Scandinavian Journal of Urology

ISSN: 2168-1805 (Print) 2168-1813 (Online) Journal homepage: http://www.tandfonline.com/loi/isju20

Low-intensity extracorporeal shockwave therapy in the treatment of postprostatectomy erectile dysfunction: a pilot study

Anders Frey, Jens Sønksen & Mikkel Fode

To cite this article: Anders Frey, Jens Sønksen & Mikkel Fode (2016) Low-intensity extracorporeal shockwave therapy in the treatment of postprostatectomy erectile dysfunction: a pilot study, Scandinavian Journal of Urology, 50:2, 123-127, DOI: 10.3109/21681805.2015.1100675

To link to this article: http://dx.doi.org/10.3109/21681805.2015.1100675

SCANDINAVIAN JOURNAL OF UROLOGY, 2016
VOL. 50, NO. 2, 123–127
http://dx.doi.org/10.3109/21681805.2015.1100675

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

Low-intensity extracorporeal shockwave therapy in the treatment of postprostatectomy erectile dysfunction: a pilot study

Anders Frey, Jens Sønksen and Mikkel Fode

Department of Urology, Herlev University Hospital, Copenhagen, Denmark

ABSTRACT

Objective: The objective was to investigate the effect and feasibility of low-intensity extracorporeal shockwave therapy (LI-ESWT) as a treatment for erectile dysfunction (ED) after bilateral nerve-sparing radical prostatectomy (RP). *Materials and methods*: Patients who had undergone robot-assisted bilateral nerve-sparing RP more than a year before entering this pilot study, had no preoperative ED and were suffering from mild to severe postoperative ED were invited to participate. Six treatments were given over a 6 week period, using the Duolith® SD1 T-Top machine. The effect of the treatment was evaluated 1 month (t1) and 1 year (t2) after the final treatment. The main outcome measure was changes in the five-item International Index of Erectile Function (IIEF-5) scores. *Results*: Eighteen patients were included in the study. However, two patients breached the protocol and consequently 16 patients were included in the analysis at t1 and 15 patients were included in the analysis at t2. At baseline the median age was 62 years (range 51 to 70 years) and the median time since surgery was 24 months (range 12 to 54 months). The median preoperative IIEF-5 score was 25 (range 22 to 25) and the median baseline IIEF-5 score was 9.5 (range 5 to 20). The median change in IIEF-5 scores was +3.5 (range −1 to 8; $p = 0.0049$) and +1 (range −3 to 14; $p = 0.046$) at t1 and t2, respectively. No severe side-effects were reported. *Conclusions*: LI-ESWT may improve erectile function after bilateral nerve-sparing RP. Based on these results, further studies in patients with ED after nerve-sparing RP are justified.

ARTICLE HISTORY
Received 5 May 2015
Revised 3 August 2015
Accepted 22 September 2015

KEYWORDS
Erectile dysfunction, extracorporeal shockwave therapy, radical prostatectomy

Introduction

Erectile dysfunction (ED) is a common side-effect after radical prostatectomy (RP), even with nerve-sparing techniques [1]. In cases where the nerves are spared, the mechanism of action is thought to be a temporary postoperative block of transmission in the cavernous nerves caused by direct trauma, stretching, heating, ischemia and local inflammation [2,3]. As functioning nerves are necessary for erections, while erections are necessary for adequate penile oxygenation, this means that the penile tissue is in a constant state of low oxygen supply during the time with nerve dysfunction [4]. This may, in turn, lead to smooth muscle apoptosis and fibrosis, which cause long-term ED [5–7]. Several symptomatic ED treatments are available; however, the loss of impulsivity in sexual relations and the cost associated with these treatments are perceived as a problem by many patients [8]. This may be especially pronounced in postprostatectomy ED as the loss of sexual function comes from one day to another. Therefore, a treatment with prolonged effect and with the potential to render additional treatments superfluous is highly desirable.

