Observational Study

Medicine®

OPEN

Ultrasound-guided intra-articular injection of hyaluronic acid and ketorolac for osteoarthritis of the carpometacarpal joint of the thumb

A retrospective comparative study

Sung Hoon Koh, MD[a], Sang Chul Lee, MD[a], Woo Yong Lee, MD, PhD[b], Jongwoo Kim, MD[c], Yongbum Park, MD[a,*]

Abstract

Intra-articular hyaluronic acid (HA) is widely used to treat symptomatic osteoarthritis (OA) in the carpometacarpal joint (CMCJ) of the thumb. However, although apparently effective and relatively safe, intra-articular HA injections act relatively slowly. Therefore, a nonsteroidal anti-inflammatory drug could be added for more prompt pain relief. The aim of this study was to compare the efficacy and safety of ultrasound (US)-guided intra-articular injection of HA and ketorolac with that of HA alone in patients with OA of the CMCJ of the thumb.

Seventy-four patients identified by chart review to have a diagnosis of OA of the CMCJ of the thumb received either a US-guided intra-articular injection of 0.5 mL of sodium hyaluronate and 0.5 mL of ketorolac (n = 38) or 0.5 mL of sodium hyaluronate and 0.5 mL of saline (n = 36). Disabilities of the arm, shoulder, and hand (DASH) and verbal numeric scale (VNS) pain scores were recorded before and 1, 3, and 6 months after injection. Univariable analyses (using the chi-squared test) and multiple logistic regression analysis were performed to evaluate the relationship between potential predictors of the outcome (treatment allocation, patient age and sex, duration of pain, and Eaton–Littler classification) and therapeutic effects.

The DASH and VNS scores were improved at 1, 3, and 6 months postinjection in both groups. The onset of pain relief was significantly more rapid (at 1 month) after the injection containing HA and ketorolac than after the injection containing HA alone. In 55.3% of cases, pain and function were improved postinjection compared with baseline and remained so for up to 6 months. The success rate was not significantly different between the assessments at 1, 3, and 6 months, and the univariable analyses did not identify any statistically significant potential predictors of the outcome. Multiple logistic regression analysis did not identify any independent predictors of a successful outcome at midterm follow-up.

The onset of analgesic action was more rapid after an injection containing HA and ketorolac than after 1 containing HA alone in patients with OA of the CMCJ of the thumb. There were no serious complications.

Abbreviations: CMCJ = carpometacarpal joint, DASH = disabilities of the arm, shoulder, and hand, HA = hyaluronic acid, NSAID = nonsteroidal anti-inflammatory drug, OA = osteoarthritis, US = ultrasound, VNS = verbal numeric scale.

Keywords: hyaluronic acid, ketorolac, osteoarthritis, ultrasonography

1. Introduction

Osteoarthritis (OA) of the carpometacarpal joint (CMCJ) of the thumb is associated with pain, reduced grip strength, loss of range of motion, and joint stiffness, leading to impaired hand function and reduced ability to perform activities of daily living.[1] There is still no curative treatment for this condition.[2] The aims of conservative treatment are to relieve pain and to preserve functionality of the thumb, including its stability, mobility, and strength.[2,3] The conservative treatments commonly used are injections (corticosteroids, hyaluronate), analgesics, education on joint protection, strengthening exercises, assistive devices, and an orthosis.[2,3]

Intra-articular corticosteroid injections can be used to treat synovitis refractory to conservative therapy, that is, activity modification, splinting, and nonsteroidal anti-inflammatory drugs (NSAIDs).[4] However, the evidence for the benefits of this treatment is mixed, and frequent use may have local side effects, including depigmentation, calcification of the periarticular soft tissue, weakening of tendons and ligaments, and several mechanical side effects, such as breakdown and loss of elasticity in the articular cartilage.[5–7] There is evidence (level IIb) suggesting that hyaluronate (hyaluronic acid [HA]) is a useful alternative to corticosteroids when treating OA of CMCJ of the thumb.[8] Although published studies are controversial, HA injections have been found to be effective in improving fine hand function for up to 6 months.[9]

Editor: Muhammad Shahzad Aslam.

The authors have no funding and conflicts of interest to disclose.

[a] Department of Physical Medicine and Rehabilitation, [b] Department of Anesthesiology, [c] Department of Family Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Republic of Korea.

[*] Correspondence: Yongbum Park, Department of Physical Medicine and Rehabilitation, Sanggye Paik Hospital, Inje University College of Medicine, Sanggye 7 dong 761-7, Nowon-gu, 139-707, Seoul, Korea (e-mail: swc328@naver.com).

Medicine (2019) 98:19(e15506)

Received: 30 November 2018 / Received in final form: 4 March 2019 / Accepted: 9 April 2019

http://dx.doi.org/10.1097/MD.0000000000015506

HA provides symptomatic relief in patients with OA and has low toxicity, but has a slow onset of action and a small effect size.[10] In previous studies, a single corticosteroid injection was superior to 3 injections of HA at 1-week intervals in reducing pain and improving hand function,[7] but the improvement was better maintained at 6 months after injections of HA than after an injection of a corticosteroid.[11] Therefore, the delayed onset of action of intra-articular injection of HA could be compensated for by administration of an agent that provides more immediate pain relief while waiting for the analgesic effects of HA to appear.

