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Treatment of chronic tendinopathies with peritendinous hyaluronan injections under sonographic guidance – an interventional, prospective, single-arm multicenter study

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Treatment of chronic tendinopathies with peritendinous hyaluronan injections under sonographic guidance – an interventional, prospective, single-arm, multicenter study

Behandlung von chronischen Tendinosen durch ultraschallgesteuerte peritendinöse Hyaluronsäureinjektion - Eine interventionelle, prospektive, einarmige multizentrische Studie

Abstract: [Translator] Chronic tendinopathies are a common problem, for which current treatment methods are often unsatisfactory. In the present study, the clinical efficacy and safety of two peritendinous injections of a 2% solution of hyaluronic acid administered at an interval of one week (OSTENIL® TENDON pre-filled syringe , TRB Chemedica AG, Haar Germany) was assessed in 35 patients who suffered from painful tendinopathy of the Achilles tendon, the common wrist extensor tendon or the peroneal tendons persistent for at least six weeks. The results showed that treatment achieves a significant pain reduction and a significant improvement in disease-related symptoms. Excellent tolerability and safety of the product were clearly demonstrated in this study.

Keywords: [Translator] Tendinopathy, tendinosis, hyaluronic acid, hyaluronan, Achilles tendon, peroneal tendon, epicondylitis, tennis elbow

Zusammenfassung: Chronische Tendinopathien sind eine häufig auftretende Problematik, die mit den gängigen Therapien oftmals nicht zufriedenstellend behandelt werden können. In vorliegender Studie wurde anhand von 35 Patienten, welche seit mindestens 6 Wochen an einer deutlich schmerzhaften Tendinopathie im Bereich der Achillessehne, des Epicondylus humeri radialis oder der Peronealsehne litten, die klinische Wirksamkeit und Sicherheit einer 2-maligen, in wöchentlichem Abstand peritendinös injizierten 2%-igen Hyaluronsäurelösung überprüft (Fertigspritze OSTENIL® TENDON, TRB Chemedica AG, Haar). Die Studienergebnisse zeigen, dass durch die Behandlung sowohl eine signifikante Schmerzreduktion als auch eine signifikante Besserung erkrankungsspezifischer Symptome erzielt wird. Die sehr gute Verträglichkeit und Sicherheit des Prüfproduktes konnte im Verlauf der Studie eindeutig belegt werden.

Schlüsselwörter: Tendinopathie, Tendinose, Hyaluronsäure, Hyaluronan, Achillessehne, Peronealsehne, Epikondylus, Tennisarm

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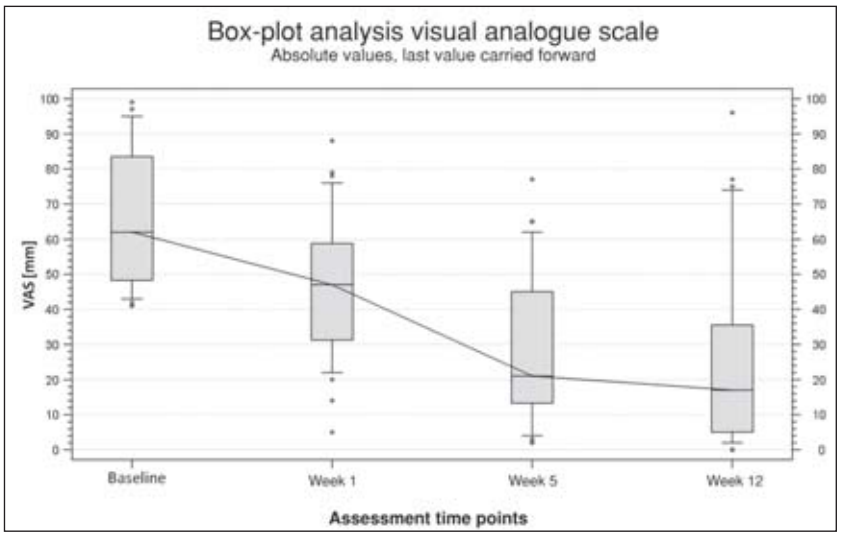

