ORIGINAL RESEARCH
Andrology

Doi: 10.4274/jus.1431
Journal of Urological Surgery, 2017;4(4):189-194

Efficacy of Low Density Linear Shockwave Treatment in Severe Arteriogenic Erectile Dysfunction Patients

Ağır Arteriyojenik Erektil Disfonksiyonlu Hastalarda Düşük Dansiteli Linear Şok Dalga Tedavisinin Etkinliği

Mehmet Giray Sönmez[1], Cengiz Kara[2]

[1]Necmettin Erbakan University Meram Faculty of Medicine, Department of Urology, Konya, Turkiye
[2]Medical Park Ankara Hospital, Clinic of Urology, Ankara, Turkiye

What's known on the subject? and What does the study add?

There are studies showing that low-intensity linear shockwave treatment (LI-ESWT) was effective and successful in erectile dysfunction (ED) due to vascular disorders, especially in arteriogenic ED. It has been claimed that LI-ESWT caused neovascularization by stimulating angiogenesis and increased endothelial cell proliferation. The efficacy of LI-ESWT + phosphodiesterase type 5 inhibitors (PDE5i) was compared with PDE5i treatment only in patients with severe ED who were diagnosed with penile arteriogenic ED based on penile Doppler ultrasonography.

Abstract

Objective: The aim of this study was to evaluate the efficacy of low-intensity linear shockwave treatment (LI-ESWT) in patients with severe arteriogenic erectile dysfunction (ED) by comparing LI-ESWT combined with daily use of phosphodiesterase type 5 inhibitors (PDE5i) with the daily use of PDE5i alone.

Materials and Methods: A total of 23 patients were included in the study. The patients were separated into two groups: LI-ESWT + tadalafil 5 mg (n=10) group and tadalafil 5 mg only group (n=13). LI-ESWT was applied once a week for four weeks. Oral tadalafil 5 mg once a day was started and continued for three months in both groups. The patients were evaluated with the International Erectile Function Index Questionnaire Erectile Function Domain (IIEF-EF), Erection Hardness Score (EHS) and Sexual Encounter Profile (SEP) 2 and 3 before treatment and the 1 and 3 months after treatment.

Results: No statistically significant difference was detected among IIEF-EF scores measured before and 1 and 3 months after treatment (p=0.091, p=0.198). At the end of the third month, IIEF score increased 4 points in LI-ESWT + tadalafil 5 mg group and 3.2 points in tadalafil 5 mg only group. No statistically significant difference was detected in EHS, and the rate of positive responses to SEP2 and SEP3 questions at the 1st and 3rd months between the groups.

Conclusion: LI-ESWT is easily applicable without any significant side effects and it has positive effects on the outcomes, however, it is not an effective treatment method in patients with severe arteriogenic ED.

Keywords: Low-intensity linear shockwave treatment, phospodiesterase type 5 inhibitors, erectile dysfunction

Öz

Amaç: Bu çalışmanın amacı, şiddetli arteriyojenik erektil disfonksiyona (ED) sahip hastalarda, fosfodiesteraz tip 5 (PDESİ) inhibitörünün (Tadalafil 5 mg) günlük kullanımı ile kombine edilen düşük dansiteli lineer şok dalga tedavisini (LI-ESWT), sadece PDESİ'nin günlük kullanımı ile kıyaslayarak LI-ESWT'nin etkinliğini değerlendirmektir.

Gereç ve Yöntem: Toplam 23 hasta çalışmaya dahil edildi. Bu hastalar LI-ESWT + tadalafil 5 mg tedavisi (n=10) uygulanan, sadece tadalafil 5 mg tedavisi uygulanan (n=13) hastalar şeklinde iki gruba ayrıldı. LI-ESWT, 4 hafta boyunca haftada bir kez uygulandı. Her iki gruptaki hastalara da

