Extracorporeal shock-wave therapy for treating chronic pelvic pain syndrome: a feasibility study and the first clinical results

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Level of Evidence 4

OBJECTIVE

To investigate the feasibility and clinical outcome of extracorporeal shock-wave therapy (ESWT) for patients suffering from chronic pelvic pain syndrome (CPPS).

PATIENTS AND METHODS

The study included 34 patients who had had CPPS for ≥ 3 months, who were investigated in two subsequent studies. ESWT was administered using a perineal approach with two different standard ESWT devices with and without an ultrasonographic positioning system. The follow-up was at 1, 4 and 12 weeks after ESWT, to evaluate the effects on pain, quality of life and voiding. Imaging studies and changes in prostate-specific antigen (PSA) were used to investigate the safety and side-effects of ESWT.

RESULTS

All patients completed the treatments and follow-up; there were statistically significant improvements in pain and quality of life after ESWT. Voiding conditions were temporarily improved but with no statistical significance. Perineal ESWT was easy and safe to administer with no anaesthesia on an outpatient basis. Side-effects could be excluded clinically, by imaging studies and by changes in PSA level.

CONCLUSION

Perineal ESWT must be considered as a promising new therapy for CPPS, in particular as it is easy to apply and causes no side-effects.

KEYWORDS

chronic pelvic pain syndrome, chronic abacterial prostatitis, shock waves

INTRODUCTION

Prostatitis is one of the most frequent outpatient urological diagnoses [1,2] and results in > 2 million visits to doctors in the USA annually [3]. Most men have the abacterial form of chronic prostatitis, or chronic pelvic pain syndrome (CPPS) [4,5]. The quality of life of affected men can be greatly impaired, in particular by pain, and the restrictions are comparable to those after a heart attack, angina pectoris and Crohn's disease [6].
The former classifications of prostatitis according to Drach et al. [7] were replaced internationally by the classification of the National Institutes of Health (NIH) [8], which distinguishes the various bacterially induced forms from the non inflammatory CPPS. Symptoms of CPPS are urinary and erectile dysfunction, pain focused in the prostate region, as well as perineal, inguinal, scrotal and suprapubic pain. The pathophysiology of CPPS has not yet been clarified. A psychiatric component might possibly play a role alongside somatic factors, and it has not been possible to detect signs of active infection or bacterial pathogens [9,10]. Locally, discussions have concerned former infections, changes to the chemical environment, hypertension of the pelvic floor muscles, changes in blood flow and neurobiological factors [11,12]. Systemically, obviously prolonged and insufficiently treated acute pain, as a negative learning process, could cause neuroplastic changes in the CNS, with an associated fixation of incurable chronic pain status [13,14].

In the final analysis, once other diseases have been excluded, the diagnosis of CPPS can only be clinically established on the basis of the typical pattern of complaint and progression. Previously there have been no causal or standardized therapeutic approaches. Analgesics, anti inflammatory agents, antibiotics, α-receptor blockers and 5α-reductase inhibitors are used alone and in various combinations [15, 17], without sufficient clarification of the evidence and effectiveness of each of these treatments. Therefore, non-drug treatment options have become increasingly important. Physiotherapy, 'trigger point' massage and electromagnetic treatment have already been used as therapies for CPPS [18,19].

Low-energy shock waves (extracorporeal shock wave therapy, ESWT) are successfully used for treating orthopaedic pain syndromes, fracture and wound healing disorders. In patients with upper arm contractures caused by a stroke, ESWT succeeded in reducing passive muscle tone, with a resulting marked improvement in the range of movement [20]. Most recently, ESWT of ischaemia induced myocardial dysfunction has achieved a significant increase in perfusion in the regions with reduced blood flow [21,22].

The possible influence of pain, local perfusion and muscle tone means that the applicability and effectiveness of perineal ESWT should be investigated in patients with CPPS.

PATIENTS AND METHODS

In the feasibility study (study 1), patients with prostatitis IIIb lasting≥ 3 months, and no evidence of bacteria in urinary and seminal culture tests, were eligible. Prostate cancer was excluded clinically and serologically. Before and after each ESWT a Doppler TRUS was used (7.5 MHz transrectal probe). The first 10 consecu-tive patients were assessed by MRI (Magnetom 1.5 T, Siemens, Germany) of the minor pelvis with an endorectal array.