An intra-articular injection containing a nonsteroidal anti-inflammatory drug (NSAID) can be considered as an alternative to corticosteroid injections, which have a number of side effects. A high drug concentration can be achieved at the point of origin of the inflammatory process after intra-articular injection of an NSAID, which could potentially have a more effective anti-inflammatory effect with fewer side effects if used in doses that result in low plasma concentrations.[12] Previous studies have not demonstrated any detrimental effects of injection of NSAIDs into articular cartilage or ligaments or any adverse effects on kinematic function of the native knee in in vivo animal models.[13–15] Ketorolac is a strong NSAID that inhibits cyclo-oxygenase and the prostaglandin enzyme system.[15] The efficacy and safety of intra-articular NSAID injections for reducing pain and functional disability in patients with OA of the knee and hip have been demonstrated during 6 months of follow-up.[12,16] However, there have been no reports on the efficacy and safety of intra-articular injection of a mixture of HA and an NSAID in patients with OA of the CMCJ of the thumb. The aims of this retrospective study were to compare the efficacy and safety of ultrasound (US)-guided intra-articular injection of HA and ketorolac with that of HA alone in patients with OA of the CMCJ of the thumb and to identify predictors of the outcome of treatment.

2. Methods

2.1. Study design

The protocol for this retrospective case–control study of medical chart data was approved by the institutional review board at Sanggye Paik Hospital. The approval included a waiver of the need for informed consent because no direct contact with the patients was required and all identifying information was removed from the data collected. Patient privacy and data confidentiality were maintained throughout the research process. Each patient received detailed information about the procedure and its expected benefits and risks, and was then asked to provide consent.

2.2. Subjects

Between 2015 and 2017, 121 patients with symptomatic OA of the CMCJ of the thumb were referred to our pain clinic and received US-guided intra-articular injection of HA and ketorolac (n = 38) or HA alone (n = 36). The diagnosis of OA of the CMCJ of the thumb was made according to the American College of Rheumatology criteria for classification of OA of the hand.[17]

The following study inclusion criteria were applied: aged 40 years or older; OA that had not responded to conservative management, including anti-inflammatory and analgesic medication or physical therapy performed for at least 4 weeks; grade II or III OA of the CMCJ of the thumb according to the Eaton–Littler radiographic criteria[18]; and pain in the CMCJ joint for at least 3 months. Patients with significant comorbidities (including rheumatologic, inflammatory, or autoimmune disease), those who had received intra-articular injections in the previous 3 months, those with a history of major trauma to the CMCJ, and those with a neurologic disorder, such as cervical radiculopathy, Parkinson disease, or stroke, were excluded.

2.3. Injection techniques

All the intra-articular injections were administered by the same physician (Yongbum Park, who has more than 10 years of experience performing US-guided procedures). All injections were administered on an outpatient basis. The US system used was an Accuvix XQ (Samsung Medison Co. Ltd, Seoul, Korea) with a linear probe at 3 to 12 MHz. The wrist is placed in the supine position for a volar approach, the volar-radial aspect of the metacarpal of the affected thumb was palpated from distal to proximal, and the transducer was oriented parallel to the metacarpal of the thumb along its volar-radial aspect.[19] Maintaining this orientation, the transducer was then slowly moved proximally or distally until a hypoechoic cleft defining the base of the metacarpal of the thumb and the distal aspect of the trapezium were identified.[19] The site where the injection was to be administered was disinfected with povidone–iodine and alcohol and then covered with a sterilization wrap containing pores to expose only the injection site. The procedure was performed while wearing aseptic gloves. The US-guided injection was performed using a plain free-hand technique. Access to the joint cavity was secured and the tip of a 25-gauge 3.8-cm needle was guided. The direction of injection from the needle tip was confirmed to be accurate on a Color Doppler image (Fig. 1). The patients received either an injection containing a mixture of 0.5 mL of sodium hyaluronate and 0.5 mL of ketorolac 30 mg/mL (the HA + ketorolac group) or a mixture of 0.5 mL of sodium hyaluronate and 0.5 mL of saline (the HA group).

The patients were asked to limit movement of the CMCJ for at least 5 to 10 minutes after the injection to allow localization of the injectate within the articular capsule. Because all the subjects did not have significant improvement through analgesics or physiotherapy treatment for 4 weeks before injection, we thought such conservative treatments during our experimental period will have very limited effects on our result. Therefore, all patients were allowed to continue treatment with analgesics and/or physiotherapy during the study period. NSAIDs were switched to acetaminophen or a fixed combination of tramadol and acetaminophen in both study groups. There were no specific additional interventions otherwise. There was no statistically significant between-group difference in the number of patients who received physiotherapy and/or analgesic medication before the trial injection (18 in the HA + ketorolac group and 16 in the HA group; $P > .05$).

2.4. Review of clinical data

A standardized chart abstraction form was used to collect data on demographics, treatments provided, pain severity, use of analgesics, and functional evaluation. All data collection and analyses were performed by an independent reviewer. Follow-up interviews were performed at 1, 3, and 6 months postinjection by nurses who were not involved in the study.

