DE GRUYTER OPEN

J Biomed Clin Res Volume 10 Number 2, 2017

DOI: 10.1515/jbcr-2017-0017

Original Articles

LOW-INTENSITY EXTRACORPOREAL SHOCKWAVE THERAPY – A NEW APPROACH IN THE TREATMENT OF ERECTILE DYSFUNCTION AFTER RADICAL PROSTATECTOMY

Boyan A. Stoykov,
Nikolay H. Kolev,
Rumen P.Kotsev,
Fahd Al-Shargabi,
Pencho P. Genov[1],
Aleksandar Vanov,
Jitian A. Atanasov,
Manish Sachdeva,
Pencho T. Tonchev[2],
Maria I. Koleva[3]

Department of Surgical Nursing, Medical University – Pleven, Bulgaria
[1]Department of Urology, UMHAT – Ruse, Bulgaria
[2]Department of Surgery, Medical University – Pleven, Bulgaria
[3]Clinic Physiomed, Pleven, Bulgaria

Corresponding Author:
Boyan A. Stoykov
Department of Surgical Nursing,
Medical University – Pleven
1, St. Kl. Ohridski Str.
Pleven, 5800
Bulgaria
e-mail: atanasovmd@yahoo.com

Received: June 15, 2017
Revision received: June 26, 2017
Accepted: February 27, 2018

Summary

The experience accumulated with low-intensity extracorporeal shock wave therapy (LI-ESWT) from international clinical trials has demonstrated its safety, efficacy and good tolerance in treatment of erectile dysfunction (ED). The aim of this retrospective study was to investigate the effect of LI-ESWT in patients with ED after bilateral nerve sparing radical surgery for prostate cancer. Twenty-seven patients underwent bilateral nerve sparing radical retropubic prostatectomy (BNSRRP) at the clinic of urology of the university hospital in Pleven between January 2016 and December 2016. Twenty-one of these patients had pre-operative preserved erectile function (EF), as reported according to the International Index of Erectile Function (IIEF-5). Postoperatively, these 21 patients experienced a mild (18-21 points) impairment of EF. In 10 patients (group 1), LI-ESWT was performed. The procedure was performed once a week for 6 weeks with a LI-ESWT (BTL 6000 SWT Topline) instrument. The reading was obtained with IIEF-5 on the third and sixth month after the end of therapy. The other 11 patients (group 2) were used as a control group and did not receive treatment. In 5 patients in group 1, a recovery of EF (> 21 points) as per IIEF-5 was recorded at the third month after treatment. In two patients, the same score was recorded at the sixth month. No improvement was seen in three men in group 1. In the controls (group 2), a spontaneous EF improvement in four patients at sixth month was registered. Despite the small number of patients and their short-term follow-up, our initial results indicate that LI-ESWT is effective, safe and well-tolerated. It could be an alternative for early penis rehabilitation in patients who have undergone BNSRRP.

Key words: erectile function, erectile dysfunction, low intensity extracorporeal shock wave therapy, bilateral nerve sparing radical retropubic prostatectomy

Introduction

Currently, the most widely used agents for the treatment of erectile dysfunction (ED) after radical prostatectomy (RP) are 5-phosphodiesterase inhibitors [1, 2]. Despite their indisputable effectiveness, these drugs cannot correct any changes that have occurred in the pathophysiology of the penis after the RP [3, 4]. This calls for finding new methods for recovering erectile function (EF) in these patients. As such, in the

recent years, wave therapy has emerged. The shock wave is a type of acoustic wave that carries certain energy and, depending on its strength, can cause destruction or stimulation of regenerative processes in tissues [5]. Mechanical transduction in soft tissues causes a cascade of biological responses [6], leading to synthesis of nitric oxide (NO) [7] on the one hand, and stimulating vascular endothelial growth factors, on the other hand. These factors cause neovascularization with subsequent improvement in blood circulation. Extracorporeal shock wave therapy was first applied in 1980 for kidney stone lithotripsy [8]. Since then, this method has been rapidly evolving, with developing devices for low-intensity extracorporeal shock wave therapy (LI-ESWT). The technique is used for treatment of musculoskeletal disorders [9], myocardial infarction [10], coronary heart disease [11], difficult wound healing [12], diabetic nephropathy [13], Peyronie's disease [14], ED [15], and others.

