

**ORIGINAL RESEARCH**

# Comparison of Peritendinous Hyaluronan Injections Versus Extracorporeal Shock Wave Therapy in the Treatment of Painful Achilles' Tendinopathy: A Randomized Clinical Efficacy and Safety Study



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**Abstract**

**Objective:** To compare the safety and efficacy of hyaluronan (HA) injections with standard extracorporeal shock wave therapy (ESWT) in the treatment of painful midportion Achilles' tendinopathy.

**Design:** Multinational, prospective, randomized controlled, blinded-observer trial.

**Setting:** Ambulatory care.

**Participants:** Adults (N=62) with Achilles' midportion tendinopathy for  $\geq 6$  weeks and a pain score of at least 40mm (Huskisson visual analog scale [VAS], 100mm) were randomized, and 59 were analyzed in the intention-to-treat data set. There were no withdrawals because of adverse effects.

**Interventions:** Two peritendinous HA injections versus 3 ESWT applications at weekly intervals.

**Main Outcome Measures:** Primary efficacy criterion was changed from the Victorian Institute of Sports Assessment—Achilles' questionnaire (VISA-A) score to the percent change in pain (VAS) at 3 months posttreatment, compared with baseline values. Main secondary parameters were VISA-A, Clinical Global Impression (CGI), and clinical parameters.

**Results:** HA treatment provided a clinically relevant improvement in Achilles' midportion tendinopathy. A large superiority of the HA group, compared with ESWT application, was observed for percent change in pain (VAS), and this superiority was proven to be statistically significant (Mann-Whitney statistic [MW]=.7507 with  $P=.0030$  lower than required  $\alpha=.025$  significance level 1-sided; Mann-Whitney  $U$  test) at 3 months posttreatment. Similar findings for HA were also observed at 4 weeks (MW=.6425,  $P=.0304$ ) and 6 months (MW=.7172,  $P=.0018$ ). Advantage of HA treatment was confirmed by VISA-A questionnaire, CGI, and clinical parameters. Ten adverse events, 4 in the HA group and 6 in the ESWT group, were reported, but none were classified as serious.

**Conclusions:** Two peritendinous HA injections showed greater treatment success in Achilles' midportion tendinopathy compared with standard ESWT.

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Tendinopathy is a broad term to describe chronic painful conditions located in and around tendons. The exact etiology, pathophysiology, and healing mechanisms of the various tendon complaints are only partly known and controversially debated. Vascularity appears increased in tendinopathy,<sup>1</sup> and the degenerative structural changes appear to disrupt the healing process of the accumulated tendon damage, leading to chronic pain and loss

of motility. The Achilles' tendon is one of those injured most often in the body,<sup>2-4</sup> with tendinopathic conditions frequently occurring at the insertional, myotendinous, or midportion locations.<sup>5</sup> Midportion Achilles' tendinopathy is most common and is involved in 55% to 65% of all Achilles' tendon injuries.<sup>3,6,7</sup>

Conservative treatment with different loading regimens is the first line of treatment, but is time-consuming and requires intensive patient compliance for several weeks or months. If this fails, surgical or nonsurgical actions are required, but have shown variable success rates.<sup>8</sup> Some treatments may cause significant side effects (eg, local tissue degradation or tendon tearing after repeated use of local steroids<sup>9-11</sup>) or adverse effects on other organ systems (eg, gastrointestinal toxicity, renal damage, or increased cardiovascular risk after intake of nonsteroidal anti-inflammatory drugs<sup>12-14</sup>), making them unsuitable for long-term use. Hyaluronan (HA) is a high-molecular weight polysaccharide naturally found in the extracellular matrix of soft connective tissues and synovial fluids of vertebrates. Because of its unique viscoelastic properties, HA is an ideal biological lubricant with known analgesic, anti-inflammatory, and antiadhesive effects.<sup>15,16</sup> It has shown efficacy in the treatment of tendon disorders by decreasing pain,<sup>17</sup> supporting tissue healing,<sup>18</sup> and improving the lubrication of the tendon.<sup>19</sup> Extracorporeal shock wave therapy (ESWT) is another option currently used in the treatment of soft tissue conditions<sup>20,21</sup> and can be regarded as one of the most frequently used treatments of tendinopathy in Europe. In clinical use, ESWT was found to inhibit pain receptors and stimulate endogenous lubrication in tendons,<sup>22-26</sup> thus making it an appropriate comparator for HA in the treatment of tendinopathy. Because direct comparisons of HA administration and ESWT application in the treatment of painful midportion Achilles' tendinopathy are lacking, we evaluated the 2 treatments in parallel in this study.

## Methods

This was a multinational, prospective, randomized, parallel-group, blinded-observer study, approved by relevant ethics committees. All patients provided written informed consent before participation. The study was conducted in accordance with the approved study protocol and the current Helsinki Declaration.

## Study participants

Patients aged between 18 and 75 years presenting with painful Achilles' midportion tendinopathy for  $\geq 6$  weeks and a pain intensity score of at least 40mm on the Huskisson visual analog scale (VAS)<sup>27</sup> (VAS pain score, 100mm) were eligible.

