

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Low-intensity extracorporeal shock wave therapy of vasculogenic erectile dysfunction – three-week treatment in a cohort of North Italian patients

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Introduction/Objective Although phosphodiesterase 5 (PDE 5) inhibitors represent the gold standard for medical treatment of erectile dysfunction (ED), they are not curative. Over the recent years, low-intensity extracorporeal shock wave therapy (LI-ESWT) has been proposed as a valid non-invasive therapy approach for ED.

The aim of our work is to assess the shortened, three-week low-intensity extracorporeal shock wave therapy of vasculogenic ED.

Methods The study involved 32 patients with an International Index of Erectile Function (IIEF) score between 5 and 20, and whose vasculogenic ED had been proven through Doppler ultrasound. All the patients had a washout period of one month after previous therapy and agreed to discontinue the PDE-5 therapy during the follow-up. The LI-ESWT was applied for three weeks, twice weekly, without repeating. The patients were evaluated at baseline, after one, three, and six months with the IIEF, Doppler ultrasound, and the Beck Depression Inventory.

Results All investigated parameters (International Index of Erectile Function, Beck Depression Inventory and penile Doppler ultrasound parameters) showed statistically significant improvement just one month after the treatment, compared to pre-treatment values, in all investigated domains. The international index of erectile function passed from baseline values of 12.75 ± 4.62 to 14.87 ± 5.04 at one month after treatment ($p < 0.01$). This trend remained positive in IIEF and all the parameters tested at the three-month and six-month follow-up.

Conclusion The shortened three-week low-intensity shock wave treatment of vasculogenic erectile dysfunction proved to be clinically effective.

Keywords: erectile dysfunction; low-intensity extracorporeal shock wave therapy; International Index of Erectile Function (IIEF); Doppler ultrasound; Beck Depression Inventory (BDI)

INTRODUCTION

Erectile dysfunction (ED) is a problem of the male population with both high prevalence and incidence worldwide. The Massachusetts Male Aging Study has reported a prevalence of ED between 5% and 35% (Northern Europe) [1]. ED is commonly associated with aging and age-related health problems, such as vascular, hormonal, neural, psychogenic factors, and side effects of therapeutic drugs [2].

Phosphodiesterase-5 (PDE-5) inhibitors, although not curative, have become a standard way of treating ED [3–6]. However, there are still some significant shortcomings of this treatment, such as side effects, drug intolerance, etc.

Low-intensity extracorporeal shock wave therapy (LI-ESWT) was introduced by Vardi et al. [7, 8] as an innovative and promising curative treatment of ED, with the possibility of avoiding side effects and drug intolerance. The majority of therapy protocols studied with non-linear LI-ESWT were based on treatments

lasting six weeks, with a three-week pause in between [8–11].

The aim of this pilot study was to investigate the effects of a three-week LI-ESWT in a cohort of patients from north-eastern Italy, all with vasculogenic ED.

METHODS

An open-label, single-arm, prospective pilot study was performed in a private urological care structure (Studio Urologico FG) in accord with the Helsinki Declaration. Thirty-two patients were enrolled in the study after obtaining their written informed consent. The inclusion criteria were as follows: history of ED for at least six months, an International Index of Erectile Function for ED (IIEF-ED) domain score between 5 and 20, responders and non-responders to PDE-5 inhibitor therapy and vasculogenic ED proven by Doppler ultrasound. All the patients had a washout period of one month after previous therapy and

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Table 1. Maximal velocity of arterial systolic flow, resistance index, Beck's Depression Inventory score, International Index of Erectile Function values before and after treatment

| Baseline values and follow-up (mean value \pm SD) | | | | | |
|---|-------------------|-------------------|-------------------|-------------------|---------|
| Variables | Baseline | 1 month | 3 months | 6 months | p* |
| Qmax | 27.59 \pm 12.55 | 37.39 \pm 17.81 | 39.43 \pm 17.22 | 39.71 \pm 17.74 | < 0.001 |
| RI | 0.67 \pm 0.08 | 0.76 \pm 0.08 | 0.79 \pm 0.06 | 0.79 \pm 0.05 | < 0.001 |
| BDI | 6.59 \pm 5.70 | 4.59 \pm 0.57 | 4.06 \pm 4.56 | 2.96 \pm 3.58 | < 0.003 |
| IIEF | 12.75 \pm 4.62 | 14.87 \pm 5.04 | 17.06 \pm 4.04 | 17.64 \pm 4.34 | < 0.004 |

Qmax – maximal velocity of arterial systolic flow; RI – resistance index; BDI – Beck's Depression Inventory score; IIEF – International Index of Erectile Function; *calculated between pre-treatment and post-treatment values after one month; no significant differences were noted between the three-month and six-month follow-ups, except from BDI

agreed to discontinue the PDI-5 inhibitor therapy during the follow-up.