Figure 1 Box plot analysis, visual analogue scale

Introduction

Overuse injuries of tendons are a common cause of painful symptoms in the extremities, particularly in young and active individuals. This is often due to increased physical stress from sports activities [1]. But tendinopathy can also occur as a result of physical work or improper loading. Pathological changes in tendons typically have a protracted course lasting 6 months or longer [2], with a smooth transition from a healthy tendon, via acute inflammatory achillodynia to chronic tendinopathy. Tendon pain that persists for a long period is particularly difficult to treat successfully. Although a wide variety of conservative treatment methods are available, few have lasting success, especially for patients with a long history of symptoms [3]. The most likely reason is that there is an aseptic inflammatory response only at the onset of the disease process. As shown in recent studies, the role of the inflammatory component becomes relatively minor already at an earlier stage of the disease, so that the anti-inflammatory characteristics of corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) do not provide effective treatment at this stage [4, 5]. In the further course of the disease, fibrosis develops with increased formation of collagen between tissue layers, which leads in turn to adhesion of the tendons and a painful reduction in the ability of the tendon to glide freely. The adhesions also result in reduced nutrition of the bradytrophic tendons, since synovial fluid is no longer distributed in sufficient quantities. This leads to metabolic disorders, with changes in fibre structure and dedifferentiation of type I collagen to type III collagen as well as sprouting of nociceptive nerve endings.

Several studies have shown that peritendinous application of hyaluronic acid (HA) is an effective therapeutic option for the treatment of chronic tendinopathy [6, 7, 8]. HA is the main component of synovial fluid, which is found in the normal tendon sheath and surrounding tissues; synovial fluid contributes to the nutrition of the tendon [9].

The viscoelastic properties of HA also have significant therapeutic effects, since HA can help to reduce the surface friction of tendons whose capacity to glide freely has been reduced by microtears and adhesions. Recent studies provide an explanation of the physical mechanism by which surface friction of tendons is reduced: the application of HA together with the formation of a network of the cells on the tendon surface result in the "gliding effect" [10,11,12].

At the cellular level, a further effect is produced by expansion of the extracellular space. Because of its high anionic charge, HA is able to bind a large quantity of water molecules, and the HA-water aggregate may swell to occupy as much as 10,000 times the volume of the HA molecule alone [13]. Due to the increased osmotic pressure, spaces form in the extracellular matrix and between the cells, contributing to an increase in cell mobility and thus leading to increased cell migration [14]. Furthermore, the tightly interlocked HA macromolecules act like a molecular sieve, which prevents free passage of inflammatory cells, prostaglandins and cytokines, and at the same time channels the transport of nutritionally important metabolites from the synovial cells to the tendon [9, 15].

In addition, HA provides an ideal environment for cell proliferation and differentiation due to its high affinity for the extracellular matrix [16, 17]. The improved environmental conditions increase cellular activity, so that the cells produce increased quantities of extracellular matrix, which in turn results in optimisation of the repair process [15]. HA also has an analgesic effect, since it has a desensitising action on nociceptive receptors [18].

Due to the favourable characteristics of HA and the lack of satisfactory therapeutic alternatives, the present study was designed to evaluate the efficacy and safety in patients with chronic tendinopathy of two peritendinous injections of HA (2 ml of 2% HA + 0.5% mannitol) at an interval of one week.

Patients and Methods

The study was an interventional, prospective, single-arm, multicenter trial. The trial was approved by an independent ethics committee, and each patient gave written consent to participation before inclusion in the trial.

A total of 35 patients aged between 18 and 75 years who suffered for at least 6 weeks from chronic tendinopathy in the mid-portion of the Achilles tendon, of the peroneal tendons or enthesitis of the lateral epicondyle of the humerus were included in the study. All patients had severe pain symptoms with a score of at least 40 mm on the visual analogue scale (Pain VAS) according to Huskisson [19].

Patients were excluded from participation if they had a concomitant disease that might interfere with the parameters to be assessed, if they had a severe systemic disease or if the trial product was contraindicated. Patients were also excluded if they had been treated with systemic or topical steroids less than 4 weeks prior to

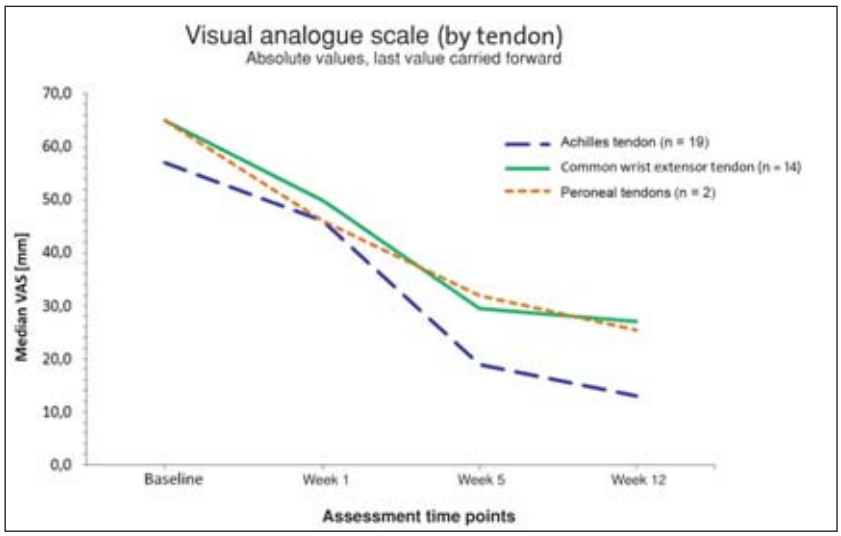

Figure 2 Visual analogue scale by tendon

the first examination, or with NSAIDs within the week prior to the start of the trial. Patients were not permitted to use any additional medications (NSAIDs in particular) or physiotherapy for the entire duration of the trial. Extreme sports as well as heavy physical activities that could have had a negative impact on the symptoms were also prohibited.