### List of abbreviations:

CGI	Clinical Global Impression
CI	confidence interval
ESWT	extracorporeal shock wave therapy
HA	hyaluronan
ITT	intention to treat
min-max	minimum-maximum
MW	Mann-Whitney
MW-U	Mann-Whitney U
VAS	visual analog scale
VISA-A	Victorian Institute of Sports Assessment—Achilles' questionnaire

Main exclusion criteria were general, severe intercurrent illnesses (eg, uncontrolled diabetes mellitus, peripheral neuropathy), any contraindications for the test products (eg, hypersensitivity, recent surgery, local osteomyelitis), concomitant diseases (eg, insertional Achilles' tendinopathy), or other conditions that could influence study evaluation or were incompatible with study procedures (eg, concomitant medications potentially interfering with the functional assessments in the study).

To avoid selection bias, verification of study entry criteria and enrollment was performed by a blinded investigator who chronologically allocated eligible patients to consecutive random codes without knowing the underlying group allocation. They were balanced randomized to either HA injection (HA group) or ESWT application (ESWT group) using a computer-generated 2-block randomization list. Patients were treated in ambulatory care at the Antwerp University Hospital (Antwerp, Belgium) and at the Praxiszentrum Orthopädie-Unfallchirurgie Nordrhein (Aachen, Germany).

## Study treatments

Study treatments were administered by independent, experienced physicians who were not involved in the general assessments of the patients. Two HA injections (HA 40mg/2mL + 10mg mannitol [Ostenil Tendon<sup>a</sup>]) were administered peritendinously at the Achilles' midportion tendon in patients in the HA group at weekly intervals under sonographic control. Patients in ESWT group received 3 ESWT sessions at weekly intervals using a piezoelectric ESWT device (PiezoSon 100 plus<sup>b</sup>) with standardized parameters (10mm penetration depth, 94° aperture angle, 4Hz pulse frequency, 1500 pulses per application). ESWT intensity levels were set to 14 and 15 (out of 20 possible intensity levels) in both centers. Intake of paracetamol, in case of unbearable pain, was allowed up to 4g daily but not within 24 hours before a study visit. Excessive sports or physical activities (eg, demanding housework) with a potentially negative impact on the treatment success were not allowed during the study.

## Effectiveness evaluations

Evaluations were performed by blinded observers. The primary efficacy criterion was percent change in pain (VAS) at 3 months posttreatment, compared with baseline values. The secondary efficacy criteria were (1) the Victorian Institute of Sports Assessment—Achilles' questionnaire (VISA-A) (VISA-A score: 0, no activity/maximum pain; 100, maximum activity/no pain),<sup>28</sup> adapted to the local language; (2) the intensity of clinical parameters (redness, warmth, swelling, tenderness on palpation, crepitus on motion, accumulation of tissue fluid), evaluated on a 5-point ordinal scale (0, none; 1, slight; 2, moderate; 3, severe; 4, extreme); and (3) patients' and investigators' overall impression of the treatment outcome (Clinical Global Impression [CGI]) using a 7-point ordinal scale (1, very much improved; 7, very much worse). A power Doppler ultrasonography was performed to evaluate the vascularization stage of the affected Achilles' tendons using the Del Buono Score System (grades I–V).<sup>29</sup>

During the treatment phase (day 0 to day 7 [visits 1–2] for the HA group; day 0 to day 14 [visit 1–3] for the ESWT group), the efficacy parameters were assessed before administration of the test product. During the treatment-free follow-up period, patients returned for 3 visits at 4 weeks (visit 4), 3 months (visit 5), and 6 months (visit 6) after the last treatment administration. At each

visit, patients self-rated their pain intensity on a horizontal VAS pain scale ranging from 0mm (no pain) to 100mm (extreme pain).

## Safety evaluations

Patients' pain during treatment application was evaluated using an 11-point ordinal scale (0, no pain; 10, extreme pain). Any adverse event occurring during the study was documented and its relation to treatment evaluated.