The purpose of this retrospective study was to establish the efficacy and safety of LI-ESWT in patients with ED after bilateral nerve sparing radical surgery for prostate cancer.

Materials and Methods

Twenty-seven patients underwent bilateral nerve sparing radical retropubic prostatectomy (BNSRRP) in the clinic of urology at the university hospital in Pleven from January 2016 to December 2016. Of these patients, only 21 had pre-operative normal EF (average 22.3 points), reported with International Index of Erectile Function (IIEF-5). According to IIEF-5, 22-25 points indicate no ED, 17-21 points – mild ED, 12-16 points – mild to moderate ED, 8-11 points – moderate ED, and 5-7 points – severe ED.

Patients were randomly selected and divided into two groups. In group 1, consisting of 10 patients, four patients had normal EF (25 points), three patients scored 24 points, two patients scored 2 points and one patient – 1 point. All participants in this group underwent LI-ESWT. In group 2, consisting of 11 patients, four patients had normal EF (25 points), three patients scored 24 points, two patients – 2 points, and two patients – 1 point. In this group, patients did not receive treatment and were used as a control group. The distribution of patients by groups and by the number of IIEF-5 points is presented in Table 1.

Table 1. Distribution of patients in groups according to number of points as per IIEF-5

Points (IIEF)	Total number of patients	Number of patients Group 1	Number of patients Group 2
25	8	4	4
24	6	3	3
23	4	2	2
22	3	1	2

The procedures were performed from the 30th postoperative day, once a week for six weeks. On the first visit, blood sugar and lipid profile were studied. At each visit, a physical examination was performed and side effects were monitored. The readings were obtained with IIEF-5 on the third and sixth month after the end of therapy. The detailed design of the study is shown in Table 2.

LI-ESWT was performed using a BTL 6000 SWT Topline apparatus with a pressure of 1.5 bar and a frequency of 12 Hz. LI-ESWT was applied on 5 places on the penis: in the proximal, medial and distal part on the dorsal surface of the penis, as well as the left and right base of the cavernous body, the penis being in a stretched position. Each point was targeted with 600 beats, a total of 3000 beats per procedure. All procedures were performed without anaesthesia in outpatient settings. Throughout the study period, patients did not use drugs that could affect their sexual function and were encouraged to maintain their normal sexual habits. The results were obtained with IIEF-5 on the third month and on the sixth month after the end of therapy.

The average age of patients was 65 years (54-71). Patients were followed for 24 weeks, and no patients dropped out of the study. Five patients had arterial hypertension, four had diabetes mellitus, three were found with dyslipidemia,

Table 2. Study design

Study design	Visit-1 1 week	Visit-2 2 week	Visit-3 3 week	Visit-4 4 week	Visit-5 5 week	Visit-6 6 week	Visit-7 after 3 months	Visit-8 after 6 months
Medical history	+	-	-	-	-	-	-	-
Physical examination	+	+	+	+	+	+	+	+
IIEF-5	+	-	-	-	-	-	+	+
Therapy	+	+	+	+	+	+	-	-
Adverse effects	+	+	+	+	+	+	+	+

+ Registered review; - Unregistered review

four had coronary heart disease and nine were smokers (up to 10 cigarettes per day).

Results

In group one, recovery of EF measured with IIEF-5 was registered in 70% of the patients, with an average score of 24 points: three patients scored 25 points, two patients – 24 points, one patient – 23 points and one patient – 22 points. In group two, recovery was registered in 44% of the patients, with a score of 23 points on the average, no patients with 25 points, one patient with 24 points, two patients with 23 points and one patient with 22 points. No adverse reactions were observed in either group. The distribution of patients by the number of IIEF-5 points and concomitant illnesses is presented in Table 3.

At the first visit (post-operative day 30), the average IIEF-5 score was 18 points in the patients in group 1. The response to treatment as per IIEF-5 was 19 points, and 17 points for non-responders. After 3 months, the average score of IIEF-5 was 21 points. Patients who responded to treatment scored 22 points, and non-responders – 19 points. After 6 months, the average score as per IIEF-5 was 23 points. Treatment responders had an average score of 24 points, and the non-responders – 20 points. The distribution of patients in group 1 according to IIEF-5 is shown in Figure 1.