Several studies have shown that low-intensity extracorporeal shockwave therapy (LI-ESWT) may represent such a treatment in non-neurogenic ED [9–13]. Meanwhile, animal studies have found that LI-ESWT may increase the rate of blood flow and regenerate nervous tissue when applied to myocardial tissue, random-pattern skin flaps and penile tissue [14–17]. This means that the treatment could theoretically ameliorate the structural changes induced following nerve-sparing RP. However, no clinical evidence of such an effect is currently available.

The aim of this pilot study was to investigate the effect and feasibility of LI-ESWT as a treatment for ED in a group of bilaterally nerve-spared RP patients.

Materials and methods

All patients in this study had undergone robot-assisted bilateral nerve-sparing RP, at Herlev University Hospital, at least 1 year before inclusion. The study was initiated in October 2012. Patients were invited to participate via telephone and received written information on the treatment. All patients provided oral consent before the first treatment. Erectile function before RP had been assessed with the five-item International Index of Erectile Function (IIEF-5) questionnaire, which provides a score between 5 and 25 [18]. Erectile function (baseline function) was assessed again before inclusion using the IIEF-5 questionnaire. In addition, patients were asked to document their use of erectogenic aids and urged not to alter their use of these while they were included in the study. Patients with a preoperative IIEF-5 score greater than 22 and an IIEF-5 score between 5 and 20 (with or without erectogenic aids)

CONTACT Anders Frey freyen60@gmail.com Department of Urology, H54F1, Herlev Hospital, Herlev ringvej 75, DK-2730 Herlev, Denmark

at inclusion were eligible for the study. Exclusion criteria included the LI-ESWT contraindications as stated by the manufacturer; hemophilia, anticoagulant therapy other than acetylic salicylic acid, a high risk of thrombosis, active cancer and systemic glucocorticoid therapy less than 6 weeks before LI-ESWT [19]. Patients were risk stratified using the D'Amico classification [20].

The treatments were performed with the Duolith® SD1 T-Top (Storz Medical, Tägerwilen, Switzerland). This machine uses an electromagnetic system to generate shockwaves, which are then focused with a parabolic reflector to an energy maximum inside the tissue. A water-based gel was used to ensure conductivity. In accordance with recommendations from the manufacturer, all patients were scheduled to receive two LI-ESWT sessions every other week for a period of 6 weeks. Each treatment session consisted of 3000 shockwaves applied to the penis with a frequency of 5 Hz in doses of 1000 shockwaves with energy densities of 20 mJ/mm^2, 15 mJ/mm^2 and 12 mJ/mm^2, applied to the root of the penis, to the shaft, and at a few millimeters proximal to the glans, respectively. Before each treatment, patients were asked if they had experienced any side-effects since the previous consultation and they were encouraged to verbalize any discomfort during sessions. In addition, all patients were instructed to contact the research team if they experienced any side-effects during the periods between treatments. Erectile function was evaluated at 1 month (t1) and again at 1 year (t2) after the last treatment session. On both occasions, patients were required to document their recent use of erectogenic aids. Patients were excluded from the analysis if they reported *de novo* use of any type of erectogenic aid during the course of this study.

Since the data was not normally distributed a Wilcoxon's signed-rank test was used to evaluate changes in IIEF-5 scores. A two-sided p value of 0.05 was considered statistically significant. As the SD for the IIEF-5 changes was unknown before the study, it was not possible to perform a standard power analysis. Instead a *post hoc* power calculation was performed based on the preliminary results and a minimal clinically relevant IIEF-5 change of 4 points. All statistical analyses were performed with R statistical software (R Foundation for Statistical Computing, 2013) [21].

All participants provided informed consent and the study was approved by the Danish data protection agency (reference no. HEH.750.19-32) in accordance with Danish law.

The main outcome measure was changes in IIEF-5 scores. Changes in IIEF-5 categories, as defined in Table 1, and a global satisfaction question ranging from "very dissatisfied" to "very satisfied", served as secondary outcome measures.

Results

Eighteen patients were included in the study. Two patients had *de novo* use of erectogenic aids at t1 and consequently a total of 16 patients was included in the analysis at t1. At t2, one patient was lost to follow-up.

