Extracorporeal shock wave therapy (ESWT) in the treatment of chronic pelvic pain syndrome in men

A prospective, randomized, placebo-controlled phase IIa/b clinical trial

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Abstract:

Background: Chronic prostatitis (CP) is divided into an inflammatory pelvic pain syndrome (NIH Category IIIa) and a non-inflammatory type (NIH Category IIIb). The symptoms associated with CP include pain in the region of the pelvis, prostate and urinary bladder as well as pain on urination without any evidence of urinary tract infection. Some CP patients have erectile dysfunction.

Materials and methods: The subjects in the clinical trial (n=60) were randomized to an intervention group (n=30) or control group (n=30) by drawing lots. Both the study group (*shock*) and the control group (*sham*) received three interventions. Using a focused shock wave handpiece and stand-off I in combination with a DUOLITH SD1 therapy system from Storz Medical, 2000 shock waves (SW) were applied to the prostate and pelvic floor muscles at a frequency of 4 Hz. In the control group (*sham*), the stand-off was replaced by a manipulated stand-off which inhibited the transmission of shock wave energy to the patient's body tissue. Subjects in the control group were unaware of this manipulation.

Results: In the experimental group (*shock*), a highly significant improvement beyond the mere placebo effect and the impact of visceral manipulation was determined in all major scores – i.e. primary endpoint: pain score (NIH-CPSI items 1-4); secondary endpoints: urinary symptoms score (NIH-CPSI items 5+6) and quality of life impact score (NIH-CPSI items 7-9). Especially in the pain domain, all patients in the experimental group achieved a longer-term (3 months after completion of treatment) improvement from baseline (mean pain domain score t0=12.10 versus t2=4.37).

Background:

The National Institute of Health (NIH) classifies prostatitis into four categories (Krieger NJ. 1999):

Acute bacterial prostatitis (ABP) (NIH Category I) is characterized by pronounced lower urinary tract symptoms (LUTS) with pain in the prostate region, along with obstructive and irritative symptoms with systemic reaction.

Chronic bacterial prostatitis (CBP) (NIH Category II) is associated with intermittent prostatic symptoms. In most cases, uropathogenic bacteria are found in the expressed prostatic secretion (EPS) and in the post-massage urine (voided bladder urine, VB_3).

Chronic prostatitis (CP) (NIH Category III) is divided into an inflammatory pelvic pain syndrome (CPPS) (NIH Category IIIa) and a non-inflammatory type (NIH Category IIIb). The symptoms associated with CP include pain in the region of the pelvic floor, prostate and

urinary bladder as well as pain on urination without any evidence of urinary tract infection (UTI). Some CP patients also have erectile dysfunction.
Asymptomatic prostatitis (AP) (NIH Category IV) is characterized by evidence of prostate inflammation. The symptoms associated with NIH Categories I to III are entirely absent.

About 10% of all men experience symptoms of prostatitis. The peak age is between 20 and 49 years and above 70 years, and the incidence rate is reported to be 3/1000 (Schaefner, et al. 2002). Evidence of bacterial prostatitis is found in only about 7% of all men, which means that approximately 3% of men develop the chronic abacterial type (NIH Categories IIIa and IIIb) or chronic pelvic pain syndrome (CPPS) (Weidner, et al. 1991).
Whereas the aetiology, pathogenesis and treatment of ABP and CBP can be clearly defined, many cases of CP/CPPS are not yet well understood in terms of their aetiology and pathophysiology. At present, five different causative factors for the development CP or CPPS are being discussed:

- Infection of the prostate with non-culturable microorganisms. Some patients with CP IIIa/CPPS exhibit prokaryotic DNA sequences as an indication of microorganisms that may cause inflammation of the organ (Schaeffer AJ. 2006) (Wagenlehner, et al. 2009).
- Functional micturition disorders with insufficient relaxation of the smooth muscles in the bladder neck region during urination. This causes an infravesical turbulent flow with reactive urine reflux into the prostate and chemically induced organ inflammation (Schaeffer AJ. 2006) with release of mediators acting as ligands on nociceptors.
- Autoimmune processes are assumed to take place owing to an increased concentration of pro-inflammatory cytokines and a concurrent reduced level of anti-inflammatory cytokines (Wagenlehner, et al. 2009).
- Uroepithelial dysfunction. A functional disorder of intravesical ion channels as that found in interstitial cystitis may also be relevant in CP/CPPS (Yilmaz, et al. 2004).
- Neurogenic inflammation. The knowledge (so far acquired by experiments only) about the development of neurogenic inflammation of the prostate, which is known to be responsible for the pathogenesis of interstitial cystitis (IC) (Sant, et al. 2007), is based on the interaction of neurokinins and mast cells. This interaction causes inflammatory processes and is associated with a sensitivity up-regulation of sensory neurons of the nervous system (Wagenlehner, et al. 2009).

The review of the 2003 Guidelines on Chronic Pelvic Pain of the European Association of Urology (EAU) has resulted in a revised nomenclature and classification in the currently applicable 2009 version. Greater importance is attached to the potential multifactorial pathoaetiology of CP/CPPS and hence to a multimodal therapy approach. This view also accounts for the fact that it is not possible in all cases to relate the existing pain to an organ as the origin of the condition. This is why the authors of the Guidelines proclaim that in cases in which this is not possible the term CP/CPPS be changed to chronic pelvic pain (CPP). This makes it clear that the pain perceived by patients may not necessarily originate in the prostate alone and that other somatic tissues such as the pelvic floor muscles may be responsible for nociception in cases of active trigger points (Travell und Simons 1983). By defining Axis VIII in its Axis Model, the EAU also considers the potential impact of psychosocial factors on the pathogenesis of CPP.

The Guidelines classify treatment recommendations for CP/CPPS (NIH Category III) into "recommended therapies", "non-recommended therapies" and "therapies for which a final assessment is not yet possible" (Wagenlehner, et al. 2009) (Fall, et al. 2010). Recommended therapies include the administration of alpha-receptor blockers, antimicrobial therapy and a multimodal symptomatic therapy approach. However, the use of alpha-receptor blockers and antimicrobial medication is rejected in patients who have undergone multiple pre-treatments, as are anti-inflammatory monotherapy, minimally invasive transurethral needle ablation of the prostate (TUNA) and invasive transurethral resection of the prostate (TURP).
Therapy methods for which a final assessment is not yet possible include transurethral microwave thermotherapy (TUMT), the use of phytotherapeutic agents, bio-feedback methods, physical therapy, acupuncture, the administration of muscle relaxants and neuromodulative substances, and neural therapeutic treatment of the pudendal nerve (Wagenlehner, et al. 2009). So far, the use of extracorporeal shock wave therapy (ESWT) has not been included in any of the categories established by the Guidelines, although several studies conducted in the last few years have provided ample evidence that ESWT can be a viable option in a multimodal therapy strategy for patients with CP/CPPS or CPP. The studies performed by Zimmermann and Zeng have demonstrated that in addition to alleviating pelvic pain extracorporeal shock wave therapy also has a positive impact on concurrent LUTS and on the quality of life (QoL) of the affected patients. Furthermore, the results of studies conducted to assess the effectiveness of ESWT in this field confirm that there is no indication whatsoever of any potential damage caused by shock waves to the prostate or adjacent structures if ESWT is performed correctly. (Zimmermann, Cumpanas

und Hoeltl, et al. 2008) (Zimmermann, et al. 2009) (Marszalek, Berger und Madersbacher 2009) (Zeng, Liang und Ye 2012)

The clinical trial conducted by the authors of this article was based on the study objectives of Zimmermann et al. (assessment of ESWT therapy effects in patients with CP/CPPS/CPP). In addition to investigating the reliability of the study results, the relation between patient-focused individualization of the shock wave dose and the outcome of the intervention had to be established. The primary endpoint of the intervention was the reduction of pain in patients with CP/CPPS/CPP, defined by the pain domain score (NIH-CPSI items 1-4). Urinary symptoms (NIH-CPSI items 5+6), quality of life impact (NIH-CPSI items 7-9) and the severity of concomitant erectile dysfunction (total IIEF score – IIEF International Index of Erectile Function) represented the secondary evaluation parameters.

