Knee Surg Sports Traumatol Arthrosc
DOI 10.1007/s00167-017-4467-0

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Short-term efficacy and safety of hyaluronic acid injection for plantar fasciopathy

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Received: 9 May 2016 / Accepted: 6 February 2017

Abstract
Purpose Plantar fasciopathy is the most common cause of plantar heel pain and is considered to be a type of enthesopathy. The short-term efficacy, safety, and dose-response relationship of high-molecular-weight hyaluronic acid (HA) was investigated in patients with plantar fasciopathy.
Methods In this multicenter, prospective, randomized, double-blind, placebo-controlled trial, 168 patients with persistent pain from plantar fasciopathy for more than 12 weeks were randomly assigned to receive 2.5 mL of 1% HA (H-HA), 0.8 mL of 1% HA (L-HA), or 2.5 mL of 0.01% HA (control group) once a week for 5 weeks. The primary endpoint was improvement in visual analogue scale (VAS) score for pain from baseline to week 5.
Results The VAS scores (least squares mean ± standard error) in each group decreased gradually after the start of treatment, a change of -3.3 ± 0.3 cm for the H-HA group, -2.6 ± 0.3 cm for the L-HA group, and -2.4 ± 0.3 cm for the control group, with the H-HA group improving significantly more than the control group ($P = 0.029$). No serious adverse events were reported. There was no difference between the groups in the incidence rates of adverse drug reactions.
Conclusion The administration of five injections of high-molecular-weight HA is an effective treatment with no serious adverse drug reactions and is a conservative treatment option for plantar fasciopathy. This treatment contributed to alleviation of pain in patients with plantar fasciopathy and improvement in their activities of daily living.
Level of evidence I.

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Published online: 02 March 2017

Keywords Plantar fascia · Heel pain · Enthesopathy · Hyaluronic acid · Double-blind · Randomized controlled trial

Introduction

The lifetime prevalence of heel pain in the general population is as high as 10% [8, 32]. The most common cause of plantar heel pain is plantar fasciopathy, which is considered to be a type of enthesopathy. Plantar fasciopathy is also a common painful condition observed in athletes who participate in running sports [4, 14, 18, 22, 29].

The aetiology of plantar fasciopathy is unclear, but obesity, prolonged standing, and reduced ankle dorsiflexion have all been implicated in its onset [31]. Inferior heel pain is usually caused by degeneration of the subcalcaneal enthesis of the plantar fascia that occurs because of overuse and fails to heal. Current conservative treatments for plantar fasciopathy include stretching exercises, night splints, shoe insoles, NSAIDs, and corticosteroid injections [2, 5, 24, 30]. Although these conservative treatments are effective in approximately 90% of patients, complete resolution of pain often takes a long time, and drug treatments may be associated with adverse drug reactions [10]. For patients with severe heel pain, local corticosteroid injections provide only short-term relief [6, 7]. However, the repeated use of such treatments is not recommended owing to the risk of fatty tissue atrophy, tendon rupture, and infection [1].

Hyaluronic acid (HA) is used as a non-operative treatment option for osteoarthritis of the knee and persistent shoulder pain [25, 33], and the efficacy and safety of HA injections for these conditions have been established by evidence-based studies. HA has also been reported to be effective in the treatment of plantar fasciopathy [11], as well as in the treatment of patellar tendinopathy and lateral epicondylitis [23, 27], which are thought to be enthesopathies similar to plantar fasciopathy.

Although the mechanism by which HA acts on enthesopathies is unknown, HA has been reported to alleviate pain [36], inhibit cartilage degeneration [15], prevent tissue adhesion [39], and inhibit the growth of blood vessels and sensory nerves [37]. Since plantar fasciopathy is a pathological condition that results from the degeneration of the fibrocartilaginous enthesis within the tendon/ligament insertion site [18, 3, 16], the major symptom is pain.

It was hypothesized in this study that HA would have an analgesic effect and alleviate symptoms in patients with plantar fasciopathy.

The objective of this study was to confirm the safety of HA and its efficacy in terms of improvement of pain after administering five doses of HA to outpatients with plantar fasciopathy, and whether this treatment leads to improvement of activities of daily living (ADL). This is the first ever, double-blind study of HA for the treatment of plantar fasciopathy to evaluate the short-term efficacy, safety, and dose-response relationship.

Materials and methods

This was a prospective, double-blind, randomized controlled trial performed at 29 study centers in Japan. Injections containing 25 mg of high-molecular-weight (2700 kDa) HA of non-animal origin (Suvenyl®; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) in 2.5 mL (H-HA), 8 mg of HA in 0.8 mL (L-HA), or 0.25 mg of HA in 2.5 mL (control group) were used in this study. The dose for the high-dose group was set to 2.5 mL of 1% HA, and a very low dose of 2.5 mL of 0.01% HA was set for the control group, since an important characteristic of HA is its viscosity, and because it is possible to inject up to 2.5 mL of the drug solution into the target site [17].

