Extracorporeal shock wave therapy in the management of midsubstance Achilles tendinopathy: the ASSERT database

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Summary

Introduction: **The present study aimed to determine the effectiveness of Extracorporeal Shock Wave Therapy (ESWT) in patients suffering from midsubstance Achilles tendinopathy in both the short and middle term.**
Methods**: Participants were recruited by different clinicians in the National Health Service (NHS) and private sector centres in the UK. All data were collected in a web-based database named ASSERT (Assessment of the Effectiveness of ESWT for Soft Tissue Injuries). The 84 participants (average age 54.30 y; range 23-77 y) were administered in a standardized ESWT protocol, and outcome measures relative to their specific condition and health status (VAS for pain perception, the VISA-A for the severity of the Achilles tendinopathy in daily life activities, and the 6 scores ofEuroQol 5D for quality of life) were collected at baseline, and again after 3, 6, 12 and 24 months following ESWT intervention.**
Results**: There was a significant amelioration over time in 5 of the 8 analyzed outcomes (all with p <0.0001), namely VAS, VISA-A, and 3 EQ-5D domains (Mobility, Pain/Discomfort, and Usual Activities scores).**
Conclusion**: ESWT showed beneficial effects on midsubstance Achilles tendinopathy over a 24 month follow-up period.**
Level of evidence: IV.

KEY WORDS: Achilles tendinopathy, extracorporeal shock wave therapy, longitudinal study, midsubstance Achilles tendinopathy.

Introduction

Achilles tendinopathy (AT) is an overuse condition accounting for up to 18% of injuries in runners and 4% of patients presenting to sports medicine clinics[1,2]. A major cause of chronic pain and functional disability, AT is a failed healing response after overuse stimulation to the tendon with no direct evidence of intra-tendinous inflammation. The tendon attempts to heal after overuse, but the healing process is incomplete and disorganised, with histological evidence of haphazard proliferation of tenocytes, intracellular abnormalities, disruption of collagen fibres, and increase in non-collagenous matrix[3]. The cause of AT is multi-factorial: overuse, adverse lower limb biomechanics, and inappropriate footwear are considered risk factors, with recent evidence of association between AT and diabetes, dyslipidaemia, inflammatory and autoimmune conditions[4]. AT could therefore be the epiphenomenal manifestation of such metabolic and immune disorders[4].
The diagnosis of AT is mainly based on history and clinical examination. Pain is the major symptom, usually at the beginning and end of a training session, with a period of diminished discomfort in between.

Over time, patients become symptomatic during exercise, and end up complaining of discomfort and disability in daily activities. In the acute phase, swelling, oedema and tenderness may be found on palpation, mostly 2–6 centimetres above the calcaneal insertion. Sometimes the fibrinogen-rich fluid around the tendon may produce fibrin and palpable crepitation. In chronic AT patients, exercise induced pain is the cardinal symptom, but crepitation and effusion are less frequent. Palpable nodular swelling may be present[5,6].

The Achilles tendon can be divided into two portions, non-insertional (proximal) and insertional (distal). The classification of AT is based on clinical, ultrasound, and MRI findings. The non-insertional region is classed as the mid-portion of the tendon, and the insertional region is referred to as being located about two centimetres above the calcaneus (pre-insertion site), with a calcaneal insertion, where the tendon is attached to the bone[7]. According to the portion involved in the tendinopathy, it is possible to classify AT in insertional Achilles tendinopathy, when the insertional region of the tendon is involved, or in midsubstance Achilles tenindopathy (MAT) when the non-insertional portion of the tendon is involved.

In MAT, the first line of management is conservative[8]. Conservative management consists of rest, modification of training activities with specific exercises, and orthoses for correction of underlying lower limb malalignment[9,10]. This management is effective in approximately 70% of patients, allowing them to return to their previous level of activity. At eight years follow-up, only 29% of patients did not respond to non-operative measures[11]. The scientific evidence on the use of NSAIDs in chronic tendinopathy is somewhat inconsistent, as inflammation is largely absent at histology in tendinopathic tendons[12].

Extracorporeal Shock Wave Therapy (ESWT) is a non-surgical to be considered treatment when conservative management fails. The rationale for the clinical use of ESWT is the stimulation of soft tissue healing and inhibition of pain receptors. However, conflicting results have been reported for the use of ESWT for the management of MAT. A randomised controlled trial[13] reported significant improvements combining ESWT with eccentric exercises, and these outcomes were especially promising in women. Also, 78% of tendons that underwent one session of low energy ESWT weekly for three weeks were improved at one year post ESWT[14]. ESWT for the treatment of MAT has been found to be effective in the short term, and the evidence is not robust enough to recommend its use for the management of tendinopathy[15]. Further standardised, long term studies are necessary to understand fully the efficacy of ESWT in the management of MAT.