Materials and methods:

Inclusion criteria for participation in the clinical trial were diagnosed CP (types IIIa and IIIb), causing pain or discomfort for three months or over, exclusion of any other disease of the urinary bladder and prostate as established by a urological consult, and the patient's unrestricted capability to consent. Exclusion criteria for enrolment were acute and chronic bacterial prostatitis (types I+II), use of medication during the duration of the trial and any other form of CP therapy. Drop-out criteria were the development of bacteriuria in the course of the trial period, lasting exacerbation of the existing problems and failure to strictly comply with the treatment intervals.

Subjects were recruited by referral from practice-based urologists and general practitioners. Examination, treatment and follow-up of patients were conducted from March 2012 until November 2013.

After having been informed in detail about the trial procedure and the intended intervention and after having decided to participate and signed the informed consent form, the subjects (n=60) were randomized to an intervention group (n=30) and a control group (n=30) by drawing lots. The original target sample size of n=80 could not be achieved. Seven subjects who had initially been enrolled had to be excluded even before the trial began because they did not meet all of the inclusion criteria (bacteria found in urine). Due to the randomization, a slightly unbalanced allocation of subjects with CP type IIIa (study group n=7 versus control group n=9) and CP type IIIb (study group n=23 versus control group n=21) to the two groups could not be avoided (Table 1). However, the distribution was not asymmetrical.

App	IIIa	IIIb	all
sham	9	21	30
shock	7	23	30
all	16	44	60

Table 1: Number of subjects by CP sub-type and treatment

As defined by the inclusion criteria, all patients had chronic abacterial prostatitis (CP type III); 16 subjects had sub-type IIIa (inflammatory) and 44 had sub-type IIIb (non-inflammatory). The distribution of the sub-types to the treatment groups did not show any asymmetry resulting from the randomization.

The mean age of the subjects in the clinical trial was 39 years (the youngest being 24, the oldest patient being 72 years of age). The inter-quartile range was 32 to 48.5 years. Due to the randomization, an unbalanced age distribution of the subjects in the two groups occurred. The control group (*sham*) included many young and some very old patients, whereas the subjects in the experimental group (*shock*) were mostly of mean age (Fig. 1).

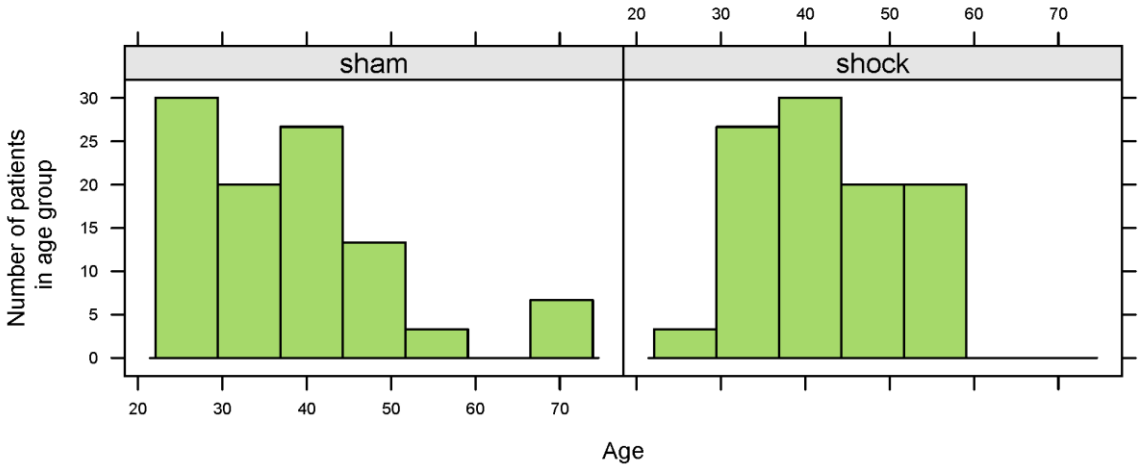

Fig. 1: Age distribution of patients in study group (*shock*) and control group (*sham*)

The histogram in Fig. 1 and the QQ plot in Fig. 2 show that the randomization resulted in an unbalanced age distribution in the two groups. The control group (*sham*) included many young and some very old patients, whereas the subjects in the experimental group (*shock*) were mostly of mean age.

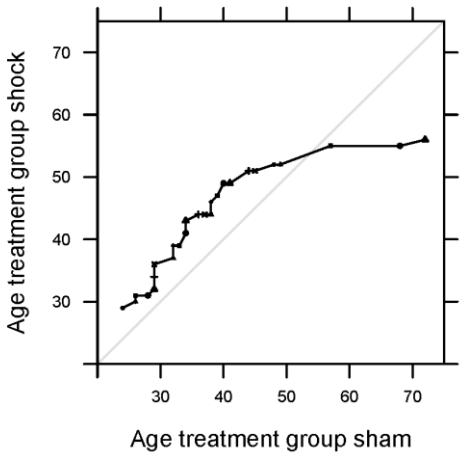

Fig. 2: QQ (quantile-quantile) plot of age distribution in the study and control groups

If the age distribution of subjects in the study group and control group had been balanced, one would have expected points above and below the bisecting line of the angle.

The Kolmogorov-Smirnov test of the two distributions shows, however, that the assumption of balanced distribution cannot be refuted (p = 0.7). This means that the comparability of the two groups is ensured.

CP-related symptoms experienced by the patients had already lasted for a median of 9.5 months (shortest duration 4 months, longest duration 52 months) before the trial began. The distribution of patients in terms of the duration of the disease does not reveal any asymmetry between the study group and control group (Fig. 3).

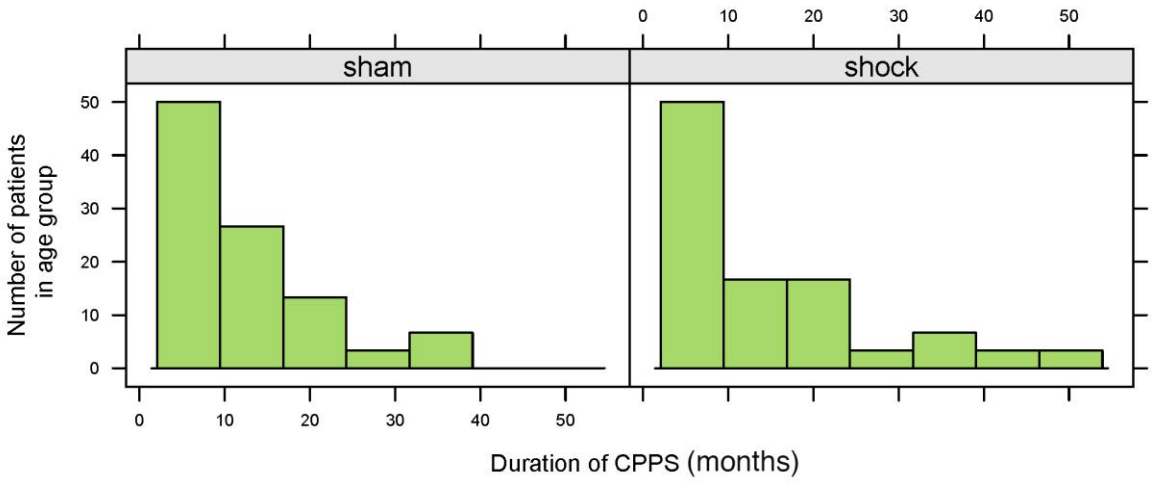

Fig. 3: Median duration of symptoms = 9.5 months

The shortest duration of symptoms was 4 months, the longest duration was 52 months. There is no indication of an unbalanced distribution of patients in terms of the pre-trial duration of symptoms between the study group and control group.