The outcomes were assessed using the disabilities of the arm, shoulder, and hand (DASH) questionnaire and verbal numeric

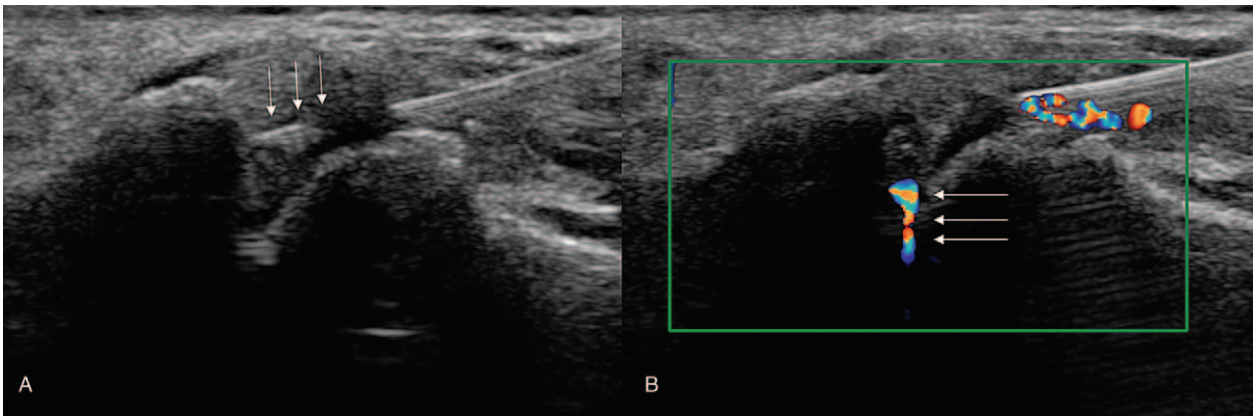

Figure 1. Ultrasound-guided CMCJ intra-articular injection. (A) The needle tip (arrows) was observed within CMCJ space. (B) Color Doppler image showing accurate intra-articular injection (arrows). CMCJ = carpometacarpal joint.

scale (VNS) for pain. The DASH tool is a 30-item disability/symptom questionnaire that assesses the patient's health status during the preceding week.[19] The items ask about the degree of difficulty in performing physical activities because of an arm, shoulder, or hand problem (21 items), the severity of pain, activity-related pain, tingling, weakness, and stiffness (5 items), as well as the impact of the problem on social activities, work, sleep, and self-image (4 items).[20] Each item has 5 response options. The scores for all items are then summed and used to calculate a DASH score ranging from 0 (no disability) to 100 (most severe disability).[20,21]

The VNS is an 11-point scale ranging from 0 ("no pain") to 10 ("the worst pain possible).[22] A successful outcome is defined as a >50% improvement in the VNS score.[20] Patients who underwent surgical treatment subsequent to their US-guided intra-articular injection or required additional NSAIDs during follow-up were considered to be treatment failures.[23] VNS and DASH were confirmed for statistical analysis and excluded afterward. Patients with a successful outcome were defined as responders and those without a successful outcome were defined as nonresponders.

Information on potential independent predictors of the outcome, that is, medications injected, patient age and sex, duration of pain, and Eaton–Littler classification, was extracted from the medical charts. The patients were classified into 4 age groups, that is, 40 to 49, 50 to 59, 60 to 69, and >70 years. The duration of OA of the CMCJ in the thumb was also investigated as a potential predictive variable, and was classified as acute (≤6 months) or chronic (>6 months).

2.5. Statistical analysis

Chi-squared and Mann–Whitney *U* tests were used to compare the characteristics of the 2 study groups, including age, sex, body mass index, Eaton–Littler classification, and duration of pain. The VNS and DASH scores recorded at each assessment point were compared by repeated-measures analysis of variance with Bonferroni correction for post hoc comparison. The chi-squared test was used to test differences in proportions. Fisher exact test was used whenever the expected value was <5. Univariable analyses were performed to evaluate the relationship between potential outcome predictors and therapeutic effect using the chi-squared test. Logistic regression analysis was performed to determine whether the medication injected, age, sex, duration of pain, and Eaton–Littler classification were independent predictors of a successful outcome. All statistical analyses were performed using SAS Enterprise Guide 4.1 (4.1.0.471; SAS Institute Inc, Cary, NC). A *P* value <.05 was considered statistically significant.

3. Results

One hundred twenty-one patients received intra-articular injections during the study period (ketorolac group, n=61; HA group, n=60), of which 74 (61%) satisfied the inclusion criteria for the study. Thirty-five patients (29%) did not complete follow-up so were excluded from the analysis. Further 12 patients (10%) who had previously undergone surgery (n=4) or had underlying rheumatoid arthritis (n=8) were excluded, leaving data for 38 patients who received an US-guided injection of HA with ketorolac and 36 who received HA only for inclusion in the analysis (Fig. 2).

The mean patient age was similar in the study groups (58.79 ± 9.82 years in the HA + ketorolac group and 58.31 ± 10.50 years in the HA group). There was no statistically significant between-group difference in sex distribution, etiology, use of analgesics, Eaton–Littler grade, or duration of pain (Table 1).

There was a significant decrease in the mean VNS score in both study groups at 1, 3, and 6 months postinjection (Table 2). At 1 month, the VNS score was significantly lower in the HA + ketorolac group than in the HA group, but there was no significant difference at 3 and 6 months. There was a significant improvement in the DASH score in both groups at 1, 3, and 6 months postinjection, with no significant between-group difference in the baseline score (Table 3).

