

Efficacy and safety of hyaluronic acid (500-730kDa) Ultrasound-guided injections on painful tendinopathies: a prospective, open label, clinical study

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Summary

Background: Tendinopathies are conditions characterized by activity-induced pain, local tenderness and swelling for which a gold standard treatment is not established yet. Hyaluronic Acid (HA) is a key-molecule in several cellular activities and it is normally present in the extra-cellular matrix of tendons and ligaments. Amongst its properties, HA injections may reduce pain and determine disease-modifying effects. This study is an investigator-initiated open-label trial conducted to investigate the efficacy and safety of HA (500-730 kDa) peritendinous injections on pain reduction in patients affected by lateral elbow, Achilles or patellar tendinopathy.

Methods: A total of 71 tendons (34 with Achilles tendinopathy, 26 with lateral elbow tendinopathy, 11 with patellar tendinopathy) of 62 patients with painful tendinopathy were treated with a cycle of ultrasound-guided peritendinous injections one injection per week for three consecutive weeks. Efficacy assessments included changes in pain intensity measured by Visual Analogue Scale (VAS) at follow-up evaluations were performed 7 (V2), 14 (V3) and 56 days after first treatment. An Ultrasound (US) assessment was also performed to evaluate changes in tendon thickness and neo-vascularization. Adverse events were recorded for safety analysis throughout the study. All results were analyzed with descriptive statistics ap-

propriate to the nature of the variables.

Results: Significant reduction in VAS ($p < 0.001$) from baseline was observed in Achilles (-6.16 ± 0.45 cm), patellar (-6.16 ± 0.72 cm) and lateral elbow (-5.33 ± 0.43 cm) tendinopathies. The sagittal thickness decreased significantly from baseline at each endpoint (V3 day 14 and V4 day 56) in each type of tendinopathy analyzed ($p < 0.05$). Neo-vascularization decreased for each tendons at V3 and V4, except for patellar tendon at V3 V1 ($p = 0.125$). Nevertheless, reduction at V4 compared to baseline remained significant ($p = 0.016$).

Conclusions: US-guided HA (500-730 kDa) peritendinous injections determine significant pain relief and reduction in tendon thickness and neo-vascularization in US evaluations. The effect of HA did not show differences regarding the site of affected tendon. The treatment proved to be safe and very well tolerated.

Level of evidence: 4.

KEY WORDS: achilles, colour power doppler, hyaluronic acid, injection, patellar, tendinopathies, tennis elbow.

Introduction

Tendinopathies are multifactorial clinical conditions, which affect millions of people, producing disability that may last for several months¹. Even mechanical overloading is considered as the main risk factor, other intrinsic and extrinsic factors may contribute to the pathogenesis^{2, 3}. In particular, poor vascularity, underload, age, gender, as well as genetic, endocrine and metabolic factors may play a central role⁴⁻⁶.

Over the last decade, various models have been proposed to explain the intrinsic pathogenic mechanism of tendinopathies, which determine the failed healing response. Chronic stages of this condition are characterized by increased tenocyte apoptosis, disarrangement of collagen fibres with decreased of type I collagen and altered type I collagen/type III collagen ratio and neoangiogenesis³.

Regardless of the cause or the type of tendon, clinical findings are quite uniform: patients refer pain at the affected tendon site, which sometimes arises during intense muscular effort or gradually if the effort is repeated and continuous; with time and continued activity, however, the pain may get worse and limit sport performance⁷.

In addition to pain, physical examination may reveal local tenderness, swelling and reduced articular range of motion⁸.

US is a valid tool to confirm the diagnosis, showing tendon thickening, focal hypo-echogenic areas with altered grey scale pattern and neovascularization detected at Power Doppler with sensitivity and specificity up to 90%⁹⁻¹².

Although several options are available to manage tendinopathies, there is currently lack of consensus on the gold standard treatment. Eccentric exercise may be beneficial to ameliorate tendon structure¹³, while the role of oral and local NSAIDs is controversial in the short-term and could lead to several side effects in the long-term¹⁴.