The subjects in the clinical trial completed the German versions of the NIH-CPSI and the International Index of Erectile Function (IIEF) questionnaires before the first treatment (t0), after the third treatment (t1) and three months (median 88.5 days / max. 102 days / min. 82 days) after completion of the third intervention (t2). A two-glass test was conducted at t0, t1 and t2, taking midstream urine samples from all patients, followed by post-massage urine samples (obtained after the midstream sample by a 3-minute rectal prostate massage with the patient in a knee-elbow position) (Seiler, et al. 2003). The two samples were analysed for signs of inflammation (leukocytes) by means of a semi-quantitative urine test strip analysis (Urisys 1100 urine analyzer from Roche), and the urine sediment was examined under the microscope to detect bacteria, if present (assessment of five meandering fields of view). After complete voiding of the bladder, transabdominal sonography was performed to measure the post-voiding residual urine volume and document the dichotomous outcome (yes/no) if the residual urine volume reached the 100 ml limit value (Gasser und Rutishauser 2005).

The subjects in the study group (*shock*) and control group (*sham*) all received three interventions. Using a focused shock wave handpiece and stand-off I in combination with a DUOLITH SD1 (serial number: TT.0133 / 2007 model) or DUOLITH SD1 »ultra« (serial number: BT.0003 / 2011 model) from Storz Medical, 2000 shock waves (SW) were applied to the prostate and pelvic floor muscles (urogenital diaphragm) at a frequency of 4 Hz via the inferior ramus of the pubis and the inferior ramus of the ischium after palpatory exploration. In the control group (*sham*), the stand-off was replaced by a manipulated stand-off which inhibited the transmission of shock wave energy to the patient's body tissue. Subjects in the control group were unaware of this manipulation. The shock wave energy applied during the treatment was increased up to a maximum level of 0.25 mJ/mm² according to the intensity of pain perceived by each individual patient as a result of the application. The total energy applied was documented in mJ/mm^2 (median total energy per application 14,110 mJ/mm^2 / minimum total energy per application 11,880 mJ/mm^2 / maximum total energy per application 15,820 mJ/mm^2). Before treatment was started, all patients were informed that the application of shock waves may cause local pain as well as referred pain, but that the effectiveness of the therapy would not depend on the pain perceived. This information about application-induced pain was provided in order not to create the impression among subjects assigned to the control group (*sham*) that they would receive placebo treatment. A maximum pain level of 6 on a visual analog scale (VAS) from 0 (no pain) to 10 (worst pain) was agreed with the patients to represent the acceptable limit level. The shock wave intensity was continually increased up to this virtual score, i.e. up to a maximum real energy

level of 0.25 mJ/mm^2. ESWT treatment was performed with the patients in a supine position. Both legs were flexed at the hip and knee (>90°). Patients were asked to maintain this position with the help of their hands during shock wave application (cf. Fig. 4).

Fig. 4: Patient positioning for ESWT treatment

This starting position at the end of the examination table, which gives the therapist free access to the urogenital diaphragm, had been determined in a preliminary study by perineal sonography with a 5 MHz ultrasound transducer and had been found to represent a reliable patient position in terms of the maximum 35 mm distance between the centre of the prostate and the skin surface and, consequently, for the standardized use of stand-off I (cf. Fig. 5). Examination and treatment of all patients in the clinical trial were performed by two therapists, with the subjects from both groups being equally assigned to the two therapists. After localization of the point of maximum pain, the position of the shock transmitter was no longer changed until the pain had subsided substantially. Re-focusing was then performed by slight angulation of the shock transmitter and by increasing the energy level, if indicated. The defined interval between the three interventions was 8 to 10 days and was observed in all participating subjects in the two groups.

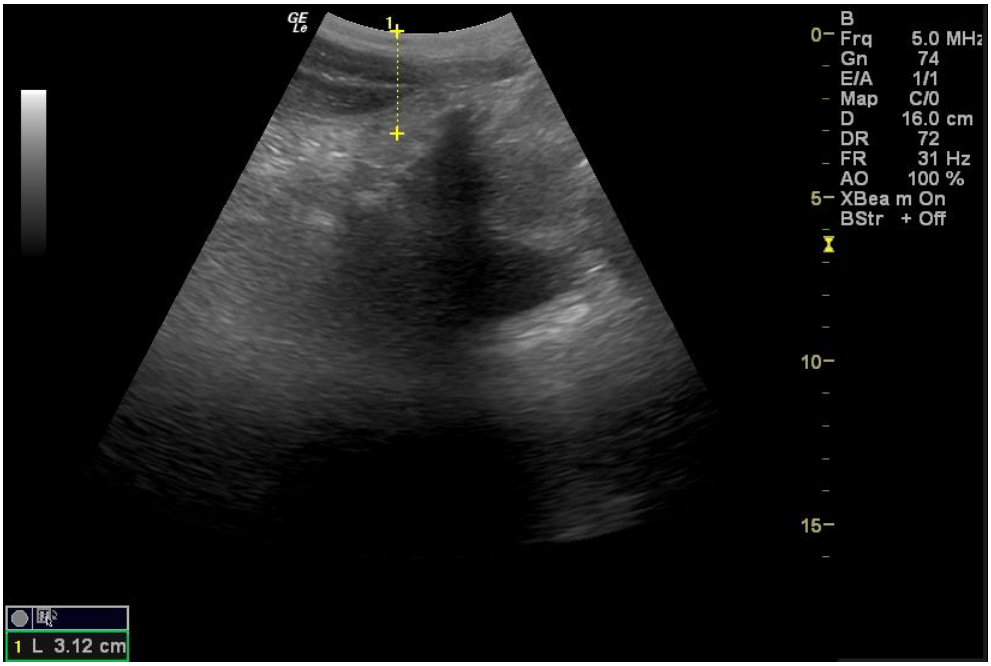

Fig. 5: Perineal sonography conducted to determine the distance between the skin surface and the centre of the target organ (prostate)

Using stand-off I, the ESWT penetration depth is 15 to 45 mm, with the focus at about 30 mm. This means that the entire organ can be reached if the prostate has a normal size and the handpiece angulation is correct.

Results:

The statistical evaluation of the collected data was performed with R [R version 3.0.2 (2013-09-25), R, 2005]. The knitr and LaTeX 2ε packages were used for compilation by Menne Biomed Consulting[1].

All patients enrolled in the study group and control group were able to participate up to the completion of the clinical trial. All data sets in the Trial Master File (TMF) were fully included in the statistical evaluation (cf. CONSORT Statement in Fig. 6).

