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ORIGINAL ARTICLE

Can low-intensity extracorporeal shockwave therapy improve erectile dysfunction? A prospective, randomized, double-blind, placebo-controlled study

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Abstract

Objective. The aim of this study was to investigate whether low-intensity extracorporeal shockwave therapy (LI-ESWT) can be used as a treatment for men with erectile dysfunction of organic origin. *Materials and methods.* This prospective, randomized, blinded, placebo-controlled study included 112 men unable to have intercourse either with or without medication. Erectile dysfunction was assessed at screening and 5, 12 and 24 weeks after treatment. Assessment was performed by interview and using the Erection Hardness Scale (EHS) and the International Index of Erectile Function (IIEF-15) questionnaire. The men were randomly assigned either to LI-ESWT (n = 51, active group) or placebo (n = 54, placebo group). They received five treatments over 5 weeks. Both the participants and the doctors were blinded to the treatment. After 10 weeks, the placebo group received active treatment (active placebo group). *Results.* Twenty-nine men (57%, active group) were able to obtain an erection after treatment and to have sexual intercourse without the use of medication. In the placebo group, only five men (9%) showed similar results (p = 0.0001). The EHS after 5 weeks showed that men in the active group experienced a significant improvement in their erectile dysfunction, but no significant result was found with the use of the IIEF – Erectile Function domain. *Conclusions.* This placebo-controlled study over 5 weeks shows that 57% of the men who suffered from erectile dysfunction had an effect from LI-ESWT. After 24 weeks, seven (19%, active group) and nine (23%, active placebo group) men were still able to have intercourse without medication. This study shows a possible cure in some patients, but more research, longer follow-up in the placebo group and an international multicentre randomized study are needed.

Keywords:

Erectile dysfunction, extracorporeal shockwave, penis

History

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Introduction

Erectile dysfunction is a male sexual dysfunction defined as a consistent or recurrent inability to attain or maintain an erection sufficient for sexual intercourse [1,2]. Erectile dysfunction is a common disorder of middle-aged men that profoundly affects their quality of life [3,4]. For the past 15 years, oral treatment with phosphodiesterase-5 (PDE-5) inhibitors or intracavernosal injection therapy with vasodilating agents has been the preferred treatment for erectile dysfunction [2].

Extracorporeal shockwave therapy (ESWT) has been used for many years in different fields. In 1980, the clinical use of extracorporeal shockwave lithotripsy as a treatment for stone disease in the upper urinary tract began and proved effective [5–7]. Throughout the years, ESWT has been modified for use in other specialities, such as in the treatment of gallstones, sialolithiasis and Peyronie's disease [8–10]. Animal studies have demonstrated neoangiogenesis in myocardial tissue and skin flaps [11,12], which invites the hypothesis that erectile dysfunction of vascular origin could be treated by ESWT [11–14].

Recent studies have shown promising results of low-intensity extracorporeal shockwave therapy (LI-ESWT) on patients suffering from mild to severe erectile dysfunction [15–17]. A randomized, double-blind, controlled study of men allocated in a two-to-one ratio to LI-ESWT or sham operation showed positive short-term clinical and physiological effects of LI-ESWT on erectile function in PDE-5 inhibitor responders [17].

The aim of the present study was to evaluate LI-ESWT given to men with erectile dysfunction in a one-to-one ratio, and then to investigate and monitor the effects of treatment on erectile function.

Materials and methods

Study population

During the period 2012–2013, 112 men with erectile dysfunction of organic origin who had responded to PDE-5 inhibitors were included in this prospective, randomized, blinded, placebo-controlled study and followed for 5 weeks.

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They had all been referred from general practitioners, were recruited from all over Denmark and participated at their own expense. The inclusion criteria were erectile dysfunction for more than 6 months, an Erection Hardness Score (EHS) less than 2 and an Index of Erectile Function (IIEF-15) score less than 20, age 18–80 years and having been in a stable relationship for more than 3 months. Men with psychogenic erectile dysfunction, neurological pathology, prior radical prostatectomy, rectal extirpation, radiation therapy to the pelvic area and recovery from any cancer within the past 5 years were excluded. Patients with heart disease prohibiting sexual activity or taking medication with antiandrogens were also excluded.

The randomization was done using a computer-generated list with random numbers.

Clinical information

The study was approved by the National Committee on Health Research Ethics and the Danish National Data Protection Agency. All men who met the criteria for participation gave written informed consent before receiving LI-ESWT. Before the first visit, all participants had answered questions about their medical and sexual history. All men were informed that the use of PDE-5 inhibitors was prohibited during the study. There was no washout period before the start of the study. At the first visit, the head urologist went through the IIEF-15 questionnaire and the EHS with every single man to ensure that all participants understood the questionnaires which would be used for later follow-up.