Correspondence: Mehmet Giray Sönmez MD, Necmettin Erbakan University Meram Faculty of Medicine, Department of Urology, Konya, Turkiye
Phone: +90 505 914 23 27 **E-mail:** drgiraysonmez@gmail.com **ORCID ID:** orcid.org/0000-0003-4615-7348
Received: 06.04.2017 **Accepted:** 31.10.2017

Cite this article as: Sönmez MG, Kara C. Efficacy of Low Density Linear Shockwave Treatment in Severe Arteriogenic Erectile Dysfunction Patients. J Urol Surg 2017;4:189-194.

günde bir defa tadalafil 5 mg tedavisi oral olarak başlandı ve tedaviye her iki grupta 3 ay devam edildi. Tedavi öncesi ve sonrası 1. ay ve 3. ayda hastalar Uluslararası Erektil Fonksiyon İndeks Formu-Erektil Fonksiyon Alanı Skoru (IIEF-EF) ve Ereksiyon Sertlik Derecesi Skoru (ESDS) seviyeleri ve Seksüel İlişki Profili (SEP) 2 ve 3 ile değerlendirildi.

Bulgular: Tedavi öncesi ve tedavi sonrası 1. ve 3. ayda ölçülen IIEF-EF skorları arasında istatiksel anlamlı fark saptanmadı (p=0,091; p=0,198). Üçüncü ay sonunda LI-ESWT + tadalafil 5 mg grubunda IIEF-EF skoru 4 puan, Tadalafil 5 mg grubunda 3,2 puan artış gösterdi. İki grup arasında 1. ve 3. ayda ölçülen ESDS, SEP2 ve SEP3 pozitif hasta oranları arasında istatistiksel olarak anlamlı fark saptanmadı.

Sonuç: LI-ESWT, ED tedavisinde kolay uygulanabilir, belirgin yan etkisi olamayan ve sonuçlar üzerinde pozitif etkisi olan bir uygulamadır. Fakat ağır arteriyojenik ED mevcut hastalarda etkin bir tedavi yöntemi değildir.

Anahtar Kelimeler: Düşük dansiteli linear şok dalga tedavisi, fosfodiesteraz tip 5 inhibitörleri, erektil disfonksiyon

Introduction

Erectile dysfunction (ED) is the inability to maintain an erection sufficient for satisfactory sexual function (1). The prevalence in males over forty years of age has been reported to be 52% in United States and 69.2% in Turkey (2). A prevalence of nearly 322 million people in 2025 is predicted (3). Penile erection occurs due to a complex interaction of psychological, neural, vascular and endocrine factors. ED is related to these multifactorial problems and its prevalence increases with age. Factors associated with vascular disorders play an important role in ED etiology. These causes are divided into three categories as arteriogenic ED, venogenic ED and mixed vasculogenic. Among vasculogenic ED causes, arteriogenic factors play an important role (1,4).

Even though phosphodiesterase type 5 inhibitors (PDE5i) are actively used as the primary option in ED treatment, the demanded response is not achieved in 40-50% of patients. Although application of vasoactive agents and penile prosthesis implantation are recommended as secondary and tertiary treatment options in irresponsive patients, patients are generally not interested in these treatments (5). Thus, treatment methods which may be tolerated easily by non-invasive patients are required.

There are studies showing that low-intensity linear shockwave treatment (LI-ESWT) is effective and successful in patients with ED due to vascular disorders, especially in those with arteriogenic ED (6,7,8). It is claimed that LI-ESWT causes neovascularization by stimulating angiogenesis and increases endothelial cell proliferation (7,9).

The aim of this study was to evaluate the efficacy of LI-ESWT in patients with severe arteriogenic ED by comparing LI-ESWT combined with the daily use of PDE5i (tadalafil 5 mg) with the daily use of PDE5i.

Materials and Methods

Patients presenting with the complaint of ED between October 2014 and December 2015 were evaluated.

A careful and detailed anamnesis was taken to eliminate psychogenic and neurological factors. Genital examination and neurological examination, including perianal sensation, anal sphincter tonus and bulbocavernosus reflex, were made. International Erectile Function Index Questionnaire - Erectile Function Domain Scores (IIEF-EF) were calculated and ED degree was determined. The patients were also evaluated with Erection Hardness Score (EHS) and sexual encounter profile (SEP) 2 and 3 before the treatment. IIEF-EF score, EHS evaluation and SEP2 and SEP3 questions are present in Table 1.