Eight patients in the HA + ketorolac group had required further injections in the month following their initial injection and 30 had not, indicating a 1-month success rate of 79%. In the HA group, 6 patients had required repeat injections and 1 patient had undergone surgery in the month after the initial injection and 29 did not require either intervention in this time, indicating a 1-month success rate of 80%. Five patients in HA + ketorolac group and 5 in the HA group required further injections in the 3 months following their initial injection and 25 and 24, respectively, did not indicating respective 3-month success rates of 66% and 67%. In the HA + ketorolac group, 4 patients had required further

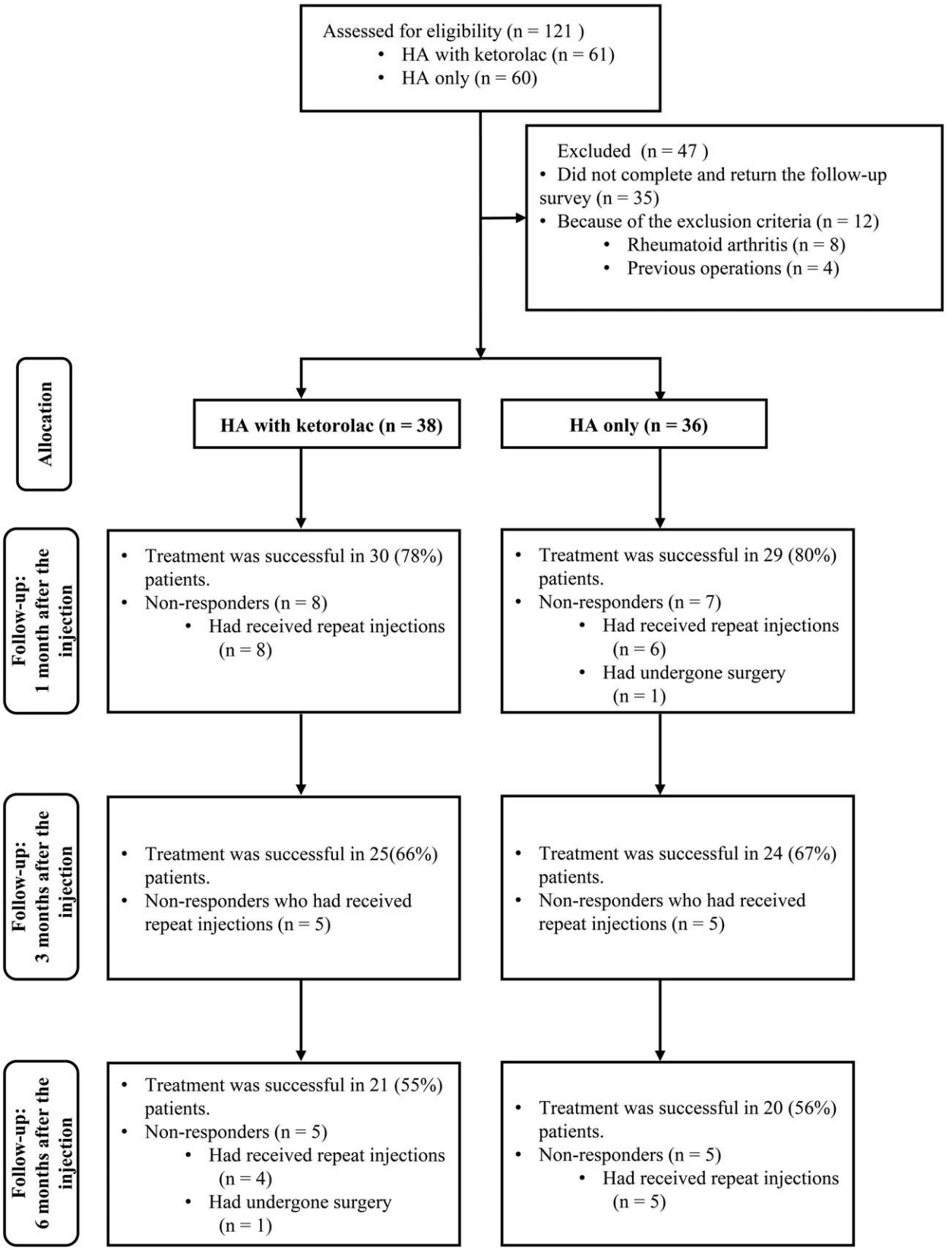

Figure 2. Flow diagram indicating progress of patients through the study. HA=hyaluronic acid.

Table 1

Patient characteristics.

	A group (N = 38)	B group (N = 36)
Sex (male/female)	9/29	8/28
Age, y	58.79 ± 9.82	58.31 ± 10.50
Pain duration, mo	6.76 ± 2.20	6.56 ± 2.27
Body mass index, kg/m^2	23.75 ± 2.32	23.99 ± 2.63
Eaton radiographic criteria (2/3)	22/16	19/17

Values are means ± standard deviation. A group: sodium hyaluronate (0.5 mL) with ketorolac. B group: sodium hyaluronate (0.5 mL) with saline (0.5 mL).

injections and 1 had undergone surgery by the 6-month follow-up and 5 patients in the HA group had required further injections, indicating respective success rates of 55% (n = 21) and 56% (n = 20; Fig. 2).