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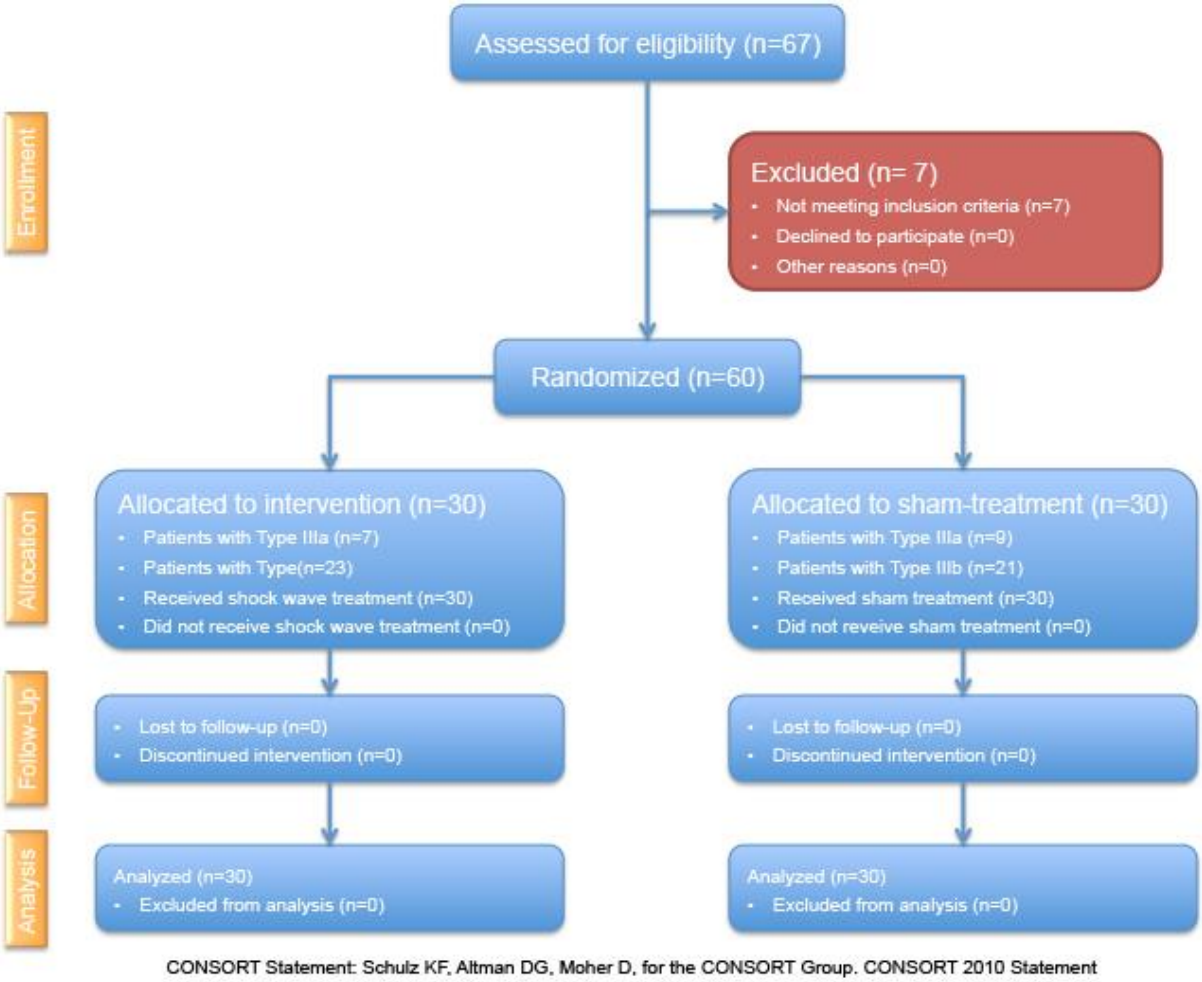

Fig. 6: CONSORT Statement of prospective, randomized, placebo-controlled clinical trial

The primary endpoint of the clinical trial was the reduction of the typical pain in patients with CP/CPPS/CPP between t0 (visit 0) and t2 (visit 2). This primary variable was defined by the pain domain score (NIH-CPSI items 1-4). The CP sub-types (IIIa or IIIb) were included as co-variables.

The evaluation of the collected data was based on a mixed model approach (Pinheiro und Bates 2000), a generalized model of the analysis of variance, in which repetitive measurements, i.e. multiple measurements, of the same score for the same subject are considered with the correct weighting.

The pain domain score (NIH-CPSI items 1-4) of patients at baseline (visit 0) was slightly higher in the experimental group (*shock*) than in the control group (*sham*). However, no significant difference was found between the two groups based on a 95% confidence interval (cf. Table 2).

visit	group	Estimate	Lower.CI	Upper.CI
visit 0	sham	11,50	10,80	12,30
visit 0	shock	12,10	11,10	13,00
visit 1	sham	9,03	8,26	9,81
visit 1	shock	5,40	4,46	6,34
visit 2	sham	8,67	7,89	9,44
visit 2	shock	4,37	3,43	5,30

Table 2: Mean pain domain scores and 95% confidence interval of pain scores

Both groups experienced a significant improvement between t0 (visit 0) and t1 (visit 1), i.e. from baseline up to the end of the third intervention. However, this improvement was substantially lower in the control group (*sham*) – with a pain domain score of 9.03 (NIH-CPSI items 1-4) (p>0.0001, 95% confidence interval) – than in the experimental group with a pain domain score of 5.40 (p>0.0001, 95% confidence interval). This trend stabilized in the three months after the end of the treatment up to the follow-up visit (t2) (cf. Fig. 7 and Table 2).

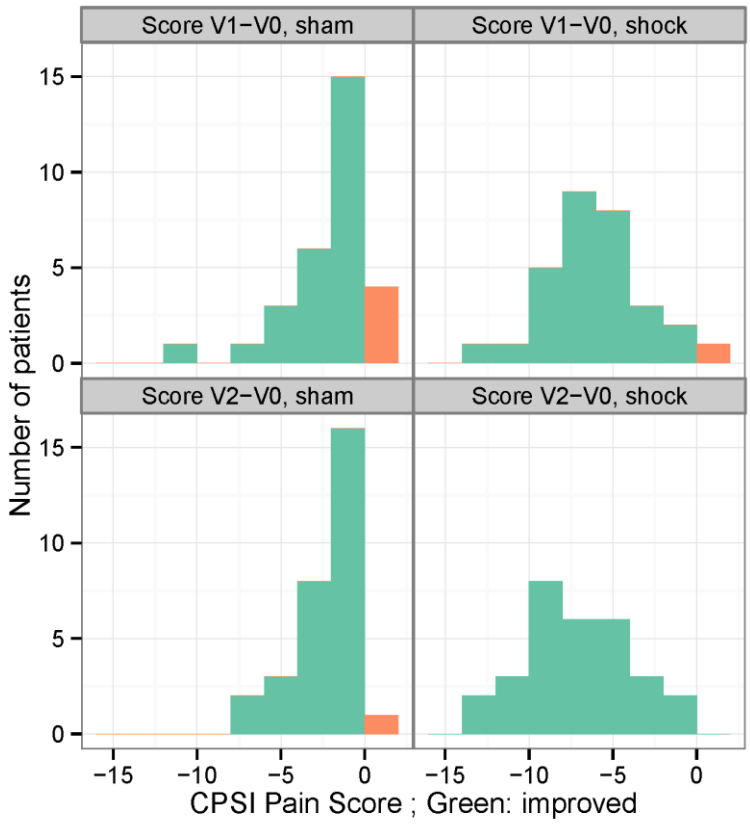

Fig. 7: Histogram of changes in the pain domain score (NIH-CPSI items 1-4)

Both groups, i.e. the experimental group (*shock*) and the control group (*sham*), experienced a reduction in the pain domain score. This reduction was significantly greater in the experimental group (*shock*) than in the control group (*sham*) – p>0.0001, 95% confidence interval.

The primary endpoint, i.e. the difference in the pain domain score (NIH-CPSI items 1-4) between t0 (visit 0) and t2 (visit 2), shows that the pain experienced by patients with CP/CPPS/CPP could be reduced to a greater extent in the experimental group (4.37) than in the control group (8.67). Consequently, the long-term effect of ESWT compared to the control group is significantly better, based on a 95% confidence interval (p>0.0001) (cf. Fig. 8).