The IIEF-15 patient questionnaire was used to assess the severity of erectile dysfunction. For the calculation, only questions 1, 2, 3, 4, 5 and 15, also known as the International Index of Erectile Function – Erectile Function domain (IIEF-ef domain), were used. A high EHS and a high IIEF-ef domain indicate good erectile function. The treatment success threshold was primarily set at EHS 3–4, which indicated that the men could have intercourse without medication. Furthermore, an increase in IIEF-ef domain score of at least 5 points was used. Assessment of erectile function was performed by interview at screening and thereafter by mail.

Study design

After ensuring that the inclusion criteria had been fulfilled, the men were randomly assigned to either active LI-ESWT treatment (active group) or placebo (placebo group) based on a randomization list that was stored in a sealed envelope. Both the men and the physicians were blinded to the allocation. Knowledge of the contents of the envelope and group assignment was available only to the Head of the Department of Urology, who was responsible for the randomization.

The participants were assessed by EHS and IIEF-ef domain at baseline and at 5 weeks. Ten weeks after study start, men in the placebo group were offered LI-ESWT and the blinded part of the study was terminated. The active placebo group were assessed at 5, 12 and 24 weeks after their treatment.

Treatments took place over a 5 week period and were carried out using a handheld Duolith® SD1 machine (Storz, Tägerwilen, Switzerland) set at 0.15 mJ/mm^2, 5 Hz, with a total of 3000 impulses, and a total energy of 12.8 J per treatment. LI-ESWT was performed in six positions on the penis (distal, centre and proximal part of each corpus cavernosum) and given by a doctor. The cap used to prevent LI-ESWT in the placebo group was positioned by the Head of the Department to ensure blinding. The machine and noise from the machine were the same in the two groups, so that neither the doctor nor the patients would know whether they received active or inactive treatment.

After the treatment each participant was asked about the effects and side-effects.

This set-up had previously demonstrated its effectiveness in a pilot study [18], where 11 (73%) out of 15 men who were treated achieved an effect. The success rate in this study and other studies [15–17] was used to calculate the power and the number of patients needed to treat in order to prove an effect in the present study. With a success rate of 60%, it was calculated that the study needed the inclusion of 80 men with no dropouts and 100 men with a dropout rate of 15% (= 2.4% one-sided, = 20%). The dropout rate in the present study was 6% (seven patients).

Data analysis

The chi-squared test was used to analyse the differences between patient groups. The level of significance for all analyses was $p < 0.05$.

Results

Baseline

In total, 112 participants were enrolled in the study. Seven of these were excluded; three owing to illness which prevented them from receiving treatment and four because they failed to return the questionnaires. After the first 5 weeks two participants from the placebo group stopped because of travel costs.

The median age was 60 years (range 37–80 years). The active group and the placebo group were similar in terms of comorbidities and use of PDE-5 inhibitors, as assessed by the questionnaires ($p = 0.56$) (Table 1).

All patients completed the treatment and none of them had any significant side-effects. In both groups, some patients reported a slight burning sensation shortly after treatment. No skin rashes or haematomas were reported during or after the treatment.

Follow-up

The EHS and the IIEF-ef domain were used to evaluate the participants after they had completed five treatments. In the active group, 29 men (57%) had an EHS of 3–4, which made it possible for them to have full sexual intercourse at 5 weeks of follow-up. Three men (6%) had an EHS of 1–2, and 19 (37%) showed no change in erectile dysfunction. In the placebo group, five men (9%) had an EHS of 3–4, seven (13%) an EHS of 1–2 and 42 (78%) had experienced no change. The difference between the two groups was

Table 1. Patient demographics and comorbidities.

	Active (ESWT) group	Placebo group	p
No. of patients (%)	51 (49)	54 (51)	0.7
Age (years), median (range)	59 (41–80)	60 (37–79)	
ED duration (months), mean (range)	57 (9–240)	64 (12–240)	
Comorbidity[a], *n* (%)	22 (43)	27 (50)	0.56
Diabetes	9 (18)	7 (13)	
Hypertension	17 (33)	20 (37)	
Heart disease	2 (4)	6 (11)	
Alcohol (units/week)	8	9	1.0
Smoker	5	9	0.39
Oral medication for ED (%)	44	47	
Good effect	25 (49)	23 (43)	0.53
Varying effect	9 (18)	9 (17)	1.0
Poor effect	8 (16)	13 (24)	0.33
Side-effects	2 (4)	2 (4)	1.0
No present medication	7 (14)	7 (13)	1.0

ESWT = extracorporeal shockwave therapy; ED = erectile dysfunction.
[a]Some of the patients had more than one comorbidity.