## Data processing and statistics

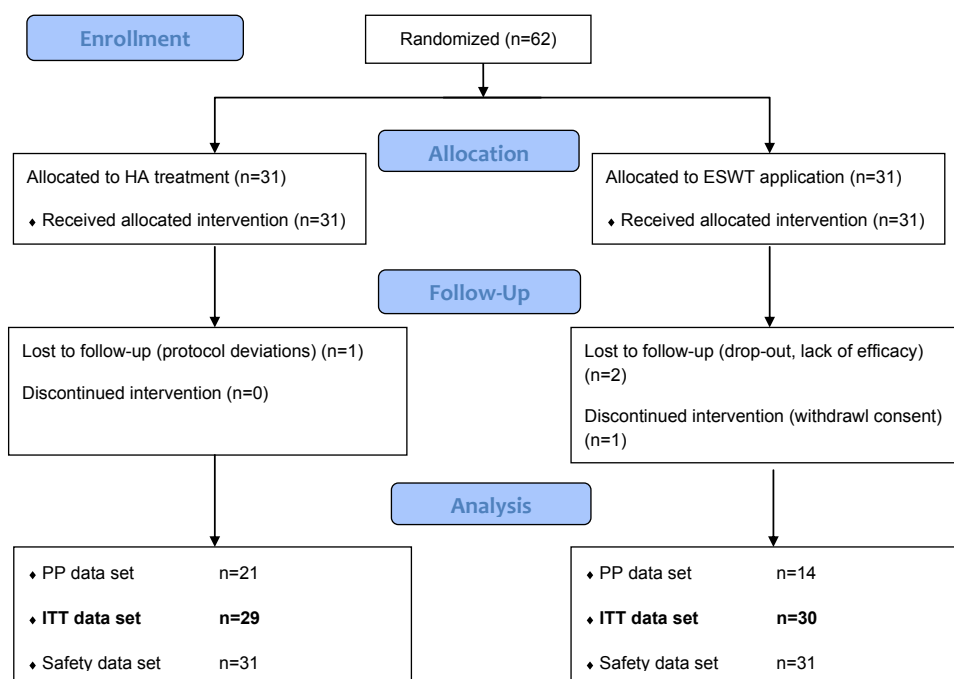
The planned sample size of 40 patients per group was determined based on previous studies<sup>30,31</sup> of similar products using a comparable design. Because patient withdrawals and data exclusions may influence study outcome, the statistical analyses were based on the intention-to-treat (ITT) data analysis set. A per-protocol analysis was only performed in the sense of a sensitivity analysis and to support the results of the ITT analysis. Missing values were replaced using the "last-value-carried-forward" principle. Treatment groups were compared using the Wilcoxon Mann-Whitney *U* (MW-U) test as a 1-sided test for superiority (significance level  $\alpha = .025$ , superiority defined for Mann-Whitney [MW] measure  $>0.5$ ), since it was assumed not to have a normal distribution. Results were interpreted to the benchmark values according to Cohen,<sup>32</sup> with the benchmark .50 indicating equality for superiority and a value of .64 signifying medium-sized superiority, defined as being medically relevant. Statistical analyses were performed by an independent biostatistician using validated computer programs (Report Version 6.7, Testimate Version 6.5<sup>o</sup>). Based on normal practice in statistics and the recommendations in the International Conference on Harmonisation E9 guideline, a criterion with the highest correlation to the parameter CGI was chosen as the primary efficacy criterion.

Because the highest correlation, verified by Pearson correlation coefficient, was found for the percent change in pain (VAS), the previous primary criterion—VISA-A at 3 months post-treatment—was changed to the percent change in pain (VAS) at 3 months posttreatment, before the frozen database was opened. Homogeneity analyses were performed for the ITT data set. Wei-Lachin procedures (global test) were performed for baseline comparability of demographic variables as a whole and the anamnestic variables as a second whole.<sup>33-35</sup> The Mann-Whitney-Wilcoxon test was performed for the baseline primary efficacy criterion (percent change in pain on the VAS). Homogeneity was judged with MW estimators as corresponding measures of relevance with their 2-sided 90% confidence intervals (CIs).

## Results

### Distribution of participants

A total of 62 patients presenting with painful Achilles' midportion tendinopathy for between 8 weeks and 14 years were consecutively included from December 2013 to March 2015 with a balanced distribution to both treatment groups. Fifty-eight patients (93.5%) received study treatment according to the randomization list and completed the study according to protocol, with the final visit of the last patient in September 2015. Reasons for early study termination in the ESWT group ( $n=3$ ) were withdrawal of consent before treatment end, loss to follow-up, and lack of efficacy, while 1 patient in the HA group was dropped because of several deviations in the selection criteria. Homogeneity between groups was proven at baseline (MW estimator within [.36; .64] and 0.5 within 90% CI) for demographic parameters (age, sex, height, weight), anamnestic criteria (medical history, activity level, the



**Fig 1** Distribution of patients (Consolidated Standards of Reporting Trials [CONSORT] flow diagram). Abbreviation: PP, per protocol.

**Table 1** Baseline patient characteristics for ITT data set

Characteristics	HA Group (n=29)	ESWT Group (n=30)
Sex		
Female	14 (48.3)	17 (56.7)
Male	15 (51.7)	13 (43.3)
Age (y)	45.8±10.0	44.8±9.6
	48.0 (19.0–62.0)	46.5 (22.0–58.0)
Height (cm)	172.7±9.3	172.9±10.7
	170.0 (155.0–197.0)	170.0 (160.0–205.0)
Weight (kg)	80.1±14.9	78.7±14.1
	82.0 (53.0–105.0)	76.0 (55.0–128.0)
Study-relevant complaints since (d)	709.0±911.9	660.9±1033.2
	346.0 (59.0–3369.0)	305.0 (113.0–5135.0)
Target side		
Right	16 (55.2)	17 (56.7)
Left	13 (44.8)	13 (43.3)
Unilateral/bilateral	19 (65.5)/10 (34.5)	24 (80.0)/6 (20.0)

NOTE. Values are n (%), mean ± SD, or median min-max.

study relevant site, use of analgesics), and for VAS pain. Statistical analyses were based on 59 patients in the ITT data set (HA group, 29; ESWT group, 30) (fig 1). Table 1 shows baseline characteristics of the ITT population.