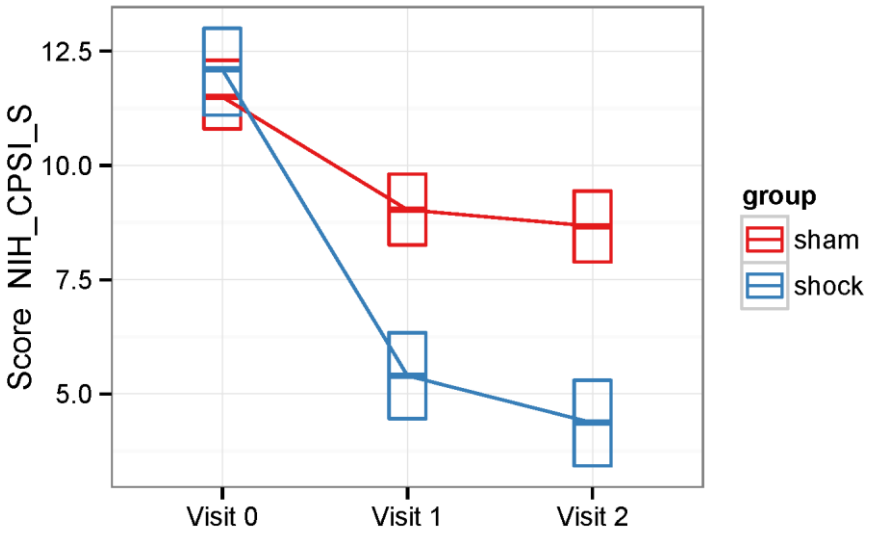

Fig. 8: Mean pain domain scores and 95% confidence interval of the pain scores in Table 2

As far as the secondary endpoints – i.e. urinary symptoms (NIH-CPSI items 5+6), quality of life impact (NIH-CPSI items 7-9), and severity of erectile dysfunction (International Index of Erectile Function) – were concerned, the following changes occurred in the study and control groups:

Based on a 95% confidence interval, there was no significant difference in the urinary symptoms (NIH-CPSI items 5+6) determined at baseline between the experimental group and the control group, although the mean total urinary domain score for NIH-CPSI items 5+6 was 1 point higher in the experimental group (*shock*=5.77) than in the control group (*sham*=4.77).

Similarly to the changes observed with respect to the pain levels, the urinary domain score significantly decreased in both groups (*shock*=1.37 versus *sham*=3.30; p>0.0001, 95% confidence interval) in the course of the treatment from t0 (visit 0) to t1 (visit 1). However, the total score for NIH-CPSI items 5+6 was 2.9 points lower in the patients who received ESWT treatment. This trend was confirmed at the follow-up t2 (visit 2) three months after

completion of the third treatment, and the difference between the two groups (*shock*=0.93 versus *sham*=3.07) had even increased to 3.1 points (cf. Table 3 and Fig. 9).

visit	group	Estimate	Lower.CI	Upper.CI
visit 0	sham	4,77	3,89	5,64
visit 0	shock	5,77	4,82	6,71
visit 1	sham	3,30	2,42	4,18
visit 1	shock	1,37	0,42	2,31
visit 2	sham	3,07	2,19	3,94
visit 2	shock	0,93	-0,01	1,88

Table 3: Mean urinary domain scores and 95% confidence interval of urinary domain score

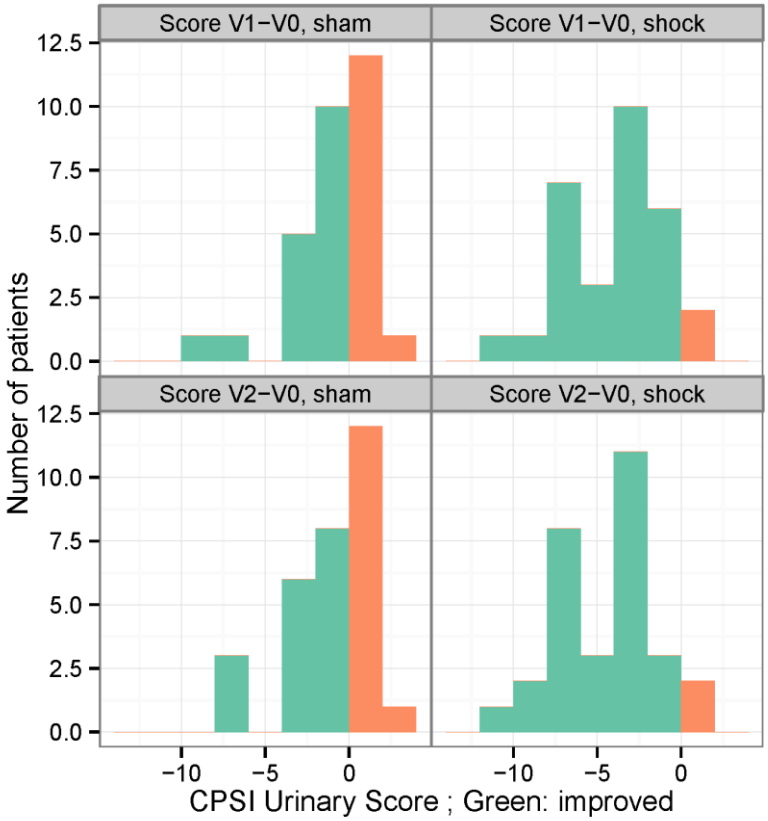

Fig. 9: Histogram of changes in the urinary domain score
(NIH-CPSI items 5+6)

Both groups, i.e. the experimental group (*shock*) and the control group (*sham*), experienced a reduction in the urinary domain score. This reduction was significantly greater in the experimental group (*shock*) than in the control group (*sham*) – p>0.0001, 95% confidence interval.

This means that the urinary domain score shows the same trend as the pain domain score (cf. Fig. 10), but has a substantially greater spread. Among other factors, this is attributable to the fact that the urinary domain comprises only two NIH-CPSI items.

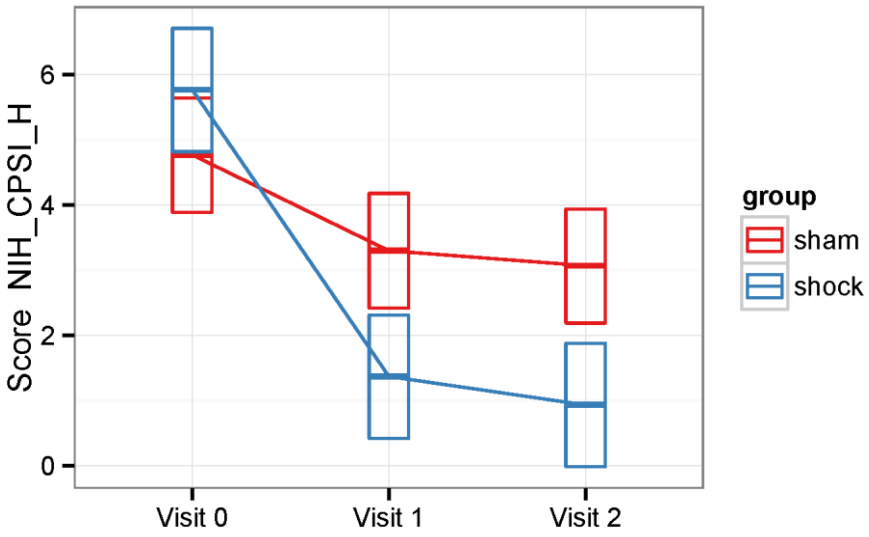

Fig. 10: Mean scores and 95% confidence interval of urinary domain scores in Table 3

A total of 16 patients (*sham*=9 versus *shock*=7) out of the 60 subjects participating in the clinical trial had leukocyturia in the post-massage urine (cf. Table 4) at the beginning of the study. Owing to the semi-quantitative collection of leukocyte counts (Urisys 1100 urine analyzer from Roche), it was not possible to use a linear model for evaluation. Consequently, a simplified assumption was used, namely that the treatment would be considered successful if the leukocyte count in the post-massage urine at t2 (visit 2) was found to be below the detection threshold (value in last column of Table 4 = 0).