At baseline, the median age was 62 years (range 51 to 70 years) and the median time since surgery was 24 months (range 12 to 54 months). According to the D'Amico classification, nine patients were treated for a low-risk prostate cancer, eight patients were treated for an intermediate-risk prostate cancer and one patient was treated for a high-risk prostate cancer. The median preoperative IIEF-5 score was 25 (range 22 to 25). The median baseline IIEF-5 score was 9.5 (range 5 to 20), with one patient using the "medicated urethral system for erections" (MUSE) and 11 using phosphodiesterase-5 inhibitors (PDE5i). At t1, the median change in IIEF-5 scores was +3.5 ($n = 16$; IQR = 4.25; SD = 2.66; $p = 0.0049$). At t2, the median change from baseline IIEF-5 scores was +1 ($n = 15$; IQR = 3.5; SD = 2.46; $p = 0.046$) (Figure 1). At t1 and t2, 11 and seven patients, respectively, reported being either satisfied or very satisfied with the treatment.

A total of seven patients improved their ED category between baseline and t1. The improvements were maintained in four of these patients at t2. One patient showed a decline in ED category between baseline and t2. However, he also terminated his use of on-demand tadalafil. One patient terminated his use of MUSE and another patient terminated his on-demand tadalafil at t1. The first maintained an increase in ED category at both t1 and t2, while the latter suffered severe ED at all time-points. At t2, three patients had discontinued their use of erectogenic aids. Two of these maintained their initial ED category and one maintained an increase in ED category. Detailed results of changes in ED categories are provided in Table 1.

Table 1. Changes in erectile function (ED) categories.

Patient no.	ED category (baseline)	ED category (t1)	ED category (t2)
1	Severe	Severe	Severe
2	Severe	Severe	Severe
3	Severe	Mild to moderate	NA
4	Moderate	Mild to moderate	Moderate
5	Moderate	Moderate	Mild to moderate
6	Mild	Mild	Mild
7	Mild	No ED	No ED
8	Severe	Severe	Severe
9	Severe	Moderate	Moderate
10	Moderate	Moderate	Moderate
11	Moderate	Moderate	Severe
12	Moderate	Mild to moderate	No ED
13	Mild to moderate	Mild	Mild
14	Mild	Mild	Mild
15	Mild	Mild	Mild
16	Moderate	Mild to moderate	Moderate

NA = not applicable.

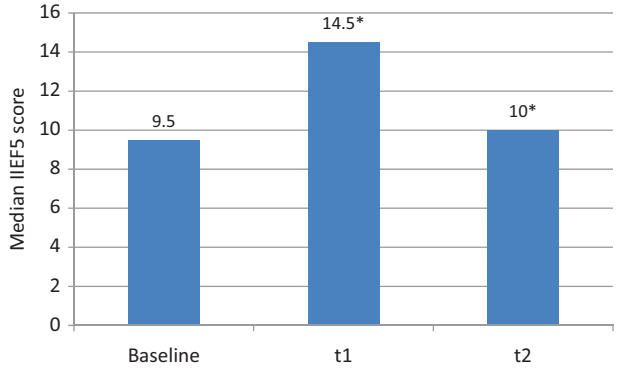

Figure 1. Median changes in International Index of Erectile Function-5 (IIEF5) scores. *$p < 0.05$.

A few patients described mild pain when the shockwave got close to the urethra during LI-ESWT. In addition, one patient experienced light soreness of the penis in the first days following each treatment. None of the reported side-effects required treatment of any kind and none of the patients decided to terminate the treatment.

The *post hoc* power analysis showed that only seven patients were needed in order to obtain a power of 90% to detect a difference of 4 points on the IIEF-5 questionnaire at t1.

