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ORIGINAL ARTICLE

Comparison of intra-articular injection of ArtiAid®-Mini with Ostenil®-Mini for trapeziometacarpal osteoarthritis: A double-blind, prospective, randomized, non-inferiority trial

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ABSTRACT

Objectives: This study aims to compare the effectiveness and safety of intra-articular hyaluronic acid (HA) injections of ArtiAid®-Mini (AAM) and Ostenil®-Mini (OM) for the treatment of trapeziometacarpal joint osteoarthritis.

Patients and methods: Between February 2018 and April 2020, this 24-week, double-blind, prospective, randomized, non-inferiority trial included a total of 17 patients (8 males, 9 females; mean age: 60.3±9.5 years; range, 42 to 76 years) who were treated with either intra-articular AAM (n=8) or OM (n=9). The primary outcome was pain according to a change in Visual Analog Scale (VAS) at 12 weeks after the last injection. The secondary outcomes included the change of VAS at Weeks 2, 4, and 24 after the injection, satisfaction, range of motion (ROM) of trapeziometacarpal joint, pinch strength, grip strength, and adverse events at Weeks 2, 4, 12, and 24 after the injection.

Results: Eight patients with AAM and eight patients with OM completed the follow-up. No significant differences in primary and secondary outcomes were observed between the two groups at baseline and each time point ($p>0.05$). The intra-group differences were significant in each time point.

Conclusion: The intra-articular injection of either AAM or OM is effective and safe for patients with trapeziometacarpal osteoarthritis up to 24 weeks.

Keywords: ArtiAid®-Mini, hyaluronic acid, Ostenil®-Mini, osteoarthritis, trapeziometacarpal.

Osteoarthritis (OA) of trapeziometacarpal (TMC) joint (rhizarthrosis) is frequent in middle and old age population. The prevalence of TMC OA in women is twice that in men, and this disease particularly affects post-menopausal females.[1] It may cause pain, deformity, and functional disability with impact on the quality of life. Conservative treatment options include non-pharmacological therapies (i.e., resting, immobilization with splint, orthoses, and physical therapies) and pharmacological treatments (i.e., analgesics, non-steroidal anti-inflammatory drugs [NSAIDs] and corticosteroid, hyaluronic acid [HA], or plate-rich plasma injection). Surgery is the last resort for patients with severe disability from OA who were failed by conservative treatments.[2]

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Hyaluronic acid is normally formed in the synovial fluid of joints and plays an important role in the biomechanics of synovial fluid by enhancing the viscoelastic and lubricating functions of the joints.[3] Thus, intra-articular HA has a significant effect on the pain and function improvement of OA and is recommended for the management of OA in knee, hip, and other joints.[4,5] Intra-articular HA injection is a safe alternative therapeutic option for TMC OA and has been widely clinically applied. However, recent meta-analysis and systemic reviews have revealed the scientific evidence on the efficacy of intra-articular HA in TMC OA as equivocal and inconclusive due to the great heterogeneity of clinical trials, and many of its effects have not been investigated clinically.[6]

Ostenil®-Mini (OM; TRB Chemedica AG, Germany) is a Conformitè Europëenne-certified viscoelastic solution for intra-articular injection which contains 10 mg/mL (1.0%) fermented sodium hyaluronate with a molecular weight of 150 KDa. In previous open-label, randomized clinical trials, Ostenil®-Mini significantly decreased pain and improved functionality of patients with TMC OA.[7-9]

ArtiAid®-Mini (AAM; Maxigen Biotech Inc., Maxigen Biotech Inc., Taiwan) is a sterile, non-pyogenic, synovial viscosupplementation acid prepared with the non-inflammatory, viscous, aqueous solution of 10 mg/mL highly purified sodium hyaluronate with a molecular weight of 60 to 120 KDa.

In the present study, we aimed to investigate the effectiveness and safety of intra-articular HA injections of AAM and OM for the treatment of TMC OA. The null hypothesis of this study was that there would be no significant difference in subjective measurement (Visual Analog Scale [VAS], satisfaction), objective measurement (range of motion [ROM], pinch and grip strength) and adverse events in TMC OA patients receiving intra-articular AAM injections compared to OM.