**VAS pain score**

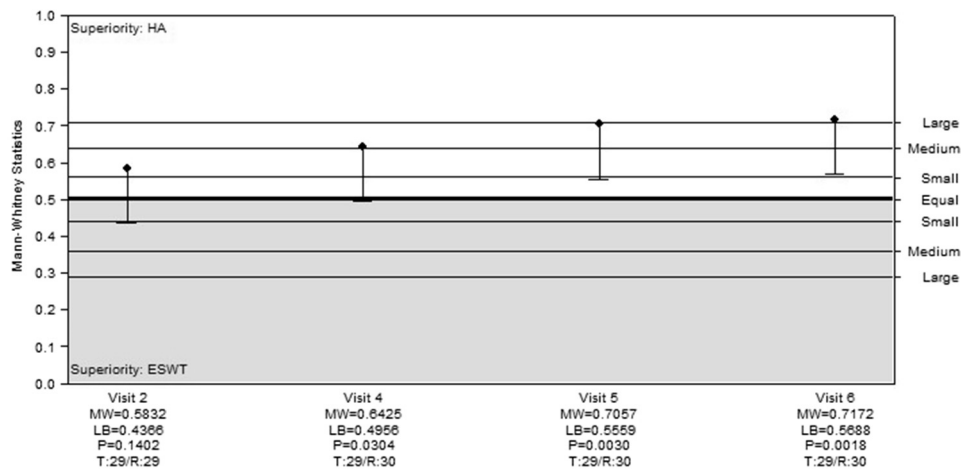
Pain decreased in both groups from the baseline median values of 63.0 (min-max 49.0–76.0) and 68.5 (minimum-maximum [min-max] 58.0–79.0) in the HA and ESWT groups, respectively. However, there was a greater improvement in the HA group at 4 weeks (HA group: median 18.0, min-max 6.0–40.0; ESWT group: median 33.0, min-max 14.0–67.0), at 3 months (HA group: median 6.0, min-max 3.0–13.0; ESWT group: median 28.0, min-max 5.0–52.0), and at 6 months posttreatment (HA group: median 3.0, min-max 1.0–7.0; ESWT group: median 22.0, min-max 1.0–57.0). Differences in VAS pain, analyzed by baseline-independent median percent changes, confirm a greater pain improvement after HA treatment (table 2). Percent pain decrease was greater in the HA group, compared with the ESWT group, after 4 weeks (–68.1% vs –47.9%), 3 months (–88.2% vs –51.6%), and 6 months (–94.9% vs –66.4%). The broad range of values (min-max) was focused in the HA group by lower/upper quartiles identifying that 75% of the patients showed improvements of at least 82.2% and 85.7% at 3 and 6 months posttreatment, respectively, whereas 75% of patients in the ESWT group showed larger variations with minimum improvement of 25.7% and 24.7% at 3 and 6 months posttreatment, respectively (see table 2). For the primary efficacy criterion, percent change in pain (VAS) from baseline to 3 months posttreatment, the HA group was shown to be largely superior compared with the ESWT group, and this was statistically significant (MW=.7057, P=.0030, CI: 97.5%) (fig 2). A sensitivity analysis with the per-protocol dataset confirmed these results (MW=.7908, P=.0016). The MW-U statistic further revealed a large superiority of the HA group at 6 months (MW=.7172, P=.0018, CI: 97.5%) posttreatment.

An originally unplanned descriptive center-specific analysis for the primary criterion, percent change in pain (VAS) from baseline

**Table 2** Main efficacy parameters for ITT data set

Parameter	Group	Day 0	Week 4	3 Months	6 Months
		Median (min-max)	Median (min-max) [LQ/UQ]	Median (min-max) [LQ/UQ]	Median (min-max) [LQ/UQ]
VAS pain (% change from baseline)	HA		–68.1 (–100.0/21.2) [–91.2/–47.4]	–88.2 (–100.0/–18.1) [–94.4/–82.2]	–94.9 (–100.0/2.2) [–98.9/–85.7]
	ESWT		–47.9 (–100.0/10.9) [–75.0/–14.8]	–51.6 (–100.0/8.6) [–91.1/–25.7]	–66.4 (–100.0/33.3) [–97.0/–24.7]
	Center 1		–59.1 (–100.0/21.2)	–86.4 (–100.0/–18.1)	–92.2 (–100.0/2.2)
	Center 2		–71.4 (–96.9/–47.4)	–91.6 (–100.0/–46.4)	–95.9 (–100.0/–68.1)
VISA-A score (score values)	HA	34.0 (0.0/74.0)	53.2 (–100.0/10.9)	88.5 (–100.0/–1.5)	88.5 (–100.0/33.3)
	ESWT	31.5 (7.0/74.0)	39.1 (–81.9/6.9)	–46.2 (–100.0/8.65)	–49.3 (–100.0/8.3)
	Center 1	8.0 (2.0/20.0)	64.0 (22.0/99.0)	73.0 (24.0/100.0)	75.0 (22.0/100.0)
	Center 2	9.0 (2.0/17.0)	50.5 (9.0/96.0)	47.5 (15.0/99.0)	52.0 (15.0/100.0)
Clinical parameter total score (score values)	HA	8.0 (2.0/20.0)	2.0 (0.0/9.0)	1.0 (0.0/4.0)	1.0 (0.0/7.0)
	ESWT	9.0 (2.0/17.0)	3.5 (0.0/12.0)	2.5 (0.0/9.0)	2.0 (0.0/10.0)
		Day 0 Median (min-max)	Day 7 Median (min-max)	Day 14 Median (min-max)	
Application pain level (score values)	HA	4.0 (0.0/10.0)	3.5 (0.0/9.0)		
	ESWT	6.0 (1.0/10.0)	6.0 (1.0/9.0)	5.0 (1.0/10.0)	

Abbreviations: LQ, lower quartile; UQ, upper quartile.