Discussion

This study represents the first attempt to treat ED following bilateral nerve sparing RP with LI-ESWT. The researchers were able to demonstrate a significant improvement in IIEF-5 scores 1 month after treatment despite the fact that three patients had terminated their use of erectogenic aids. Improved erectile function was observed regardless of ED category at baseline. At 1 year following treatment, the median IIEF-5 score remained statistically significant even though three more patients had terminated their use of erectogenic aids and one of the initial responders was lost to follow-up. The treatment was found to be safe and to cause minimal discomfort for the patients.

As described in the Introduction, ED is a common side-effect of RP, probably owing to structural changes in nerves and penile tissue. Ongoing efforts to improve nerve sparing have not yet resolved the problem [1]. Moreover, attempts at restoring spontaneous erections through scheduled post-operative treatment with erectogenic aids – so-called ''penile rehabilitation'' – have generally been disappointing [22]. This means that current treatments for post-RP ED are symptomatic, in the form of PDE5i, vacuum erection devices, MUSE, injection therapies and penile implants.

The potential mechanism of action for LI-ESWT in the treatment of ED is unknown, but based on the current literature it is hypothesized that the shockwaves trigger cellular pathways which increase the expression of growth factors and endothelial nitric oxide synthase, resulting in subsequent angiogenesis and regeneration of nerve fibers [23–25]. Regarding penile tissue, studies in a streptozotocin-induced diabetic rat model have shown that LI-ESWT can have a regenerative effect on both the endothelia and the nitric oxide synthase-producing nerve fibers in the corpus cavernosum [14,15]. Although these findings have yet to be reproduced in clinical trials, this could offer an explanation for the increase in erectile function observed with the treatment.

However, when considering the use of LI-ESWT, one must keep in mind that the treatment is relatively time consuming for both the patient and the practitioner. Depending on the time spent on commuting to the hospital, it was estimated that each patient spent a combined 8–12 h on receiving the treatment. This is only justifiable if LI-ESWT provides a clinically significant and sustained improvement in erectile function. Therefore, it is important to note that only two patients were categorized as having no ED after LI-ESWT and that the majority of patients achieved only marginal improvements in ED category that would still require them to use erectogenic aids to engage in intercourse. In this regard, previous studies investigating the effects of LI-ESWT in patients with non-neurogenic ED have shown conflicting results [9–13].

On the positive side, Vardi and co-workers have published results from two studies investigating the effects of LI-ESWT in men with organic ED who were responders to PDE5i before inclusion. The first was a pilot study in 20 patients, who showed improvements in both total IIEF scores and IIEF ED domain scores ($p < 0.001$ for both) 1 month after the final treatment [10]. A subsequent randomized trial in 67 men receiving either LI-ESWT or a sham treatment showed significantly greater improvements in IIEF ED domain scores in the treatment group compared to the sham group (6.7 vs 3.0; $p = 0.032$). In addition, improvements were observed in penile hemodynamics in the treatment group [11]. Another study by the same group investigated the effects of LI-ESWT in 29 PDE5i non-responders with a mean baseline IIEF ED domain score of 8.8. Here, an increase in mean IIEF ED domain scores to 12.3 along with an increase in maximal penile blood flow was observed ($p < 0.0001$ for both). When patients were allowed to use PDE5i for a month after the first follow-up, IIEF ED domain scores increased substantially to 18.8 [9].

However, when Yee and co-workers randomized 58 patients with organic ED to either sham treatment or LI-ESWT following a similar protocol, no differences were found in either IIEF-5 scores or erection hardness scale scores. In a subgroup analysis, the investigators found significant changes in IIEF-5 scores for patients with severe ED at baseline ($p = 0.001$). Unfortunately, it is unclear whether the patients were still on their ED medication [12].

The previously discussed studies all used the Omnispec® ED1000 (Medispec, Yehud, Israel). Meanwhile, a recent study by Olsen and colleagues used the Duolith SD1 T-Top, as in the present study. They included 105 patients and randomized them to either LI-ESWT or sham therapy. Five weeks after the final treatment, no difference in IIEF ED domain score changes was observed between the groups. However, on the erection hardness scale questionnaire significantly more patients in the LI-ESWT group had improved their scores to 3 or 4 (erections hard enough for penetration) ($p = 0.0001$) [13].