Table 3. Distribution of patients by IIEF-5 score and concomitant illness

Patients	Recovery of EF in Group 1	Recovery of EF in Group 2
Number of patients	7	4
Average age	63.5	64
Age range	54-69	56-71
Follow up (weeks)	24	24
Diseases carrying risk	**Number of patients**	**Number of patients**
Hypertension	3 (43%)	2 (50%)
Diabetes type II	2 (29%)	2 (50%)
Hyperlipidemia	2 (29%)	1 (25%)
Coronary heart disease	3 (43%)	1 (25%)
Smoking	5	4
Points (IIEF)	**Number of patients**	**Number of patients**
25	3	0
24	2	1
23	1	2
22	1	1

As for group 2 patients, the average score

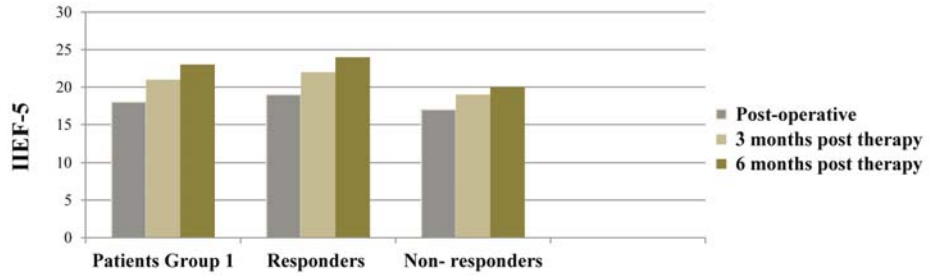

Figure 1. Distribution of patients in group 1 according to IIEF-5

of IIEF-5 was 18 points on post-operative day 30. As per IIEF-5, patients who responded to treatment scored 20 points and non-responders scored 17 points. After 3 months, the average score as per IIEF-5 was 20 points. Responders scored 21 points and non-responders – 19 points. After 6 months, the average score of IIEF-5 was 21 points and in patient responding to treatment, the average of IIEF-5 was 23 points, and in non-responders it was 20 points. The distribution of IIEF of patients in group 2 is shown in Figure 2.

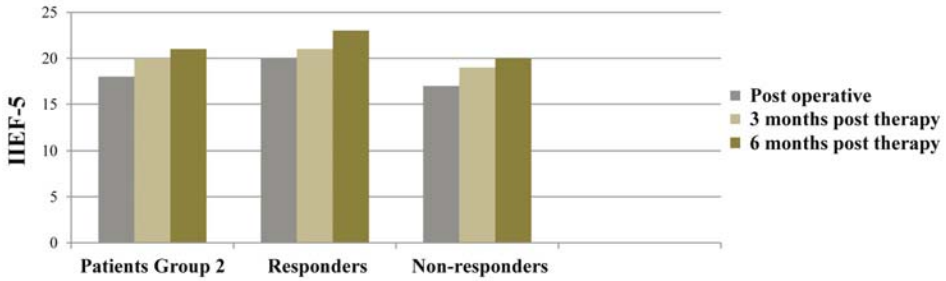

Figure 2. Distribution of group 2 patients according to IIEF-5

Discussion

For the first time in the world literature, the use of LI-ESWT in treatment of ED was explained in 2010 by Vardi et al. (2010) [16]. The experience gained over the last 17 years with LI-ESWT from international clinical trials has demonstrated its undeniable safety, efficacy and good tolerance in ED treatment [17]. Table 4 shows all studies using LI-ESWT to treat ED.

The results of our retrospective study correspond to those in the world literature. In group 1, patients who underwent LI-ESWT, there was a 63% better recovery of erectile function as compared to group 2 patients, who did not receive treatment. These results in the treatment of ED after BNSRRP with LI-ESWT are promising. It is well tolerated by patients and does not cause significant side effects [29, 30].

Conclusions

Despite the small number of patients and their short-term follow-up, our initial results indicate that LI-ESWT is effective, safe and well tolerated. It could be an alternative for early penis rehabilitation in patients who have undergone bilateral nerve sparing radical retropubic prostatectomy. To confirm the results, we need a long follow-up study involving a larger number of patients.