**Fig 2** VAS pain percent change from baseline. Last value carried forward, HA (test) versus ESWT (reference) (data set: ITT). MW-U test at day 7 (visit 2), 4 weeks (visit 4), 3 months (visit 5), and 6 months (visit 6) posttreatment, one-sided, 97.5% CI. Results were interpreted based on the following benchmark values: .36 medium-sized inferiority, .44 small inferiority, .50 equality, .56 small superiority, .64 medium-sized (relevant) superiority, and .71 large superiority.<sup>32</sup> Abbreviations: LB, lower bound; R, reference; T, test.

(fig 3), revealed comparable values for HA patients but different values for ESWT patients (see table 2). Differences in pain intensity between center 1 and center 2 were only 5.2% and 3.7% in HA groups at 3 and 6 months posttreatment, respectively, but were 42.3% and 39.2% in ESWT groups at 3 and 6 months posttreatment, respectively.

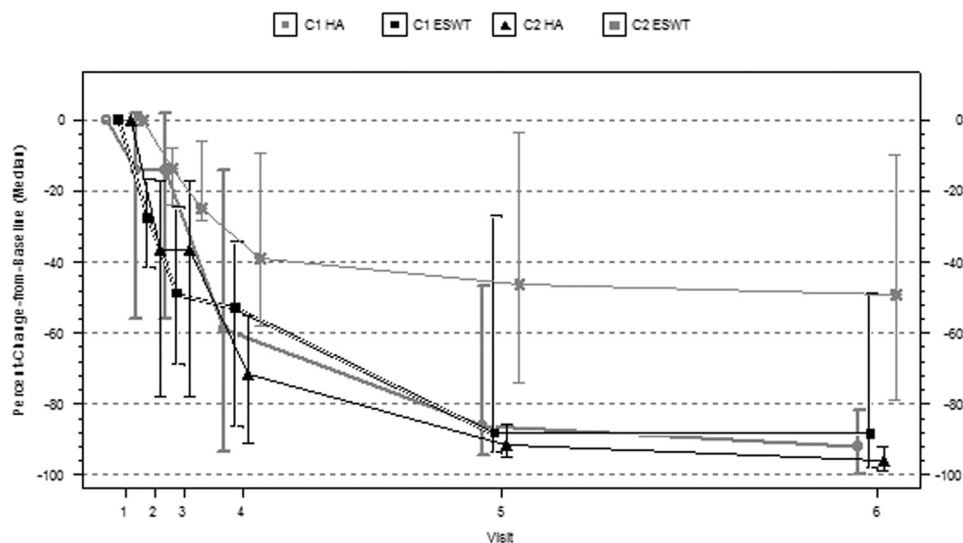
### Victorian Institute of Sports Assessment—Achilles' questionnaire

Results were positive in both treatment groups, but the outcome was more favorable in the HA group throughout the posttreatment phase. Initial median VISA-A scores improved in the HA group, compared with the ESWT group, at 4 weeks (13.5 score points higher), 3 months (25.5 score points higher), and 6 months (23.0 score points higher) (see table 2). The number of improved

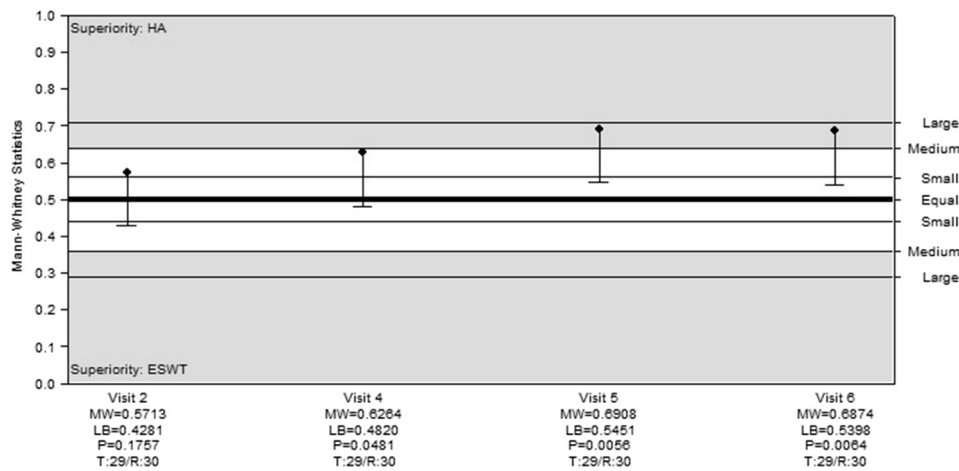
patients (increase in score values compared with baseline values) was higher in the HA group after 4 weeks (HA group: 93.1%; ESWT group: 86.7%), 3 months (HA group: 96.6%; ESWT group: 86.7%), and 6 months (HA group: 96.6%; ESWT group: 93.3%). In the MW-U analysis, a significant, large-sized superiority of the HA group over the ESWT group was demonstrated at 3 months (MW = .6908,  $P = .0056$ , CI: 97.5%) and 6 months (MW = .6874,  $P = .0064$ , CI: 97.5%) posttreatment. Small and medium superiority of the HA group was observed on day 7 and 4 weeks post-treatment (fig 4).