Hormone tests and other laboratory tests, including follicle-stimulating hormone, luteinizing hormone, testosterone, prolactin, and blood glucose tests, urinalysis, kidney and liver function tests, lipid profile and complete blood count of the patients were evaluated.

Penile Doppler ultrasonography (PDU) was performed in all patients with suspected vasculogenic ED.

Table 1. Scores for erectile dysfunction evaluation parameters

IIEF-EF score
≤5: No attempts at intercourse
6-10: Severe ED
11-16: Moderate ED
17-21: Mild to moderate ED
22-25: Mild ED
≥26: "Normal" erectile function
EHS
Grade 1: Tumescence but no rigidity
Grade 2: Tumescence with minimal rigidity
Grade 3: Rigidity sufficient for sexual intercourse
Grade 4: Fully rigid erection
SEP2
In the past 4 weeks, were you able to penetrate your partner?
Yes/No
SEP3
Have you had an erection long enough for you to have successful intercourse?
Yes/No

IIEF-EF: The International Erectile Function Index Questionnaire - Erectile Function Domain Score, EHS: Erection Hardness Score, SEP2: Sexual Encounter Profile 2, SEP3: Sexual Encounter Profile 3, ED: Erictile dysfunction

Before the PDU, 60 mg papaverine HCl was intracavernosally injected using a 26-gauge 2 mL injector from the proximal 1/3 part of the penis. Then, at the 5th, 10th, 15th and 20th minutes, arterial and venous penis flows were evaluated. Acuson S2000, 9 MHz linear probe (Siemens Medical, Erlangen, Germany) was used for measurements. In patients with a peak systolic blood flow velocity below 30 cm/second, arterial insufficiency (arteriogenic ED), in patients with end-diastolic flow velocity, venous insufficiency (venogenic ED) and in patients with both of these problems, the diagnosis of mixed ED was established.

A total of 23 patients in severe ED group with an IIEF-EF score of 10 and below and having arteriogenic ED based on PDU result were included in the study. These patients were separated into two groups: LI-ESWT + tadalafil 5 mg treatment (n=10) group and tadalafil 5 mg only (n=13) group. LI-ESWT (RENOVA, Direx Medical Systems, Israel) was applied once a week for four weeks in four different anatomic areas: the right and left corpus cavernosum and the right and left penile crura. The treatment was performed as follows: 5000 waves of 0.09 mJ/mm^2, 300 intensity waves/min (5 Hz), 40 mm deep, in four areas (cavernosum right, left waves on each side 900, and left and right crus waves 1600 on each side); each session lasting 20 min with a one-week interval between each session (7,8). 5 mg tadalafil treatment was orally started once a day in both groups and the treatment was continued for three months. In the first and third months after treatment, the patients were re-evaluated with IIEF-EF score, EHS, SEP 2 and 3.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Necmettin Erbakan University Local Ethics Committee (approval number: 2017-822). Consent according to Helsinki Declaration was taken from the patients.

Inclusion Criteria

Patients over 20 years of age who were followed up for at least three months and had ED lasting more than three months, had a IIEF-EF score of ≤10, penile arterial deficiency based on PDU, EHS ≤2, no neurological, hematological, oncological or psychiatric disorder or penile anatomic anomaly and not using antiandrogen and not receiving radiotherapy were included in the study. All individuals who participated in the study were informed about the study and their written consents were obtained.

Statistical Analysis

LI-ESWT + tadalafil and tadalafil only groups were statistically compared. The chi-square (χ^2) test was used for analysis of the relationship between categorical variables. For comparisons between two groups, Student's t test and Mann-Whitney U test were used as appropriate. Two-Way ANOVA was used to assess the changes in pre-treatment and post-treatment variables. A p value of less than 0.05 was considered statistically significant. Statistical evaluation of data was made using SPSS 15 for Windows.

