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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 ≥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,[1] and the degenerative structural changes appear to disrupt the healing process of the accumulated tendon damage, leading to chronic pain and loss

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

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.[8] Some treatments may cause significant side effects (eg, local tissue degradation or tendon tearing after repeated use of local steroids[9-11]) or adverse effects on other organ systems (eg, gastrointestinal toxicity, renal damage, or increased cardiovascular risk after intake of nonsteroidal anti-inflammatory drugs[12-14]), 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.[15,16] It has shown efficacy in the treatment of tendon disorders by decreasing pain,[17] supporting tissue healing,[18] and improving the lubrication of the tendon.[19] Extracorporeal shock wave therapy (ESWT) is another option currently used in the treatment of soft tissue conditions[20,21] 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,[22-26] 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 ≥6 weeks and a pain intensity score of at least 40mm on the Huskisson visual analog scale (VAS)[27] (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[a]]) 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[b]) 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),[28] 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).[29]

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