PATIENTS AND METHODS

Study design and study population

This multi-center, double-blind, comparative, prospective, positive-control, randomized, non-inferiority trial was conducted at Department of Orthopedics of two tertiary care centers between February 2018 and April 2020. All patients with TMC OA were screened. Inclusion criteria were as follows: aged 35 years and above; having clinical symptoms (TMC joint pain, joint stiffness, decreased mobility, deformity, instability, functional impairment) and radiological observations indicative and typical of TMC OA (Eaton and Litter Stage II or III); having a VAS score of pain ≥4 for over three months; pain-resistant to well-conducted medical treatments (rest, physical therapy, orthosis, analgesics or NSAID) or intolerant of medical complications and willing to discontinue medications except for acetaminophen or acetylsalicylic acid (<325 mg/day), could practice contraception during the study; and could understand and receive the protocol and signed the informed consent. Exclusion criteria were as follows: having bilateral TMC OA; having known alcoholism; having previous HA injection less than six months ago; having previous intra-articular injections of corticosteroids or glycosaminoglycans less than three months ago; having known allergy to hyaluronate or one of the products; having localized infection; having hemarthrosis or joint effusion, joint infection, immunodeficiency, cachexia, and uncontrolled diabetes or using anticoagulant; having coexisting interphalangeal OA; having previous thumb or wrist surgery; pregnant or lactating; and unable to follow the protocol according to the investigators' judgment. Finally, a total of 17 patients (8 males, 9 females; mean age: 60.3±9.5 years; range, 42 to 76 years) including eight with AAM and nine with OM were included (Figure 1).

Randomization

A computer-based program was used to randomly assign the enrolled patients to one of the two treatment groups, namely, AAM (n=8) or OM (n=9) in a 1:1 ratio. Assignment remained unknown to the patients and clinical evaluators throughout the duration of their participation in this study.

Study schedule (Study timetable)

Screening stage

Pre-trial evaluations included individual data collection (age, sex, body weight, body height,

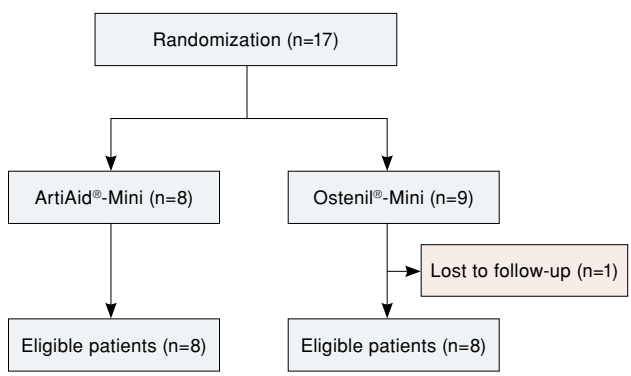

FIGURE 1. Study flowchart.

TABLE I
Study timetable

	Screening stage	Therapeutic intervention	Evaluation stage			
	-14 to -1 day	Week 1-2±3 days	Week 4±7 days	Week 6±7 days	Week 14±7 days	Week 26±7 days
Verification inclusion/exclusion criteria	x					
Patient history	x					
Clinical examination	x					
Radiological examination	x					
Injection		x				
Adverse events		x	x	x	x	x
Functional assessment	x		x	x	x	x
Visual Analog Scale	x		x	x	x	x
Range of motion	x		x	x	x	x
Pinch strength	x		x	x	x	x
Grip strength	x		x	x	x	x
Satisfaction			x	x	x	x

body mass index, smoking, alcohol consumption, and affected hand), medical and surgical history taking, and radiological examination with Eaton and Little classification scale, numerical pain rating scale (VAS, which scales the patients' pain from 0 to 10, with 0 being "no pain" and 10 indicating greatest pain intensity), ROM of TMC joint (flexion/extension and abduction), pinch and grip strength tests, and satisfaction surveys (scaled from 1 to 5, with 1 representing the greatest unsatisfaction) (Table I).

Therapeutic intervention

The patients were injected with HA of either 1 mL of AAM (10 mg/mL) or 1 mL or OM (10 mg/mL) according to their allocation. The injection material was drawn into a standard 1 mL syringe, out of sight of the patient and clinical evaluator. An opaque label was placed on the syringe to cover the injection material and ensure blinding during the injection. All the injections were administered by a single experienced specialist and performed under ultrasound-guided procedures (5-10 MHz, SonoSite, Bothell, WA, USA) following a previous technique.[10] All participants received a second injection after one week.

Functional outcomes and safety assessment

All the patients were scheduled for follow-up visits at Weeks 2, 4, 12, and 24 after the second injection. The VAS (0-10), satisfaction survey (1-5), and ROM of TMC joint and grip and pinch strength tests were repeated in the same way as the initial assessment. Pre-trial evaluations, functional outcomes and safety assessment for study participation were screened and assessed by a single orthopedic surgeon and a hand therapist, who was blinded to the method of injection applied and had no involvement in the injection procedure.