Results

The mean age of the patients in LI-ESWT + tadalafil and tadalafil groups was 52.7 (44-64) years and 54.2 (38-67) years, respectively (p=0.32).

No statistically significant differences were detected in the details of patient characteristics in two groups. Details of patient characteristics in the groups are shown in Table 2.

Table 2. Details of patient characteristics in the groups

	LI-ESWT + tadalafil 5 mg	Tadalafil 5 mg	p
Number (%)	10 (41.6)	13 (58.3)	
Mean age	52.7 (44-64)	54.2 (38-67)	0.32
Hypertension (%)	7 (70)	8 (61.5)	0.26
Diabetes mellitus (%)	6 (60)	7 (53.8)	0.34
Heart disease (%)	4 (40)	5 (38.4)	0.22
Dyslipidemia	3 (30)	4 (30.7)	0.42
Body mass index >30 (%)	4 (40)	4 (30.7)	0.17
ED duration >3 years (%)	8 (80)	10 (76.9)	0.59

ED: Erectile dysfunction, LI-ESWT: Low density linear shockwave treatment

In LI-ESWT + tadalafil 5 mg and tadalafil 5 mg only groups, the median IEEF-EF scores were as follows: before treatment: 7.1 (5-10), 7.6 (6-10) (p=0.26), 1 month after treatment: 10.6 (7-14), 9.35 (6-13) (p=0.1), and 3 months after treatment: 11.1 (7-14), 10.8 (7-13) (p=0.21), respectively. No statistically significant difference was detected in IIEF-EF scores measured before treatment and 1 and 3 months after treatment. At the end of the third month, the mean IIEF-EF score increased 4 points in LI-ESWT + tadalafil 5 mg group and 3.2 points in tadalafil 5 mg only group (p=0.33). In both evaluations made in 1 and 3 months after treatment, there were two (20%) patients with an EHS score of >2 in LI-ESWT + tadalafil 5 mg group and three patients in tadalafil 5 mg only group. No statistically significant difference was detected in EHS score in 1 and 3 months after treatment between the groups (p=0.16 and p=0.16, respectively). No statistically significant difference was detected in the rate of patients reporting positive responses to SEP2 and SEP3 in 1 and 3 months after treatment between the groups (p=0.25 and p=0.25, respectively). Pre- and after-treatment IIEF-EF

scores and EHSs, and the rate of patients who reported positive responses to SEP2 and SEP3 are given in Table 3. None of the patients reported a significant side effect or discomfort due to LI-ESWT treatment.

Table 3. International Erectile Function Index Questionnaire – Erectile Function Domain Score, Erection Hardness Score and Sexual Encounter Profile 2, Sexual Encounter Profile 3 positive patient ratios before and after treatment

	LI-ESWT + tadalafil 5 mg	Tadalafil 5 mg	p
Basal IIEF-EF score (median)	7.1 (5-10)	7.6 (6-10)	0.26
1st month IIEF-EF score (median)	10.6 (7-14)	9.35 (6-13)	0.1
3rd month IIEF-EF score (median)	11.1 (7-14)	10.8 (7-13)	0.21
Basal EHS >2 number of patients (%)	0 (0)	0 (0)	
1st month EHS >2 number of patients (%)	2 (20)	3 (23)	0.16
3rd month EHS >2 number of patients (%)	2 (20)	3 (23)	0.16
Basal SEP2 (+) number of patients (%)	1 (10)	1 (7.6)	0.25
1st month SEP2 (+) number of patients (%)	2 (20)	3 (23)	0.16
3rd month SEP2 (+) number of patients (%)	2 (20)	3 (23)	0.16
Basal SEP3 (+) number of patients (%)	0 (0)	0 (0)	
1st month SEP3 (+) number of patients (%)	1 (10)	1 (7.6)	0.25
3rd month SEP3 (+) number of patients (%)	1 (10)	1 (7.6)	0.25