The proportions of patients in the 2 study groups with a >50% improvement in the VNS score are shown in Fig. 3. The HA + ketorolac group showed a higher treatment success rate at 1, 3, and 6 months, but the difference was not statistically significant. At 6 months, the treatment success rate was 55% in the HA + ketorolac group and 56% in the HA group. There was no clinically meaningful reduction in the proportion of patients who required additional analgesia (NSAIDs or opioids) in either study group at 6 months postinjection.

Univariate and multivariate logistic regression analyses did not identify age, sex, duration of pain, use of analgesics, injection method, or number of injections received to be independent predictors of treatment outcome ($P > .05$; Tables 4 and 5).

No systemic adverse events were reported. There were 5 reports of a mild, transient sensation of pain, and heaviness in the injected joint in the HA + ketorolac group that typically lasted for 2 to 4 days but did not affect the ability to perform activities of daily living. No septic complications were reported.

4. Discussion

This is the first trial to demonstrate the clinical efficacy and safety of intra-articular injection of HA and ketorolac for OA of the CMCJ in the thumb. We found that this injection provided pain relief and improved function in patients who had been refractory to analgesics and physical therapy. In addition, the pain reduction effect at 1 month after intra-articular injection of HA + ketorolac was superior to that of injection of HA alone. Our results suggest that the combined injection may be more beneficial for OA of the CMCJ in the thumb than injection of HA alone in terms of providing more rapid relief of pain and improving the functionality of the hand.

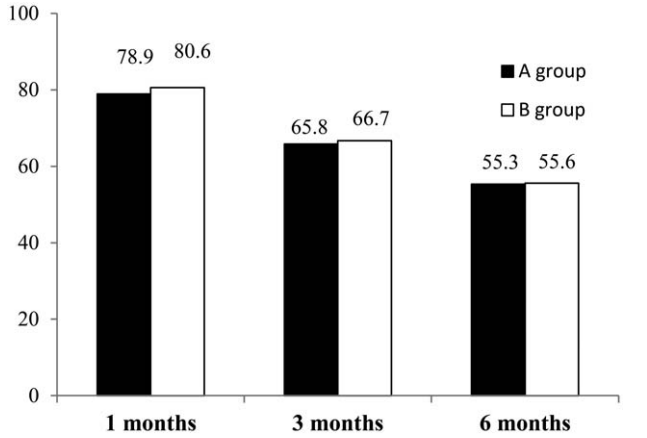

Figure 3. Illustration of significant pain relief (≥50% reduction in verbal numerical scale from baseline). A group: sodium hyaluronate (0.5 mL) with ketorolac; B group: sodium hyaluronate (0.5 mL) with saline (0.5 mL).

HA has an important role in maintaining homeostasis in the joints and is naturally present in synovial fluid.[24] HA concentrations are decreased in the joints of patients with OA.[25] HA is also an effective lubricant and shock absorber, and assists retention of fluid, especially in weight-bearing joints.[25] Therefore, HA is now widely used in injectable form to alleviate pain and improve function in joints with OA and has few adverse effects.[26]

In addition to the physical benefits afforded by an increased concentration of HA in synovial fluid, there is research evidence

Table 2

VNS of the carpometacarpal joint osteoarthritis of the thumb preinjection and postinjection.

	Before injection	1 mo after last injection	3 mo after last injection	6 mo after last injection
A group	6.35 ± 1.16	2.48 ± 1.32*,†	2.81 ± 1.57*	2.80 ± 1.76*
B group	6.37 ± 1.04	3.39 ± 2.01*	2.83 ± 1.72*	2.82 ± 1.62*

Values are means ± standard deviation. A group: sodium hyaluronate (0.5 mL) with ketorolac. B group: sodium hyaluronate (0.5 mL) with saline (0.5 mL).
VNS = verbal numeric pain scale.
* $P < .05$ comparison of VNS score with baseline.
† $P < .05$ A group vs B group.

Table 3

DASH of the carpometacarpal joint osteoarthritis of the thumb preinjection and postinjection.

	Before injection	1 mo after last injection	3 mo after last injection	6 mo after last injection
A group	31.29 ± 5.09	23.29 ± 5.84*	20.73 ± 5.42*	19.04 ± 7.66*
B group	32.53 ± 4.63	24.42 ± 5.84*	21.86 ± 5.84*	19.79 ± 5.98*

Values are means ± standard deviation. A group: sodium hyaluronate (0.5 mL) with ketorolac. B group: sodium hyaluronate (0.5 mL) with saline (0.5 mL)
DASH = disabilities of the arm, shoulder, and hand.
* $P < .05$ comparison of Harris hip score with baseline.

Table 4

Univariable analysis for possible outcome predictors for injection effectiveness at follow-up.

Characteristic	Responders (N = 41)	Non-Responders (N = 33)	*P* value
US-guide IA injection			
A group	21 (51.2)	17 (51.5)	
B group	20 (48.8)	16 (48.5)	.980
Gender			
Male	10 (24.4)	7 (21.2)	
Female	31 (75.6)	26 (78.8)	.747
Age			
40–49	10 (24.4)	7 (21.2)	
50–59	12 (29.3)	11 (33.3)	
60–69	13 (31.7)	9 (27.3)	
>70	6 (14.6)	6 (18.2)	.932
Duration			
<6 month	13 (31.7)	10 (30.3)	
>6 month	28 (68.3)	23 (69.7)	.897
Eaton radiographic criteria			
2	23 (56.1)	18 (54.5)	.894
3	18 (43.9)	15 (45.5)	

A group: sodium hyaluronate (0.5 ml) with ketorolac (0.5 ml).
B group: sodium hyaluronate (0.5 ml) with saline (0.5 ml).