Functional outcome assessment

The primary outcome was VAS at 12 weeks after the initial injection time. The VAS was also assessed at Weeks 2, 4, and 24. The secondary outcomes were satisfaction survey, ROM of TMC joint, and grip and pinch strength, all of which were assessed at Weeks 2, 4, 12, and 24 after the initial injection.

Safety assessment

Related adverse events according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes were as follows: gastrointestinal disorders, cardiac disorders, vascular disorders, respiratory, thoracic and mediastinal disorders, nervous system disorders, skin and subcutaneous tissue disorders, musculoskeletal and connective tissue disorders, renal and urinary disorders, infections and infestations, and hypersensitivity reaction. These data were collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction.[11]

Statistical analysis

Statistical analysis was performed using the SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA). Continuous data were expressed in mean ± standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. Between groups comparison was analyzed using the independent t-test, whereas the difference between baseline and each post-injection point in each group were assessed by a paired t-test. Categorical data between the groups were compared through the chi-square or Fisher exact test. Post-hoc test was carried out to determine the factors of significance. A p value of <0.05 was considered statistically significant.

RESULTS

All patients completed the pre-injection assessment and tolerated the procedure well. One patient in the OM group did not attend to follow-up visit and, thus, was excluded. Finally, eight (100%) patients in the AAM group and eight (89%) patients in the OM group completed the 24-week follow-up assessment. Two (25%) patients in the AAM group and one (13%) patient in the OM group were classified as Eaton and Litter Stage II. Six (75%) patients in the AAM group and seven (87%) patients in the OM group were classified as Eaton and Litter Stage III. Left hand involvement was observed in three (37.5%) patients in the AAM group and eight (100%) patients in the OM group. Systemic comorbidities were found in eight (100%) patients in the AAM group and five (62.5%) patients in the OM group. No significant differences in demographic characteristics were observed between the two treatment groups (Table II).

Subjective measurement

Visual Analog Scale

The mean subjective VAS scores at baseline and Weeks 2, 4, 12, and 24 after the injection were 5.6±0.5, 2.6±1.6, 2.0±1.2, 0.9±0.8, and 0.5±0.8 in the AAM group, respectively, and 5.9±1.1, 1.9±1.1, 1.9±1.1, 1.1±1.0, and 0.4±1.7 in the OM group, respectively. No significant differences were observed between the groups at baseline and each time point. Significant intra-group differences in the mean VAS scores were found in both treatment groups. The mean VAS score was significantly improved up to 12-week post-injection in the AAM group and 24-week post-injection in the OM group (Table III).

TABLE II
Baseline demographic of participants

	ArtiAid®-Mini (n=8)			Ostenil®-Mini (n=8)			
Characteristics	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			59.5±10.5			59.9±9.0	0.711
Sex							0.131
Male	2	25.0		5	62.5		
Female	6	75.0		3	37.5		
Body height (m)			1.6±0.1			1.6±0.1	0.629
Body weight (kg)			62.0±11.3			68.8±10.0	0.224
Body mass index			23.5±3.0			25.4±2.3	0.176
E-L classification							0.522
II	2	25.0		1	12.5		
III	6	75.0		7	87.5		
Smoker	0	0.0		0	0.0		
Alcohol consumption							1
0 glasses/day	8	100.0		7	87.5		
1-5 glasses/day				1	12.5		
Affected limb							0.2
Right	3	37.5		0	0.0		
Left	5	62.5		8	100.0		

SD: Standard deviation; m: Meter; kg: Kilogram; E-L: Eaton and litter. Between-groups analyses were carried out by the independent t-test, chi-squared or Fisher exact test.

Satisfaction survey

No significant differences in the satisfaction measurement were observed between and within the two groups (Table III).

Objective measurement

Range of motion of trapeziometacarpal joint

No significant differences in flexion, extension, and abduction were observed between the groups at baseline and each post-injection time point. The flexion, extension, and abduction of TMC joint significantly improved at two-week post-injection in both groups. In the AAM group, extension at 24-week post-injection was significantly improved compared to that at two-, four-, and 12-week post-injection. In both groups, the abduction of TMC joint at 24-week post-injection was improved significantly compared to that at two-week post-injection (Table III).