ID	group	t0 (visit 0)	t1 (visit 1)	t2 (visit 2)	success
CPPS000	sham	250	0	0	0
CPPS006	sham	250	100	25	1
CPPS010	sham	250	500	250	1
CPPS019	sham	250	100	500	1
CPPS022	sham	250	250	100	1
CPPS025	sham	500	250	500	1
CPPS031	sham	500	25	250	1
CPPS057	sham	500	10	250	1
CPPS059	sham	250	250	100	1
CPPS004	shock	500	0	0	0
CPPS008	shock	250	0	0	0
CPPS011	shock	250	25	0	0
CPPS015	shock	250	25	0	0
CPPS037	shock	500	0	75	0
CPPS044	shock	250	500	75	1
CPPS051	shock	500	100	0	0

Table 4: List of all patients having leukocyturia in the post-massage urine at baseline t0 (visit 0), sorted by trial groups

The fourfold table created on the basis of these findings (cf. Table 5) was analysed for

deviations from the equal distribution by conducting a chi-square (X^2) test. Due to the low case number, a Monte Carlo simulation was used in the chi-square (X^2) test.

	0	1
sham	1	8
shock	5	2

Table 5: Fourfold table for the assessment of the treatment success rated in terms of the elimination of leukocyturia in the post-massage urine, defined as leukocyte count = 0 at t2 (visit 2)

Based on the outlined statistical analysis of leukocytes in the post-massage urine, there are indications ($p>0.04$ in the fourfold table test) that leukocyturia diagnosed at baseline can be reduced as a result of the treatment (leukocytes in post-massage urine below the semi-quantitative detection threshold). Although the leukocyte count is an important parameter – especially because it is the only factor not subject to the patient's subjective assessment – this analysis must not be overestimated due to the very small sample size.

Owing to the randomization and based on a 95% confidence interval, the quality of life score (NIH-CPSI items 7-9) did not show any significant difference between the control group (*sham*=8.97) and the experimental group (*shock*=8.87) at baseline. The trend observed in the analysis of the pain domain and urinary domain scores was also confirmed for NIH-CPSI items 7-9 (cf. Table 6 and Fig. 11).

visit	group	Estimate	Lower.CI	Upper.CI
visit 0	sham	8,97	8,22	9,71
visit 0	shock	8,87	8,04	9,69
visit 1	sham	6,77	6,02	7,51
visit 1	shock	3,80	2,98	4,62
visit 2	sham	6,53	5,79	7,28
visit 2	shock	2,90	2,08	3,72

Table 6: Mean QoL scores and 95% confidence interval of QoL scores

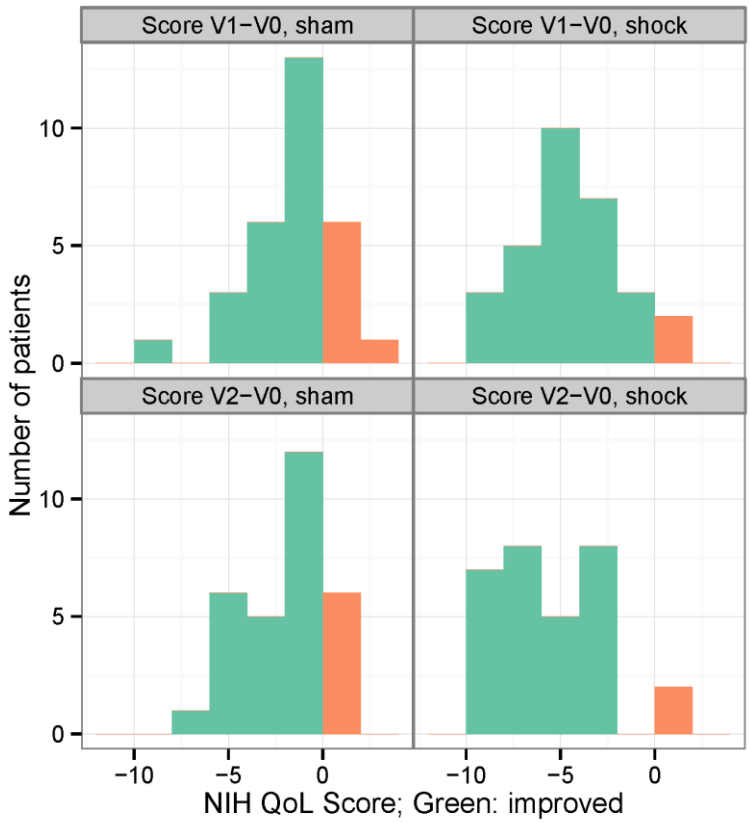

Fig. 11: Histogram of changes in the quality of life score from baseline t0 (visit 0)

Starting with quality of life scores of 8.97 (*sham*) and 8.87 (*shock*) at baseline, both the control group and the experimental group experienced an improvement in their quality of life between t0 (visit 0) and t1 (visit 1) and – as a long-term effect – t2 (visit 2). In fact, the QoL score had decreased to 6.53 (*sham*) versus 2.90 (*shock*) by t2. Although the reduction in the QoL score from t0 to t2 was 3.5 points higher in the experimental group than in the control group ($p>0.0001$, 95% confidence interval), this result should be interpreted with great caution because, firstly, the therapeutic attention and care given to patients in the course of the intervention may already have had a positive impact on the QoL score and, secondly, the possibility of insufficient blinding of the placebo group cannot be excluded (cf. Fig. 12).

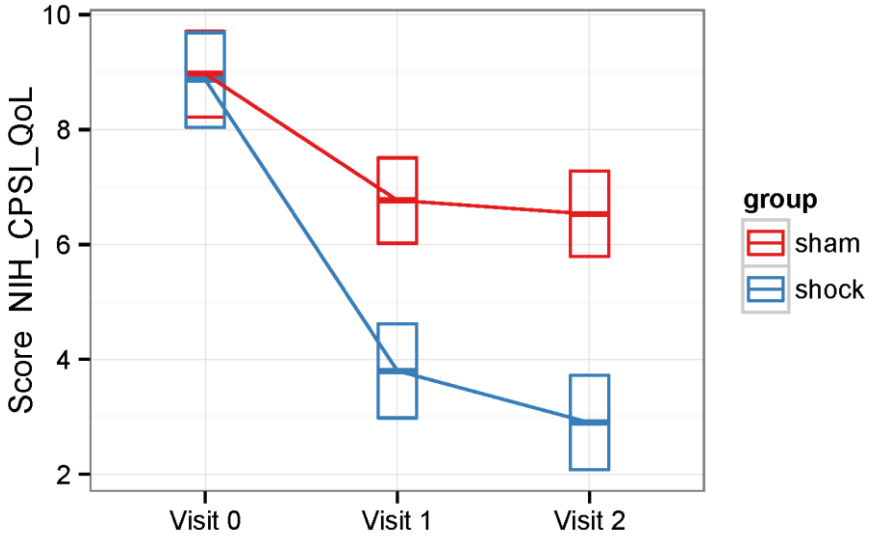

Fig. 12: Mean QoL scores and 95% confidence interval of QoL scores
The 95% confidence intervals represent the spread between patients.