The present study (ASSERT) was established to evaluate the effectiveness of ESWT in patients with MAT in whom ESWT had been administered in a standardized fashion, and had been followed up over 24 months. The reduction of severity of symptoms, the relief of pain, and the improvement of the quality of life were evaluated. The study also aimed to analyse whether differences existed between male and female patients, and between females before and after the menopause, and whether age and previous treatments undertaken could have played a role in influencing the effectiveness of ESWT.

Methods

The ASSERT database collected information concerning the effectiveness of ESWT across the UK. The ESWT machines were standardised and a standardized treatment protocol, together with standardised baseline measurements and outcome assessment and time points in centres across the UK, were adopted to aid validity[16].

Recruitment

Participants were enrolled from both the National Health Service (NHS) and private sector centres in the UK. Clinicians recruited participants presenting with midsubstance Achilles tendinopathy, and for whom ESWT was designated as the treatment choice.

Participants

Participants were included if they were over the age of 18 and had: a diagnosis of MAT which had been confirmed by the recruiting clinician; undergone a course of conservative therapy which had not been effective in relieving symptoms; been recommended to receive ESWT at one of the recruiting centres; not been diagnosed with inflammatory arthropathy; and demonstrated the ability to give informed consent.

A total of 94 participants were enrolled (52 males; 42 females), and of those 84 participants (45 males; 39 females) met the inclusion criteria and were considered for analysis (Tab. I).

This study has been designed and conducted in accordance with the principles of the Declaration of Helsinki and it has been approved by the Local Ethics Committee (11/LO/0253). A written informed consent was obtained by each participant[17].

Use of ESWT machine

Standardisation of the machine and the process of administration of ESWT had been agreed to ensure generalisability, consistency, and reproducibility of the results. All clinicians using the Swiss DolorClast device (Electro Medical Systems SA, Nyon, Switzerland) and Storz devices (Storz Medical AG, Tägerwilen, Switzerland) received training and certification to ensure adherence to the proposed protocol. All clinicians followed a standardised method to administer the ESWT[18]. This included delivering an initial 500 sensitising impulses at a low pressure (1.5 bar of air pressure). This reduces the pain which patients experience during the treatment. Based on patient feedback, the clinician increased the air pressure to 2.5 bar or above. The total dose of impulses remained

Table I. Sample of participants.

	n	Age (y)	Number of previous treatments
		Mean (range)	Mean (range)
Participants enrolled	94	53.91 (23-77)	1.65 (0-4)
Male	52	55.28 (23-77)	1.64 (0-4)
Female	42	52.34 (32-76)	1.67 (0-4)
Post menopause	25	58.16 (51-76)	1.57 (0-4)
Pre menopause	17	43.25 (32-50)	1.80 (0-4)
Participants considered for the analyses	84	54.30 (23-77)	1.66 (0-4)
Male	45	55.56 (23-77)	1.64 (0-4)
Female	39	52.87 (32-76)	1.68 (0-4)
Post menopause	24	58.33 (51-76)	1.60 (0-4)
Pre menopause	15	43.50 (32-50)	1.79 (0-4)

constant at 2500 per session, with one session a week for three consecutive weeks, with a maximum gap between treatments of two weeks.

Database

The ASSERT database is a web based system (www.assert.org.uk) from which the clinician received a study number for each participant[16]. Only unidentifiable information with the patients' study number was entered into the database. Sensitive data is held on secure servers. Following informed consent, the clinician recorded the following information: 1) Diagnosis: this was formulated on clinical grounds and some clinicians also used imaging to confirm the diagnosis; 2) Area treated/condition presented with; 3) Date of presentation of symptoms; 4) Date of treatment with ESWT; 5) Code for clinicians centre; 6) Centre where treatment was administered; 7) Previous treatments prior to consultation; 8) Side treated; 9) Dates when ESWT was administered; 10) Baseline scores recorded: EuroQol questionnaire scores (EQ-5D)[19], VAS for pain[20], and VISA questionnaire for Achilles tendinopathy (VISA-A)[21]; 11) Follow-up scores at 3, 6, 12 and 24 months post treatment; 12) Satisfaction: rated poor, satisfactory, good or excellent; 13) Time to effective treatment; 14) Recurrence of the condition; 15) Complications; 16) Adverse events.

Baseline and follow-up assessments

After having obtained written informed consent, the treating clinician undertook baseline assessments. The follow-up assessments were instead performed after 3, 6, 12 and 24 months' post treatment. The coordinators of ASSERT undertook all follow-up assessments via email, telephone or post.