Corticosteroid injections are widely used in clinical practice. Recent findings demonstrate that corticoid injection are worse than most conservative interventions in the long-term¹⁵ they could weak tendon structure enhancing the risk of tendon rupture¹⁶. Several studies have shown that peritendinous application of hyaluronic acid (HA) is an effective therapeutic option for the treatment of chronic tendinopathy^{17, 18}.

Hyaluronic acid (HA) is one of the main components of synovial fluid, which is produced in the normal tendon sheath and it is a main component of tendon extracellular matrix¹⁹. *In vitro* models suggest that HA may increase tenocyte viability and collagen I production and deposition, with positive collagen I/collagen III ratio in a dose-dependent manner²⁰. Its viscoelastic properties permit to reduce the surface friction of tendons increasing the gliding ability. It has been demonstrated that the application of HA, together with the formation of a network of the cells on the tendon surface, results in the "gliding effect"^{21, 22}.

The aim of this prospective, open label, single-centre study was to evaluate the efficacy and safety of three US-guided peritendineous injections of 2 mL of medium weight HA (500-730 kDa) at an interval of one week on pain relief in patients affected by Achilles and patellar or lateral elbow tendinopathies.

Methods

Study design

This was an investigator-initiated, prospective, open-label, single-centre clinical study that evaluated the efficacy of HA US-guided peritendineous injections on pain reduction at rest and on movement in patients with painful tendinopathies.

The study was approved by the local Ethical Committee and was conducted ethically according to international standards²³. Written informed consent was obtained from each patient before the inclusion.

Patients

All patients were enrolled over a 5-year period (2009 - 2013). Male or female patients aged ≥ 18 years in the symptomatic phase of chronic Achilles, patellar or lateral elbow tendinopathies (characterized by the

presence of at least one among: tendon swelling, pain on palpation, pressure and/or prehension, painful limited range of motion) for ≥ 6 weeks and a pain score of at least 50 mm on VAS, confirmed by US evaluation, non-responders to conventional therapies for more than one month, were eligible.

Patients with recent tendon surgery, pregnant or breast-feeding and patients with diabetes (glycated haemoglobin > 6.7) were excluded from the study. Patients were also excluded if had been treated with systemic or topical steroids less than 1 month prior to inclusion or with NSAIDs therapies less than 10 days before inclusion. During the study, the use of any pain medication or physical therapy were not allowed. Demographic characteristics of patients and the presence of concomitant hypothyroidism, diabetes and/or hypercholesterolemia were collected.

Study treatment

Sixty-two evaluable subjects were included (mean age 46.26) for a total of 71 treated tendons, classified as lateral elbow, Achilles or patellar tendinopathies. Patients received 3 ultrasound-guided injection of 2mL HA (500-730 kDa, Hyalgan®, Fidia Farmaceutici SpA, Abano Terme, Italy) once a week for 3 consecutive weeks.

Each injection was administered with a 25 Gauge needle approximately oriented 45° between the sagittal and coronal planes. Ultrasound imaging of treated tendons allowed examination of tendon morphology, detecting the areas of tendon degeneration and tendon thickness. Neovascularization was assessed using Power Doppler imaging. The procedure was performed with a high-frequency (5-18 MHz) linear probe (MyLab25 Gold, Esaote SpA, Italy) and to be sure of the reproducibility of the assessment, the osteotendinous junction was chosen as a reference in probe positioning.

Description of ultrasound guided injection scheme:

To treat patellar tendon, 2 mL of HA were injected distally the lower pole of the patella with the needle oriented in cranio-caudal direction at an angle of 45° to the Hoffa's body.

For the Achilles tendon, 2 mL of HA were injected about 1 cm from the calcaneal insertion site and proceeding proximally with the needle at an angle of 45° in the direction of Kager's triangle.

For the epicondyle, 2 mL of HA were injected distal to the bone insertion site in the forearm direction, between the extensor carpi radialis brevis and the finger extensor digitorum communis tendon.

Efficacy and Safety assessments

The primary endpoint was pain intensity changes from baseline (V1), assessed by VAS (0-10 cm) in which 0 represents 'no pain' and 10 represents 'extreme pain' at each study timepoint (V2 day 7, V3 day 14 and V4 day 56). Secondary variables were changes in tendon thickness measured by US and in

Table I. Demographic characteristics of sample.