Table 2. Effect of LI-ESWT based on EHS and IIEF-ef domain between the active group and the placebo group at the 5 week follow-up.

	Active (ESWT) group	Placebo group	p
Number of patients (%)	51 (49)	54 (51)	
EHS at 5 weeks, response rate (%)	51 (100)	54 (100)	
0	19 (37)	42 (78)	0.0001
1–2	3 (6)	7 (13)	0.53
3–4	29 (57)	5 (9)	0.0001
IIEF-ef domain score change at 5 weeks (%)	44 (86)	51 (94)	
<5 points	25 (57)	32 (63)	
≥5 points	15 (34)	11 (22)	0.67
≥10 points	4 (9)	8 (16)	

LI-ESWT = low-intensity extracorporeal shockwave therapy; EHS = Erection Hardness Score; IIEF-ef domain = International Index of Erectile Function – Erectile Function domain.

statistically significant at the EHS levels 0 and 3–4 ($p = 0.0001$), but not at the EHS level 1–2 (Table 2).

In the active group, the EHS response rate was 80% at week 12 and 70% at week 24. In the active placebo group, the EHS response rate was 85% at week 12 and 75% at week 24. In the period between weeks 12 and 24, the number of men who achieved an EHS score of 3–4 declined in both groups, from 12 (28%) to seven (19%) in the active group and from 12 (28%) to nine (23%) in the active placebo group (Table 3). There was no significant difference between the two groups in terms of IIEF-ef domain after week 5. The IIEF domain score improved by at least 5 points in 19 men (43.2%) in the active group and in 19 men (37.1%) in the placebo group (Table 2). Compared with baseline IIEF-ef domain scores, 13 men (22%) in the active group had achieved an increase of 5 or more points and 10 men (28%) had achieved an increase of more than 10 points at 12 weeks. At week 24, 12 (32%) still showed scores of 5 or above and six (15%) still showed scores greater than 10 (Table 3). In the active placebo group, a trend towards better results after active treatment was observed at the follow-up in week 5; thus, 14 men (33%) had scores greater than or equal to 5 and 14 men (33%) had achieved an increase of more than 10 points. At week 24, 15 (38%) still showed scores of 5 or above and seven (17%) still showed scores above 10 (Table 3).

Discussion

In this 5 week placebo-controlled study, LI-ESWT helped 57% of patients with erectile dysfunction of organic origin to have intercourse without medication. Worldwide, growing numbers of men are suffering from diseases such as diabetes, hypertension and heart disease, which contribute to the development of erectile dysfunction [4]. For many years, oral treatment with PDE-5 inhibitors, injection therapy with alprostadil, vacuum constriction devices and surgical treatment have been the available treatment methods for erectile dysfunction [1]. However, these treatments do not help patients to achieve spontaneous erection, and the medications are contraindicated in some conditions and may have side-effects. Several studies have therefore investigated other

Table 3. Follow-up data in the active group and the placebo group after both had received extracorporeal shockwave therapy (ESWT).

	Active (ESWT) group	Active placebo group
No. of patients	51	52[a]
EHS at 5 weeks, response rate (%)	51 (100)	52 (100)
0	19 (37)	6 (11)
1–2	3 (6)	18 (35)
3–4	29 (57)	28 (54)
EHS at 12 weeks, response rate (%)	41 (80)	44 (85)
0	7 (18)	5 (11)
1–2	22 (54)	27 (61)
3–4	12 (28)	12 (28)
EHS at 24 weeks, response rate (%)	36 (70)	39 (75)
0	6 (17)	8 (21)
1–2	23 (64)	22 (56)
3–4	7 (19)	9 (23)
IIEF-ef domain score change at 5 weeks, response rate (%)	44 (86)	42 (81)
<5 points	25 (57)	14 (33)
≥5 points	15 (34)	14 (33)
≥10 points	4 (9)	14 (13)
IIEF-ef domain score change at 12 weeks, response rate (%)	46 (90)	45 (86)
<5 points	23 (50)	20 (44)
≥5 points	13 (28)	16 (36)
≥10 points	10 (22)	9 (20)
IIEF-ef domain score change at 24 weeks, response rate (%)	38 (75)	40 (77)
<5 points	20 (53)	18 (45)
≥5 points	12 (32)	15 (38)
≥10 points	6 (15)	7 (17)

Data are shown as *n* (%).
EHS = Erection Hardness Score; ESWT= extracorporeal shockwave treatment; IIEF-ef domain = International Index of Erectile Function – Erectile Function domain.
[a]Two dropouts due to travel costs.

treatment modalities for erectile dysfunction, such as LI-ESWT, which is a promising new, minimally invasive method with almost no side-effects [14–19].