The severity of erectile dysfunction (ED) can be graded according to the International Index of Erectile Function (IIEF). Based on the total IIEF score of the questionnaire, the following severity grades can be distinguished: 1-7 severe ED, 8-11 moderate ED, 1-16 mild to moderate ED, 17-21 mild ED, and 22-25 no erectile dysfunction. ED classification in terms of the underlying aetiology is not possible with the IIEF. Although there was no significant difference in the mean IIEF scores between the two groups at baseline (95% confidence interval) (cf. Table 7), the fact that only 32 out of the 60 subjects participating in the trial had an abnormal score (*sham*=14 and *shock*=18) (cf. Table 8) should be taken into consideration in the assessment of the IIEF score.

visit	group	Estimate	Lower.CI	Upper.CI
visit 0	sham	20,80	19,40	22,10
visit 0	shock	19,80	18,30	21,20
visit 1	sham	21,20	19,90	22,60
visit 1	shock	21,50	20,00	22,90
visit 2	sham	21,30	20,00	22,70
visit 2	shock	22,30	20,90	23,70

Table 7: Mean IIEF scores and 95% confidence interval of IIEF scores

group	1-7	8-11	12-16	17-21	22-25
sham	0	1	5	8	16
shock	0	0	7	11	12

Table 8: ED grading, sorted by treatment groups

ED grading: 1-7 severe ED, 8-11 moderate ED, 1-16 mild to moderate ED, 17-21 mild ED, 22-25 no erectile dysfunction (highlighted in yellow).

Contrary to the CP/CPPS- or CPP-related occurrence of ED reported in the literature (Zimmermann, Cumpanas und Hoeltl, et al. 2008) (Wagenlehner, et al. 2009) (Schaefner, et al. 2002) (Schaeffer AJ. 2006), only just over 50% (n=32) of the patients examined in the clinical trial had any signs of ED. In 19 (*sham*=8 and shock=*11*) out of these 32 subjects, the ED was graded as mild, and even in these 19 cases it cannot be excluded that the initial pain and lower urinary tract symptoms (LUTS) may have contributed to an impairment of erectile function, which would then mean that the improvement in the primary endpoint during the therapy may have had a positive impact on the ED score without the ESWT having had any influence on a causal aetiological factor of erectile dysfunction (cf. Figs. 13+14).

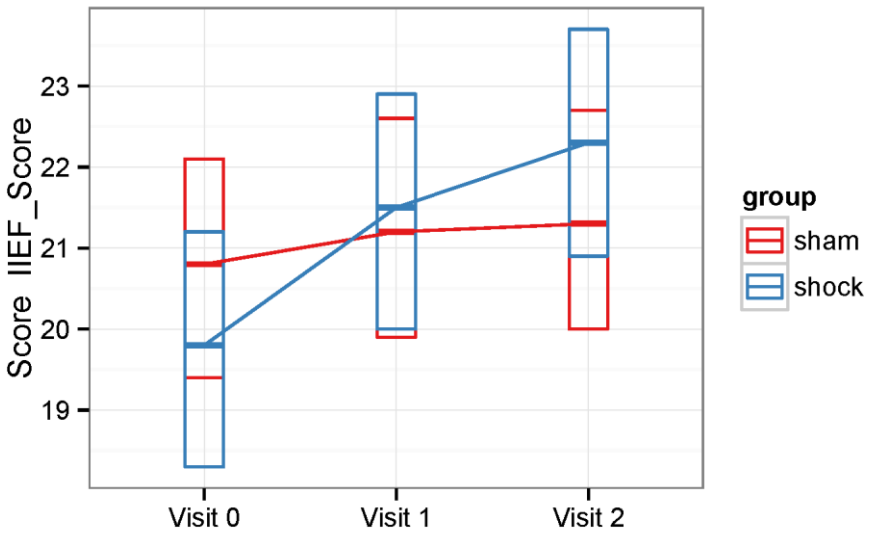

Fig. 13: Mean IIEF scores and 95% confidence interval of IIEF scores

The improvement in the IIEF score is statistically significant, but it contributes to the total score only to a minor extent. Since many of the IIEF scores were close to the maximum score even at baseline, no significant change in the total score was to be expected for these patients.

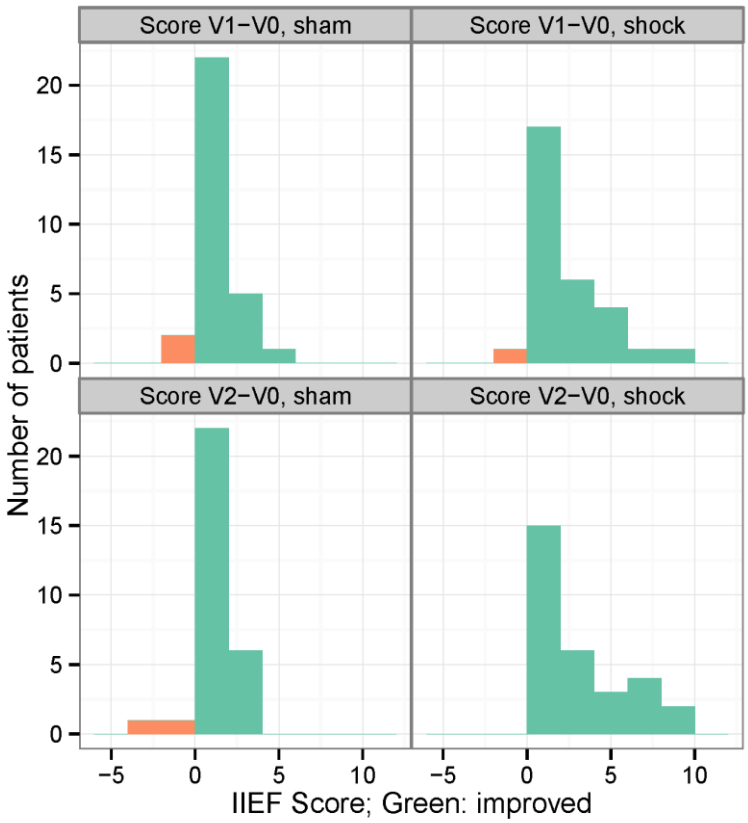

Fig. 14: Histogram of the changes in the total IIEF score from baseline at t0 (visit 0)

The total IIEF score at t2 (visit 2) had improved from baseline at t0 (visit 0) both in the control group and in the experimental group (*sham*=21.3 and *shock*=22.3). In the experimental group (*shock*), the increase in the total score was two points higher than in the control group (*sham*). As a result, the long-term therapy effect is considered to be significant (p>0.0001, 95% confidence interval).

Even if the applied total energy (mJ/mm^2) did not represent any primary or secondary endpoint of the clinical trial, the development of the total energy per treatment will be analysed below to draw field-oriented conclusions for the use of ESWT in patients with CP/CPPS or CPP.

Contrary to the dosage indications published to date for the treatment of CP/CPPS or CPP (Zimmermann, Cumpanas und Hoeltl, et al. 2008) (Zimmermann, Cumpanas und Miclea, et al. 2009) (Zeng, Liang und Ye 2012) (Marszalek, Berger und Madersbacher 2009), we decided to conduct the clinical trial with a more individualized dosage that was adapted to the patient's specific perception of pain. The energy flow was limited to a maximum of 16,350 mJ/mm^2 per treatment (SW=2000 at a frequency of 4 Hz and maximum 0.25 mJ/mm^2). The mean total energy in the first treatment was 13,502 mJ/mm^2 and could be increased in the course of the second and third treatment – compared to the first intervention – by 275 mJ/mm^2 and 411 mJ/mm^2, respectively (cf. Fig. 15). The mean spread across patients in the clinical trial was 1,556 mJ/mm^2, i.e. approximately 11% of the mean

energy. Considering the substantial spread of pain scores generally encountered, this spread is very small. This is indicative of a very reliable and reproducible application.