Outcome assessment

The EQ-5D[19] and VAS for pain[20] were completed alongside the VISA-A[21].

The EQ-5D is a standardised measure of health status developed by the EuroQol Group to provide a simple, generic measure of health for clinical and economic appraisal. For the present study, the version 3L (EQ-5D-3L) was used. This is a simple questionnaire composed by 5 items with a 3-point scale answer for each item, and designed for completion by the person being treated. Each one of the 5 items respectively investigate 5 dimensions of the quality of life that are (1) mobility, (2) self-care, (3) usual activities, (4) pain/discomfort, and (5) anxiety/depression. A score from 1 (best score) to 3 (worst score) is assigned for each dimension. The EQ-5D also includes a scale, named EQ-5D Thermometer Scale, that allows to obtain a global score to generally describe the quality of life of the patient. It consists of a vertical line, 100 mm in length, anchored by 2 word descriptors at each end, that are "the worst health you can imagine" and "the best health you can imagine". The patient is asked to mark on the line the point that he feels represents his perception of his current health status. The score ranges from 0 (worst health status) to 100 (best health status), and it is computed by measuring the distance (in mm) between the end of the line marked with "the worst health you can imagine" and the mark on the line indicated by the patient.

The VAS for pain (or Visual Analog Scale for pain) is very similar to the EQ-5D Thermometer Scale but it focuses the attention only on the pain perceived by the patient, and not on the overall quality of life. It consists in a horizontal line, 100 mm in length asked the patient "How severe is your pain today?". The line

is anchored by 2 word descriptors at each end, that are "no pain" and "very severe pain". The patient marks on the line the point that he/she feels represents their current perception of his pain intensity, and the score, from 0 (no pain) to 100 (very severe pain), is computed as the measurement of the distance (in mm) between the end of the line marked with "no pain" and the point on the line indicated by the patient.

The VISA-A is a validated questionnaire assessing the severity of Achilles tendinopathy[21]. It consists of 10 items evaluating the self-reported perception of pain and the consequent limitation in performing different tasks (e.g. walking, single leg heel raises, etc.). The score, from 0 (high severity) to 100 (no severity), is computed as summation of the score of each item.

Statistical analysis

A Linear Mixed Model analysis (LMM) with Maximum Likelihood method was performed to evaluate the significant effects over time produced by ESWT in the treatment of the MAT. To perform the LMM analysis, 2 fixed factors were considered: Time factor (fixed factor: T0 *vs* T3 *vs* T6 *vs* T12 *vs* T24) to investigate differences over time, and Gender factor (fixed factor: male *vs* female) to investigate differences between male and female patients' outputs. The interaction Timex Gender was analysed as well. The VAS score, VISA-A score, and the 6 scores obtained by the EQ-5D were considered as dependent variables for the analysis. If two or more of the follow-up datasets were missing the patient was excluded.

Age and the number of previous treatments performed were considered as covariates in the analysis to verify whether these factors could have influenced the VAS, VISA-A and EQ-5D scores over time.

Subsequently, another LMM analysis was performed on the female participants to evaluate differences between women with and without menopause over time. This analysis was performed using 2 fixed factors: Time factor (fixed factor: T0 *vs* T3 *vs* T6 *vs* T12 *vs* T24), and menopause factor (fixed factor: Menopause *vs* No-menopause), and the interaction Timex Menopause was also considered. As for the previous LMM analysis, VAS, VISA-A, and the 6 scores of the EQ-5D were considered as dependent variables for the analysis.

Given the multiple dependent variables, the Bonferroni correction was used to adjust the *p*-value. Bonferroni correction indicated an adjusted *p*-value <0.006 for significance for both the LMM analyses.

When a significant effect over time was detected, Bonferroni *post-hoc* analyses adjusted for multiple comparison was used to perform comparisons in pair among the different time of assessments.

All the analyses were performed with the statistical software SPSS 20 (IBM Corporation, Chicago, IL, USA).

Results

There was a significant decrement over time of the VAS score ($F_{4,198}$= 50.237; p<0.0001), with no significant differences between genders ($F_{1,82}$= 0.002; p=0.963) as well as in the interaction Timex Gender ($F_{4,198}$=2.196; p=0.071).

The VISA-A showed a significant increment of the score over time ($F_{4,193}$= 47.892; p< 0.0001), with no significant differences between the two genders ($F_{1,83}$=0.021; p=0.886) and in the interaction Timex Gender ($F_{4,193}$=1.204; p=0.310).