Both patients and were masked to the assigned treatment throughout the study follow-up. However, because the HA injections were distinguishable by the physicians who gave the injections, the patient assessments (including assessment of local symptoms and ADLs) and safety assessments were done by different physicians blind to the study treatment. Physicians injected the drug solution in accordance with the procedure stipulated for this study, and patient blinding was ensured by blocking visual access to the injection procedure by having patients lie in a supine position. Eligible patients were randomly assigned to one of the three groups (random assignment 1:1:1) via a central enrolment center by use of permuted-block randomization (blocks of size 6). Patients received 5 weekly injections (1 injection per week for 5 weeks) of the investigational drug without local anaesthetic. The patient lay supine with the knee flexed to 90°. The investigational drug was injected above the plantar fascia from the medial aspect to avoid pain (Fig. 1). Clinical evaluation was conducted before investigational drug injection at baseline and every week until week 5. Safety was assessed through physical examinations and laboratory blood tests at baseline and every week until week 5.

Patients

Diagnosis of plantar fasciopathy depended on subcalcaneal heel pain on standing for long periods or on walking, running, or starting to walk, with tenderness around the medial attachment site of the plantar fascia to the calcaneus. Patients with pain due to nerve pressure or with disorders such as tarsal tunnel syndrome, partial rupture of

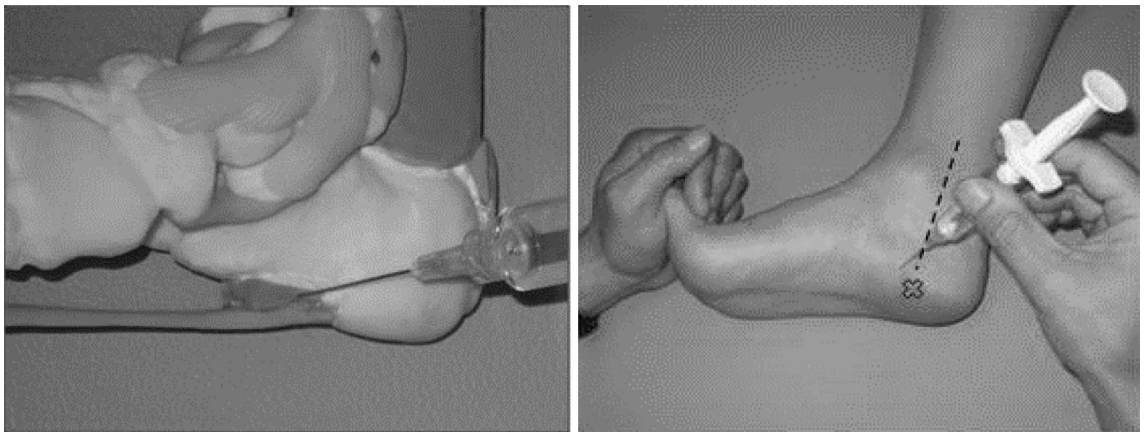

Fig. 1 Method used to inject HA into loose, connective tissue at the point of attachment of the plantar fascia and the medial calcaneal tubercle. Dorsiflexion of the toes makes an outline of the plantar fascia leading toward the point of tenderness. The point of tenderness at the attachment of the plantar fascia to the medial calcaneal (marked with a *cross*) generally lies on a vertical line distal to the posterior border of the medial malleolus (*dotted line*). The investigational drug was injected above the plantar fascia from the medial aspect, aiming at loose, connective tissue distally adjacent to the point of attachment of the plantar fascia to the medial calcaneal tubercle. HA was not injected into the substance of the tendon

muscle or tendon such as posterior tibial tendon dysfunction and reflex sympathetic atrophy, or plantar fibromatosis were excluded. To be eligible for enrolment, patients were to be ≥20 and <75 years of age, to have had symptoms of plantar fasciopathy for ≥12 weeks, and to have a visual analogue scale (VAS) score for their average pain over several days of ≥4 cm at enrolment. Patients were excluded if they had received local injections of HA, corticosteroids or anaesthetic, or had received corticosteroids (orally, rectally, or intravenously) within 2 weeks before study treatment; had received extracorporeal shockwave therapy within 12 weeks before study treatment; or had previously received surgical treatment for the foot used in the study.

Concomitant therapies of local HA, corticosteroid, or anaesthetic injections, application of topical corticosteroids in the affected area, use of corticosteroids (orally, rectally, or intravenously), surgical procedures, extracorporeal shockwave therapy, and use of other investigational drugs were prohibited from 2 weeks before treatment with the investigational drug until the end of the study. The use of NSAIDs, physical therapy, and orthotic treatment was permitted from 1 week before treatment with the investigational drug until the end of the study, provided the dosage and administration were not changed and treatment with any NSAID or therapy was not initiated. Patients were instructed to avoid changing activity during the study period. To assess changes in activity level, patients were asked to complete a standardized questionnaire in which the length of time patients spent on activities such as walking and running was monitored and evaluated according to a 5-step scale.

Outcome measures

The primary endpoint was an improvement in VAS score for pain from baseline to week 5 (final observation was 1 week after the final injection). Patients were asked to rate their average pain over a period of several days from 0 (no pain) to 10 cm (most severe pain). Individual patient VAS scores were measured to the first decimal place, and results (means and standard error) were rounded to one decimal place for analysis and reporting.

