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REVIEW ARTICLE

Controversies in low intensity extracorporeal shockwave therapy for erectile dysfunction

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Introduction

Despite major advances in the field of erectile dysfunction (ED) in the past decades, the current treatment paradigm is far from perfect and all available treatments have significant limitations. Oral PDE-5 inhibitors are commonly offered as initial treatment. Although highly effective in many patients, they do not alter the underlying pathophysiology of the erectile mechanism, which may continue on its downward spiral [1]. In addition, select PDE-5 inhibitors may still be costly. Furthermore, PDE-5 inhibitors may have undesirable adverse effects such as dyspepsia, headache, flushing, and dizziness [1, 2]. Another effective treatment for ED is intracavernosal injections (ICI) which includes monotherapy or a combination of prostaglandin E1, papaverine, and phentolamine. Despite a response rate of up to 90%, the thought of inserting a needle to the penis is undesirable to many patients. Furthermore, ICI can lead to penile pain, priapism, and fibrosis [2], further leading to treatment discontinuation. Intraurethral suppository is another non-invasive alternative with a moderate 43–60% success rate [2]. However, this option is often expensive and difficult to apply. Vacuum constriction devices are the least expensive option, incurring only a one-time cost of $150–$450 for unlimited short-term erections of ~20–30 min [2]. Vacuum constriction devices are typically cumbersome to use and have numerous unpleasant side effects such as transient penile petechiae, ejaculatory difficulties, and numbness [2]. Finally, surgical insertion of a penile prosthesis is a very viable option for men with any stage of ED. While a penile prosthesis provides a high rate of patient satisfaction, it is an invasive surgical procedure [2]. Penile prostheses have multiple potential complications as well that are beyond the scope of this article. In summary, all current treatment options for vasculogenic ED have multiple limitations, including decreased sexual spontaneity, local side effects, risk of priapism, compliance difficulties, and inability to reverse the underlying pathophysiology.

Low intensity extracorporeal shockwave therapy (Li-ESWT) is a novel treatment for ED that aims to reverse the pathophysiology of ED at the cellular level to provide long-term improvement and return of spontaneous erectile function [3]. Because Li-ESWT is minimally invasive, it is touted to be readily accepted and have minimal side effects.

Li-ESWT for erectile dysfunction

Li-EWST has been shown to positively affect the pathophysiology in various human disease states. Li-ESWT has been shown to alleviate cardiac myocardial ischemia and promote neovascularization, resulting in decreased chest pain and improved cardiac function in patients with angina pectoris and myocardial ischemia [4, 5]. Li-ESWT has also been shown to improve wound healing and decrease vein harvest site complications for patients undergoing coronary artery bypass graft surgery [6]. In patients with chronic diabetic foot ulcers, Li-ESWT increases local tissue perfusion and improves healing [7]. In urology, Li-ESWT has been evaluated a potential treatment option for Peyronie's disease, but success has been limited [1].

Several in vitro studies have demonstrated that Li-ESWT improves erectile machinery at the cellular level. Lin et al. [8] showed that Li-ESWT causes microtrauma, which induces neovascularization and increases expression of vascular endothelial growth factors (VEGF) and their receptor Flt-1.6 in erectile tissues. Other in vitro studies found that Li-ESWT directly increases NO synthesis in penile tissues, facilitating corporal smooth muscle relaxation and increased blood flow [9, 10]. These properties make Li-ESWT a promising modality for the treatment of vasculogenic ED.

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Table 1 Summary of all randomized controlled trials of Li-ESWT on erectile

	Previous PDE-5 inhibitor usage	Treatment group size	Follow-up	Number of sessions	Shocks per session	Energy/session (mL/mm2)	IIEF–EF	IIEF–EF–MCID	EHS >3	Hemodynamic evaluation
Olsen et al. [19]	Not specified	51	6 months	5 vs 0	3000	0.15	No	No	Yes	None
Vardi et al. [3]	PDE-5I Responder	46	3 months	12 vs 0	1500	0.09	Yes	NR	Yes	Veno-occlusive strain gauge plethysmography
Kalyvianakis [12]	PDE-5I Responder	30	12 months	12 vs 0	1500	0.09	Yes	Yes	NR	Triplex penile US
Fojecki [16]	Combined	63	1 month	5 vs 0	600	0.09	No	No	No	None
Kitrey [11]	PDE-5I Refractory	42	1 month	12 vs 0	1500	0.09	Yes	Yes	Yes	Veno-occlusive strain gauge plethysmography
Yee et al. [14]	Combined	30	1 month	12 vs 0	1500	0.09	SHIM used	NR	No	None
Fojecki et al. [17]	Combined	52	12 months	0+5 vs 5+5	600	0.09	No	No	No	None
Kalyvianakis [12]	PDE-5I Responder	21	6 months	6+6 vs 6+12	5000	0.05	Yes	Yes	NR	Triplex penile US
Srini e al. [18]	PDE-5I Responder	95	12 months	12 vs 0	NR	NR	Yes	NR	Yes	None

NR not reported

Li-ESWT has been available since 1990 [7], but it has only recently gained attention as a novel treatment for ED. Since the first randomized controlled trial on Li-ESWT for ED was published in 2012 [3], numerous groups have published their experience using this modality (see Table 1). Most studies demonstrate some clinical or physiologic improvement in patients with vasculogenic ED in the absence other etiologies such as malignancy and neurological conditions. Despite this interest, there are numerous limitations to these studies and many questions regarding this novel treatment modality remains unanswered. We herein address the controversies surrounding Li-ESWT for ED.