Age	N	62
	Mean (SD)	46.26 (12.53)
	Median	46.00
	(Min, Max)	(16.71)
Gender	Male	47 (75.81%)
	Female	15 (24.19%)

Power Doppler signal of the target tendon (severity was classified as: 0= "No vascularization", 1= "Mild", 2= "Moderate" and 3= "Severe"), according to Hoksrund et al.²⁴ at V3 and V4. Moreover, a clinical evaluation of tendinopathy based on redness, warmth, swelling, tenderness, crepitus during movement and peritendinous effusion was performed at any study visit. Adverse events related and not related to the study drug were assessed for safety. Table I summarises demographic characteristics of sample.

Statistical Analysis

Statistical analysis was performed using SAS® software release for Windows® (SAS Institute, Inc, Cary, North Carolina, USA). There was no control group and a statistical calculation of sample size was not performed. The population size was enough to guarantee a 5% significance level. All statistical tests were 2-sided. To assess changes in pain and tendon characteristics at each endpoint, both the *Student's t test* and the *Wilcoxon Signed Rank Test* were used, considering

significant p-values ≤0.05. Finally, for each endpoint, an ANCOVA model was constructed to estimate the mean of the differences between the final and the initial assessments, adjusting for the following independent variables present at baseline: sex, age, type of tendon treated, number of infiltrations performed and number of risk factors.

Safety population included all patients receiving at least 1 injection while Efficacy included all patients receiving at least 1 injection with at least 1 post-baseline value. Safety and Efficacy Populations were comparable.

Results

Baseline characteristics

Sixty-two patients were included in the database, and 71 tendons were treated: 47.9% Achilles tendons (14 left and 20 right), 36.6% lateral epicondyles (6 left and 20 right) and 15.5% patellar tendons (4 left and 7 right)

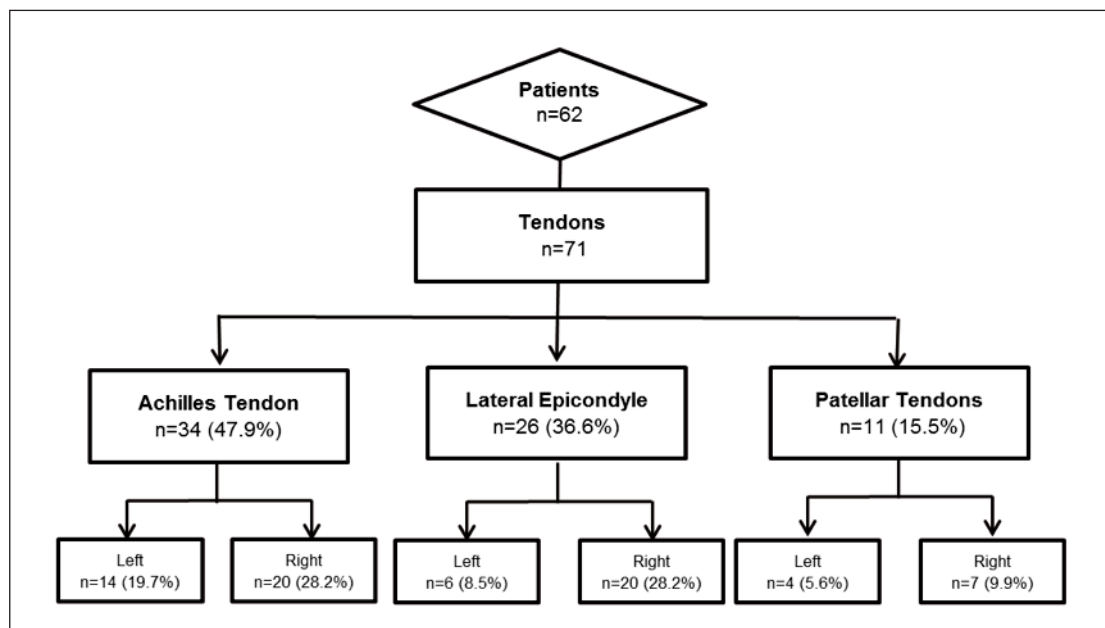


Figure 1. Subject disposition.

right) (Fig. 1). Of the 62 patients included in the study, 47 were males (75.8%) and 15 females (24.2%). The mean age was 46.3 years (± 12.5) (Tab. I).