Secondary endpoints were improvements in Roles and Maudsley score, ADLs, and local symptoms. The Roles and Maudsley score measures patients' satisfaction. In this score, patients assessed their outcomes as excellent (no pain, full movement and full activity), good (occasional discomfort, full movement and full activity), fair (some discomfort after prolonged activity), or poor (pain-limiting activities). The ADLs and local symptoms were assessed by the evaluating physician as follows. The local symptoms of spontaneous pain, tenderness, provoked pain, first-step pain, and exercise pain were assessed using a 5-step scale: no pain, mild pain, moderate pain, severe pain, or intolerable pain. The ADLs of stair climbing, walking, and running were assessed using a 5-step scale: without difficulty, with some difficulty, with difficulty, with much difficulty, or unable to do.

Ethical approval

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the institutional review boards at each center. A written

informed consent was obtained from each patient before enrolment. This study is registered with identifier number Japic-CTI 101090.

Please see the "Appendix" section for a full list of institutions at which this study was conducted together with the ID number of each IRB approval.

Statistical analysis

All analyses were modified intention-to-treat (ITT) analyses performed using SAS version 8.2 (SAS Institute, Cary, NC, USA). The modified ITT population included all randomized patients who received an investigational drug and had at least one post-baseline assessment. For the primary efficacy analysis, analysis of covariance was used to compare the change in VAS scores from baseline to week 5 adjusted by the baseline VAS score between the HA groups (H-HA or L-HA) and the control group. A closed testing procedure was used to control for multiplicity. At first, the H-HA group and the control group were compared; if a significant difference was found ($P < 0.05$), then the L-HA group and the control group were compared. Missing values were imputed using the last observation carried forward. It was assumed from the results of an earlier pharmacological study [17] that the difference in mean change of VAS scores at week 5 between the H-HA and control groups would be −1.5 cm with a standard deviation of 2.4 cm. Under these assumptions, 42 patients per group would be required to provide 80% power with a two-sided 5% alpha using Student's *t* test. To account for possible drop-out, allowance was made for at least 50 patients to be randomly assigned to each group. Sample size calculations were performed with nQuery Advisor 5.0 (Statsols, Cork, Ireland).

Results

A total of 168 patients was enrolled. Figure 2 represents the flow of participants during the study. The first patient was enrolled in April 2010 and the last patient completed treatment in December 2010. Of the 168 patients enrolled, 166 received at least 1 injection of the investigational drug and were included in the final analysis. The demographic characteristics at baseline are shown in Table 1. No noteworthy changes in activity levels, including times spent walking and running, were observed during the study period in any of the patients.

Primary efficacy endpoint

The VAS score in each group decreased gradually after initiation of treatment (Fig. 3). In the control group, the mean VAS score decreased from 6.7 ± 0.2 cm at baseline to 4.3 ± 0.3 cm at week 5. The improvement in VAS score from baseline to week 5 (primary endpoint) was significantly greater in the H-HA group (−3.3 ± 0.3 cm) than in the control group (−2.4 ± 0.3 cm) ($P = 0.029$, Fig. 3). There was no significant difference between the improvement in VAS score in the L-HA group (−2.6 ± 0.3 cm) and of that in the control group (n.s., Fig. 3).

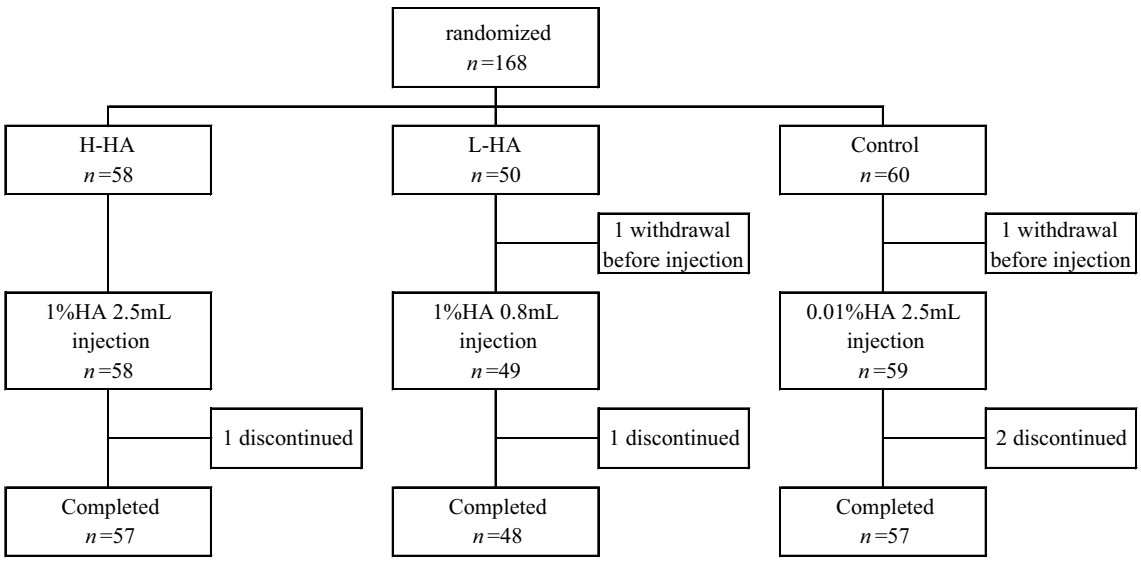

Fig. 2 Distribution of study patients from enrolment to completion of the study. H-HA = group injected with 2.5 mL of 1% HA; L-HA = group injected with 0.8 mL of 1% HA; control = group injected with 2.5 mL of 0.01% HA

