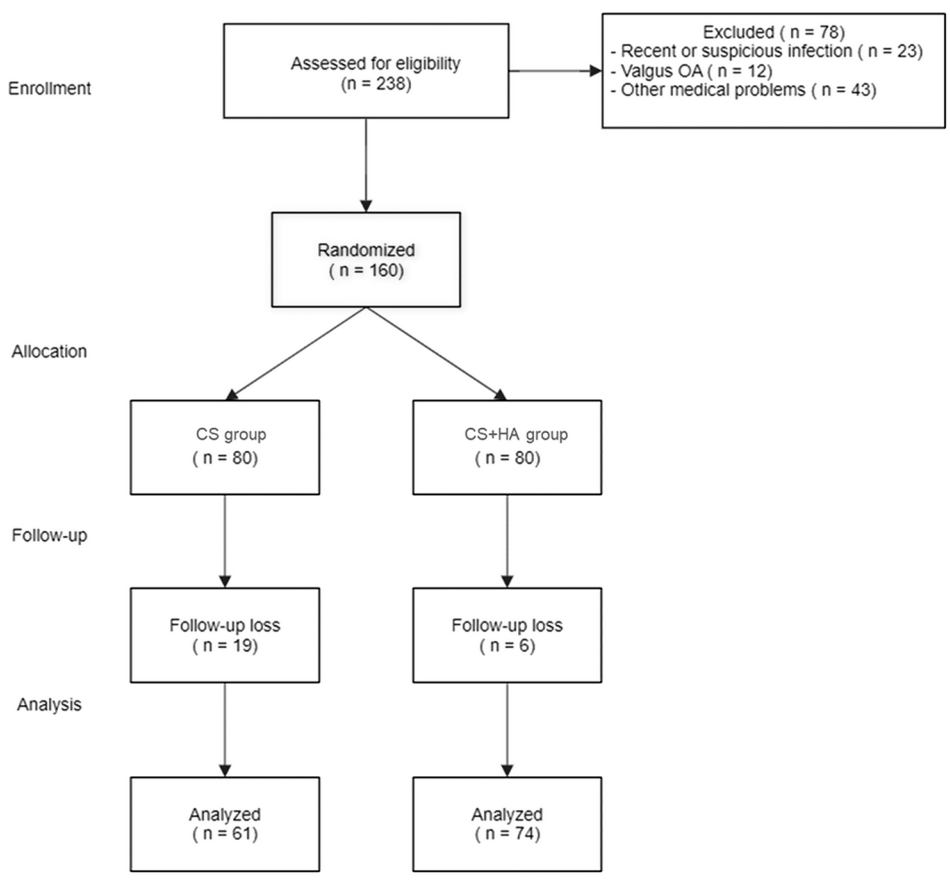

Fig. 1 Flow diagram of patient enrollment

Table 2 Demographic data

	CS group (*n* = 61)	CS + HA group (*n* = 74)	*p*-value
Age (years)*	60.5 ± 9.46 (29–82)	58.8 ± 9.84 (38–86)	0.319
Sex (male / female)	39 (60.9%) / 22	43 (58.1%) / 31	0.490
BMI (kg/m^2)*	25.7 ± 3.0	25.5 ± 3.6	0.698
Modified Takakura classification			0.942
2	35 (57.4%)	45 (62.2%)	
3A	14 (23.0%)	15 (20.3%)	
3B	8 (13.1%)	8 (10.8%)	
4	4 (6.6%)	5 (6.8%)	

BMI, body mass index

*The continuous values are presented as means ± standard deviations with ranges and categorical values as numbers and percentages

Table 3 Mean changes between baseline versus 6 and 12 weeks after injection

	Outcomes (95% CI)	CS group	CS + HA group	*p*-value
From baseline to 6 weeks	AOS	1.48 ± 37.64 (-11.11, 8.16)	-21.15 ± 23.59 (-26.61, -15.68)	< 0.01*
	VAS	-1.69 ± 1.16 (-1.99, -1.39)	-1.26 ± 1.00 (-1.49, -1.03)	0.023*
	SF-36	12.41 ± 14.74 (8.63, 16.18)	10.67 ± 9.97 (8.35, 12.98)	0.416
From baseline to 12 weeks	AOS	0.61 ± 35.23 (-8.42, 9.63)	-20.74 ± 27.89 (-27.20, -14.28)	< 0.01*
	VAS	-1.84 ± 1.42 (-2.20, -1.47)	-1.92 ± 1.33 (-2.29, -1.61)	0.731
	SF-36	9.86 ± 18.31 (5.17, 14.57)	13.23 ± 13.04 (10.21, 16.25)	0.215