The exclusion criteria were the following: psychogenic ED, neurologic comorbidities, documented hypogonadism (total testosterone serum levels under 10 nmol/L), prior radical prostatectomy, and recovery from any cancer within the past five years.

Treatment protocol

Low-intensity shock wave therapy was delivered using a special probe attached to a compact electrohydraulic unit with a focused shockwave source (Omnispec ED1000, Medispec Ltd, Germantown, MD, USA). Only standard ultrasound gel was applied between contact surfaces. The penis was manually stretched, and the prepuce retracted; the shockwaves were delivered to the distal, mid, and proximal penile shaft, and to the left and right crura.

Each LI-ESWT session lasted for 20 minutes, and comprised 300 shocks per treatment point (a total of 1,500 per session), at an energy density of 0.09 mJ/mm² and a frequency of 120/min. The volume of penile tissue that was exposed to shockwaves at each site was cylindrical (diameter: 18 mm; height: 100 mm). The treatment protocol consisted of two treatment sessions per week, for three weeks, without repeating the treatment after three weeks, which is the key difference compared to the previous study protocols with non-linear LI-ESWT [11, 12].

During the treatment period, no psychological intervention or support was provided, and patients were required to maintain their normal sexual habits.

Study protocol

The IIEF was used for the symptomatic evaluation of patients with ED, as this is a widely accepted measurement tool with a high degree of sensitivity and specificity for detecting treatment-related changes in the erectile mechanism [13, 14]. A standard tool was used for the psychological evaluation of patients, the Beck Depression Inventory (BDI) score, and a clinical evaluation was performed on all patients [15]. A grey scale ultrasound followed by a penile Doppler dynamic ultrasound with alprostadil 10 μ g intracavernosal injection was performed. Measurements of peak systolic (Qmax) and end-diastolic velocities were obtained in each cavernosal artery at five-minute intervals for a total of 30 minutes. A peak systolic velocity of less

than 35 cm/second was used as the threshold for arterial insufficiency. An end-diastolic velocity greater than 5 cm/second was used to predict venous incompetence. Moreover, resistance index (RI) was evaluated and considered to be pathologically reduced when lower than 0.75. A complete study protocol was carried out before the treatment and during the follow-up. A follow-up was carried out one month, three months, and six months after treatment, using IIEF-5 and BDI questionnaires and recording changes in dynamic Doppler ultrasound parameters.

Statistical analysis was performed with a repeated measures analysis of variance (ANOVA). Linear regression analysis was used to prove the correlation between the variables. Statistical difference was considered significant when $p < 0.01$.

RESULTS

The study protocol was applied to 32 middle-aged men (mean: 57.62 \pm 7.98; range: 38–68 years) with vasculogenic ED for a mean of 35.2 months. The data regarding pre- and post-therapy IIEF, duplex Doppler ultrasound, RI, and BDI are shown in Table 1.

A statistically significant improvement in all the investigated parameters can be seen one month after treatment, compared to the pre-treatment values, in all investigated domains. The IIEF passed from baseline values of 12.75 \pm 4.62 to 14.87 \pm 5.04 at one month after treatment ($p < 0.01$). The BDI basic values passed from 6.59 \pm 5.70 to 4.59 \pm 0.57 after the first months from the treatment ($p < 0.01$). As of penile color Doppler ultrasound parameters, both Qmax and RI values showed a statistically significant improvement at first month after treatment ($p < 0.01$). There was no deterioration of the investigated values during the follow-up.

There is a significant correlation between the improvement in IIEF and Qmax (Figure 1), and a negative correlation between IIEF and BDI (Figure 2). Multiple significant correlations between IIEF, Qmax, and RI are shown in Figure 3.