Table 1 Characteristics of patients at baseline

	H-HA ($n=58$)	L-HA ($n=49$)	Control ($n=59$)
Age, mean (range), years	50.4 (20–73)	52.0 (24–74)	54.1 (27–74)
Women, no. (%)	39 (67.2)	33 (67.3)	39 (66.1)
Height, mean ± SD, cm	161.2 ± 9.2	159.2 ± 9.0	160.9 ± 8.0
Weight, mean ± SD, kg	64.7 ± 13.2	62.3 ± 12.1	63.5 ± 10.7
BMI, mean ± SD, kg/m^2	24.8 ± 4.1	24.5 ± 3.6	24.5 ± 3.4
Duration of symptoms, median (interquartile range), days	220.5 (161–422)	211.0 (118–466)	246.0 (137–409)
Disease reason, no. (%)			
Occupation	18 (31.0)	19 (38.8)	17 (28.8)
Sport	14 (24.1)	13 (26.5)	10 (16.9)
Other	26 (44.8)	17 (34.7)	32 (54.2)
Previous corticosteroid treatment within 6 weeks, no. (%)	0	1 (2.0)	3 (5.1)
VAS, mean ± SD, cm	6.6 ± 1.7	6.6 ± 1.9	6.7 ± 1.5

SD standard deviation, *BMI* body mass index, *VAS* Visual Analogue Scale (0–10 cm)

Secondary efficacy endpoints

Each of the secondary endpoints, including Roles and Maudsley score, local symptoms, and ADLs, tended to improve in each group but showed no significant difference (Table 2; Fig. 4).

Safety evaluation

No serious adverse events were reported during the study period. Adverse drug reactions were reported in a total of 13 patients (7.8%) and were generally mild or moderate in severity. There was no marked difference between any of the groups in the incidences of adverse drug reactions (Table 3). Most of the patients recovered from injection site pain within several days. No laboratory test abnormality was reported as an adverse event.

Discussion

The most important finding of the present study was that improvement in the VAS score for pain in patients with plantar fasciopathy was significantly greater in the H-HA group than in the control group. A dose-dependent improvement in pain was also observed, with more pronounced improvement in the H-HA group as compared with the L-HA group. Secondary endpoints, including Roles and Maudsley score, local symptoms, and ADLs, were also improved in each group, with the H-HA group in particular tending to have more improved outcomes. Outcomes were also improved by an injection of 0.01% HA (control group); therefore, the intervention of the injection itself may have potential to improve pain and ADLs. Considering all of these results together, 2.5 mL of 1%

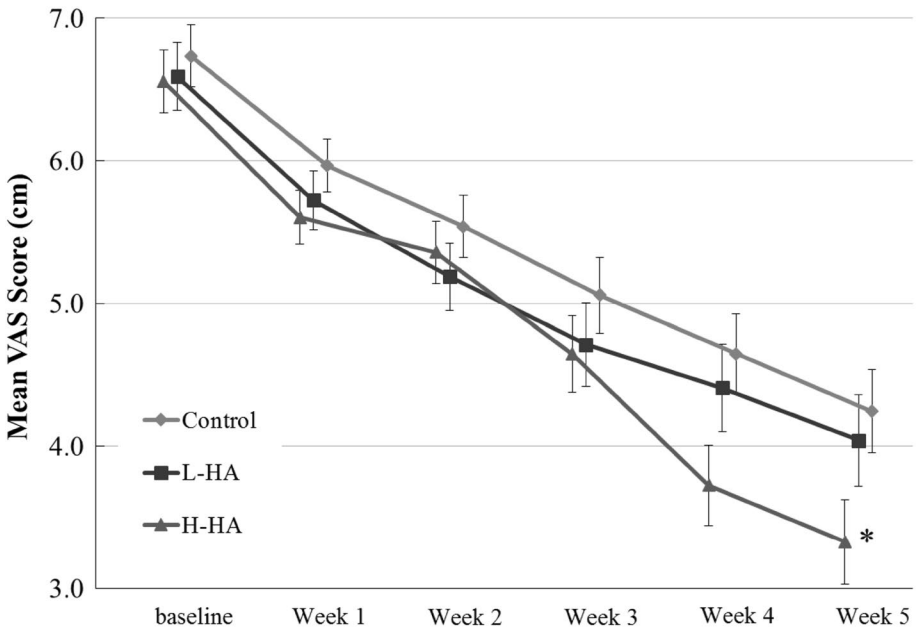

Fig. 3 VAS scores for pain across assessment points (least *squares* mean ± standard error). H-HA = group injected with 2.5 mL of 1% HA (*triangles*); L-HA = group injected with 0.8 mL of 1% HA (*squares*); Control = group injected with 2.5 mL of 0.01% HA (*diamonds*). Analysis of covariance was used to compare the change in VAS scores from baseline to week 5 adjusted by the baseline VAS score. *$P<0.05$ versus control group

Table 2 Secondary efficacy endpoints

	H-HA ($n=58$)	L-HA ($n=49$)	Control ($n=59$)
Roles and Maudsley score, no. (%)	13 (22.4)	6 (12.2)	9 (15.3)
Local symptoms, no. (%)			
Spontaneous pain	16 (27.6)	7 (14.3)	14 (23.7)
Tenderness	25 (43.1)	13 (26.5)	18 (30.5)
Provoked pain	14 (24.1)	9 (18.4)	11 (18.6)
First-step pain	18 (31.0)	19 (38.8)	19 (32.2)
Exercise pain	23 (39.7)	17 (34.7)	12 (20.3)
ADLs, no. (%)			
Walking	9 (15.5)	9 (18.4)	7 (11.9)
Running	19 (32.8)	13 (26.5)	17 (28.8)
Stair climbing	11 (19.0)	10 (20.4)	10 (16.9)

The number of patients who improved by two or more assessment levels from baseline to week 5

HA (H-HA) could be the optimal dose for treating plantar fasciopathy.