The main risk factor present in the study population was hypercholesterolemia (16.1%) followed by hypothyroidism (9.7%). Diabetes was absent in 98.4% of the patients (Fig. 2).

Clinical outcomes

Pain decreased significantly from baseline at each endpoint (V2 day 17, V3 day 14 and V4 day 56) in each type of tendinopathy analysed ($p < 0.001$) (Fig. 3). Specifically, in patients affected by Achilles tendinopathy, the mean VAS value was 7.92 cm (± 1.44) and it progressively decreased at V2 (7.59 cm ± 0.97 ; $p < 0.001$), V3 (3.91 cm ± 2.08 ; $p < 0.001$) and V4 (2.02 cm ± 2.10 ; $p < 0.001$). Similarly, in patients affected by patellar tendinopathy the mean VAS value was (7.59 cm ± 0.97) and it progressively decreased at V2 (5.32 cm ± 1.60 ; $p < 0.001$), V3 (3.95 cm ± 1.64 ; $p < 0.001$) and V4 (2.50 cm ± 2.16 ; $p < 0.001$). In lateral elbow tendinopathy, the mean VAS value was 8.19

cm (± 0.79) and it progressively decreased at V2 (5.25 cm ± 1.80 ; $p < 0.001$), V3 (3.39 cm ± 1.91 ; $p < 0.001$) and V4 (1.74 cm ± 2.17 ; $p < 0.001$)

Results from the ANCOVA model, after adjustment by sex, age, type of treated tendon, number of injections and number of risk factors, showed that the reduction in pain intensity was similar for each tendon and that there were no significant differences between types of treated tendon ($p > 0.05$) (Tab. II).

Ultrasonographic examination

The sagittal thickness decreased significantly from baseline at each endpoint (V3 and V4) in each type of tendinopathy analysed ($p < 0.05$). At baseline, mean sagittal thickness of Achilles tendon was 9.41 mm (± 2.38) at baseline, while it was 8.44 mm (± 2.59) at V3 and 8.31 mm (± 2.28) at V4. Mean sagittal thickness of patellar tendon was 7.09 mm at baseline (± 1.65), while it was 6.55 mm (± 1.36) at V3 and 6.16 mm (± 1.58) at V4. For lateral elbow tendon, mean sagittal thickness was 6.20 mm (± 0.78) at baseline, while it was 5.80 mm (± 0.94) at V3 and 5.32 mm