Before the present study was undertaken, a pilot study was performed in which a group of 15 men followed the same protocol. After treatment, 11 of these men (73%) were able to have intercourse without medication [18]. In four men (27%), the improvement in erectile function was maintained after 24 months. The benefit of LI-ESWT has previously been demonstrated in a randomized, double-blind, sham-controlled study which, however, used another machine and treatment interval [15]. The present study used shockwaves generated electromagnetically and the men attended one session per week for 5 weeks. The Vardi group [15] used shockwaves generated by an electrohydraulic unit, and the waves were delivered using a broader probe than the one used in the present study. In the study by Vardi, two treatment sessions were given per week for 3 weeks, the treatments were repeated after a 3 week treatment-free interval, and the probe was applied to the same places on the penis as well as to the crura [15]. In an open-label, single-arm prospective study, Vardi and co-workers [16] showed a 50% improvement in achieving erection without any PDE-5 inhibitors at 6 months of follow-up. The present study and the studies by Vardi [15,16] are not completely comparable owing to differences in the number of patients, treatment sites (Vardi includes treatment of the crura), probe sizes (much larger probe used by the Vardi group), total number of treatments (the Vardi group used 12 treatments) and machines, as explained above.

The outcome was determined by the use of the IIEF-ef domain and EHS. The IIEF-15 has been validated in Denmark but the EHS has not. At the 5 week follow-up, 57% of the patients receiving ESWT had an EHS greater than 2, which is sufficient for full sexual intercourse ($p < 0.05$). However, there was a fall in EHS at the 24 week follow-up, where 28% still had a score greater than 2. This could indicate a need for possible follow-up treatments. Some of the patients improved their score, but not enough for full sexual intercourse. It is likely that some patients require a larger number of treatments, possibly a higher dose of therapy or a combination with medication to achieve sufficient results. Further studies are needed in this field. Unfortunately, this study did not demonstrate a treatment benefit as expressed in a higher IIEF-ef domain score. Considering the treatment success threshold, the results are not significant. However, a positive effect was found in about 20% of the treated men over the 24 weeks of follow-up. The participants seemed to have some problems understanding the questionnaires, even after being instructed by a doctor on the first day of inclusion. It was the IIEF-15 that caused problems, which became clear when the researchers calculated the results and talked to the participants. However, when seeing the results of the EHS, which clearly show EHS 3–4 in 57% of the active group at week 5 and 19% at week 24, and knowing that the starting values of EHS were below 0–2, something had clearly changed for these men. Further randomized, placebo-controlled studies are needed in this area, and attention should be given to the questionnaires and the interviews to ensure that the results reflect the participants' outcomes in their most accurate forms.

One limitation of this study is the lack of penile haemodynamic or other objective measurements, but another study has shown that ESWT exerts a genuine effect on the erectile mechanism by improving penile blood flow [17]. Another limitation is the lack of a fully blinded 24 week follow-up. However, previous studies have shown that there was no change in the placebo group in terms of clinical situation or questionnaire scores [17]. When an interim analysis was performed after 10 weeks, men in the placebo group were promised that if there was an effect in the active treatment group, they would also be offered active treatment.

The strength of the present study is that it is a prospective, randomized study for which motivated men were recruited from different social strata with no racial variation.

The effect of LI-ESWT on erectile dysfunction has not been clearly determined. The basis for its use as a treatment for erectile dysfunction is the notion that it could induce the release of endothelial nitric oxide synthase, vascular endothelial growth factors and proliferating cell nuclear antigen and thus enhance neovascularization. Research suggests that neovascularization has been achieved within the field of cardiology [19]. Studies of these factors in erectile dysfunction are still pending. Studies have shown partial improvement of erectile dysfunction in a diabetic rat model treated with ESWT or stem cells [13,20], and neoangiogenesis in corpora cavernosa in normal rats and diabetic rats treated with ESWT compared with controls [13].

In conclusion, this study has shown that 57% of patients with erectile dysfunction of organic origin had an effect from LI-ESWT after 5 weeks. After 24 weeks, seven men (19%) in the active group and nine (23%) in the active placebo group) were still able to have intercourse without medication. The study showed the same response in the placebo group when this group was treated with active LI-ESWT. The treatment is patient friendly, has no side-effects requiring treatment and can be used for all patients. The present study underlines that there is a need for further research and randomized, international and multicentre studies in this area.

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