The efficacy and safety of HA for treating arthritic conditions has been established, and HA is approved for that use in many countries. In this study, no serious adverse events were reported in any of the groups. The most common adverse drug reaction was injection site pain, and in this respect, there was no difference between any of the groups. The results of this study therefore suggest that multiple HA injections are safe for treating patients with plantar fasciopathy (at least up to five injections).

The effect of HA in patients with enthesopathies has been examined previously. Higashiyama et al. reported that HA injections for the treatment of plantar fasciopathy ameliorated clinical symptoms in all patients, although there was no control group [38]. Muneta et al. reported that HA injected for the treatment of patellar tendinopathy was effective at relieving clinical symptoms [23]. Petrella et al. investigated the efficacy of two injections of HA or placebo in patients with lateral epicondylitis, and reported a significant reduction in pain in the HA group as compared with the control group [22]. Administration of a single injection of HA to patients with lateral epicondylitis, patellar tendinopathy, insertional Achilles tendinopathy, or plantar fasciitis was recently reported to result in similar improvements after injection, and no major safety problems were observed [17]. Therefore, several reports have shown that HA can be expected to be an effective treatment for enthesopathies.

Histopathologically, numerous small blood vessels and nerves are present in the loose, connective tissue close to the subcalcaneal enthesis of the plantar fascia, and degenerative changes in the fibrocartilage of the dorsal enthesis are characterized by the appearance of clusters of cartilage cells and longitudinal fissures [16]. Although the precise mechanism of action of HA on plantar fasciopathy is unclear, it was speculated that the mechanism involves HA's analgesic effect, inhibition of cartilage degeneration, and inhibition of blood vessel/sensory nerve growth.

Table 3 Summary of adverse drug reactions

	H-HA ($n=58$)	L-HA ($n=49$)	Control ($n=59$)
Injection site pain	3 (5.2)	2 (4.1)	4 (6.8)
Injection site swelling	0 (0)	1 (2.0)	0 (0)
Peripheral edema	0 (0)	0 (0)	1 (1.7)
Plantar fasciitis*	0 (0)	1 (2.0)	0 (0)
Pain by manipulation	1 (1.7)	0 (0)	0 (0)

*Worsening of plantar fasciopathy. Values are the number (%) of patients

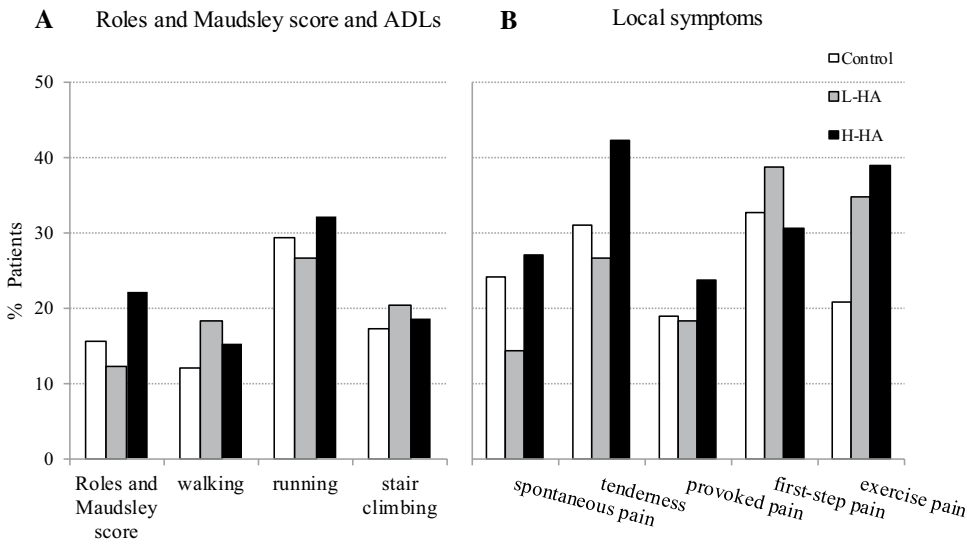

Fig. 4 Results of secondary endpoints. **a** Percentage of patients whose Roles and Maudsley score and ADLs improved by two or more assessment levels from baseline to week 5. **b** Percentage of patients whose local symptoms improved by two or more assessment levels from baseline to week 5. H-HA = group injected with 2.5 mL of 1% HA; L-HA = group injected with 0.8 mL of 1% HA; control = group injected with 2.5 mL of 0.01% HA

Therefore, attention was focused on the region around the enthesis, and HA was injected above the plantar fascia from the medial aspect, aiming at the loose, connective tissue.