Table 5

Multiple logistic regression analysis for possible outcome predictors for injection effectiveness at follow-up.

Characteristic	OR	95% CI	*P* value
A vs B group	0.928	0.351–2.459	.882
Gender	1.106	0.352–3.476	.863
Age	1.016	0.967–1.067	.526
Duration	1.076	0.859–1.347	.525
Eaton classfication	1.262	0.472–3.371	.623

95% CI = 95% confidence interval, OR = odds ratio.

indicating additional chondroprotective effects, inhibition of immune cells and inflammatory mediators, stimulation of synthesis of proteoglycans and endogenous HA by chondrocytes, and antinociceptive effects.[26] However, the evidence for the ability of intra-articular injection of HA to relieve pain into the CMCJ is mixed. Stahl et al[9] reported that HA injections and corticosteroid injections were both effective in reducing pain in 52 patients with grade 2 OA of the CMCJ during 6 months of follow-up but that HA was more effective in improving some of the fine functions of the hand for up to 6 months. Fuchs et al also compared the effects of HA with those of corticosteroids in a prospective randomized trial in which patients were treated with either 3 intra-articular injections of HA or 3 intra-articular injections of corticosteroids.[11] Effective pain relief and improvement in joint function was achieved in both of the study groups. In the present study, pain relief and functional improvement were maintained in both treatment groups throughout the 6-month study period.

HA is a symptomatic slow-acting drug with low toxicity, but has a small effect size in OA.[11] Moreover, the initial pain reduction effect of HA is lower than that of corticosteroids. Fuchs et al reported that injection of corticosteroids relieved pain more rapidly than injection of HA in patients with OA of the CMCJ of the thumb, with a maximum effect at 2 to 3 weeks after initiation of treatment. In the absence of rapid pain relief, compliance with ongoing treatment may be reduced. Therefore, when injecting intra-articular HA, an additional agent with a rapid onset of analgesic effect should be included.

Addition of a corticosteroid to an HA injection has been found to shorten the delay in onset of analgesic effect in patients with OA of the knee.[27–29] Fraser et al[28] reported that pain intensity decreased more rapidly in a group of patients treated with a combination of HA and dexamethasone and suggested that an intra-articular injection of HA and a steroid might act synergistically. Grecomore et al,[29] who performed experiments in a sheep model, suggested that intra-articular HA might be less effective in an inflamed joint than in a noninflamed joint. They reported that the mean fractional turnover rate of radiolabeled HA injected into inflamed joints was almost twice that in noninflamed joints. These findings support the notion that controlling inflammation in joints with OA might improve the effectiveness of intra-articular injection of HA.[27]

Although intra-articular corticosteroid injections have been widely used because of the relative ease and safety of the technique, a number of potential complications can arise, including fat atrophy, hyperpigmentation or hypopigmentation of the adjacent skin, tendon rupture, and avascular necrosis.[30] NSAIDs are the medications most commonly prescribed for oral treatment of OA. NSAIDs are not corticosteroids, so do not have the adverse effects of corticosteroids but still have strong anti-inflammatory effects.[31] Nevertheless, long-term use of oral NSAIDs is associated with gastrointestinal and renal complications, especially in the elderly.[31] When administered directly to a specific anatomic site, an NSAID is likely to produce higher local tissue concentrations with fewer systemic complications.[31] A previous study reported that injection of

both HA and ketorolac provided better pain relief and more functional improvement than injection of HA alone for up to 3 weeks in patients with degenerative OA of the knee.[27] In the present study, we found a significant decrease in VNS and DASH scores from 1 month post-treatment in our HA + ketorolac group.

Various factors affecting successful clinical treatment will be analyzed in this research. Mallinson et al[32] found that no relationship between the treatment response and findings on US imaging, which demonstrates the ongoing challenges in identifying the patients with OA of the CMCJ of the thumb who may benefit the most from joint injection therapy.[32,33] There is limited literature supporting a relationship between radiological severity and treatment response. Day et al[34] demonstrated that corticosteroid injection with splinting provided reliable, long-term relief in patients with Eaton–Littler grade I arthritis of the CMCJ of the thumb, but not in patients with severe disease. Khan et al[35] found that the duration of symptomatic improvement following unguided injection of triamcinolone and an anesthetic agent decreased as the radiological severity increased. In this study, the radiologic severity of OA did not have an effect on the clinical results, probably because of exclusion of patients with Eaton–Littler grade I and IV diseases. Further studies of the clinical effects of HA + ketorolac injection in patients with different Eaton–Littler grades are needed to establish appropriate treatment guidelines.

The most severe complications associated with the use of ketorolac are acute renal failure and an increased risk of bleeding.[36] However, when it is used appropriately, the risk of renal failure is no greater than that associated with other pain medications.[37] Feldman et al[38] reported that parenteral administration of ketorolac for 5 days or less was associated with the same rate of renal failure (1.1%) as that reported for parenteral opioids. The antiplatelet effect of NSAIDs has been well documented in the literature.[27,28] Strom et al[39] found a weak association between ketorolac and gastrointestinal bleeding (odds ratio: 1.3), especially when the medication was administered for more than 5 days, at doses >105 mg daily, and in patients aged 65 years and older. There were no such side effects in our study; however, we acknowledge that care is needed when administering these injections in older patients and in those with renal or gastrointestinal conditions. Five patients who received the combination injection in our study developed focal postinjection pain that typically lasted for 2 to 4 days. A study of intra-articular injection of ketorolac into the knee also reported focal postinjection knee pain,[27] which could reflect the concentration of ketorolac used. However, in our study, this side effect was self-limiting and resolved spontaneously in all cases. We believe that this postinjection pain is not a serious problem. Nevertheless, the optimal concentrations and volumes of ketorolac that can be administered for OA of the CMCJ of the thumb need to be determined in further studies.