References

1. Hatzimouratidis K, Burnett AL, Hatzichristou D, McCullough AR, Montorsi F, Mulhall JP. Phosphodiesterase type 5 inhibitors in postprostatectomy erectile dysfunction: a critical analysis of the basic science rationale and clinical application. Eur Urol. 2009;55(2):334-47.

Table 4. Studies using LI-ESWT for treatment of ED

Study	Year	Country	Disease	Energy (mJ/mm^2)	Number of shocks	Number of therapies per week	Number of regions	Number of weeks	Questionnaires	p-value after therapy
Olsen et al [18]	2015	Denmark	ED*	0.15	3000	1	6	5	IIEF§, EHS**	0.67
Frey et al [19]	2015	Denmark	ED after RP‡‡	NA††	3000	2	3	6	IIEF	0.0049
Bechara et al [20]	2015	Argentina	ED	0.09	5000	1	4	4	IIEF	NA
Chung and Cartmill [17]	2015	Australia	ED	0.25	3000	2	4	6	IIEF	<0.05
Pelayo-Nieto et al [21]	2015	Mexico	ED	0.09	5000	1	4	4	IIEF	0.013
Srini et al [22]	2015	India	ED	NA	NA	NA	NA	NA	IIEF, EHS	0.0001
Yee et al [23]	2014	Hon Kong	ED	0.09	1500	2	5	9	IIEF, EHS	0.001
Palmieri et al [24]	2012	Italy	ED + PD†	0.25	2000	1	NA	4	IIEF, QL§§	<0.05
Vardi et al [25]	2012	Israel	ED	0.09	1500	2	5	9	IIEF, EHS	0.0322
Zimmermann et al [26]	2009	Australia	ED + CPPS‡	0.25	3000	1	NA	4	IIEF	0.034
Chitale et al [14]	2010	Great Britain	ED + PD	NA	3000	1	NA	6	IIEF	0.249
Poulakis et al [27]	2006	Germany	ED + PD	0.17	2000	1	NA	5	IIEF	0.205
Skolarikos et al [28]	2005	Greece	ED + PD	NA	3000	NA	NA	6	IIEF	0.06

*ED – erectile dysfunction;
§IIEF – International Index of Erectile Function;
**EHS – erection hardness score;
‡‡RP – radical prostatectomy;
††NA – not applicable;
†PD – Peyronie‘s disease;
§§QL – quality of life;
‡CPPS – chronic pelvic pain syndrome