The Omnispec ED1000 and the Duolith SD1 T-Top use the same technique to generate the shockwaves. However, based on the studies, it remains unclear whether there are clinically significant differences between the machines. This issue will need to be resolved with a head-to-head study. Likewise, no studies have investigated whether there is a dose dependency when treating ED with LI-ESWT, and energy densities are primarily based on the patients' expected pain tolerance and follow recommendations from the manufacturer. It is possible that more treatment sessions or higher energy densities could result in better outcomes. Based on the results of this study, this may be especially relevant in post-RP patients.

Major weaknesses of this study include the use of erectogenic aids in the study population, the lack of a control group and the small patient cohort. It would have been preferable to restrict all use of erectogenic aids during the study period. However, since most patients where dependent on these treatments for erections at baseline, it would not be

ethically justifiable to inflict a potential significant negative impact on their sexual capabilities for a pilot study. With regard to the missing control group, it is important to keep in mind that the study was planned as a pilot study with the intent of assessing a possible treatment effect. As such, it would have been premature to perform a randomized trial. In addition, it would have been difficult to interpret a comparison with a simple no-treatment group as men opting for LI-ESWT are likely to be more motivated for sexual activity than those who are not interested in the treatment. When considering a possible placebo effect, a study by Montorsi et al. investigating the effects of PDE5i in RP patients found that this resulted in a 1 point increase in the IIEF-ED domain [26]. Thus, this is unlikely to account for the entire effect in the present study. For the purpose of this study, all patients had to be beyond the first year after their RP. This measure was taken to ensure that patients were at a steady state with regard to their erectile capabilities. However, there was a substantial spread in time since surgery between patients and it is possible that applying LI-ESWT at an earlier stage after the surgery could prevent penile fibrosis caused by long-term hypoxia from missing erections. Finally, with regard to the study size, the *post hoc* power analysis showed that the study was large enough to detect a relevant change in IIEF-5 score. This power analysis may not apply in the randomized controlled trial setting, where the number of subjects needed would be greater.

In conclusion, LI-ESWT may improve erectile function after bilateral nerve-sparing RP; however, the improvements did not allow for unassisted erections sufficient for intercourse in most patients. Based on the results, further studies in patients with ED after nerve-sparing RP are justified. Such studies should explore intensified treatment protocols and focus on clinically relevant outcomes. With the current level of evidence, LI-ESWT should be performed only for research purposes following RP.

Acknowledgements

The Duolith® SD1 T-Top was kindly put at our disposal by Storz Medical.

Declaration of interest

Jens Sønksen is a speaker for Eli Lilly, Coloplast and Astellas, a shareholder for Multicept, and acts as an advisory board member for Eli Lilly, Astellas and Menarini. Mikkel Fode is a speaker for Eli Lilly, Coloplast and Astellas, and acts as an advisory board member for Eli Lilly and Menarini.