Pinch strength

No significant differences in the pinch strength were observed between the groups at baseline and 2-, 4-, 12-, and 24-week post-injection. For both groups, the pinch strength of TMC joint was significantly improved at each follow-up time point compared to baseline. In the AAM group, the pinch strength improved significantly after 24 weeks

TABLE III
Outcome measurement

	Baseline	Post-injection 2 weeks	4 weeks	12 weeks	24 weeks
Measure follow-up	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Visual Analog Scale					
ArtiAid®-Mini	5.6±0.5	2.6±1.6[a]	2.0±1.2[a]	0.9±0.8[a,b,c]	0.5±0.8[a,b,c]
Ostenil®-Mini	5.9±1.1	1.9±1.1[a]	1.9±1.1[a]	1.1±1.0[a,b,c]	0.4±0.7[a,b,c,d]
p	0.954	0.287	0.784	0.594	0.700
Flexion (degrees)					
ArtiAid®-Mini	12.8±2.1	14.3±1.2[a]	14.8±0.7[a]	14.9±0.4[a]	15.0±0.0[a]
Ostenil®-Mini	11.6±1.1	14.3±1.0[a]	14.1±1.3[a]	14.9±0.4[a]	15.0±0.0[a]
p	0.213	>0.999	0.267	>0.999	>0.999
Extension (degrees)					
ArtiAid®-Mini	47.5±3.8	51.9±5.3[a]	52.8±4.5[a]	53.8±4.4[a]	58.6±6.5[a,b,c,d]
Ostenil®-Mini	44.4±8.2	51.1±6.1[a]	49.6±8.4[a]	52.5±5.4[a]	55.0±6.6[a]
p	0.469	0.808	0.371	0.619	0.285
Adduction (degrees)					
ArtiAid®-Mini	52.5±2.7	56.5±3.1[a]	59.5±6.1[a]	58.9±3.8[a]	62.8±4.8[a,b]
Ostenil®-Mini	53.3±4.2	56.1±4.9[a]	57.6±4.4[a]	60.0±3.8[a]	61.6±2.3[a,b]
p	0.864	0.951	0.526	0.562	0.499
Pinch (kg)					
ArtiAid®-Mini	3.9±0.5	4.8±0.9[a]	4.7±0.4[a]	4.9±0.7[a]	5.3±0.6[a,b,c]
Ostenil®-Mini	5.0±2.2	4.9±1.1[a]	5.7±2.0[a]	5.9±2.5[a]	7.1±2.7[a,b,c]
p	0.314	0.907	0.788	0.958	0.290
Grip (kg)					
ArtiAid®-Mini	17.9±3.0	19.7±2.4[a]	19.8±2.4[a]	21.1±1.8[a]	22.9±3.7[a,b,c]
Ostenil®-Mini	21.7±6.2	24.4±6.6[a]	24.8±6.5[a]	26.5±7.9[a]	28.4±10.3[a]
p	0.494	0.402	0.074	0.099	0.195
Satisfaction					
ArtiAid®-Mini		4.0±0.0	4.0±0.0	4.0±0.0[a]	4.0±0.0
Ostenil®-Mini		3.9±0.4	4.0±0.0	4.0±0.0	4.1±0.4
p		0.351	NaN	NaN	0.351

NaN: Not a number; a,b,c,d: Different superscript numbers indicate a statistically significant difference across time points by *post-hoc* test.

compared to at two- and four-week post-injection. These findings were also observed in the OM group (Table III).

Grip strength

No significant differences in the grip strength were observed between the groups at baseline and 2-, 4-, 12-, and 24-week post-injection. Significant intra-group differences in the grip strength were found in both groups in each time point compared to baseline. In the AAM group, the grip strength improved significantly at 24 weeks compared to at two- and four-week post-injection (Table III).

Adverse events

During follow-up, one patient had incontinence and vaginal disease in the AAM group, and one patient had balanoposthitis in the OM group. These conditions were not related to HA injection. No nematoma, tendon laceration, nerve injury, vascular damage, infection, and other complication were observed.

Final outcome

Finally, eight patients in the AAM group and eight patients in the OM group completed the follow-up in this study through clinical examination. No significant differences in the VAS, satisfaction, ROM of TMC joint (flexion, extension, and abduction), and pinch and grip strength were observed between the groups at baseline and each time point. The VAS score improved significantly at two-week post-injection and continued throughout the follow-up period. The flexion, extension, abduction, and pinch and grip strength were significantly improved at two-week post-injection.

DISCUSSION

In the present study, we compared the outcomes of ultrasound-guided intra-articular HA injections of AAM to OM for the treatment of carpometacarpal OA. In our study, there was no statistically significant difference in the subjective measurement (VAS, satisfaction), objective measurement (ROM, pinch and grip strength) and adverse events between the two groups at baseline and each follow-up time point.