2. Dimitrov P, Panchev P, Simeonov P, Vasilev V, Georgiev M, Yanev K. Prostate carcinoma – staging and possibilities for operative treatment. Medical science. 2008;2:51-5.
3. Walsh PC. Radical prostatectomy for localized prostate cancer provides durable cancer control with excellent quality of life: a structured debate. J Urol. 2000;163(6):1802-7.
4. Hatzichristou D, d'Anzeo G, Porst H, Buvat J, Henneges C, Rossi A, et al. Tadalafil 5 mg once daily for the treatment of erectile dysfunction during a 6-month observational study (EDATE): impact of patient characteristics and comorbidities. BMC Urol. 2015;15:111.
5. Rassweiler JJ, Knoll T, Köhrmann KU, McAteer JA, Lingeman JE, Cleveland RO, et al. Shock wave technology and application: an update. Eur Urol. 2011;59(5):784-96.
6. Frairia R, Berta L. Biological effects of extracorporeal shock waves on fibroblasts. A review. Muscles Ligaments Tendons J. 2011;1(4):138-47.
7. Förstermann U, Sessa WC. Nitric oxide synthases: regulation and function. Eur Heart J. 2012;33(7):829-37.
8. Chaussy C, Brendel W, Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. Lancet. 1980;13(2):1265-8.
9. Hazan-Molina H, Reznick AZ, Kaufman H, Aizenbud D. Periodontal cytokines profile under orthodontic force and extracorporeal shock wave stimuli in a rat model. J Periodontal Res. 2015;50(3):389-96.
10. Becker M, Goetzenich A, Roehl AB, Huebel C, de la Fuente M, Dietz-Laursonn K, et al. Myocardial effects of local shock wave therapy in a Langendorff model. Ultrasonics. 2014;54(1):131-6.
11. Yang P, Guo T, Wang W, Peng YZ, Wang Y, Zhou P, et al. Randomized and double-blind controlled clinical trial of extracorporeal cardiac shock wave therapy for coronary heart disease. Heart Vessels. 2013; 28(3):284-91.
12. Hayashi D, Kawakami K, Ito K, Ishii K, Tanno H, Imai Y, et al. Low-energy extracorporeal shock wave therapy enhances skin wound healing in diabetic mice: a critical role of endothelial nitric oxide synthase. Wound Repair Regen. 2012;20(6):887-95.
13. Hanna M, Pedersen D, Lund M, Marcussen N, Lund L. Low energy ESWT, a novel treatment for diabetic nephropathy (animal study). J Endourol. 2012;26:16-22.
14. Chitale S, Morsey M, Swift L, Sethia K. Limited shock wave therapy vs sham treatment in men with Peyronie's disease: results of a prospective randomized controlled double-blind trial. BJU Int. 2010;106(9):1352-6.
15. Abu-Ghanem Y, Kitrey ND, Gruenwald I, Appel B, Vardi Y. Penile low-intensity shock wave therapy: a promising novel modality for erectile dysfunction. Korean J Urol. 2014;55(5):295-9.
16. 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(2):243-8.
17. Chung E, Cartmill R. Evaluation of clinical efficacy, safety and patient satisfaction rate after low-intensity extracorporeal shockwave therapy for the treatment of male erectile dysfunction: an Australian first open-label single-arm prospective clinical trial. BJU Int. 2015;115(Suppl 5):46-9.
18. 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(4):329-33.
19. Frey A, Sonksen J, Fode M. Low-intensity extracorporeal shockwave therapy in the treatment of postprostatectomy erectile dysfunction: a pilot study. Scand J Urol. 2016;50:123-7.
20. Bechara A, Casabe A, De Bonis W, Nazar J. Effectiveness of lowintensity extracorporeal shock wave therapy on patients with erectile dysfunction (ED) who have failed to respond to PDE5i therapy. A pilot study. Arch Esp Urol. 2015;68(2):152-60.
21. Pelayo-Nieto M, Linden-Castro E, Alias-Melgar A, Espinosa-Pérez Grovas D, Carreño-de la Rosa F, Bertrand-Noriega F, et al. Linear shock wave therapy in the treatment of erectile dysfunction. Actas Urol Esp. 2015;39(7):456-9.
22. Srini VS, Reddy RK, Shultz T, Denes B. Low intensity extracorporeal shockwave therapy for erectile dysfunction: a study in an Indian population. Can J Urol. 2015;22(1):7614-22.
23. 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(10):1041-5.
24. Palmieri A, Imbimbo C, Creta M, Verze P, Fusco F, Mirone V. Tadalafil once daily and extracorporeal shock wave therapy in the management of patients with Peyronie's disease and erectile dysfunction: results from a prospective randomized trial. Int J Androl. 2012;35(2):190-5.

25. 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(5):1769-75.
26. Zimmermann R, Cumpanas A, Miclea F, Janetschek G. Extracorporeal shock wave therapy for the treatment of chronic pelvic pain syndrome in males: a randomised, double-blind, placebo-controlled study. Eur Urol. 2009;56(3):418-24.
27. Poulakis V, Skriapas K, de Vries R, Dillenburg W, Ferakis N, Witzsch U, et al. Extracorporeal shockwave therapy for Peyronie's disease: an alternative treatment? Asian J Androl. 2006;8(3):361-6.
28. Skolarikos A, Alargof E, Rigas A, Deliveliotis C, Konstantinidis E. Shockwave therapy as first-line treatment for Peyronie's disease: a prospective study. J Endourol. 2005;19(1):11-4.
29. Kolev N, Atanasov J, Dunev V, Stoykov B, Kotsev R, Vanov A, et al. Open Retropubic and Robot-Assisted Radical Prostatectomy in Prostate Carcinoma: Advantages of Methods. Journal of Biomedical and Clinical Research. 2016;9(2):145-9.
30. Hinev A, Hadjiev V, Kolev N. Validation of preoperative nomograms predicting lymph node involvement in prostate cancer: a Bi-institutional study. Eur Urol. 2011;60(6):1310-1.