We decided to administer a single injection in the CMCJ of the thumb because of the small synovial space involved and cost considerations. Roux et al[40] reported that no significant differences between 1, 2, and 3 injections of intra-articular HA in 42 patients with hand OA at follow-up 3 months postinjection. Furthermore, previous studies have reported that a single injection has sufficient therapeutic efficacy.[9,10]

This study has some limitations to be acknowledged. The first is its retrospective design. Although we selected the subjects using the extensive inclusion and exclusion criteria described in the "Methods" section, there could still have been a degree of selection bias. However, we believe that this shortcoming would have been offset by standardization of the collection of demographic, clinical, and imaging data before treatment and at each follow-up visit. Furthermore, we could not exclude the possibility that some of the patients received other treatments, such as medication or physical therapy, during the follow-up period, despite having a history of being refractory to them, and it is difficult to completely exclude the possibility that these treatments affect the outcomes. Second, the 6-month follow-up period was relatively short. However, because the procedure was not repeated during this time, our results reflect the clinical efficacy of a single treatment and exclude the cumulative effects of multiple procedures. Third, the treatment procedures were performed by the same physician, which may limit the generalizability of the study findings. Fourth, the study contained a relatively small sample size and did not include a control group that received no treatment. A randomized double-blind controlled study in a large population of patients would be necessary to validate our present findings

In conclusion, intra-articular HA has been widely used in the symptomatic management of OA of the CMCJ in the thumb. Although these injections act relatively slowly, they appear to be effective at improving function and pain and are a relatively safe treatment option. In this study, treatment of OA of the CMCJ of the thumb with an injection containing HA and ketorolac allowed a more rapid onset of analgesia than HA alone. Therefore, there are no contraindications, it is recommended that an NSAID be added when administering an HA injection to provide more rapid pain relief.

Author contributions

Data curation: Sang Chul Lee.
Formal analysis: Jongwoo Kim.
Methodology: Woo Yong Lee.
Writing – original draft: Sung Hoon Koh.
Writing – review & editing: Yongbum Park.

References

[1] Bagis S, Sahin G, Yapici Y, et al. The effect of hand osteoarthritis on grip and pinch strength and hand function in postmenopausal women. Clin Rheumatol 2003;22:420–4.
[2] Spaans AJ, van Minnen LP, Kon M, et al. Conservative treatment of thumb base osteoarthritis: a systematic review. J Hand Surg Am 2015;40:16–21.
[3] Gillis J, Calder K, Williams J. Review of thumb carpometacarpal arthritis classification, treatment and outcomes. Can J Plast Surg 2011;19:134–8.
[4] Bakri K, Moran SL. Thumb carpometacarpal arthritis. Plast Reconstr Surg 2015;135:508–20.
[5] Van Heest AE, Kallemeier P. Thumb carpal metacarpal arthritis. J Am Acad Orthop Surg 2008;16:140–51.
[6] Tehranzadeh J, Booya F, Root J. Cartilage metabolism in osteoarthritis and the influence of viscosupplementation and steroid: a review. Acta Radiol 2005;46:288–96.
[7] Bahadir C, Onal B, Dayan VY, et al. Comparison of therapeutic effects of sodium hyaluronate and corticosteroid injections on trapeziometacarpal joint osteoarthritis. Clin Rheumatol 2009;28:529–33.
[8] Zhang W, Doherty M, Leeb BF, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a task force of the EULAR standing committee for international clinical studies including therapeutics (ESCISIT). Ann Rheum Dis 2007;66:377–88.
[9] Stahl S, Karsh-Zafrir I, Ratzon N, et al. Comparison of intraarticular injection of depot corticosteroid and hyaluronic acid for treatment of degenerative trapeziometacarpal joints. J Clin Rheumatol 2005;11:299–302.