DISCUSSION

Our results show a significant change in both IIEF and BDI scores, and an improvement in Qmax and RI. Significant improvement remained during the follow-up.

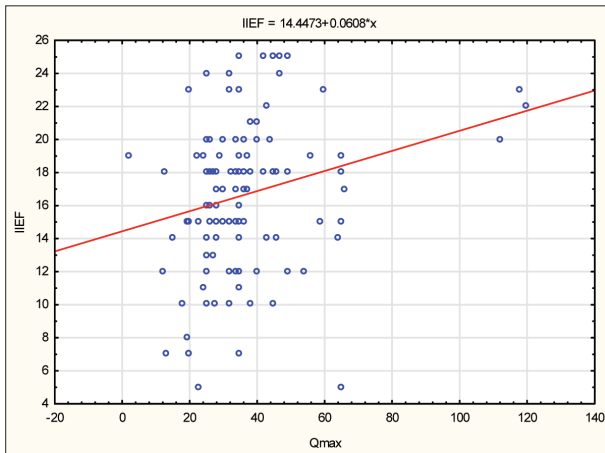


Figure 1. Correlation between the adjusted maximal velocity of arterial systolic flow parameters and the changes in International Index of Erectile Function scores

Qmax – maximal velocity of arterial systolic flow score;
IIEF – International Index of Erectile Function

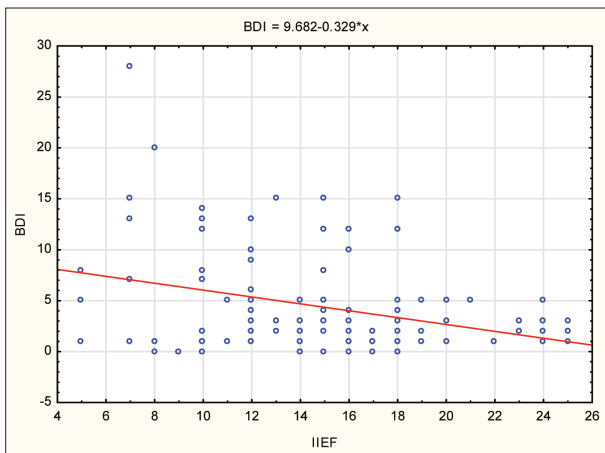


Figure 2. Correlation between the adjusted Beck's Depression Inventory scores and the changes in International Index of Erectile Function scores

BDI – Beck's Depression Inventory score;
IIEF – International Index of Erectile Function

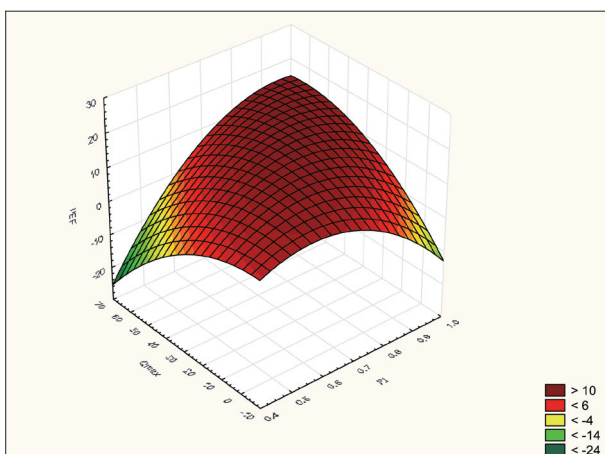


Figure 3. Multiple correlation between the changes in the maximal velocity of arterial systolic flow and resistance index values and the changes in International Index of Erectile Function scores

Qmax – maximal velocity of arterial systolic flow score;
RI – resistance index; IIEF – International Index of Erectile Function

Low intensity shock wave therapy is promising, although the exact mechanism used by LI-ESWT to induce the tissue changes is not known. Thanks to the release of neo-angiogenic factors and the subsequent neovascularization of the treated tissue, LI-ESWT leads to tissue regeneration [16]. Indeed, it has been shown that this low-intensity energy acts on vascularization, inducing a non-enzymatic production of physiologic amounts of nitric oxide [17]. Thus, the latest studies show that IIEF scores increase after treatment with LI-ESW [18]. Even though PDE-5 inhibitors represent the first-line therapy for ED by increasing the IIEF score, they do not represent a curative approach. The increase in IIEF does not last over time; rather, it is strictly limited to the assumption of PDE-5 inhibitors. In addition, some ED patients respond poorly to PDE-5 and need other, more invasive treatments [9, 11, 12].