As has been previously reported, subcalcaneal heel spurs are comparable to the peripheral osteophytes of articular cartilage found in patients with osteoarthritis, and the degenerative changes at the plantar fascia enthesis, such as cell clusters and longitudinal fissures, resemble those in osteoarthritic cartilage [16]. Taking these results together, plantar fasciopathy can be viewed as an osteoarthritis-like pathological condition. Therefore, since HA has shown effectiveness in the treatment of osteoarthritis of the knee, similar effectiveness in plantar fasciopathy is plausible.

Local anaesthetic was not used in this study because this may lead to bias as it is highly possible that an injection of local anaesthetic alone can lead to an improvement in the symptoms of plantar fasciopathy. In spite of this, the VAS scores for pain in the control group gradually decreased more than expected. The results of the control group are reasonable in that clinical evidence of a placebo effect has been reported in the treatment of osteoarthritis, especially for invasive routes of delivery [41]. However, it was suspected that this may not be merely due to a placebo effect but also to the effects of factors such as the removal of adhesion and washing of the region around the enthesis.

The efficacy of the HA injections varied, and no effect or a worsening effect was occasionally observed in this study. It was considered possible that in these cases, HA was not delivered accurately to the correct region. An ultrasound-guided technique would be helpful to solve the technical problem of accurately injecting into the region [26, 13].

There are many available treatment options for plantar fasciopathy, but there is currently no established standard treatment. Recently, the results of platelet-rich-plasma treatment and extracorporeal shockwave therapy have been reported for the treatment of plantar fasciopathy. However, platelet-rich-plasma treatment and extracorporeal shockwave therapy still remain controversial [22, 38, 20, 21, 28, 35, 40]. When conservative treatment fails to relieve inferior heel pain, surgery may be considered. However, because of persistent pain associated with surgery, which occurs in up to a quarter of patients surgically treated for heel pain [4, 9], and the potential risks of complications including nerve injury in endoscopic release, patients, especially athletes, are often interested in treatment options other than surgery [12, 19, 34]. It is thus believed that HA injection, with its demonstrated efficacy and safety and its ease of use in routine medical practice, can become an alternative treatment for patients with plantar fasciopathy.

After simple administration of five doses of HA to outpatients, it was confirmed that the H-HA dose in particular enabled a significant improvement in pain based on change in VAS scores, and it was demonstrated that HA possesses outstanding safety, and that Roles and Maudsley score, local symptoms, and ADLs scores were also improved. These results indicate that HA—with its simple administration method—has the potential to become a new alternative to corticosteroid therapy for routine clinical treatment before considering surgery and for improving ADLs in patients with plantar fasciopathy. HA treatment may allow patients with plantar fasciopathy to extend their time until surgery or to evade surgery altogether.

One limitation of this study was that the observation period was short. A longer term study of HA for the treatment of plantar fasciopathy is warranted.

Conclusion

This study is the first ever, prospective, double-blind, randomized controlled trial in which patients with plantar fasciopathy received up to five injections of HA. Injection of high-molecular-weight HA is an effective treatment for plantar fasciopathy without any serious adverse drug reactions.

Acknowledgements We thank the study investigators, their staff, and their patients for participating in this clinical study. The following investigators participated in the study: Jun Tsujino, Keijinkai Teine Keijinkai Hospital; Satoru Nakajo, Nakajo Orthopaedic Clinic; Atsushi Kita, Japanese Red Cross Sendai Hospital; Masahito Hatori, Tohoku University School of Medicine; Kazuo Ohuchi, Fukushima Medical University; Satoru Ozeki, Koshigaya Hospital, Dokkyo University School of Medicine; Akihiro Tsuchiya, Funabashi Orthopaedic Sports Medicine Center; Masato Takao, Teikyo University School of Medicine; Michiyasu Kayaoka, Tokyo Rosai Hospital; Yasunori Tsukimura, Kitasato Institute Hospital; Hisateru Niki, St. Marianna University School of Medicine; Atsushi Kato, Ando Orthopaedics Hospital; Ikuo Wada, Nagoya City University Hospital; Tatsuya Koike, Osaka City University Graduate School of Medicine; Hiroshi Nakajima, Otemae Hospital; Mitsuo Kinoshita, Osaka Medical College; Yoshitaka Ishizaki, Higashiosaka City General Hospital; Ichiro Higashiyama, Matsukura Hospital; Masatoshi Naito, Fukuoka University Faculty of Medicine; Toshio Inoue, Hakujyuji Hospital; Hiroshi Tsurukami, Tsurukami Orthopaedic Clinic; Shunji Oba, Oba Orthopaedics. This study was funded by Chugai Pharmaceutical Co., Ltd. (Chugai). Investigational drugs were provided at no cost by Chugai. Publication of this article was not contingent upon approval by Chugai.

Compliance with ethical standards

Conflict of interest Yoshinori Takakura has received consulting fees from Chugai. Tsukasa Kumai, Norihiro Samoto, Atsushi Hasegawa, Hideo Noguchi, Atsushi Shiranita, Masaharu Shiraishi, Satoshi Ikeda, and Kazuya Sugimoto received grants from Chugai as study investigators. Yasuhito Tanaka declares no conflict of interest.

Funding This study was funded by Chugai Pharmaceutical Co., Ltd. (Chugai). Investigational drugs were provided at no cost by Chugai. Publication of this article was not contingent upon approval by Chugai.