IIEF-EF score: The International Erectile Function Index Questionnaire - Erectile Function Domain Score, LI-ESWT: Low density linear shockwave treatment, EHS: Erection Hardness Score, SEP2: Sexual Encounter Profile 2, SEP3: Sexual Encounter Profile 3

Discussion

ED treatment options have quite increased in time. PDE5i, intracavernosal injections and penile prostheses are used for treatment in general. Though these treatments are effective and safe, they are "optional" therapies. Although these treatments aim to improve sexual function and erection quality, their improving effects on erection mechanism are generally not permanent or natural. Search for a better treatment for spontaneously re-providing sexual activity in males is the next step in ED management. No significant progress has been achieved although researches on stem cell treatment or gene therapy are being continued (10).

Organic and psychological factors are the main underlying causes in ED etiology. Organic factors play a significant role in the etiology and vasculogenic factors primarily cause ED. Thus, diseases causing vascular pathologies are the main risk factors for vasculogenic ED and, ED risk increases nearly 1.5-4 times in the presence of these risk factors (11,12). Vasculogenic ED occurs with the relaxation problem in endothelium-dependent or endothelium-independent smooth muscle cells and atherosclerotic obstruction in cavernous arteries. As atherosclerosis affects the whole vascular system in the body, the earliest symptom is expected to occur in the artery with the smallest lumen diameter. Atherosclerosis-related symptoms in penile artery are observed in early period since the lumen of penile artery is also narrow (13,14).

Insufficient penile artery flow is responsible for 55% of EDs and severe penile arterial flow inadequacy in 90% of patients in whom a response to treatment cannot be achieved with PDE5i (15).

LI-ESWT has been used as a new therapy for ED in the last 10 years. Clinical studies and reports on this subject have increased especially in recent years. This means that LI-ESWT has gradually gained acceptance both by doctors and the patients (16).

Pelayo-Nieto et al. (8) applied LI-ESWT with 5000 shockwaves to 15 patients with mild-moderate ED once a week for four weeks and detected an increase of 5.46 (14.23-19.69) points in IIEF scores ($p<0.013$) and 33% recovery in patients with a EHS below 2 ($p<0.01$) in the evaluation they made at the end of the first month of treatment.

Vardi et al. (17) applied a total of six sessions of LI-ESWT (twice in three weeks) for nine weeks after administration of PDE5i treatment for a month in a sham-controlled study they made. According to the evaluation made one month after treatment, there was an increase of 6.7 points in IIEF score in the treatment group and 3 points in sham group ($p=0.0322$). Therate of patients with an EHS of 3 and above increased to 77.5% and the penile blood flow increase was also found to be significant in the treatment group. In the evaluation made in the third month, it was reported that IIEF score increased another two points.

Bechara et al. (7) applied LI-ESWT (four weeks, 5000 shockwaves once a week) in 20 patients irresponsive to PDE5i treatment. They reported a rate of response to treatment of 60% and an increase of 5.8 points in IIEF-5 score. The rate of patients reporting positive responses to SEP2 and SEP3 also increased at a statistically significant level. It was reported that only 20% of patients in this study (n=4) were in severe ED group and 3 out of 8 patients not responding to treatment (37.5%) were in severe ED group.

Chung and Cartmill (18) reported that IIEF score increased ≥5 points in 60% of patients in the evaluation made six weeks later on 30 patients who received LI-ESWT (3000 shockwaves, 6 weeks, once in two weeks).

In their placebo-controlled study, Olsen et al. (19) evaluated patients 5, 12 and 24 weeks after LI-ESWT (3000 shockwaves, 5 weeks) treatment lasting five weeks. Patients who had an EHS below 2 before the treatment were included in both groups. While the rate of patients with an EHS between 3 and 4 was 57% in the fifth week in LI-SWT group, it was measured as 54% in placebo group. These rates decreased in the 24th week to 19% and 23%, respectively. No significant difference was detected in IIEF scores between the two groups.