After the pilot study by Vardi et al. [7], which took into consideration the patients who had previously responded to PDE-5 inhibitor therapy, Gruenwald et al. [10] applied LI-ESWT to patients who had responded poorly to PDE-5 inhibitor therapy. By using the same protocol as in the first study on 29 patients, they concluded that LI-ESWT was again beneficial for this kind of patient, as it had a physiological effect on the erectile mechanism [10].

After those preliminary studies, others were done, but almost all studies on LI-ESWT for ED had the same duration and applied the same treatment doses. The treatment protocol mostly considered the application of LI-ESWT twice a week for three weeks, with re-treatment for another three weeks after a three-week pause. The number of shocks applied was almost always 300 per treatment point with an energy flux density of 0.09 mJ/mm² [9].

A very recent study carried out at the Mayo Clinic applied low-energy shock wave therapy to alleviate renal dysfunction in renovascular disease. They treated pigs' kidneys with renal artery stenosis using low-energy shock waves twice a week for only three consecutive weeks, without repeating. Twenty-six pigs were randomized to atherosclerotic renal artery stenosis (ARAS) or normal controls, treated or untreated with LI-ESWT. The results were amazingly positive. A three-week low-intensity shockwave therapy attenuated renovascular hypertension, normalized stenotic kidney microvascular density and oxygenation, stabilized function, and alleviated fibrosis. This was associated with upregulation of the vascular endothelial growth factor expression that was decreased by ARAS, with increased angiotensin-1, and downregulation of hypoxia-induced factor-1. Moreover, LI-ESWT improved the expression of endothelial nitric oxide synthase that was diminished in ARAS. No detectable injury to the kidney was observed [19].

The encouraging results from this and all the previous studies led us to conduct a prospective pilot study, applying the three-week low-intensity shockwave therapy to patients with ED in order to examine if the shortened therapy could have the same effect as the repeated three-week therapy.

Our primary end points were the change in IIEF-5 and in the penile color Doppler values given through the Qmax and RI values, as well as the BDI score.

The IIEF-5 questionnaire is a widely accepted measurement tool with a high degree of sensitivity and specificity for detecting treatment-related changes in the erectile mechanism [13, 14].

The BDI is one of the most widely used psychometric tests for measuring the severity of depression. The BDI was originally developed to provide a quantitative assessment of the intensity of depression. As it is designed to reflect the depth of depression, it can monitor changes over time and provide an objective measurement for judging improvement and the effectiveness of treatment methods [15]. A systematic review by McCabe [20] showed how ED leads to poor sexual relationships and poor sexual satisfaction, diminished confidence, low self-esteem, and symptoms of depression. After any kind of treatment, there were significant improvements for the baseline regarding most of these parameters, except for overall life satisfaction and overall relationship satisfaction [20]. Although the BDI has its limitations, as do all questionnaires, considering that the person completing it may exaggerate or minimize their score, we considered BDI as an important aspect of treatment success. As far as we know, this is the first study to date that uses BDI in evaluating the results of LI-ESWT to treat ED.

The immediate, statistically significant increase in all variables after the one-month follow up showed that this shortened therapy was efficient in improving erectile function, and that the effects of angiogenesis could be clinically important after the three-week therapy, without repeating.

The fact that the basic BDI values did not show the presence of depression in our patients, excluded the fact that ED was due to depression in our cohort. This also excluded the possible placebo effect that could be expected from our study protocol. The BDI score, although in the normality range at basic values, lowered even more at the six-month follow-up. The mean BDI scores changed from 6.59 ± 5.70 before treatment to 2.96 ± 3.58 at the six-month follow-up, which was statistically significant. Patients sometimes need time to develop self-confidence and improve general well-being after suffering depression-like symptoms for a long time before the therapy. This could be especially true for those patients who did not respond to PDI-5 therapy before the LI-ESWT, and who had lost faith in clinical improvement, considering that, to date, PDI-5 therapy is the gold standard for treating ED. Our results showed an immediate effect on BDI scores after one month, which was maintained after six months without any additional active intervention.