### Clinical parameters and CGI

A cumulative analysis of all clinical parameters (sum score ranging from 0 [no complaints] to 20 [extreme]) showed that most patients in the 2 groups improved over time (see table 2).



**Fig 3** VAS pain percent change (median, quartiles) from baseline (center specific) at day 7 (visit 2), 4 weeks (visit 4), 3 months (visit 5), and 6 months (visit 6) posttreatment. Last value carried forward (data set: ITT). Abbreviations: C1, center 1; C2, center 2.



**Fig 4** VISA-A scores as changes from baseline. MW-U test at day 7 (visit 2), 4 weeks (visit 4), 3 months (visit 5), and 6 months (visit 6) posttreatment. Last value carried forward, HA (test) versus ESWT (reference) (data set: ITT), one-sided, 97.5% CI. Abbreviations: LB, lower bound; R, reference; T, test.

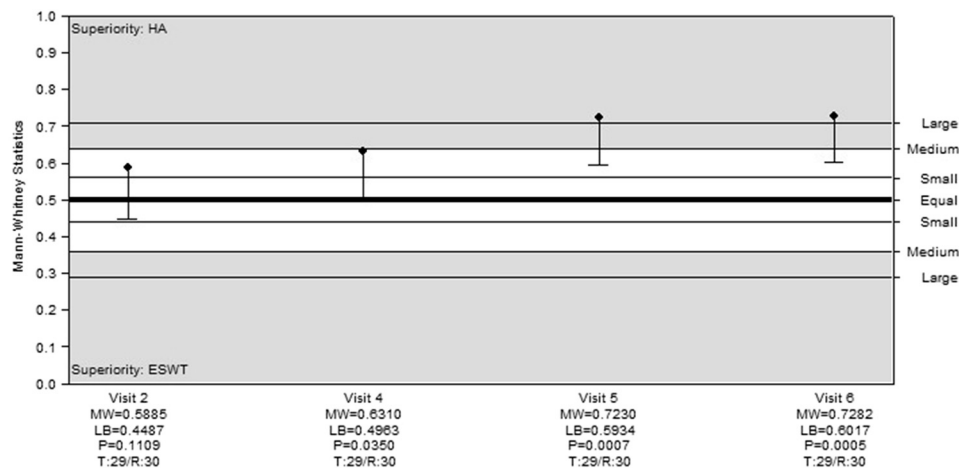
The improvement was comparable at 4 weeks (HA group: 86.2%; ESWT group: 83.3%) and 6 months (HA group: 89.7%; ESWT group: 86.7%). At 3 months, more patients with improvement were seen in the HA group (93.1% vs 76.7%). A small-sized nonsignificant superiority was observed in the MW-U test for the HA group at 3 months (MW=.5667,  $P=.1915$ , CI: 97.5%) and 6 months (MW=.5534,  $P=.2425$ , CI: 97.5%) posttreatment.

The overall treatment success (CGI) was well correlated with the investigators' and participants' evaluation and rated very positively in both treatment groups. Compared with baseline, the number of patients reporting a marked improvement (ranging from "minimally" to "very much" improved) was higher in the HA group, compared with the ESWT group, at 4 weeks (89.7% vs 80.0%), 3 months (100.0% vs 73.3%), and 6 months (96.6% vs 80.0%). In the MW-U analysis, a significant superiority of the HA group was proven at 3 months (MW=.7230,  $P=.0007$ , CI: 97.5%) and 6 months (MW=.7282,  $P=.0005$ , CI: 97.5%)

posttreatment in both evaluations (investigators and participants) (fig 5).

### Other parameters

Vascularization at study relevant site was comparable in both treatment groups: at 6 months posttreatment, 51.7% of participants in the HA group and 42.3% in the ESWT group were free of neovascularization within the tendon. Advantage of HA treatment was also supported by lower pain levels during administration. HA injections were associated with lower pain during administration, compared with ESWT application, at day 0 and day 7 (see table 2). Evaluation of "return to work" and "restart of sporting activities" could only be analyzed descriptively, as only 1 patient was certified sick during the study and returned to work before study termination, while most patients did not stop their sporting activities. Since analgesic intake was required by only 1 patient, no differences between treatment groups were analyzed.



**Fig 5** CGI patients' ratings as changes from baseline. MW-U test at day 7 (visit 2), 4 weeks (visit 4), 3 months (visit 5), and 6 months (visit 6) posttreatment (1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; 7, very much worse). Absolute values, last value carried forward, HA (test) versus ESWT (reference) (data set: ITT), one-sided, 97.5% CI. Abbreviations: LB, lower bound; R, reference; T, test.

## Safety

A total of 10 adverse events were reported in a total of 8 participants (12.9%): 3 patients (4.8%) in the HA group (4 adverse events) and 5 patients (8.1%) in the ESWT group (6 adverse events). None of these were considered serious. Eight adverse events were judged as not device or procedure related, and only 2 were thought to have a causal relationship with the study treatments. One participant reported transient, moderate tendon pain after HA injection on day 1, and another participant reported transient, moderate application site pain lasting 2 days after ESWT treatment. A single intake of paracetamol was necessary in 1 patient in the HA group.