The EQ-5D Anxiety/Depression score did not show significant changes over time ($F_{4,188}$=0.783; p=0.538), and no differences were found between genders ($F_{1,64}$=0.936; p=0.337). Similarly, no differences were found in the interaction Timex Gender ($F_{4,188}$=0.449; p=0.773). Conversely, a significant reduction over time were found in the EQ-5D Mobility score ($F_{4,198}$=19.973; p<0.0001), but no significant differences were found between the two genders ($F_{1,76}$ =0.430; p=0.514) and in the interaction Time Gender ($F_{4,197}$=0.126; p=0.973). A significant reduction over time was found also in the EQ-5D Pain/Discomfort score ($F_{4,201}$= 42.964; p<0.0001), with no significant differences between the two genders ($F_{1,77}$=0.004; p=0.951) and in the interaction Timex Gender ($F_{4,201}$=1.210; p=0.308). There was a significant reduction over time of the EQ-5D Usual Activities score ($F_{4,203}$=38.043; p<0.0001), with no significant differences between the two genders ($F_{1,80}$= 0.087; p=0.769) and in the interaction Timex Gender ($F_{4,203}$= 3.667; p=0.007; not significant because of the Bonferroni correction). The EQ-5D Self-Care did not show significant differences both in Time ($F_{4,222}$= 0.611; p=0.655) and Gender ($F_{1,65}$=0.842; p=0.362), and in the interaction Time Gender ($F_{4,222}$= 1.297; p=0.272). The EQ-5D Thermometer Scale analysis did not show significant differences in Time, ($F_{4,185}$= 3.537; p=0.008), and no differences were found between genders ($F_{1,69}$= 0.846; p=0.361) and in the interaction Timex Gender ($F_{4,185}$= 0.267; p=0.899).

The number of previous treatments and the age of the patients, used as covariate of the analysis, were not significant, indicating that these factors did not exert any significant influence.

Similarly, the LMM analysis for the female patents showed no significant differences between women with and without menopause, as well as in the interaction Timex Menopause in any of the 8 analysed variables.

All the data are reported as means ± SD in Table II with the results of the *post-hoc* analysis.

Discussion

ESWT administered according to the protocol described was associated with a significant beneficial effect in 5 of the 8 analysed variables. In particular, these positive effects are obtained after only 3 months, with additional ameliorations after this peri-

Table II. Results relative to the effects over time with the post-hoc analyses outputs.

Tests		T0	T3	T6	T12	T24	Overall significance in time	Comparisons in pair - significance
		Means (Range)[N]	Means (Range)[N]	Means (Range)[N]	Means (Range)[N]	Means (Range)[N]		
VAS	Scores	49.83(1-100) [78]	19.47 (0-78) [57]	19.13 (0-92)[52]	14.19 (0-90) [43]	4.83 (0-77)[36]	$p< 0.0001$	T0 *vs* T3, T6, T12, T24 T3 *vs* T24 T6 *vs* T24
	Difference with baseline score	-	-30.36	-30.70	-35.65	-45.00		
VISA-A	Scores	47.39 (10-90) [75]	67.91 (6-100) [54]	70.57 (0-100)[49]	83.44 (15-100)[43]	88.97 (33-100) [36]	$p< 0.0001$	T0 *vs* T3, T6, T12, T24 T3 *vs* T12, T24 T6 *vs* T12, T24
	Difference with baseline score	-	+20.52	+23.18	+36.06	+41.59		
EQ-5D Anxiety/Depression	Scores	1.21(1-2) [78]	1.13 (1-2) [54]	1.16 (1-3) [51]	1.12 (1-2) [43]	1.08 (1-2) [36]	Not significant	
	Difference with baseline score	-	-0.08	-0.05	-0.09	-0.12		
EQ-5D Mobility	Scores	1.64 (1-2) [78]	1.37 (1-2) [54]	1.35(1-3) [51]	1.16(1-2) [43]	1.03 (1-2) [36]	$p< 0.0001$	T0 *vs* T3, T6, T12, T24 T3 *vs* T24 T6 *vs* T24
	Difference with baseline score	-	-0.27	-0.29	-0.48	-0.61		
EQ-5D Pain/Discomfort	Scores	2.06(1-3) [78]	1.59 (1-2) [54]	1.55(1-3) [51]	1.28 (1-3) [43]	1.11(1-3) [36]	$p< 0.0001$	T0 *vs* T3, T6, T12, T24 T3 *vs* T12, T24 T6 *vs* T12, T24
	Difference with baseline score	-	-0.47	-0.52	-0.79	-0.95		
EQ-5D Usual Activities	Scores	1.81 (1-3) [78]	1.33(1-3) [54]	1.33(1-3) [51]	1.12 (1-2) [43]	1.03 (1-2) [36]	$p< 0.0001$	T0 *vs* T3, T6, T12, T24 T3 *vs* T24 T6 *vs* T24
	Difference with baseline score	-	-0.47	-0.47	-0.69	-0.78		
EQ-5D Self-Care	Scores	1.03(1-2) [78]	1.00 (1-1) [54]	1.02 (1-2) [51]	1.02 (1-2) [43]	1.00(1-1) [36]	Not significant	
	Difference with baseline score	-	-0.03	-0.01	-0.01	-0.03		
EQ-5D Thermometer Sc.	Scores	74.44 (27-100) [78]	77.31 (3-100) [54]	81.71 (20-100) [51]	81.51 (28-100) [43]	85.14 (60-100) [36]	Not significant	
	Difference with baseline score	-	2.88	7.27	7.08	10.70		