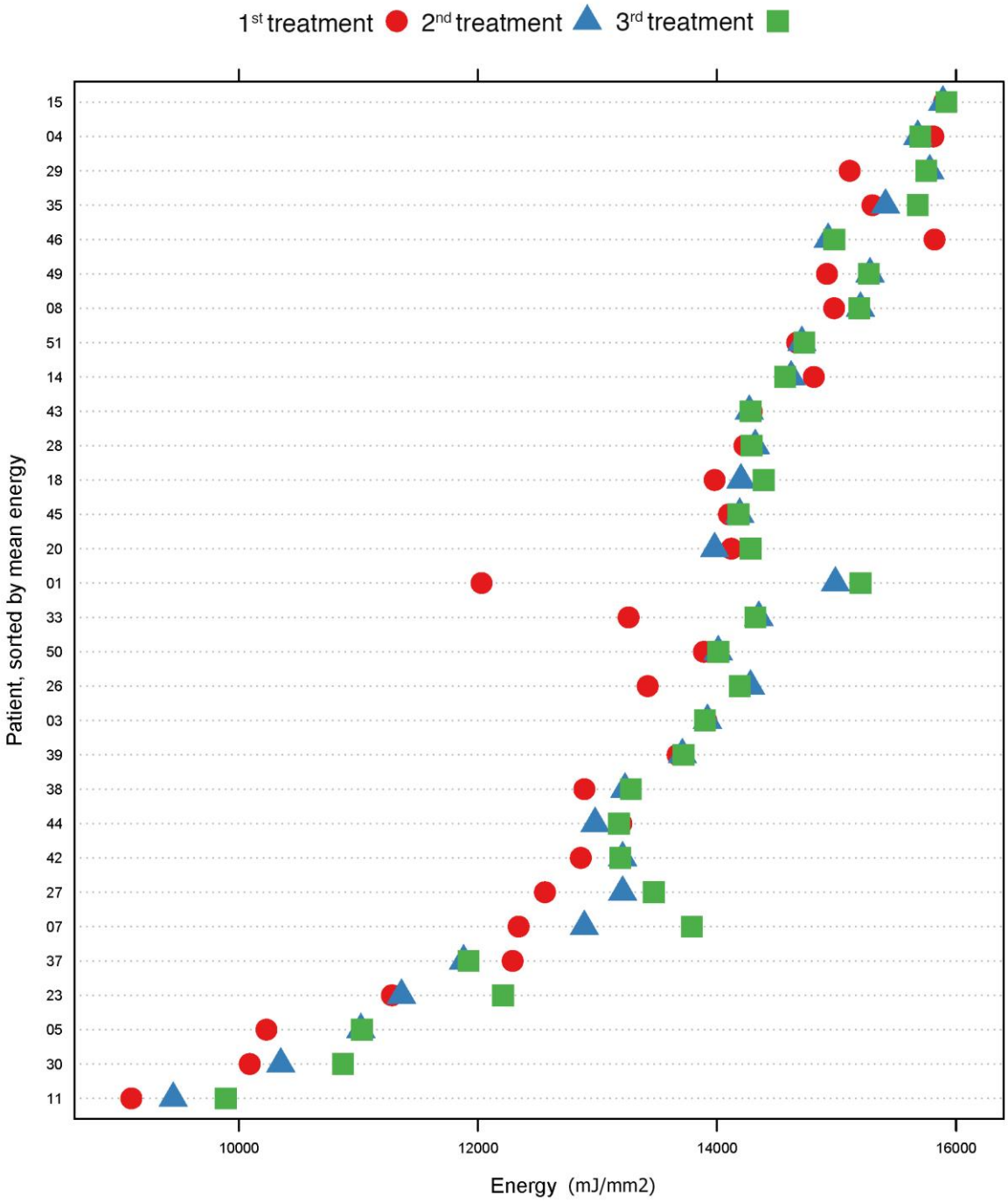

Fig. 15: Total energy applied in the three treatments (mJ/mm^2)

The vertical axis is sorted by the mean total energy / patient and treatment. The spread for a specific patient is very small, compared to the spread across patients. The increase in the total energy / patient is indicative of a nociceptive habituation effect (gate-control mechanism).

Discussion:

Almost all NIH-CPSI and IIEF scores calculated in the course of the clinical trial were found to have improved, both in the control group and in the experimental group, compared to the individual domain scores determined at baseline. To a certain extent, these improvements may be attributable to a placebo effect and to the selective inclusion of patients into the trial. Moreover, one should also bear in mind that the prostatic massage performed to collect the post-massage urine represents a manual mobilization and visceral manipulation which may have a sustained beneficial effect on the investigated primary and secondary target parameters, as confirmed by various studies conducted in the past few years (FitzGerald, Anderson und Potts 2009) (Marx, et al. 2013).

However, in the experimental group (*shock*), a highly significant improvement beyond the mere placebo effect and the impact of visceral manipulation was determined in all major scores – i.e. primary endpoint: pain score (NIH-CPSI items 1-4); secondary endpoints: urinary symptoms score (NIH-CPSI items 5+6) and quality of life impact score (NIH-CPSI items 7-9). Especially in the pain domain, all patients in the experimental group achieved a longer-term (3 months after completion of treatment) improvement from baseline (mean pain domain score t0=12.10 versus t2=4.37). With this improvement, the total pain score in the experimental group was 4.8 points lower than the pain domain score in the control group.

Furthermore, erectile dysfunction (ED) diagnosed in just over 50% (n=32) of the subjects participating in the clinical trial and its severity (total IIEF score – International Index of Erectile Function) significantly decreased in the experimental group compared to the total score at baseline and to the mean total score in the control group at t2 (*sham*=21.3 versus *shock*=22.3). However, this development should be interpreted with great caution because, firstly, many patients had IIEF scores close to the maximum score even at baseline, and, secondly, the pathoaetiology underlying the erectile dysfunction was not investigated in any of the cases. Consequently, the potential impact of ESWT on erectile dysfunction remains utterly uncertain and we do not know whether the improvement in the total IIEF score may be attributable to the alleviation of pain and the improved quality of life.

Limitations of the clinical trial:

Although, retrospectively, the study design of the clinical trial was very good, patient compliance was exceptionally high (no *missing data*) and treatment of the control group (*sham*) was conducted in full symmetry as far as possible, asymmetry between the experimental group and the control group could not be completely excluded. Patients in the control group did not perceive any pain during the treatment, which meant that pain as a

major determining factor in selecting the dosage – including the sham dosage – could not be used as a reference. Moreover, the primary and secondary domain scores analysed to evaluate the therapy outcome were based on a purely subjective assessment by patients and need to be considered with caution. The only objective parameter – namely the reduction in the leukocyte count in the post-massage urine – could only be used for statistical evaluation in patients with CP type IIIa. Although this parameter was found to have substantially improved in the experimental group compared to the control group, the number of investigated subjects (n=16) was far too low to make a reliable statement concerning the inflammation-induced changes in the organ. The total sample size (n=60) complies with the requirements for a phase IIa/b clinical trial. An advanced trial should now be conducted with a greater sample size to investigate the therapy outcome of ESWT compared to the "therapies recommended" by the European Association of Urology (EAU) and to analyse the cost-effectiveness of the different therapy modalities in terms of a resource-oriented treatment of patients.

Funding and approval:

The clinical trial was funded entirely by the Transfer Institute for Clinical Anatomy of Steinbeis University Berlin (SHB) and approved by the University's Ethics Commission. No third-party funds were provided. The shock wave therapy systems employed in the clinical trial (DUOLITH SD1 and DUOLITH SD1 »ultra«) were made available on a cost-neutral basis by Storz Medical AG based in Tägerwilen (Switzerland).

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