## Discussion

To our knowledge, this is one of the first studies where the benefits of HA treatment were compared directly to ESWT application in the treatment of symptomatic midportion Achilles' tendinopathy. Both treatments were tested in their standard and recommended application, with 2 peritendinous HA injections and 3 ESWT applications at weekly intervals.

Specific baseline characteristics that could influence differences in outcomes across sites were minimized (eg, by careful uniform center staff training, regular monitoring visits, comparable sample sizes, and source of patient recruitment). Balanced homogeneity of both treatment groups was demonstrated in center-specific analysis for demographic and anamnestic characteristics. The impact of these factors on differences in pain intensity between center 1 and center 2 was regarded as negligible. Therefore, treatment-specific heterogeneity in the ESWT group resulting from application-specific medical treatment, as this is a daily routine in medical practices, was taken into consideration. Because this study was powered to detect outcome differences and not site differences, the influence of site-specific application should be evaluated in other clinical studies with adjusted sample sizes.

The considerable decrease in pain intensity from baseline to study termination in both groups justifies the use of these modalities in the treatment of Achilles' midportion tendinopathy. However, the HA-treated patients showed much higher pain relief and a significant advantage compared with the ESWT group throughout the study. Superiority of HA treatment was even observed 1 week after the first administration.

The advantage of HA treatment was further substantiated by results of the VISA-A score, clinical parameters, and CGI. The percent change in pain and VISA-A scores revealed clinically relevant results in patients receiving HA treatment and were underscored by the CGI, which revealed a superiority of HA treatment by investigators' and patients' evaluations at all follow-up visits. Assessment of clinical parameters resulted in observed superiority and proven noninferiority at 3 and 6 months posttreatment for almost all parameters. At all visits during the treatment period, patients rated pain intensity during HA injections as lower than application pain during ESWT treatment.

The results of this clinical study confirm the positive effects on treatment outcome after HA injection or ESWT application in Achilles' midportion tendinopathy.<sup>17,20,21</sup> A very recent publication<sup>36</sup> of preliminary results at 3 months' follow-up evaluation

provides the first information about a prompt clinical improvement from HA treatment compared with ESWT. The results confirm a significant improvement in pain and function in both treatment groups at 3 months' follow-up, but this was achieved using an additional HA injection (3 instead of 2) or ESWT application (4 instead of 3).

Our clinical trial shows that using the recommended treatment schemes for HA injections (2 injections) and ESWT application (3 applications)—that is, fewer treatments, a shorter treatment period, and less efforts and costs for the patients—the HA group obtained clinically relevant results throughout the study, with a significant superiority, compared with the ESWT group, for the primary efficacy criterion of percent change in pain intensity (VAS) at all study visits. The advantages and greater benefits from HA treatment clearly outweigh the small risk of adverse events for this treatment modality, and results are regarded as generalized because of appropriate study design.

## Study limitations

A double-blind study design was not possible because both treatments were tested in their standard and recommended application. However, to avoid bias, the application was performed by a single investigator per center, and the evaluation of patients was performed by a blinded observer.

## Conclusions

Two peritendinous HA injections resulted in significant symptomatic pain relief and improvement in function in patients with Achilles' midportion tendinopathy, with a low risk for adverse events.

## Suppliers

- Ostenil Tendon; TRB Chemedica AG.
- ESWT device: PiezoSon 100 plus; Richard Wolf GmbH.
- Report Version 6.7, Testimate Version 6.5; IDV Datenanalyse und Versuchsplanung.

## Keywords

Achilles tendon; High-energy shock waves; Hyaluronic acid; Rehabilitation; Tendinopathy