Routine blood variables and PSA levels were determined before and after each ESWT. The patients received six ultrasonographically controlled ESWT treatments (each 2000 impulses, positive energy flow density of 0.11 mJ/mm ^{2}, frequency 3 Hz) within 2 weeks using a perineal approach while supine,and using a standard ESWT device with integrated US system (Minilith SL1, Storz Medical, Tägerwilen, Switzerland). The SW focus was placed intraprostatically under real-time US guidance and moved to scan virtually the whole gland.

The follow-up was at 1, 4 and 12 weeks after ESWT. For the duration of the study additional drug intake was excluded. The grade of pain was evaluated using a visual analogue scale (VAS, 0–10). The CPPS-related complaints were investigated by validated questionnaires (voiding with the IPSS; specific complaints with the NIH chronic Prostatitis Symptom Index, CPSI) with the main focus on sideeffects and applicability.

In study 2, after the positive outcome of the study 1, some of the tests were omitted and the treatment schedule was optimized. The inclusion criteria were similar to study 1. Other treatments or drug intake were excluded during the study period. The patients received one perineally applied ESWT treatment weekly (each 3000 impulses, total energy flow density 0.25 mJ/m ^{2}, 3 Hz) for 4 weeks. The device used for the study was a standard electromagnetic SW device with a focused SW source (Duolith SD1, Storz Medical). The focal zone penetration depth was 30–50 mm. Therefore, and according to the experience based on the use of real-time inline US, the SW focus could be placed in the prostate from the perineum with no US positioning system. The Duolith, with the smaller SW transducer, was used to achieve further simplification of ESWT. The follow-up schema was similar to that in study 1. Paired *t*-tests were used for the statistical analysis.

RESULTS

In study 1, 14 patients (mean age 49.7 years, range 36–62) were treated as outpatients; the treatment was well tolerated, and anaesthesia was not required. The duration of ESWT was 12 min each. There were no apparent side-effects and all patients completed the treatment course and the follow-up. Of the 14 patients, 11 had less pain and a lower rate of CPPS-specific complaints at 12 weeks after ESWT. The overall pain reduction rate was 44% (7.0 to 3.9) The NIH-CPSI improved by 22.5% (from 10.0 to 7.3) and the IPSS was reduced in 10 of the 14 patients.

The MR images before ESWT in all patients were inconspicuous, except for isolated and minimal inflammatory changes; in particular it was possible to exclude more significant changes as the cause of the symptoms. The follow-up MRI was at a median (range) of 69.3 (48, 19–193) days after the first ESWT, and thus at a mean of 48 days after completing ESWT. No intraprostatic or periprostatic changes were diagnosed in any of the patients after ESWT.

Immediately before and after each treatment, TRUS of the prostate were done, including colour Doppler TRUS; the echogenicity of the prostate tissue and the perfusion were determined. There were no apparent changes to the echo pattern of the prostate after ESWT. Immediately after ESWT the colour Doppler image showed a significant increase in perfusion, with a rise in peak flow of up to 100%, which had returned to normal values 2 days later. No sustained perfusion changes were detected on Doppler TRUS.

The PSA level before the start of treatment were all in the age-correlated normal range (0.5–2.7 ng/mL). Neither the level on the day of ESWT nor those 2 days later showed any significant change. Almost 40% of any increases were within a fluctuation range of < 10%, and < 17% showed a transient PSA increase of > 10%. The other patients had no increases in PSA level, or indeed reductions, after ESWT (Fig. 1). The PSA profiles did not correlate with the clinical results and relevant tissue changes were excluded

FIG.1. The changes in PSA level during ESWT

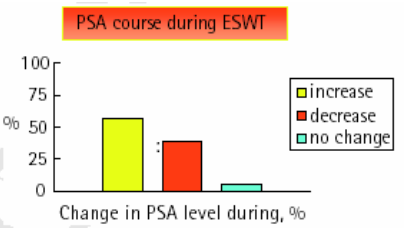
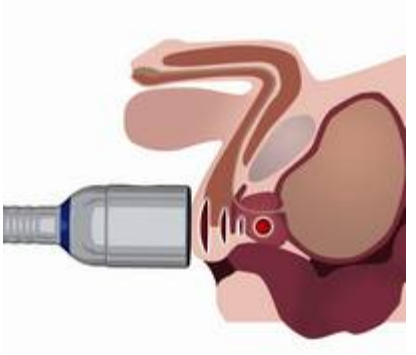


FIG.2. The perineal SW approach (intraprostatic focus).