A positive physiological effect on cavernosal tissue is certainly proven by hemodynamic values. As with the Doppler findings, we witnessed an increase in Qmax at the one-month follow-up. This increase was the greatest the first month after treatment, with a slightly greater value at the three-month and six-month follow-up. This represents direct proof that the shortened course of therapy with low-intensity shock waves improves the hemodynamic values of the penis, and that this effect can be observed quite

soon after treatment. Vardi et al. [7, 8] stated that most of the treated men reported improvements in erectile function between treatment sessions 6 and 8, which is probably the time needed for LI-ESWT to induce the physiological changes. Nevertheless, those values remained the same with a small but significant increase over three and six months, which is indicative of the durability of the shortened treatment.

We used a scientifically tested machine that had already been proven through 'sham control' to have certain positive effects on penile hemodynamics over a longer follow-up period. Recently, Fojecki et al. [21] showed that exposure to two cycles of linear ESWT to treat ED was not superior to one cycle at the six-month and 12-month follow-up. Although they used a different machine with a linear probe and a five-week treatment session, the number of shockwaves and the energy flux density were the same.

Our patient cohort was mostly homogenous when considering cardiovascular risk factors. Three men had arterial hypertension in medical therapy, one had insulin-dependent diabetes mellitus, and one of the patient's ED was due to previous pelvic trauma. We included patients who had responded, partially responded, or had not responded to previous PDI-5 therapy. This is based on previous studies that showed that LI-ESWT could have beneficial effects on both PDI-5 responders and non-responders [7, 10].

The main limitations of our study were certainly the low number of patients and the lack of a sham-controlled arm. Although the study population comprised only 32 men, this was sufficient to determine whether or not our shortened treatment could have a positive physiological effect on cavernous tissue. Bearing in mind that this was a pilot study, and that Vardi's first study was carried out on a smaller patient cohort, without a sham-controlled arm, these limitations should be considered relative. We would like to emphasize that the most striking clinical observation was that almost every participant gave highly positive feedback on the treatment.

CONCLUSION

The efficacy of a short course of the LI-ESWT therapy to manage ED was confirmed. The LI-ESWT was successful in improving symptomatic, vasculogenic and psychological aspects of vasculogenic ED. Although additional investigations are necessary, the initial results of our study are promising, improving the position of LI-ESWT in the guidelines for curative treatment options for patients with vasculogenic ED.

NOTE

This paper forms part of a doctoral thesis by Dr. Goran Arandelović with the title "The effects of three-week low intensity shock wave therapy on erectile dysfunction."