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## References

1. Peers KH, Brys PP, Lysens RJ. Correlation between power Doppler ultrasonography and clinical severity in Achilles tendinopathy. *Int Orthop* 2003;27:180-3.
2. Alfredson H, Lorentzon R. Chronic Achilles tendinosis: recommendations for treatment and prevention. *Sports Med* 2000;29:135-46.
3. Kvist M. Achilles tendon injuries in athletes. *Sports Med* 1994;18:173-201.
4. Paavola M, Kannus P, Paakkala T, Pasanen M, Järvinen M. Long-term prognosis of patients with Achilles tendinopathy. An observational 8-year follow-up study. *Am J Sports Med* 2000;28:634-42.
5. Carmont MR, Maffulli N. Management of insertional Achilles tendinopathy through a Cincinnati incision. *BMC Musculoskelet Disord* 2007;8:82.
6. Järvinen M, Jozsa L, Kannus P, Jarvinen TL, Kvist M, Leadbetter W. Histopathological findings in chronic tendon disorders. *Scand J Med Sci Sports* 1997;7:86-95.
7. Järvinen TA, Kannus P, Maffulli N, Khan KM. Achilles tendon disorders: etiology and epidemiology. *Foot Ankle Clin* 2005;10:255-66.
8. Roche AJ, Calder JD. Achilles tendinopathy: a review of the current concepts of treatment. *Bone Joint J* 2013;95-B:1299-307.
9. Childress MA, Beutler A. Management of chronic tendon injuries. *Am Fam Physician* 2013;87:486-90.
10. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. *Lancet* 2010;376:1751-67.
11. Speed CA. Fortnightly review: corticosteroid injections in tendon lesions. *BMJ* 2001;323:382-6.
12. Åström M, Westlin N. No effect of piroxicam on Achilles tendinopathy. A randomized study of 70 patients. *Acta Orthop Scand* 1992;63:631-4.
13. Mehallo CJ, Drezner JA, Bytowski JR. Practical management: nonsteroidal antiinflammatory drug (NSAID) use in athletic injuries. *Clin J Sport Med* 2006;16:170-4.
14. Rossignol M, Abouelfath A, Lassalle R, et al. The CADEUS study: burden of nonsteroidal anti-inflammatory drug (NSAID) utilization for musculoskeletal disorders in blue collar workers. *Br J Clin Pharmacol* 2009;67:118-24.
15. Fraser JR, Laurent TC, Laurent UB. Hyaluronan: its nature, distribution, functions and turnover. *J Intern Med* 1997;242:27-33.
16. Necas J, Bartosikova L, Brauner P, Kolar J. Hyaluronic acid (hyaluronan): a review. *Vet Med (Praha)* 2008;53:397-411.
17. Lynen N. Treatment of chronic tendinosis with peritendinous hyaluronan injections under sonographic guide—an interventional, prospective, single-arm multicenter study [German]. *Orthopädische und Unfallchirurgische Praxis* 2012;10:400-4.
18. Voigt J, Driver VR. Hyaluronic acid derivatives and their healing effect on burns, epithelial surgical wounds, and chronic wounds: a systematic review and meta-analysis of randomized controlled trials. *Wound Repair Regen* 2012;20:317-31.
19. Oh CH, Oh JH, Kim SH, Cho JH, Yoon JP, Kim JY. Effectiveness of subacromial anti-adhesive agent injection after arthroscopic rotator cuff repair: prospective randomized comparison study. *Clin Orthop Surg* 2011;3:55-61.
20. Furia JP. High-energy extracorporeal shock wave therapy as a treatment for chronic noninsertional Achilles tendinopathy. *Am J Sports Med* 2008;36:502-8.
21. Rasmussen S, Christensen M, Mathiesen I, Simonson O. Shockwave therapy for chronic Achilles tendinopathy: a double-blind, randomized clinical trial of efficacy. *Acta Orthop* 2008;79:249-56.
22. Ogden JA, Tóth-Kischkat A, Schultheiss R. Principles of shock wave therapy. *Clin Orthop Relat Res* 2001;(387):8-17.
23. Rompe JD, Furia J, Maffulli N. Eccentric loading versus eccentric loading plus shockwave treatment for midportion Achilles tendinopathy: a randomized controlled trial. *Am J Sports Med* 2009;37:463-70.
24. Takahashi N, Wada Y, Ohtori S, Moriya H, Wada Y. Second application of low-energy shock waves has a cumulative effect on free nerve endings. *Clin Orthop Relat Res* 2006;443:315-9.
25. Wang CJ. Extracorporeal shockwave therapy in musculoskeletal disorders. *J Orthop Surg Res* 2012;7:11.
26. Zhang D, Kearney CJ, Cheriyan T, Schmid TM, Spector M. Extracorporeal shockwave-induced expression of lubricin in tendons and septa. *Cell Tissue Res* 2011;346:255-62.
27. Huskisson EC. Measurement of pain. *Lancet* 1974;2:1127-31.
28. Robinson JM, Cook JL, Purdam C, et al. Victorian Institute of Sport Tendon Study Group. The VISA-A questionnaire: a valid and reliable index of the clinical severity of Achilles tendinopathy. *Br J Sports Med* 2001;35:335-41.
29. Del Buono A, Chan O, Maffulli N. Achilles tendon: functional anatomy and novel emerging models of imaging classification. *Int Orthop* 2013;37:715-21.
30. Meloni F, Milia F, Cavazzuti M, et al. Clinical evaluation of sodium hyaluronate in the treatment of patients with supraspinatus tendinosis under echographic guide: experimental study of periarticular injections. *Eur J Radiol* 2008;68:170-3.
31. Merolla G, Bianchi P, Porcellini G. Ultrasound-guided subacromial injections of sodium hyaluronate for the management of rotator cuff tendinopathy: a prospective comparative study with rehabilitation therapy. *Musculoskelet Surg* 2013;97(Suppl 1):S49-56.
32. Colditz GA, Miller JN, Mosteller F. Measuring gain in the evaluation of medical technology. The probability of a better outcome. *Int J Technol Assess Health Care* 1988;4:637-42.
33. Lachin JM. Some large-sample distribution-free estimators and tests for multivariate partially incomplete data from two populations. *Stat Med* 1992;11:1151-70.
34. Thall PF, Lachin JM. Analysis of recurrent events: nonparametric methods for random-interval count data. *J Am Stat Assoc* 1988;83:339-47.
35. Wei LJ, Lachin JM. Two-sample asymptotically distribution-free test for incomplete multivariate observations. *J Am Stat Assoc* 1984;387:653-61.
36. Frizziero A, Vittadini F, Barazzuol M, et al. Extracorporeal shockwaves therapy versus hyaluronic acid injection for the treatment of painful noncalcific rotator cuff tendinopathies: preliminary results. *J Sports Med Phys Fitness* 2016 Apr 12 [Epub ahead of print].