Ethical approval The study was performed in accordance with the ethics principles of the Declaration of Helsinki and was conducted with the approval of the institutional review boards at each of the centers where the study was performed.

Informed consent Informed consent was obtained from all individual participants included in this study.

Appendix

This study was conducted at the following institutions after receiving IRB approval: Teine Keijinkai Hospital (ID: TKH2010-06), Nakajo Orthopaedic Clinic (ID: NJ-20100324), Japanese Red Cross Sendai Hospital (ID: SD-20100420), Tohoku University School of Medicine (ID: 101004), Fukushima Medical University (ID: TI22002), Higashimaebashi Orthopaedic Clinic (ID: HM-20100319), Koshigaya Hospital, Dokkyo University School of Medicine (ID: 10-01), Ishii Orthopaedic and Rehabilitation Clinic (ID: IS-20100319), Funabashi Orthopaedic Sports Medicine Center (ID: FS-20100318), Teikyo University School of Medicine (ID: TK-20100401), Tokyo Rosai Hospital (ID: RS-20100721), Kitasato Institute Hospital (ID: KK-20100617), Shiraishi Orthopaedic Pain Clinic (ID: SS-20100311), St. Marianna University School of Medicine (ID: A2036-Unv.), Ando Orthopaedics Hospital (ID: AD-20100709), Nagoya City University Hospital (ID: 11-10-0006), Osaka City University Graduate School of Medicine (ID: OC-20100625), Otemae Hospital (ID: OT-20100319), Osaka Medical College (ID: 10-1-08-0260), Higashiosaka City General Hospital (ID: TS-20100326), Matsukura Hospital (ID: MK-20100421), Nara Prefecture General Medical Center (ID: NK-20100318), Nara Medical University (ID: 10-002), Kyushu Rosai Hospital (ID: KR-20100511), Fukuoka University Faculty of Medicine (ID: 10-003), Hakujyuji Hospital (ID: HJ-20100309), Ken-Ai Memorial Hospital (ID: KA-20100330), Tsurukami Orthopaedic Clinic (ID: TR-20100401), and Oba Orthopaedics (ID: OB-20100610).

References

1. Acevedo JI, Beskin JL (1998) Complications of plantar fascia rupture associated with corticosteroid injection. Foot Ankle Int 19(2):91–97
2. Ball EM, McKeeman HM, Patterson C, Burns J, Yau WH, Moore OA, Benson C, Foo J, Wright GD, Taggart AJ (2013) Steroid injection for inferior heel pain: a randomised controlled trial. Ann Rheum Dis 72(6):996–1002
3. Benjamin M, Toumi H, Ralphs JR, Bydder G, Best TM, Milz S (2006) Where tendons and ligaments meet bone: attachment sites ('entheses') in relation to exercise and/or mechanical load. J Anat 208(4):471–490
4. Buchbinder R (2004) Clinical practice. Plantar fasciitis. N Engl J Med 350(21):2159–2166
5. Cole C, Seto C, Gazewood J (2005) Plantar fasciitis: evidence-based review of diagnosis and therapy. Am Fam Physician 72(11):2237–2242
6. Coombes BK, Bisset L, Vicenzino B (2010) Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. Lancet 376(9754):1751–1767
7. Crawford F, Atkins D, Young P, Edwards J (1999) Steroid injection for heel pain: evidence of short-term effectiveness. A randomized controlled trial. Rheumatology (Oxford) 38(10):974–977
8. Crawford F, Thomson C (2003) Interventions for treating plantar heel pain (Review). Cochrane Database Syst Rev. 3: CD000416. Review. (2010) Update. Cochrane Database Syst Rev 1:CD000416
9. Davies MS, Weiss GA, Saxby TS (1999) Plantar fasciitis: how successful is surgical intervention? Foot Ankle Int 20(12):803–807
10. Davis PF, Severud E, Baxter DE (1994) Painful heel syndrome: results of nonoperative treatment. Foot Ankle Int 15(10):531–535
38. de Vos RJ, Weir A, van Schie HT, Bierma-Zeinstra SM, Verhaar JA, Weinans H, Tol JL (2010) Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. JAMA 303(2):144–149
11. Higashiyama I, Kumai T, Hayashi K, Shinohara Y, Matsuda T, Tanaka Y, Takakura Y (2007) Effect of hyaluronic acid for plantar fasciitis. J Jpn Soc Surg Foot (Edinb) 28:25–28 (**Japanese**)
12. Jerosch J, Schunck J, Liebsch D, Filler T (2004) Indication, surgical technique and results of endoscopic fascial release in plantar fasciitis (E FRPF). Knee Surg Sports Traumatol Arthrosc 12(5):471–477
13. Kane D, Greaney T, Bresnihan B, Gibney R, FitzGerald O (1998) Ultrasound guided injection of recalcitrant plantar fasciitis. Ann Rheum Dis 57(6):383–384
14. Kibler WB, Goldberg C, Chandler TJ (1991) Functional biomechanical deficits in running athletes with plantar fasciitis. Am J Sports Med 19(1):66–71
15. Kikuchi T, Shimmei M (1994) Effects of hyaluronan on proteoglycan metabolism of rabbit articular chondrocytes in culture. Jpn J Rheumatol 5:207–215
16. Kumai T, Benjamin M (2002) Heel spur formation and the subcalcaneal enthesis of the plantar fascia. J Rheumatol 29(9):1957–1964
17. Kumai T, Muneta T, Tsuchiya A, Shiraishi M, Ishizaki Y, Sugimoto K, Samoto N, Isomoto S, Tanaka Y, Takakura Y (2014) The short-term effect after a single injection of high-molecular-weight hyaluronic acid in patients with enthesopathies (lateral epicondylitis, patellar tendinopathy, insertional Achilles tendinopathy, and plantar fasciitis): a preliminary study. J Orthop Sci 19(4):603–611
18. Leach RE, DiIorio E, Harney RA (1983) Pathologic hindfoot conditions in the athlete. Clin Orthop Relat Res 177:116–121
19. Lutter LD (1986) Surgical decisions in athletes' subcalcaneal pain. Am J Sports Med 14(6):481–485
20. Martinelli N, Marinozzi A, Carnì S, Trovato U, Bianchi A, Denaro V (2013) Platelet-rich plasma injections for chronic plantar fasciitis. Int Orthop 37(5):839–842
21. Mishra A, Woodall J Jr, Vieira A (2009) Treatment of tendon and muscle using platelet-rich plasma. Clin Sports Med 28(1):113–125
22. Moretti B, Garofalo R, Patella V, Sisti GL, Corrado M, Mouhsine E (2006) Extracorporeal shock wave therapy in runners with a symptomatic heel spur. Knee Surg Sports Traumatol Arthrosc 14(10):1029–1032