CI, confidence interval; AOS, ankle Osteoarthritis Scale; VAS, visual analogue scale; SF-36, short form-36

p values of < 0.05 were considered significant (marked as asterisk, "*")

MCID of each clinical parameter

The calculated MCID values for AOS, VAS, and SF-36 at each time point are shown in Table 4. Approximately half of the patients in both groups did not achieve the MCID for AOS (39% in the CS group and 49% in the CS + HA group at 6 weeks; 31% in the CS group and 39% in the CS + HA group at 12 weeks). For VAS, over 70% of patients in both groups achieved the MCID (76% in the CS group and 80% in the CS + HA group at 6 weeks; 76% in the CS group and 72% in the CS + HA group at 12 weeks). For SF-36, 48% in the CS group and 47% in the CS + HA group achieved the MCID at 6 weeks, and

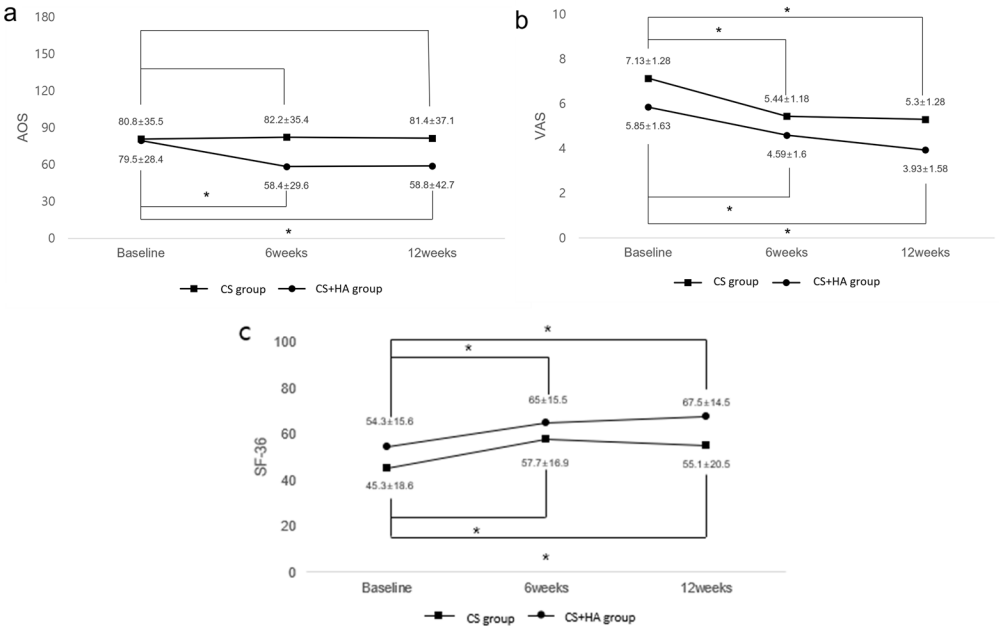

Fig. 2 Clinical results including Ankle Osteoarthritis Scale (**A**), Visual Analogue Scale (**B**), Short Form-36 (**C**) between the groups. Results are presented as mean values ± standard deviations at each time point

* Values followed by an asterisk denote significant differences (adjusted *p*-value according to post-hoc test was used, < 0.016*)*

47% in the CS group and 58% in the CS + HA group at 12 weeks.

Discussion

This randomized controlled trial compared the efficacy of dual intra-articular injections of CS + HA versus a single injection of CS in patients with ankle OA. The primary outcome, AOS scores, showed significantly greater improvement in the CS + HA group compared to the CS group at both 6 and 12 weeks. Secondary outcomes, including VAS and SF-36 scores, also showed significant improvements in both groups, with the CS + HA group generally exhibiting more substantial and sustained benefits, particularly in early-stage OA. The results suggest that dual injections provide superior and longer-lasting pain relief and functional improvement compared to corticosteroid alone, making it a more effective treatment option for ankle OA.