REFERENCES

- Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: Results of the Massachusetts Male Aging Study. *J Urol.* 1994; 151(1):54–61.
- Shabsigh R, Kimoto Y, Amar E, Hackett G, Jarow JP, Mirone V, et al. Economical aspects in sexual dysfunctions. In: Lue TF, Basson R, Rosen R, Giuliano F, Khoury S, Montorsi F (Eds.) *Sexual Medicine, Sexual Dysfunctions in Men and Women.* Health Publications, Paris; 2004:139–160.
- Aversa A, Bruzziches R, Vitale C, Marazzi G, Francomano D, Barbaro G, et al. Chronic sildenafil in men with diabetes and erectile dysfunction. *Expert Opin Drug Metab Toxicol.* 2007; 3(3):451–64.
- Porst H, Rajfer J, Casabe A, Feldman R, Ralph D, Vieira LF, et al. Long-term safety and efficacy of tadalafil 5 mg dosed once daily in men with erectile dysfunction. *J Sex Med.* 2008; 5(9):2160–9.
- Vardi Y, Appel B, Ofer Y, Gruenwald I, Dayan L, Jacob G. Effect of chronic sildenafil treatment on penile endothelial function: a randomized, double-blind, placebo-controlled study. *J Urol.* 2009; 182(6):2850–5.
- Hatzichristou D, d'Anzeo G, Porst H, Buvat J, Hennes C, Rossi A, et al. Tadalafil 5mg 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.
- 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.
- 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.
- Clavijo RI, Kohn TP, Kohn JR, Ramasamy R. Effects of Low-Intensity Extracorporeal Shockwave Therapy on Erectile Dysfunction: A Systematic Review and Meta-Analysis. *J Sex Med.* 2017; 14(1):27–35.
- 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(1):259–64.
- Zou ZJ, Tang LY, Liu ZH, Liang JY, Zhang RC, Wang YJ, et al. Short-term efficacy and safety of low-intensity extracorporeal shock wave therapy in erectile dysfunction: a systematic review and meta-analysis. *Int Braz J Urol.* 2017; 43(5):805–21.
- Lu Z, Lin G, Reed-Maldonado A, Wang C, Lee YC, Lue TF. Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis. *Eur Urol.* 2017; 71(2):223–33.
- Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology.* 1997; 49(6):822–30.
- Rosen RC, Cappelleri JC, Gendrano N 3rd. The international Index of Erectile Function (IIEF): a state of the science review. *Int J Impot Res.* 2002; 14(4):226–44.
- Beck AT, Ward C, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961; 4:561–71.
- Romeo P, Lavanga V, Pagani D, Sansone V. Extracorporeal shock wave therapy in musculoskeletal disorders: a review. *Med Princ Pract.* 2014; 23(1):7–13.
- Mariotto S, Cavaliere E, Amelio E, Ciampa AR, de Prati AC, Marlinghaus E, et al. Extracorporeal shock waves: from lithotripsy to anti-inflammatory action by NO production. *Nitric Oxide.* 2005; 12(2):89–96.
- 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.
- Zhang X, Krier JD, Amador Carrascal C, Greenleaf JF, Ebrahimi B, Hedayat AF, et al. Low-Energy Shockwave Therapy Improves Ischemic Kidney Microcirculation. *J Am Soc Nephrol.* 2016; 27(12):3715–24.
- McCabe MP, Althof SE. A systematic review of the psychosocial outcomes associated with erectile dysfunction: does the impact of erectile dysfunction extend beyond a man's inability to have sex? *J Sex Med.* 2014; 11(2):347–63.
- Fojecki GL, Tiessen S, Ooster PJS. Effect of Linear Low-Intensity Extracorporeal Shockwave Therapy for Erectile Dysfunction: 12-Month Follow-Up of a Randomized, Double-Blinded, Sham-Controlled Study. *Sex Med.* 2018; 6(1):1–7.

Екстракорпорални ударни таласи ниског интензитета за третман васкулогене еректилне дисфункције – тронедељна терапија на групи болесника из североисточне Италије

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САЖЕТАК

Увод/Циљ Инхибитори фосфодиестеразе типа 5 (*PDE5-Is*) представљају златни стандард у медикаментозној терапији еректилне дисфункције. Упркос томе, медикаментозни третман не представља терапију којом се може трајно излечити еректилна дисфункција. Циљ наше студије је испитати скраћену тронедељну терапију екстракорпоралним ударним таласима ниског интензитета васкулогене еректилне дисфункције.

Метод Студија је укључила 32 болесника са међународним индексом еректилне функције између 5 и 20, са потврђеном васкулогеном еректилном дисфункцијом на доплер ултразвуку. Болесници су имали паузу у трајању од једног месеца од претходне терапије и били су сагласни да прекину терапију *PDE5* инхибиторима у периоду праћења после третмана. Применили смо екстракорпоралне ударне таласе ниског интензитета у трајању од три недеље, два пута недељно, без понављања. Болесници су оцењивани пре терапије, један месец, три и шест месеци после терапије међународним ин-

дексом еректилне функције, доплер ултразвуком и Бековим упитником за депресију.

Резултати Сви испитани параметри (Међународни индекс еректилне функције, Беков упитник за депресију, параметри доплер ултразвука пениса) показали су позитивну статистички значајну промену после само једног месеца од терапије. Међународни индекс еректилне функције је забележио пораст првог месеца после терапије и поео се са основних вредности од $12,75 \pm 4,62$ на $14,87 \pm 5,04$ ($p < 0,01$). Овај позитиван тренд се задржао како на Међународном индексу еректилне функције тако и на свим тестираним параметрима после три и шест месеци праћења.

Закључак Скраћена тронедељна терапија екстракорпоралним ударним таласима ниског интензитета примењена на васкулогену еректилну дисфункцију показала се клинички ефективном.

Кључне речи: еректилна дисфункција; екстракорпорални ударни таласи ниског интензитета; међународни индекс еректилне функције; доплер ултразвук; Беков упитник за депресију