[10] Figen Ayhan F, Ustün N. The evaluation of efficacy and tolerability of Hylan G-F 20 in bilateral thumb base osteoarthritis: 6 months follow-up. Clin Rheumatol 2009;28:535–41.
[11] Fuchs S, Monikes R, Wohlmeiner A, et al. Intraarticular hyaluronic acid compared with corticoid injections for the treatment of rhizarthrosis. Osteoarthr Cartil 2006;14:82–8.
[12] Unlu Z, Ay K, Tuzun C. Comparison of intra-articular tenoxicam and oral tenoxicam for pain and physical functioning in osteoarthritis of the knee. Clin Rheumatol 2006;25:54–61.
[13] Shapiro PS, Rohde RS, Froimson MI, et al. The effect of local corticosteroid or ketorolac exposure on histologic and biomechanical properties of rabbit tendon and cartilage. Hand (N Y) 2007; 2:165–72.
[14] Riggin CN, Tucker JJ, Soslowsky LJ, et al. Intra-articular tibiofemoral injection of a nonsteroidal anti-inflammatory drug has no detrimental effects on joint mechanics in a rat model. J Orthop Res 2014;32: 1512–9.
[15] Galán-Herrera JF, Poo JL, Maya-Barrios JA, et al. Bioavailability of two sublingual formulations of ketorolac tromethamine 30 mg: a randomized, open-label, single-dose, two-period crossover comparison in healthy Mexican adult volunteers. Clin Ther 2008;30:1667–74.
[16] Park KD, Kim TK, Bae BW, et al. Ultrasound guided intra-articular ketorolac versus corticosteroid injection in osteoarthritis of the hip: a retrospective comparative study. Skeletal Radiol 2015;44: 1333–40.
[17] Altman RD, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum 1990;33:1601–10.
[18] Eaton R, Littler JW. Ligament reconstruction for the painful thumb carpometacarpal joint. J Bone Joint Surg 1973;55A:1655–66.
[19] Umphrey GL, Brault JS, Hurdle MF, et al. Ultrasound-guided intra-articular injection of the trapeziometacarpal joint: description of technique. Arch Phys Med Rehabil 2008;89:153–6.
[20] Gummesson C, Atroshi I, Ekdahl C. The disabilities of the arm, shoulder and hand (DASH) outcome questionnaire: longitudinal construct validity and measuring self-rated health change after surgery. BMC Musculoskelet Disord 2003;4:11.
[21] Beaton DE, Katz JN, Fossel AH, et al. Measuring the whole or the parts? Validity, reliability, and responsiveness of the disabilities of the arm, shoulder and hand outcome measure in different regions of the upper extremity. J Hand Ther 2001;14:128–46.
[22] Hartrick CT, Kovan JP, Shapiro S. The numeric rating scale for clinical pain measurement: a ratio measure? Pain Pract 2003;3:310–6.
[23] Keen HI, Lavie F, Wakefield RJ, et al. The development of a preliminary ultrasonographic scoring system for features of hand osteoarthritis. Ann Rheum Dis 2008;67:651–5.
[24] Fam H, Bryant JT, Kontopoulou M. Rheological properties of synovial fluids. Biorheology 2007;44:59–74.
[25] Moran SL, Duymaz A, Karabekmez FE. The efficacy of hyaluronic acid in the treatment of osteoarthritis of the trapeziometacarpal joint. J Hand Surg Am 2009;34:942–4.
[26] Heyworth BE, Lee JH, Kim PD, et al. Hylan versus corticosteroid versus placebo for treatment of basal joint arthritis: a prospective, randomized, double-blinded clinical trial. J Hand Surg Am 2008;33:40–8.
[27] Lee SC, Rha DW, Chang WH. Rapid analgesic onset of intra-articular hyaluronic acid with ketorolac in osteoarthritis of the knee. J Back Musculoskelet Rehabil 2011;24:31–8.
[28] Fraser JR, Kimpton WG, Pierscionek BK, et al. The kinetics of hyaluronan in normal and acutely inflamed synovial joints: observations with experimental arthritis in sheep. Semin Arthritis Rheum 1993;22:9–17.
[29] Grecomore G, Piccione F, Letizia G. Therapeutic synergism between hyaluronic acid and dexamethasone in the intraarticular treatment of osteoarthritis of the knee: a preliminary open study. Curr Med Res Opin 1992;13:49–55.
[30] Hameed F, Ihm J. Injectable medications for osteoarthritis. PM R 2012;4 (suppl):S75–81.
[31] Reuben SS, Connelly NR. Postoperative analgesia for outpatient arthroscopic knee surgery with intraarticular bupivacaine and ketorolac. Anesth Analg 1995;80:1154–7.
[32] Mallinson PI, Tun JK, Farnell RD, et al. Osteoarthritis of the thumb carpometacarpal joint: correlation of ultrasound appearances to disability and treatment response. Clin Radiol 2013;68:461–5.
[33] Dekker J, Boot B, van der Woude LH, et al. Pain and disability in osteoarthritis: a review of biobehavioral mechanisms. J Behav Med 1992;15:189–214.
[34] Day CS, Gelberman R, Patel AA, et al. Basal joint osteoarthritis of the thumb: a prospective trial of steroid injection and splinting. J Hand Surg 2004;29:247–51.
[35] Khan M, Waseem M, Raza A, et al. Quantitative assessment of improvement with ingle corticosteroid injection in thumb CMC joint osteoarthritis? Open Orthop J 2009;3:48–51.
[36] Sawyer GA, Anderson BC, Raukar NP, et al. Intramuscular ketorolac injections in the athlete. Sports Health 2012;4:319–27.
[37] Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest 2008; 133(suppl):299S–339S.
[38] Feldman HI, Kinman JL, Berlin JA, et al. Parenteral ketorolac: the risk for acute renal failure. Ann Intern Med 1997;126: 193–9.
[39] Strom BL, Berlin JA, Kinman JL, et al. Parenteral ketorolac and risk of gastrointestinal and operative site bleeding: a post marketing surveillance study. JAMA 1996;275:376–82.
[40] Roux C, Fontas E, Breuil V, et al. Injection of intra-articular sodium hyaluronidate (Sinovial) into the carpometacarpal joint of the thumb (CMC1) in osteoarthritis. A prospective evaluation of efficacy. Joint Bone Spine 2007;74:368–72.