In study 2, 20 patients (mean age 42.2 years, range 21–59) were included (May to August 2006). All patients completed the follow-up. The mean (range) duration of CPPS was 7.7 (3–24) months. The ESWT (duration17 min) was well tolerated as an outpatient session, with no anaesthesia, and no sideeffects were apparent.

The positioning of the SW transducer was simple and secure, due to the anatomical conditions and a suitable focal penetration depth (Fig. 2). The use of an additional positioning system to ensure the correct transducer placement was unnecessary.

All patients had a response on the pain VAS and the NIH-CPSI; both reductions were statistically significant (P< 0.001). The change in IPSS was not statistically significant (P= 0.669; Table 1).

TABLE 1

Sample time, weeks	IPSS	NIH-CPSI	VAS
Before ESWT	10,5	19,9	5,3
1	6,4	11,3	2,9
4	6,7	11,0	2,5
12	10,5	14,4	3,3
P	>0,05	<0,001	<0,001

TABLE 1

The results of study 2

DISCUSSION

To date there are only hypothetical models for the pathogenesis of CPPS, and thus both patients and doctors must find their own ways to treat this illness. The drug-based CPPS treatment regimens used to date have only minimal if any treatment effect. Offering drug-based therapy over a long period, particularly to the large proportion of young patients with CPPS, is not desirable, irrespective of the drug involved.

CPPS is probably manifested as a myofascial pain syndrome with an abnormal tone of the periprostatic musculature, and a neurological component has become increasingly apparent, associated with dysfunctional effects [23,24]. Many of the complaints are closely connected to the autonomous nervous system, and the interplay between smooth and cross-striated muscles. Acute and chronic inflammations occurring via the sympathetic endplate might be involved, leading to the endogenous generation of pain via nociceptive nerve endings and receptors. Furthermore, certain kinds of psychological stress can lead to abnormal electromyographic activity and to myofascial pain syndromes [25].

It therefore appears possible to treat many of the disorders associated with CPPS using myofascial trigger points, cognitive behavioural therapy, and biofeedback and relaxation training [26].

ESWT-associated pain alleviation based on hyperstimulation of nociceptors was intended to interrupt the flow of nerve impulses [27,28]. This mechanism does not explain the longer-term effect of the SWs, because the local changes preventing pain sensations from being created are only relatively transient and there is no enduring modulation in the sensitivity of the treatment area. Furthermore, ESWT-induced revascularization processes can alleviate pain and help to heal tissue [29]. There are reductions in muscle tone and spasticity [20] and a stimulation of microvascularization after applying SWs.

SW possibly influence the neuroplasticity of the 'pain memory'. According to this concept, the lack of effective therapy over a significant period of sustaining pain results in a development of a 'pain memory' as a mis-derived learning process due to the reinforcement of negative impulses in the brain and their long-term fixation. ESWT, by minimal pain impulses, could be disrupting the former pain memory and achieving a 'reprogramming'. This approach might explain, for example, why it is possible to influence an area of pain located some distance from the treatment locus.

The periprostatic pelvic floor muscles are also influenced by the therapy, therefore local muscle relaxation could be causing the disorder, improving as the result of a reduction in functional muscle shortening.

The intensity of pain associated with CPPS was reduced in the present study by about half; the maximum alleviation was at 4 weeks after the end of treatment, and the pain increased again by 12 weeks after ESWT, although a significant effect from the treatment remained apparent. As was to be expected, the alleviation of pain resulted in an improvement in the patients' specific quality of life. Based on comparable studies, the duration of follow-up was restricted to 12 weeks.

The pain reduction by SWs remains effective over a period of several weeks. Therefore it can be presumed that the underlying effective mechanisms are not just local alterations, but associated with many factors, and that it is currently not possible to precisely define or ascribe individual degrees of importance to the underlying mechanisms.

The lack of side-effects specific to the therapy and the absolute lack of problems in applying the therapy mean that, in theory, it would be possible to repeat the ESWT cycle at any time. The treatment regimen, defined by empirical means so far, can be adapted in the light of the results at any time, should this approach appear to offer prospects for success. In future, it might be possible to significantly extend the intervals between treatments possibly to achieve a longer-lasting treatment effect.
Interestingly, there was a temporary and considerable (although not statistically significant) improvement in subjective urination conditions in most patients in both studies. The subjectively perceived urination quality is only indirectly related to the other variables assessed, and therefore this was an unexpected finding. It is possible that the aforementioned local changes also had an effect on urination behaviour. In the future therefore, a group of patients should have a urodynamic evaluation before and after ESWT, to obtain data which could be used for deriving objective results about this, because evaluating the IPSS alone is insufficient and, above all, is not objective enough. Possibly, these results could mean that ESWT might be used for treating illnesses primarily associated with urinary disorders.