References

1. Tal R, Alphs HH, Krebs P, Nelson CJ, Mulhall JP. Erectile function recovery rate after radical prostatectomy: a meta-analysis. J Sex Med 2009;6:2538–46.
2. Masterson TA, Serio AM, Mulhall JP, Vickers AJ, Eastham JA. Modified technique for neurovascular bundle preservation during radical prostatectomy: association between technique and recovery of erectile function. BJU Int 2008;101:1217–22.
3. Burnett AL. Rationale for cavernous nerve restorative therapy to preserve erectile function after radical prostatectomy. Urology 2003;61:491–7.
4. Kim N, Vardi Y, Padma-Nathan H, Daley J, Goldstein I, Saenz de Tejada I. Oxygen tension regulates the nitric oxide pathway. Physiological role in penile erection. J Clin Invest 1993;91:437–42.
5. Moreland RB. Is there a role of hypoxemia in penile fibrosis: a viewpoint presented to the Society for the Study of Impotence. Int J Impot Res 1998;10:113–20.
6. Iacono F, Giannella R, Somma P, Manno G, Fusco F, Mirone V. Histological alterations in cavernous tissue after radical prostatectomy. J Urol 2005;173:1673–6.
7. Mulhall JP, Slovick R, Hotaling J, Aviv N, Valenzuela R, Waters WB, et al. Erectile dysfunction after radical prostatectomy: hemodynamic profiles and their correlation with the recovery of erectile function. J Urol 2002;167:1371–5.
8. Hedelin H, Stroberg P. Treatment for erectile dysfunction based on patient-reported outcomes: to every man the PDE5 inhibitor that he finds superior. Drugs 2005;65:2245–51.
9. Gruenwald I, Appel B, Vardi Y. Low-intensity extracorporeal shock wave therapy – a novel effective treatment for erectile dysfunction in severe ED patients who respond poorly to PDE5 inhibitor therapy. J Sex Med 2012;9:259–64.
10. Vardi Y, Appel B, Jacob G, Massarwi O, Gruenwald I. Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. Eur Urol 2010;58:243–8.
11. Vardi Y, Appel B, Kilchevsky A, Gruenwald I. Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. J Urol 2012;187:1769–75.
12. Yee CH, Chan ES, Hou SS, Ng CF. Extracorporeal shockwave therapy in the treatment of erectile dysfunction: a prospective, randomized, double-blinded, placebo controlled study. Int J Urol 2014;21:1041–5.
13. Olsen AB, Persiani M, Boie S, Hanna M, Lund L. Can low-intensity extracorporeal shockwave therapy improve erectile dysfunction? A prospective, randomized, double-blind, placebo-controlled study. Scand J Urol 2015;49:329–33.
14. Qiu X, Lin G, Xin Z, Ferretti L, Zhang H, Lue TF, et al. Effects of low-energy shockwave therapy on the erectile function and tissue of a diabetic rat model. J Sex Med 2013;10:738–46.
15. Liu J, Zhou F, Li GY, Wang L, Li HX, Bai GY, et al. Evaluation of the effect of different doses of low energy shock wave therapy on the erectile function of streptozotocin (STZ)-induced diabetic rats. Int J Mol Sci 2013;14:10661–73.
16. Nishida T, Shimokawa H, Oi K, Tatewaki H, Uwatoku T, Abe K, et al. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. Circulation 2004;110:3055–61.
17. Yan X, Zeng B, Chai Y, Luo C, Li X. Improvement of blood flow, expression of nitric oxide, and vascular endothelial growth factor by low-energy shockwave therapy in random-pattern skin flap model. Ann Plast Surg 2008;61:646–53.
18. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 1999;11:319–26.
19. Storz Medical. Duolith SD1 T-Top user manual. Tägerwilen, Switzerland: Storz Medical; 2009.
20. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969–74.
21. R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2011.
22. Fode M, Ohl DA, Ralph D, Sonksen J. Penile rehabilitation after radical prostatectomy: what the evidence really says. BJU Int 2013; 112:998–1008.
23. Wang CJ, Kuo YR, Wu RW, Liu RT, Hsu CS, Wang FS, et al. Extracorporeal shockwave treatment for chronic diabetic foot ulcers. J Surg Res 2009;152:96–103.
24. Nurzynska D, Di MF, Castaldo C, Arcucci A, Marlinghaus E, Russo S, et al. Shock waves activate in vitro cultured progenitors and precursors of cardiac cell lineages from the human heart. Ultrasound Med Biol 2008;34:334–42.

25. Aicher A, Heeschen C, Sasaki K, Urbich C, Zeiher AM, Dimmeler S. Low-energy shock wave for enhancing recruitment of endothelial progenitor cells: a new modality to increase efficacy of cell therapy in chronic hind limb ischemia. Circulation 2006;114:2823–30.

26. Montorsi F, Nathan HP, McCullough A, Brock GB, Broderick G, Ahuja S, et al. Tadalafil in the treatment of erectile dysfunction following bilateral nerve sparing radical retropubic prostatectomy: a randomized, double-blind, placebo controlled trial. J Urol 2004;172:1036–41.