After checking the inclusion and exclusion criteria, each patient received a peritendinous injection (with ultrasound guidance) of 2 ml of the trial product (40 mg HA + 10 mg of mannitol) around the affected tendon. A second injection was made after an interval of one week. During the treatment phase, trial parameters were recorded before the first injection and then before the second injection. Further measurements were made at 5 and 12 weeks after the start of treatment.

The time course of pain symptoms was assessed with the Pain VAS (100 mm), in which 0 represents 'no pain' and 100 represents 'extreme pain' [19].

The clinical parameters typical for tendinopathy (redness, warmth, swelling, tenderness, crepitus during movement and peritendinous effusion) were recorded at all time points. A 5-point ordinal scale was used to assess intensity (0 = none, 1 = slight, 2 = moderate, 3 = substantial, 4 = extreme) of each clinical parameter.

The overall impression of treatment success (clinical global impression, CGI) was measured using a 7-point ordinal scale (1 = very much improved, 2 = much improved, 3 = slightly improved, 4 = unchanged, 5 = slightly worse, 6 = much worse, 7 = very much worse). This assessment was made by both the investigator and the patient at 1, 5 and 12 weeks after the start of treatment.

A patient questionnaire was used to assess the patient's perception of the extent to which his daily life, leisure activities and work were restricted. This assessment was made using a 5-point ordinal scale (0 = no restriction, 1 = slight restriction, 2 = moderate restriction, 3 = substantial restriction, 4 = extreme restriction) at all time points. Safety aspects were evaluated by documenting all adverse events.

Statistical analysis

Since this was a pilot study, there was no control group and a statistical calculation of sample size was not performed. The number of participants was chosen to guarantee a reliable analysis. For assessment and analysis of the safety and effectiveness of the trial product, data from all 35 patients were analysed. Missing data were replaced according to the 'Last Observation Carried Forward' (LOCF) principle.

The Pain VAS value at 5 weeks after the start of treatment was used as the primary measure of efficacy. Secondary parameters included clinical parameters, the CGI, patient questionnaire for all time points, and the VAS score at 1 and 12 weeks after the start of treatment.

An intra-group comparison for the primary endpoint was performed with the 2-sided Wilcoxon-Pratt test. The alpha level was defined as alpha = 0.05. All secondary parameters were analysed with the 2-sided sign test, alpha = 0.05, for intra-group comparisons between baseline and follow-up parameters.

Results

In the period from 3 February to 30 May 2011, a total of 35 patients with a mean age of 45.9 ± 10.6 years (± SD) were included in the study. Seventeen (51.4 %) of the patients were female and 18 (48.6 %) were male.

Tendinopathy was localised in the mid-portion of the Achilles tendon in 19 patients (54.3%), at the lateral epicondyle of the humerus in 14 patients (40.0%) and in the peroneal tendon in 2 patients (5.7%). Patients had suffered from chronic tendinopathy for a median period of 12.3 ± 17.9 months.

Assessment of pain symptoms with the VAS showed a significant improvement compared to baseline ($p < 0.0001$) at 5 weeks after the start of treatment. At the time of enrolment, patients rated pain with a median intensity of 62 ± 18.9 mm, but at 5 weeks the score was only 21 ± 21.3 mm (Fig. 1). The significant decrease in pain intensity was maintained in the long term, since further significant improvement of the VAS score was found at 12 weeks, with a median of 17 ± 26.2 mm ($p < 0.0001$).

Specific analysis by tendon showed a significant improvement of pain in all affected tendons (Fig. 2). The most pronounced improvement was found in patients with Achilles tendinopathy. These patients reported pain intensity before the first injection with a median VAS score of 57 ± 19.1 mm, but during treatment this improved to a median of 19 ± 19.9 mm at 5 weeks and 13 ± 20.1 mm at 12 weeks after the start of treatment.

Patients with tendinopathy localised to the lateral epicondyle of the humerus reported a median VAS score of 65 ± 19.9 mm at the initial assessment, which improved to 29 ± 21.0 mm and 29 ± 31.1 mm at the first and second follow-up assessments.