p value for significance after Bonferroni correction is <0.006.

od, during the 24 months of observation. ESWT produced significant positive effects in reducing pain, and improving the ability of the patients to manage everyday life, as indicated by the significant amelioration in the various scores. The quality of life and the health status were significantly improved after ESWT, as suggested by the overall improvement of EQ-5D scores, with the only exception of Anxiety/Depression and Self-Care dimensions' scores. However, the baseline scores of these two dimensions (Tab. II) were substantially low, and remained low for the duration of the follow-up. The non-significant change was probably attributable to the low impact of MAT on these 2 dimensions since the baseline assessment.

Another clinically important finding was the time necessary to obtain significant benefits on health status and pain relief. There was a significant improvement three months after the last session of ESWT in VAS, VISA-A, EQ-5D Mobility, EQ-5D Pain/Discomfort, and EQ-5D Usual Activities. Given these results, ESWT can be considered a valid and effective method for the treatment of MAT. The use of previous treatments, the age, the gender and the presence/absence of menopause exert no significant influence on the efficacy of ESWT. The influence of these factors was generally not considered in previous studies, and could represent an additional strength for the use of this modality in the management of MAT, regardless of gender or age.

ESWT is a safe and non-invasive treatment for people suffering from chronic MAT in which conservative methods have been unsatisfactory[22]. It has been reported that the evidence for ESWT in mid-portion AT is currently very limited[23]. However, the results of the present study are in accordance with a number of systematic reviews for the treatment of Achilles tendinopathy[24-26] which identify that there is consistent evidence on the effectiveness of ESWT in the management of patients with chronic Achilles tendinopathies. More specifically, Foldager et al.[27] found that ESWT significantly benefits both insertional and non-insertional AT; Saxena et al.[14] showed reduced pain and improved function 1 year after ESWT. It has been reported that an increase in the VISA-A between 12[28,29] and 20[30] is clinically relevant. The results of the present study demonstrate that the improvement in pain and function improve over time. Two years post treatment the pain has reduced significantly and the function has improved dramatically, a mean increase of 42 in the VISA-A between the baseline and the score at 24 months.

Kearney and Costa[24] identified that there was a consensus that functional treatment methods, including shockwaves, should be used before surgical methods for treating Achilles tendinopathy. However, there was a lack of detailed information on study results, and no statistical comparisons and different treatment protocols were used. For this reasons, more high-quality and well-conducted studies are necessary. In particular, a database such as ASSERT could be a valid method for the systematic collection of large amount of data and for the standardization of procedures to obtain strong evidences in this field.

This study is not a randomised controlled trial. However, Level I studies have been conducted in the present field, and have shown that ESWT, when administered according to well established protocols, is safe and effective in the management of the condition at hand. The National Institute for Health and Clinical Excellence (NICE) suggested that the effectiveness of ESWT in "real life" would have needed to be evaluated in a pragmatic fashion, using standardised protocols and well validated clinically relevant outcome measures. The ASSERT protocol is NICE compliant, and satisfies the requirements set out by NICE[31].

Many different clinicians were involved in administering the ESWT treatment, after appropriate certified training and standardisation of the protocol, and the effects of ESWT treatment were evaluated by independent individuals. This increases the generalizability of the present findings, and, in this respect, should be considered a major strength of the present study. Also, all patients had previously failed a variety of conservative management means, and this was a major criterion to be recruited in the present study.

In conclusion, when administered in a standardised fashion to an unselected population of patients suffering from midsubstance Achilles tendinopathy, ESWT therapy is safe and effective in alleviating symptoms for up to 24 months.

Compliance with ethical standards

Conflict of interest

All Authors declare no conflict of interest.

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Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research com-

mittee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

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

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