The interpretation of these results is limited to the extent that the patients studied in the present study did not primarily have a urinary disorder. Numerous studies in orthopaedics, urology and, most recently, cardiology have shown ESWT to have an extremely low spectrum of side-effects. This experience was confirmed again in the present study. TRUS after each ESWT made it possible to reliably exclude short-term changes, while MRI of the minor pelvis also allowed subsequent changes to be excluded. As a result, it is possible to assume that perineal ESWT can be applied with no risks.

The increased intraprostatic perfusion detected by Doppler TRUS immediately after ESWT, but no longer detectable 2 days later, is possibly due to short-term vasodilatation after exposure to SWs, attributable to a stimulation of local nitric oxide production. The difficulty involved in defining completely identical areas before and after ESWT means that the reproducibility of this method is low. In view of the perfusion measurement of very small intraprostatic blood vessels, it is only possible to obtain limited additional information using Doppler TRUS.

The PSA level after ESWT was measured to seek possible changes resulting from the treatment. The PSA levels showed a nonspecific profile, with only slight or completely absent fluctuations, both several minutes after and 48 h after ESWT. In addition to the clinical procedure, and Doppler TRUS, PSA was a further indicator that there is no reason to expect any relevant tissue damage, and that perineal ESWT can be regarded as a safe treatment. The results of the pilot study meant that no check on PSA levels associated with treatment was subsequently required.

The positioning of the SW focal zone within the prostate as the primary target organ was assessed in the first study by real-time inline US integrated in the therapy head. Due to the unambiguous anatomy in the lithotomy position, placing the therapy head on the perineum made it possible to reach the target structures of the prostate and the pelvic floor with a largely identical setting of the focal penetration depth, reliably and with no problems. Possible mis-positioning and resulting treatment to the wrong structures were excluded. The use of a US-based location system, as used initially, is therefore unnecessary for treating CPPS. Thus it was possible to use a significantly smaller device (Duolith SD1 vs Minilith) that is faster and easier to operate, with no US unit, in the follow-up study.

The selection of the number of treatments, the treatment distance and the number of pulses per session was made after preliminary clinical studies of other applications, and could only be defined empirically at first. The energy floe density of 0.11 mJ/mm ^{2} made it possible to assume that the probability of tissue damage could be practically excluded, and that the probability of a possible therapeutic effect would be sufficiently high.

The treatment regimen of the pilot study was adjusted to match reports of successful treatment from comparable orthopaedic studies; the total number of applied pulses remained unchanged (12 000) although the application period was doubled (from 2 to 4 weeks). This was intended to increase the effect on the tissue. The effectiveness of different treatment intervals and frequencies must be investigated further to define optimum treatment regimens for the desired local ESWT effects.

This also represents one of the limiting factors in our study. There are no reference factors for the treatment from comparable clinical studies. It is not possible to define treatment parameters and target criteria from the animal model, for example. Therefore, it was essential for the study to be orientated to the clinical procedure, and we think that all the control mechanisms required for this new indication for ESWT were implemented.

Few patients have been treated to date, but it was possible to achieve a statistically significant difference in the variables of pain alleviation and specific quality of life. The study had no control group, which represents a limitation. An initial control factor in this case was that comparably good results could be achieved in two study centres with totally different general conditions and study personnel. However, objective conditions and results are required for verification of the study. As some target variables tended to show a return to baseline levels, although only to a minor extent, a longer follow-up should be selected in future to assess the durability of the results. Patients with an initially good response could be treated as often as required if there was a subsequent recurrence of the disorder.

In conclusion, ESWT could be important for treating CPPS as it is easy and straightforward to apply and with practically no side-effects. With ESWT it was possible for the first time to establish a rapid and therefore financially appealing outpatient therapeutic option for CPPS, using a standard unit, with a treatment that can be repeated as often as required, and which requires little time or personnel costs.

A double-blind placebo-controlled study, including a sham treatment in the control group, for the further evaluation of this method, including an extended follow-up, has been completed in the meantime. Until the results of that trial are available the new technology should be applied only under investigational conditions.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **CPPS**, chronic pelvic pain syndrome; **ESWT**, extracorporeal shock-wave therapy; **NIH-CPSI**, National Institutes of Health – Chronic Pain Symptom Index; **VAS**, visual analogue scale