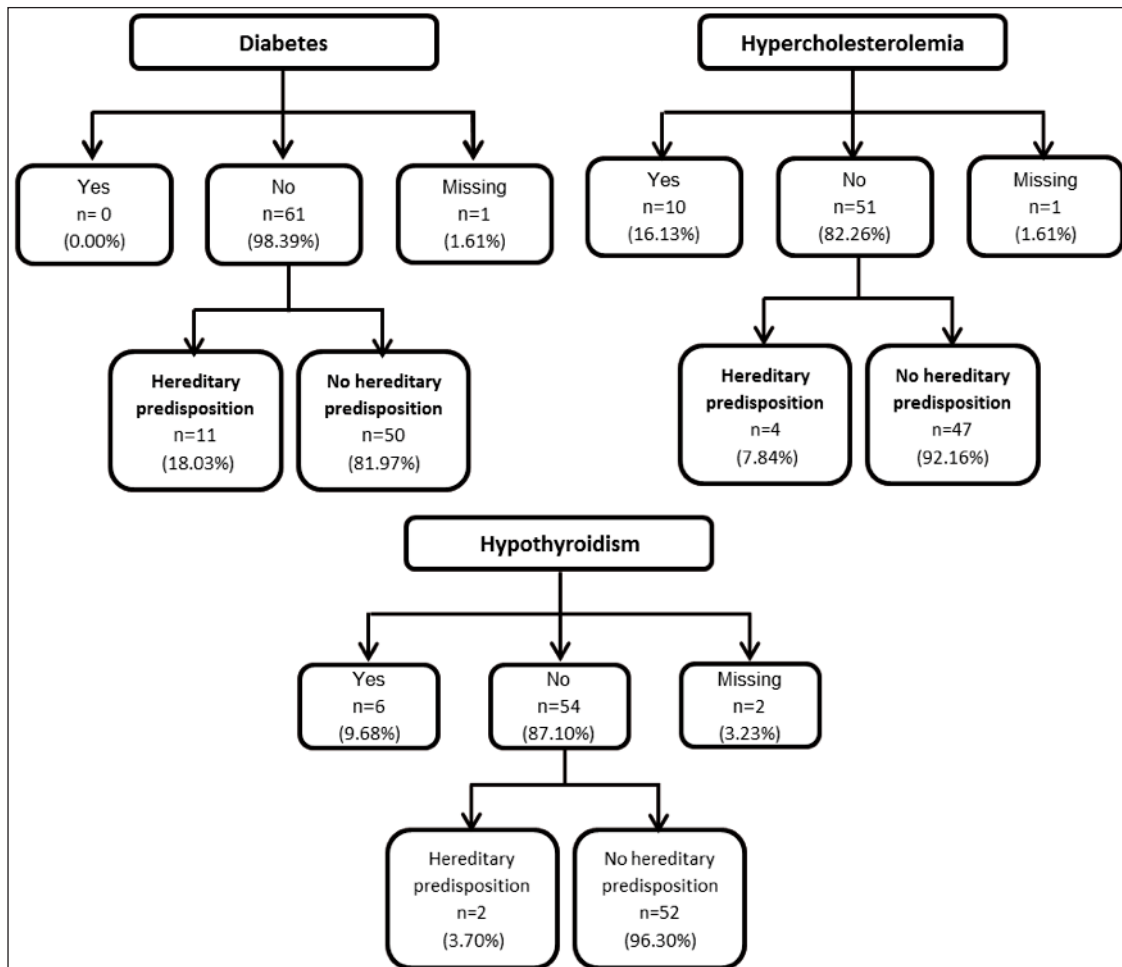


Figure 2. Distribution of diabetes, hypercholesterolemia and hypothyroidism on study population.

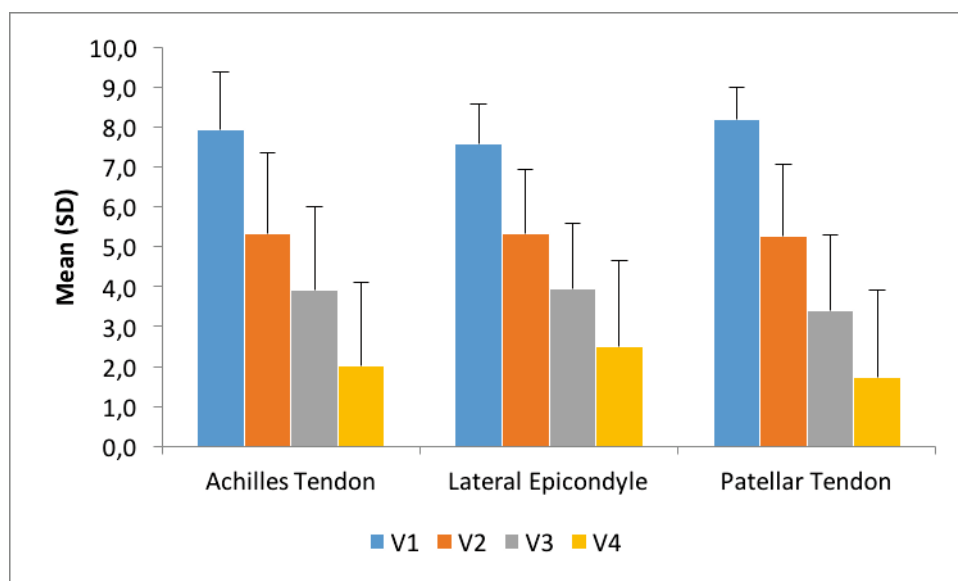


Figure 3. Mean pain intensity on VAS at each evaluation, by site of treated tendon. Legend: V1 Baseline; V2 Day 7; V3 Day 14; V4 Day 56.