Srini et al. (20) applied LI-ESWT to patients responding to PDE5i and reported that 78% and 71% of patientshad a EHS between 3 and 4 in the first and fifth months, respectively.

Reisman et al. (21) reported that there was an increase of 8.5 points in IIEF-5 score in severe ED patients after LI-ESWT. It was reported that the rate of patients reporting positive responses to SEP3 increased from 25% to 60% in the first month.

Yee et al. (22) reported that there was no significant difference in IIEF and EHS scores between treatment and sham groups 13 weeks after LI-ESWT.

Although there been studies reporting that LI-ESWT provided a benefit in ED treatment, there are differences between the results. The reason for this may be the application of this treatment without separating ED patients into specific groups and application of different shockwaves for different durations with different protocols during the treatment. Moreover, in different studies, whether or not PDE5i was used before and during treatment may also have resulted in differences (7,17,18,19,20,21,22). Therefore, we tried to specify ED patients in our study and patients in severe ED group found to have arterial insufficiency based on penile Doppler ultrasonography results were included in the study group. We evaluated whether LI-ESWT treatment created a difference or not by giving PDE5i to both groups during the treatment. No significant LI-ESWT treatment-related side effect was observed in any of the previous studies, and in our study.

In a meta-analysis made quite recently, it was reported that IIEF of the patients in mild ED group increased significantly ($p<0.0001$) but a significant increase was not observed in IIEF in severe and moderate ED patients ($p=0.30$ and $p=0.49$, respectively). Additionally, in this study, it was reported that increased number of shockwaves and treatment periods less than 6 weeks cause a better therapeutic efficiency (23).

We applied 5000 shockwaves once a week for four weeks in our study. There was no difference between the two groups in diseases which could create vascular pathology. However, although we additionally gave tadalafil 5 mg/day to our LI-ESWT patient group, no significant difference was detected in IIEF score between them and the group given tadalafil 5 mg/day only. While IIEF-EF score increased 4 points in LI-ESWT + tadalafil group at the end of the third month, it increased 3.2 points in tadalafil group.

We assume that the main reason behind the significant difference found between the two groups after the treatment is the inclusion of severe arteriogenic ED patients in the study. Similarly, Bechara et al. (7) reported that 3 out of 4 patients in severe ED group were irresponsive to LI-ESWT. In addition, the form of LI-ESWT protocol and treatment duration are controversial in many studies (8,17,18,19). However it has been reported that treatment lasting longer than six weeks did not have a positive effect on the results (23). There is no study comparing the treatments lasting 4, 5 and 6 weeks. Thus, we have not found a difference between treatment responses since the LI-ESWT protocol we applied for four weeks was not satisfactory. A satisfactory recovery may not have occurred in the results since the rate of the presence of the diseases which could result in vascular pathologies was high in both groups.

These results showed that LI-ESWT + tadalafil treatment does not have any effect in patients with severe ED penile arterial insufficiency compared to tadalafil treatment only. Therefore, we assume that penile prosthesis treatment would be more appropriate in patients with severe ED, penile arterial insufficiency and in those not benefiting from medical treatment. LI-ESWT treatment is not reimbursed by the Ministry of Health of Turkiye and the cost of four-week treatment is nearly 4000 Turkish Liras (1072$) per patient. Its high cost makes the applicability of this treatment more difficult.

Study Limitations

Low number of patients, presence of diseases which may cause vascular pathologies in our patients (i.e. diabetes mellitus, hypertension and coronary heart disease) and the cost of the treatment can be counted among our limitations for applying the treatment only four weeks and for not increasing the number of LI-ESWT sessions.

Conclusion

LI-ESWT can be applied without any significant side effects and has positive effect on the results. However, it provides no advantage in patients with severe ED or penile arterial insufficiency. Studies separating larger number of participants into more specific ED groups are required to evaluate the treatment efficacy better.

Ethics

Ethics Committee Approval: The study was approved by the Necmettin Erbakan University Local Ethics Committee (approval number: 2017-822).