Patients with affected peroneal tendons showed an improvement in the median VAS score from an initial value of 65 ± 19.8 mm to 26 ± 31.8 mm at 12 weeks after the first treatment.

With regard to clinical parameters, complete resolution of peritendinous fluid accumulation was found in all patients (100%) at 12 weeks after the start of treatment. Almost all patients showed complete improvement of redness (96.9%), warmth (96.9%) and crepitation during movement (93.8%). Almost 2/3 of the patients (60%) experienced a reduction in tenderness, while 66% of patients had less swelling at 12 weeks after the start of treatment.

The CGI was very well correlated for both the investigators and the patients. The investigators reported a clinical global improvement at in 88.6% of patients at one week, at 5 weeks in 91.4% of patients and at 12 weeks in 93.8% of patients. The patients reported a clinical global improvement at one week in 82.9% of cases, at 5 weeks in 88.6% of cases and at 12 weeks in 87.5% of cases.

One week after the first injection, many patients (45.7%) reported a significant improvement, and five weeks after the start of treatment, a large number (40.0%) reported a slight improvement compared to the initial findings. At the check-up at 12 weeks after the start of treatment, the majority of patients reported that their symptoms were 'much improved' or 'very much improved' (31.3% each).

This positive assessment was also reflected in the evaluation of the patient questionnaire. At all time points, there was a significant improvement in the restriction of daily activities ($p < 0.0001$), leisure activities ($p < 0.0001$) and at work ($p < 0.0018$).

A total of 14 adverse events were reported by 11 (31.4%) patients. None of these events were associated with the trial product. The peritendinous injections of HA were well tolerated by all patients.

Discussion

Treatment of chronic tendinopathies often represents a significant problem for the physician. Injections of corticosteroids, which are commonly used, have a particularly limited efficacy in chronic tendinopathies, and may have significant side effects. For example, symptoms often recur shortly after treatment with lipid-soluble corticosteroids [20]. In particular, frequent use of corticosteroids may be accompanied by peritendinous crystalline deposits that can make the tendon brittle and prone to rupture [21]. Regular administration of NSAIDs, which are commonly used to treat tendinopathy, may have gastrointestinal side effects among others.

HA is a naturally occurring biological substance, which is a major component of ligaments, cartilage and synovial structures [22]. Furthermore, HA is very effective in the treatment of osteoarthritis, and has few side effects [23]. In the present study, 2 ml of a 2% HA solution were used. Based on the therapeutic regimen for HA treatment of osteoarthritis, two injections were performed at an interval of one week. The injections were administered around the tendon under ultrasound guidance.

In the evaluation of treatment outcomes, it was found that treatment of painful chronic tendinopathy with peritendinous injection of HA significantly reduced pain symptoms. This is probably due in part to the tightly interlocked HA macromolecules, which specifically prevent free passage of inflammatory cells, prostaglandins and cytokines [15], and partly to the effect of the mannitol, added to the formulation which traps oxygen free radicals [24]. It should also be noted that all patients enrolled in the trial had suffered from painful tendinopathy for at least 12 months, and their pain improved in a short time with HA treatment.

Similarly, there was also a significant improvement in the clinical findings associated with tendinopathy. In particular, there were significant improvements in non-structural alterations, although tissue swelling, an indication of structural reorganisation of the tendon, was still present in two thirds of the patients at the final examination at 12 weeks after the start of treatment. Despite the swelling of the tendon and/or the peritendinous tissues, there were no lasting symptoms of clinical inflammation or irritation. This may be explained by reduction in friction and peritendinous adhesions due to the HA injections [10, 11, 12].

With regard to the long-term effects of the HA treatment, it was found that even at the time of the follow-up at 12 weeks after the start of treatment, there was still a lasting effect with clear improvement of the previous symptoms. This is probably due to the high concentration of HA that was used and stabilisation of the HA with the excipient mannitol. The high concentration of HA probably contributed to the excellent results achieved in the present study. The favourable outcome of the treatment regimen was sustained for a relatively long follow-up period, although it consisted of only two HA injections at an interval of one week.

Summary and Clinical Significance

The results of this study indicate that two injections of a 2% HA solution administered at an interval of one week represent a very effective therapeutic option for treatment of chronic tendinopathy. Treatment with 2% hyaluronic acid resulted in a rapid and sustained reduction in pain as well as a significant improvement of clinical symptoms. Excellent tolerability and safety of the product were clearly demonstrated in this study. None of the adverse events was associated with the use of the trial product. Further clinical studies with larger patient groups and a longer period of assessment should be conducted in the near future to confirm the present findings.

Conflict of interest. Dr. Lynen acted as a medical expert for this clinical trial. OUP

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