The results of our study are consistent with previous researches [27, 45, 46]. A meta-analysis of eight randomized controlled trials found that combined intra-articular injection of CS and HA resulted in greater short-term (2–4 weeks) and long-term (24–26 or maximum 52 weeks) reductions in WOMAC pain scale scores compared with HA alone for knee OA [27]. Another study showed significant pain relief with dual injections of HA and CS compared to a single CS injection for post-traumatic subtalar OA [47]. Despite some variations in results, the dual injection method was generally preferred. Notably, no previous studies have investigated this approach for the ankle OA.

Several conservative treatment options have been introduced for ankle OA, and an intra-articular injection is commonly indicated for patients showing inadequate response to medication [48]. Corticosteroid is one of the most commonly used agent because of their rapid onset of action and cost-effectiveness [49, 50]. However, recent studies have reported that its effects last only up to 4 weeks and that its adverse effects include cartilage and soft tissue destruction and cytotoxic effects on chondrocytes. Furthermore, infections, calcifications, and acute synovitis have been reported. Consequently, the execution of multiple corticosteroid injection poses challenges.

HA is a component of normal synovial fluid, in which it acts as a viscosity enhancer and volume expander, thus contributing to shock absorption [51]. In terms of pharmacokinetics, intra-articular HA remains effective for varying periods, depending on the molecular weight of the formulation and types of joints treated. The clinical effects of HA tend to act from days to several weeks. Kim et al. [24] reported HA products with an average molecular weights of ≥ 300 kDa have been effective in reducing pain at 12 weeks after the last injection for knee OA. Accordingly, the relevant product item and follow-up period was determined. Furthermore, Kotz et al. [52] reported in a multicenter study that the effects of intra-articular HA were maintained up to 12 months after injection in 55% of 108 patients with knee OA. Although various studies have reported varying durations for the