(±0.87) at V4 (Fig. 4).

Regarding vascularity measured by Power Doppler, it was observed a significant decrease for each tendon at V3 and V4, except for patellar tendon from V3 to V1 (p=0.125). Nevertheless, reduction at V4 compared to baseline remained significant (p=0.016). (Fig. 5)

Safety

No serious adverse events were recorded. Two patients reported transient adverse events during the study, one mild endometriosis and one mild episode of lumbosciatic syndrome, neither of them related to the study medication. The peritendinous injections of HA were well tolerated by all patients.

Discussion

Although tendinopathies are a common complaint, accounting for 30% of all musculoskeletal consultations with a general practitioner, a gold standard treatment has not been identified yet²⁵.

Hyaluronic acid has already been shown to be safe

and effective in treating osteoarthritis^{26, 27}, while few studies have examined its effectiveness in tendon disorders.

The main objective of this study was to evaluate the efficacy and safety of HA injections of LMW-HA on pain reduction at rest and on movement in patients with painful tennis elbow, Achilles and patellar tendinopathies.

Kumai et al.²⁸ found that a single injection of a high molecular weight (HMW) HA (2700 kDa), determined a prompt decrease in pain in 62 patients affected by Achilles, patellar and tennis elbow insertional tendinopathies in the short-term (1 week after injection). Similarly, these study results indicate that symptom relief is achieved immediately after the first injection. Furthermore, in our study, we observed that pain continue to decrease until the last follow-up (56 days). This may indicate that a cycle of 3 injections of 500-730 kDa HA may determine long-term decrease in pain intensity in patients affected by chronic tendinopathies non-responders to conventional therapies

In accordance with our findings, Frizziero et al.²⁹, found that 3 injections of 500-730 kDa compared to low-energy extracorporeal shock-wave treatment (ESWT) pro-

Table II. Result from ANCOVA model in which the reduction in pain intensity was similar for each site and that there were no significant differences between types of treated tendon (p>0.05).

Type of treated tendon	Mean (SD)	Lower 95%	CL Upper 95%	CL P-value
Achilles Tendon	-6.16 (0.45)	-7.05	-5.26	0.326
Lateral Epicondyle	-5.33 (0.43)	-6.20	-4.46	0.994
Patellar Tendon	-6.16 (0.72)	-7.59	-4.73	-

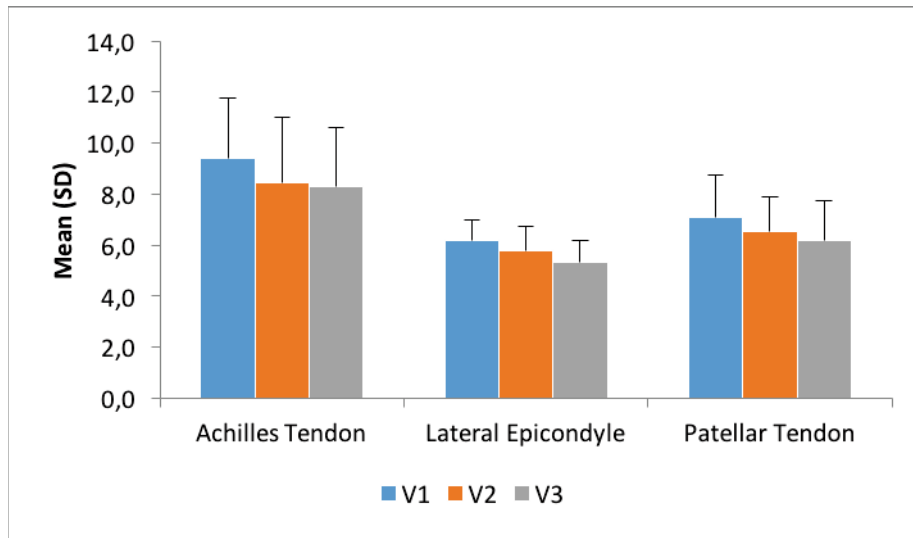


Figure 4. Mean sagittal thickness on US at each evaluation by site of treated tendon. Legend: V1 Baseline; V3 Day 14; V4 Day 56.