Informed Consent: Consent form was filled out by all participants.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.G.S., C.K., Concept: M.G.S., C.K., Design: M.G.S., C.K., Data Collection or Processing: M.G.S., C.K., Analysis or Interpretation: M.G.S., C.K., Literature Search: M.G.S., C.K., Writing: M.G.S., C.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Hatzimouratidis K. Reply to Pero Bokarica's letter to the editor re: K. Hatzimouratidis, I. Eardley, F. Giuliano, I. Moncada, A. Salonia. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. European Association of Urology Website. http://uroweb.org/guideline/male-sexual-dysfunction/. Updated 2015. Eur Urol 2015;68:e78.
2. Akkus E, Kadioglu A, Esen A, Doran S, Ergen A, Anafarta K, Hattat H; Turkish Erectile Dysfunction Prevalence Study Group. Prevalence and correlates of erectile dysfunction in Turkey: a population-based study. Eur Urol 2002;41:298-304.
3. Ayta IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. BJU Int 1999;84:50-56.
4. Ciftci H, Gumus K, Yagmur I, Sahabettin S, Çelik H, Yeni E, Savas M, Gulum M. Assessment of Mean Platelet Volume in men with vasculogenic and nonvasculogenic erectile dysfunction. Int J Impot Res 2015;27:38-40.
5. Dhir RR, Lin HC, Canfield SE, Wang R. Combination therapy for erectile dysfunction: an update review. Asian J Androl 2011;13:382-390.
6. Lei H, Liu J, Li H, Wang L, Xu Y, Tian W, Lin G, Xin Z. Low-intensity shock wave therapy and its application to erectile dysfunction. World J Mens Health 2013;31:208-214.
7. Bechara A, Casabé A, De Bonis W, Nazar J. Effectiveness of low-intensity 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;68:152-160.
8. Pelayo-Nieto M, Linden-Castro E, Alias-Melgar A, Espinosa-Pérez Grovas D, Carreño-de la Rosa F, Bertrand-Noriega F, Cortez-Betancourt R. Linear shock wave therapy in the treatment of erectile dysfunction. Actas Urol Esp 2015;39:456-459.
9. Wang CJ, Wang FS, Yang KD, Weng LH, Hsu CC, Huang CS, Yang LC. Shock wave therapy induces neovascularization at thetendon-bone junction: a study in rabbits. J Orthop Res 2003;21:984-989.
10. 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;55:295-299.
11. Kefi A, Demir Ö, Seçil M, Esen A. Doppler ultrasonography in erectile dysfunction patients with risk factors. Turk J Urol 2005;31:202-206.
12. Martin-Morales A, Sanchez-Cruz JJ, Saenz de Tejada I, Rodriguez-Vela L, Jimenez-Cruz JF, Burgos-Rodriguez R. Prevalence and independent risk factors for erectile dysfunction in Spain: results of the Epidemiologia de la Disfuncion Erectil Masculina Study. J Urol 2001;166:569-574.
13. Persu C, Cauni V, Gutue S, Albu ES, Jinga V, Geavlete P. Diagnosis and treatment of erectile dysfunction-a practical update. J Med Life 2009;2:394-400.
14. Montorsi P, Montorsi F, Schulman CC. Is erectile dysfunction the "tip of the iceberg" of a systemic vascular disorder? Eur Urol 2003;44:352-354.
15. Rogers JH, Karimi H, Kao J, Link D, Javidan J, Yamasaki DS, Dolan M, Laird JR, Low RI. Internal pudendal artery stenoses and erectile dysfunction: correlation with angiographic coronary artery disease. Catheter Cardiovasc Interv 2010;76:882-887.
16. 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;71:223-233.
17. 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;187:1769-1775.
18. 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):46-49.
19. 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;49:329-333.
20. 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;22:7614-7622.
21. Reisman Y, Hind A, Varaneckas A, Motil I. Initial experience with linear focused shockwave treatment for erectile dysfunction: a 6-month follow-uppilot study. Int J Impot Res 2015;27:108-112.
22. 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;21:1041-1045.
23. 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;71:223-233.