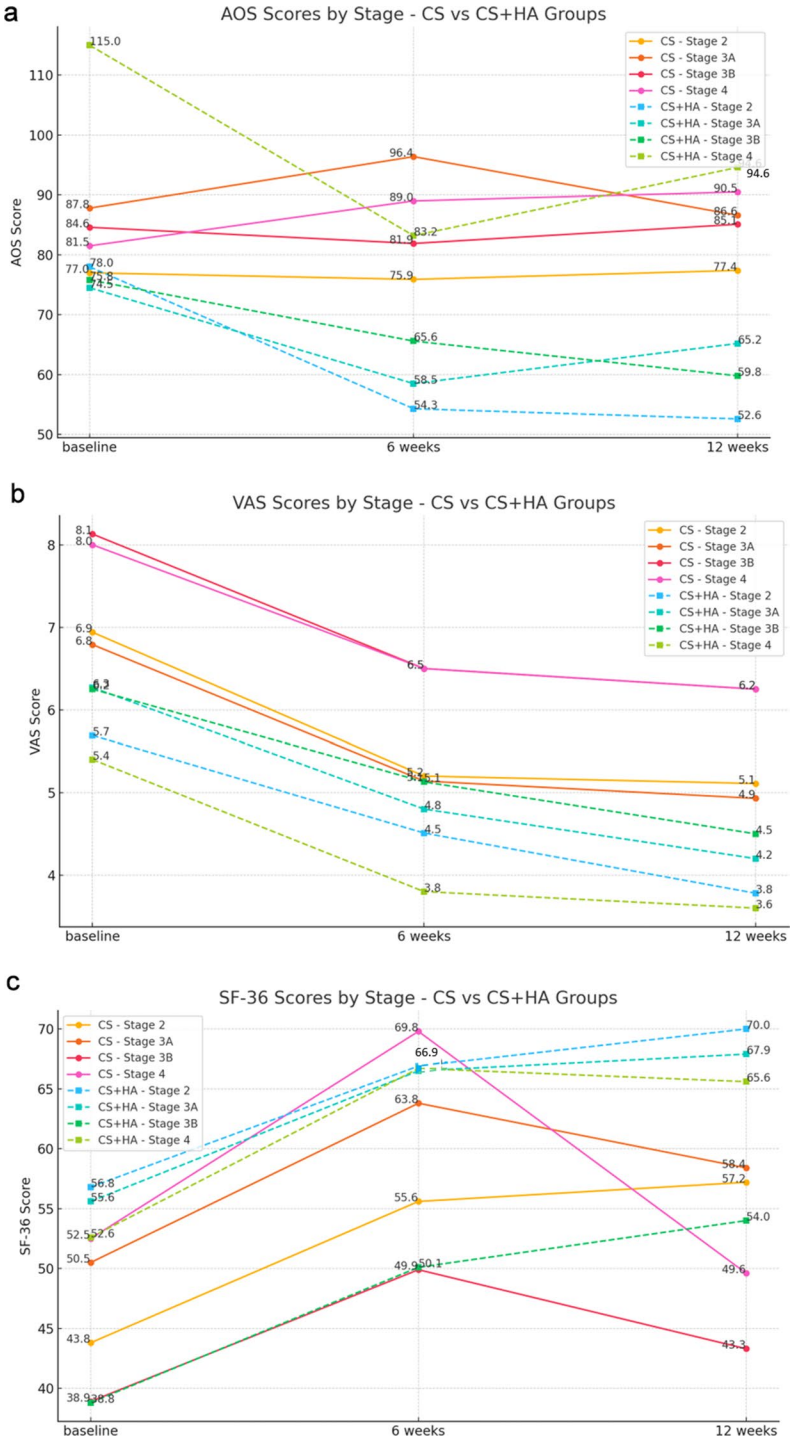

Fig. 3 Illustrations of the changes in clinical outcomes (AOS, VAS, and SF-36) by group and time point across different OA stages are presented. Solid lines represent the CS group, while dotted lines represent the CS + HA group, showing the overall trend. All changes are depicted as differences from baseline

effects of HA, our study adopted the 12-week follow-up period, which might be considered an enough period that can distinguish a shorter duration of CS monotherapy and long-term effects of dual therapy, given the short-term effects of CS monotherapy. 12-week period was considered as a common timeframe suggested by various studies [24, 53, 54]. In our study, we also verified the benefits of HA or HA + CS injection regimen for ankle OA and demonstrated treatment safety, optimal dosage [20, 55].

It is acknowledged that the difference in the number of injections between the two groups, which could

Table 4 Calculated MCID values based on SD approach

		AOS	VAS	SF-36
CS	6 weeks after injection	18.82	0.58	7.37
	12 weeks after injection	17.11	0.71	4.96
CS + HA	6 weeks after injection	11.76	0.50	9.16
	12 weeks after injection	13.95	0.67	6.52

MCID, minimum clinically important difference; SD, standard deviation; AOS, ankle Osteoarthritis Scale; VAS, visual analogue scale; SF-36, short form-36

be perceived as a limitation in maintaining the parallel design of this study. However, this imbalance was deliberately chosen based on some studies supporting the efficacy of multiple HA injections. A systemic review and meta-analysis by Concoff et al. [22] found that three weekly injections of HA provided significantly greater pain relief and functional improvement than a single injection. In addition, Witteveen et al. [23] reported that three weekly injections of HA resulted in better clinical outcomes than a single injection in patients with OA. Although this resulted in a different number of injections between two groups, the authors chose to provide an effective treatment regimen that reflects clinical practice and increase the potential benefits.

A low incidence of side effects has been reported with intra-articular HA injection [56]. Special caution is required for acute pseudo-septic arthritis or a synovial flare [57]. Its clinical presentation is similar to infectious arthritis, but its mechanism is known to be related to high production of proinflammatory cytokines and hypersensitivity reactions; hyaluronan and CD44 have a ligand-receptor association that may increase the recruitment of inflammatory cells [58]. Because it is not a self-limiting disease, anti-inflammatory treatment is necessary in many cases. Once septic arthritis is excluded, intra-articular corticosteroid could be one of the treatment options [57, 59, 60]. On the other hand, the possible adverse effect related to CS includes cartilage deterioration, especially with repeated uses. One relevant study has shown that CS may lead to accelerated cartilage breakdown with frequent injections [53]. In order to prevent its effect, in this study, single usage of CS is determined. There have been no documented side effects specific to the combination use of CS and HA in previous studies. Therefore, special cautions were prepared to address the side effects commonly associated with each individual injection. Fortunately, none of the major adverse effects previously mentioned were reported throughout this study.