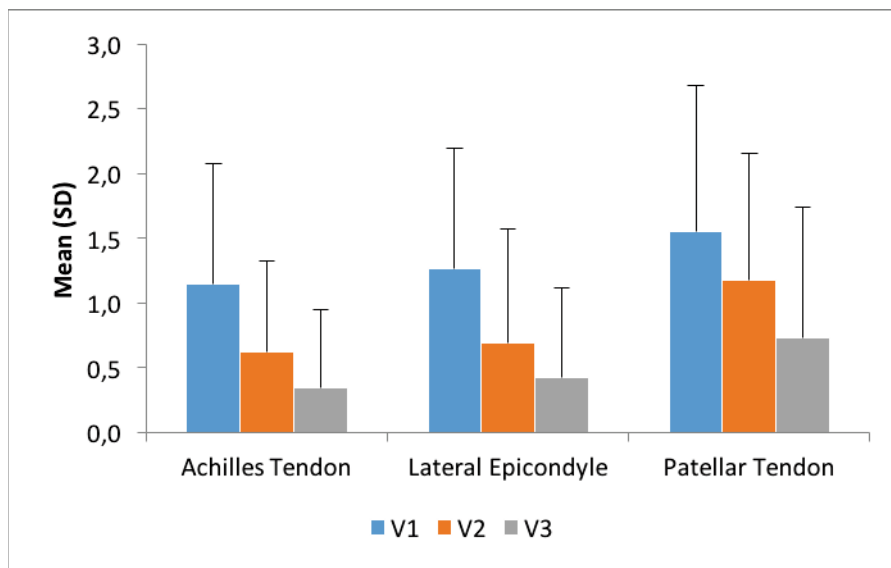


Figure 5. Mean vascularization on US at each evaluation by site of treated tendon. Legend: V1 Baseline; V3 Day 14; V4 Day 56.

vide prompt clinical improvement that last until 3 months of follow-up in rotator cuff tendinopathy. Similar results were obtained also in mid-portion Achilles tendinopathy, in which 2 injections of a combination HA and mannitol were found to be superior to ESWT³⁰. The Authors found 51.7% of participants in the HA group and 42.3% in the ESWT group were free of neovascularization within the tendon at Power Doppler US evaluation³⁰. Our findings confirm the significant reduction in neovascularization detected at Power Doppler at V3 and V4 compared to baseline, except for V3 in patients treated for patellar tendinopathy, while reduction in V4 was significant.

Furthermore, it was observed a significant reduction in tendon thickness at V3 and V4 compared to the baseline that were similar and not dependent on the tendon.

The amelioration in US parameters could be partially explained by reduction in friction and peritendinous adhesions due to the lubricant action of HA. These results may also indicate a possible “structure-modifying effect” here of HA (500-730kDa) on tendon, which need to be confirmed by further studies. The present study has the following 4 main limitations: the lack of a control group and randomization, the short-term follow-up and the lack of functional outcomes

specific for each tendon considered in this study. However, HA resulted efficient in short-term pain reduction and safe, without relevant adverse effects related to the molecule in the treatment of tendon pathology.

Conclusions

US-guided peritendinous injections of hyaluronic acid (500-730 kDa) in Achilles and patellar tendinopathy and lateral epicondylitis resulted in significant pain relief, decrease in tendon thickness and neovascularization without differences regarding the affected tendon object of this study.

These clinical findings and the absence of adverse events, may confirm that hyaluronic acid represent a safe and effective option in the managements of painful tendinopathies.

Conflict of interest

This study was an investigator initiated study carried out in accordance with internationally recognized standards, such as the Declaration of Helsinki and the ICH's Guideline for Good Clinical Practice. The Authors declare that they have no conflict of commercial interest. Nicola Giordan is an employee of Fidia Farmaceutici S.p.A. All Authors state, however, that Fidia Farmaceutici S.p.A. did not solicit this research project or protocols with investigators or institutions. Fidia Farmaceutici S.p.A. was not responsible for the initiation of the study and did not participate in the scientific design of the trial, in the creation of the protocol, management of the study, data analysis, reporting and in the decision to submit the manuscript for publication.

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