In an open-label, prospective clinical study, 20 patients experiencing painful TCM joint OA received two to three intra-articular injections of 10 mg/mL sodium hyaluronate (OM) at weekly intervals.[7] A significant reduction in pain and an increase in grip strength (pulp and lateral pinch) were observed at the final evaluation three months after the injection, and no adverse effects were reported. In a single-blind, randomized-controlled trial assessing the efficacy and tolerability of intra-articular sodium hyaluronate (OM) and triamcinolone acetonide for the treatment of rhizarthrosis, maximum pain relief was achieved after two to three weeks in the triamcinolone acetonide group and 26 weeks in the sodium hyaluronate group.[8] Improvements in lateral and pinch strength, abduction/adduction, and opposition were observed in both groups, and lateral pinch strength was significantly better in the sodium hyaluronate group than in the triamcinolone acetonide group. Bahadir et al.[9] published an open-label, evaluator-blinded, randomized clinical study to compare three weekly injections of sodium hyaluronate (OM) (5 mg/0.5 mL) with one injection of triamcinolone acetonide (20 mg/0.5 mL). The final results showed that the VAS pain score significantly improved within six months in the triamcinolone acetonide group and 12 months in the sodium hyaluronate group. Both groups exhibited a significantly stronger grip, but not pinch. The Duruöz Hand Index was improved significantly in the triamcinolone acetonide group. These findings suggest the effects of OM on decreasing pain and improving joint mobility which may last for several months after the treatment cycle. In the present study, the comparison between AAM and OM revealed their identical improving effects on VAS score, satisfaction, ROM of TMC joint, and pinch and grip strength. The AAM provided more rapid pain relief than OM at 12-week post-injection, although no significant differences were observed within the two groups. The improvements in flexion, adduction, and pinch strength were also identical in both groups, while the extension and grip strength were rapidly improved at 12-week post-injection in the OM group.

Hyaluronic acid is naturally present in synovial fluid and maintains hemostasis in the joint.[12] The HA concentrations are decreased in OA joints.[13] Different HA formulations present varying properties depending on their concentration and molecular weight. The HA is classified into three molecular weight groups: low (<1,500 KDa), intermediate (1,500-3,000 KDa), and high (>3,000 KDa). The size of HA has a direct impact on its binding affinity to CD-44 receptors. High-molecular-weight HA (HMWHA) is favorable for the increased production of inflammatory cytokines and chemokines, recruitment of inflammatory mediators, formation of blood vessels,

and CD-44-mediated effects of chondroprotection, proteoglycan/glycosaminoglycan synthesis, anti-inflammatory, subchondral bone compliancy, mechanical, and analgesic. The HMWHA provides greater therapeutic benefits than low-molecular-weight HA (LMWHA), but no consensus has been reached regarding the clinical efficacy difference between these two.[14,15] The HMWHA and HA cross-linked formulation are more frequently associated to local reactions and post-injection flares than intermediate or low MWHA.[16,17] In the present study, the effectiveness and safety of AAM and OM, both LMWHA, were confirmed.

No evidence is available regarding the direct influence of the number of joint injections on the occurrence of side effects.[18] A study compared the therapeutic mid-term effect of a single intra-articular HA injection versus three injections of LMWHA.[19] Both groups experienced pain relief, disability improvement was found mainly in the group receiving three injections, and no significant differences in evaluated outcomes were observed between the groups. The present study used two injections of intra-articular HA and attained significant and lasting pain and function improvements.

The injection of intra-articular HA under ultrasound guidance is simple, rapid, economic, and safe. It allows the easy visualization of the joint and ensures that the HA is injected properly inside the joint cavity.[20] In a prospective study, Karalezli et al.[21] showed that pain and discomfort were frequent during injection and reported a major degree of pain experience by the subjects in the non-fluoroscopy control group. In the present study, the whole injection procedure was under ultrasound guidance and performed by an empirical physician.

Nonetheless, this study has some limitations. First, the sample size is relatively small and the study did not include a control group receiving placebo. As a result, the validity and generalizability of the results should be interpreted cautiously. Second, the study was performed at two tertiary medical centers, and only patients with Eaton and Litter Stage II-III were recruited. Therefore, the results cannot be generalized to the entire populations with different degrees of radiologically evident severity. Further multi-center studies with a large sample size are required.

In conclusion, our study results show that the effectiveness and safety of AAM administered once a week for two weeks are comparable with those of OM. Further studies are warranted to draw more reliable conclusions on this subject.

Ethics Committee Approval: The study protocol was approved by the Institutional Review Board of the E-Da Hospital Ethics Committee (date: 07.12.2017, no: EMRP03106N). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Manuscript drafting, Analysis of data: P.H.W.; Acquisition of data: C.H.W.; Acquisition of data: C.H.M.; Analysis of data: Y.C.C.; Full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, study design: P.T.W., I.M.J. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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