23. Muneta T, Koga H, Ju YJ, Mochizuki T, Sekiya I (2012) Hyaluronan injection therapy for athletic patients with patellar tendinopathy. J Orthop Sci 17(4):425–431
24. Neufeld SK, Cerrato R (2008) Plantar fasciitis: evaluation and treatment. J Am Acad Orthop Surg 16(6):338–346
25. Neustadt D, Caldwell J, Bell M, Wade J, Gimbel J (2005) Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: a randomized, controlled, multicenter trial. J Rheumatol 32(10):1928–1936
26. Park YB, Choi WA, Kim YK, Lee SC, Lee JH (2012) Accuracy of blind versus ultrasound-guided suprapatellar bursal injection. J Clin Ultrasound 40(1):20–25
27. Petrella RJ, Cogliano A, Decaria J, Mohamed N, Lee R (2010) Management of tennis elbow with sodium hyaluronate periarticular injections. Sports Med Arthrosc Rehabil Ther Technol 2:4
28. Ragab EM, Othman AM (2012) Platelets rich plasma for treatment of chronic plantar fasciitis. Arch Orthop Trauma Surg 132(8):1065–1070
29. Rathleff MS, Mølgaard CM, Fredberg U, Kaalund S, Andersen KB, Jensen TT, Aaskov S, Olesen JL (2015) High-load strength training improves outcome in patients with plantar fasciitis: a randomized controlled trial with 12-month follow-up. Scand J Med Sci Sports 25(3):e292–e300
30. Rathleff MS, Thorborg K (2015) 'Load me up, Scotty': mechanotherapy for plantar fasciopathy (formerly known as plantar fasciitis). Br J Sports Med 49(10):638–639
31. Riddle DL, Pulisic M, Pidcoe P, Johnson RE (2003) Risk factors for plantar fasciitis: a matched case-control study. J Bone Jt Surg Am 85-A(5):872–877
32. Riddle DL, Schappert SM (2004) Volume of ambulatory care visits and patterns of care for patients diagnosed with plantar fasciitis: a national study of medical doctors. Foot Ankle Int 25(5):303–310
33. Saito S, Furuya T, Kotake S (2010) Therapeutic effects of hyaluronate injections in patients with chronic painful shoulder: a meta-analysis of randomized controlled trials. Arthritis Care Res (Hoboken) 62(7):1009–1018
34. Schepsis AA, Leach RE, Gorzyca J (1991) Plantar fasciitis. Etiology, treatment, surgical results, and review of the literature. Clin Orthop Relat Res 266:185–196
35. Speed C (2014) A systematic review of shockwave therapies in soft tissue conditions: focusing on the evidence. Br J Sports Med 48(21):1538–1542
36. Tamoto K, Nochi H, Tokumitsu Y (1994) High molecular weight hyaluronic acids inhibit interleukin-1-induced prostaglandin E_2 generation and prostaglandin E_2-elicited cyclic AMP accumulation in human rheumatoid arthritis synovial cells. Jpn J Rheumatol 5:227–236
37. Tang T, Muneta T, Sekiya I (2008) Fibrous change of the infrapatellar fat pad due to strenuous running exercise and its treatment with intraarticular hyaluronan injection in a rat model. J Med Dent Sci 55(1):163–173
39. Weiss C, Levy HJ, Denlinger J, Suros JM, Weiss HE (1986) The role of Na-hylan in reducing postsurgical tendon adhesions. Bull Hosp Jt Dis Orthop Inst 46(1):9–15
40. van der Worp H, van den Akker-Scheek I, van Schie H, Zwerver J (2013) ESWT for tendinopathy: technology and clinical implications. Knee Surg Sports Traumatol Arthrosc 21(6):1451–1458
41. Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M (2008) The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheum Dis 67(12):1716–1723