Several studies on HA injections have indicated a link between OA stages and treatment effectiveness. One such study found that early- and mid- stage knee OA (Kellgren-Lawrence stage 2 or 3) exhibited greater clinical improvements compared to end-stage OA [61, 62]. In a prospective study by Lee et al. [19], 37 patients with ankle OA received three weekly HA injections. The study compared baseline AOS, VAS, and AOFAS ankle-hindfoot scores with those at 6 months after injection across different OA stages. The results suggested that clinical outcomes worsened with advancing stages, with HA injections reducing pain more effectively in early or intermediate-grade ankle OA. Our study found similar results: patients in the CS + HA groups with early-stage OA (Stage 2 and 3 A) showed significant clinical improvements, while those with end-stage OA (Stage 3B and 4) did not. Thus, we believe that CS provides effective short-term pain relief, while HA offered longer-term benefits.

In the present study, MCID values provide a critical benchmark for assessing the clinical significance of treatment outcomes. MCID values were calculated using both anchor-based and distribution-based methods. These values indicate that a significant proportion of patients experienced clinically meaningful improvements following the dual intra-articular injection, particularly in terms of pain relief and quality of life. These results are consistent with previous research indicating that achieving the MCID reflects meaningful clinical improvements [40, 41].

Our study has several limitations. First, although this was a randomized controlled trial, the difference in the number of injections between the two groups is a limitation. The CS group received one injection while the CS + HA group received three, which affects the blinding process. However, since the participants were not informed of the regimen and number of injections, we consider this study to be single-blind. In addition, the use of three HA injections as a control could address this limitation. Second, the relatively short follow-up period limits our ability to comment on the long-term effects of HA. One literature [49] suggests that the effects of HA begin to manifest 1 week after injection and peak between 5 and 13 weeks. Given the challenges of long-term follow-up for nonsurgical treatments, we chose 6- and 12-week follow-up visits to assess effectiveness. The reason we did not set a follow-up period longer than 12 weeks is that we determined CS would not be effective beyond this point. Therefore, we believed that this period would show the long-term effects we aimed. However, further studies with longer follow-up period over 12 weeks would strengthen our conclusions. Third, baseline scores before injection differed between the two groups. To address this, we compared median changes between pre- and post-treatment status rather than absolute values. Lastly, the discrepancy in the final number of patients enrolled (61 in the CS group versus 74 in the CS + HA group) was due to factors such as patient dropout and exclusion based on eligibility after randomization, not a flaw in the study design. Despite these differences, we maintained rigorous randomization

and blinding protocols to minimize bias. We believe that further studies with longer follow-up periods and larger sample sizes are recommended to further validate these findings and explore the long-term effects of this treatment regimen.

Conclusion

This randomized controlled trial demonstrates that dual intra-articular injections of corticosteroid and hyaluronic acid (CS + HA) provide superior pain relief and functional improvement compared with a single corticosteroid (CS) injection in patients with ankle osteoarthritis. Despite the limitations, our study supports the efficacy and safety of dual injections as a more effective treatment option for ankle OA.

Abbreviations

CS	Corticosteroid
HA	Hyaluronic acid
TA	Tibialis anterior
OA	Osteoarthritis
AOS	Ankle osteoarthritis scale
VAS	Visual analog scale
SF-36	Short form of 36
PCS	Physical component summary
ANOVA	Analysis of variance
MCID	Minimum clinically important differences

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-025-08488-0.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

Not applicable.

Author contributions

CHP participated in study conception and design, contributed data analysis. JJP contributed to data collection. IHW and JJP interpretated data. IHW drafted and revised the article. CHP finally approved the article to be published.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

The study adheres to CONSORT guidelines.

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles described in the Declaration of Helsinki. Prior to commencement, the study protocol was reviewed and approved by Yeungnam University Hospital Institutional Research Ethics Committee (Approval number: YUMC 2019-09-063-011). The recruited patients provided written informed consent prior to enrollment.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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