Controversies regarding Li- ESWT for ED

Reporting inconsistency

Grade A level (highest level possible) means that current literature evidence is satisfactory and that future evidence is unlikely to change any recommendation. This implies that there are numerous well-designed and adequately powered blinded randomized control trials that provide consistent results. The evidence for Li-ESWT and ED does not yet meet this standard. A list of current randomized controlled trials of Li-ESWT for ED (Table 1) will illustrate the variation in treatment protocols and reporting of outcomes.

In terms of patient satisfaction, the International Index of Erectile Function–Erectile Function domain score (IIEF–F) is often used and is a validated instrument to evaluate ED. The minimally clinically important difference (MCID) to demonstrate treatment efficacy is generally accepted to be a change of 3 points for mild ED, 5 for moderate ED, and 7 for severe ED. Another commonly used scoring tool is the Erection Hardness Score (EHS). In this system, achieving a score of 3 out of 4 was considered a significant clinical response because it is considered to be adequate for penetration. The Sexual Health Inventory for Men (SHIM), another validated questionnaire, was used in several of the trials. While these are all validated questionnaires, the difference in reporting of outcomes between studies of Li-ESWT makes it difficult to pool results into a single conclusion.

To be an effective treatment that reverses the pathophysiology of ED, Li-ESWT should have objective evidence demonstrating clinical improvement in penile blood flow or rigidity. However, these end-points were not evaluated in the majority of the trials conducted. Among the trials that do evaluate penile blood flow, the methodology varied. Vardi et al. [3] and Kitrey et al. [11] evaluated hemodynamics using veno-occlusive strain gauge plethysmography and found a significant increase in maximum and resting penile blood flow in the treated group, which was not seen in the control group. Kalyvianakis et al. [12] and Kalyvianakis et al. [13] used

triplex penile ultrasound and found significant improvement in the penile peak systolic velocity and resistive index in the treatment group but not the sham group.

The ideal patient

The optimal candidate for Li-ESWT is yet to be determined. Currently, only vasculogenic ED patients have been evaluated as candidates for Li-ESWT. Non-vasculogenic ED patients (i.e., patients with male hypogonadism, psychogenic ED, structural abnormalities) were excluded in the studies listed in Table 1. It is currently unclear which candidate within this heterogenous group of patients benefits the most from treatment. Several studies demonstrated a greater response in patients with severe ED. Yee et al. [14] noted significant improvement in IIEF–EF score in patients with severe ED (10.1 vs. 3.2 $p = 0.003$), but not in patients with mild or moderate ED. Kitrey et al. [11] demonstrated that Li-ESWT increased the IIEF–EF score by 5 points vs 0 for the sham group in patients with PDE-5 inhibitor refractory ED; 40% of this group had a change above MCID. This group also experienced improvements in penile blood flow on penile flow mediated dilatation technique (FMD) and 54% were able to achieve an EHS of 3 or higher after treatment. On the contrary, Kitrey et al. [15], in a follow-up survey of previous trials, showed that severe ED was a predictor for disease regression: of the 57% of responders with severe ED, less than half were able to maintain their benefit at 12 and 24 months after treatment.

The optimal treatment protocol

An ideal treatment protocol should theoretically maximize benefit while minimizing cost and unnecessary procedures. Currently, this has not been established for Li-ESWT for ED. In general, increased number of treatment sessions tend to lead to greater benefit with no increase in side effects. Fojecki et al. [16, 17] treated patients with the lowest number of total shocks. They were unable to demonstrate any significant benefit in terms of IIEF–EF or EHS with 5 or 10 weekly treatment sessions of 600 shocks per session. Trials that were able to demonstrate significant differences in either IIEF–EF or EHS performed at least 12 sessions of 1500 shocks each at 0.09 mL/mm^2. (Table 1) The only dose-response study was a 2-phase study by Kalyvianakis et al. [13]. In this study, 42 patients were randomized into 6 + 6 treatment sessions or 12 + 6 treatment session with 5000 shocks per session at 0.05 mL/mm^2. First and second treatment phase were performed 6 months apart to allow for evaluation between phases. In a pooled analysis of 6 vs.12 (6 + 6 sessions or 12 sessions after phase 1) vs18 (12 + 6 sessions) total sessions, there was significant change in IIEF–EF score in all three groups with the 18-session group seeing the most substantial benefit. The mean change in IIEF–EF score for 6, 12, and 18 sessions was + 3.1, + 5.2, and + 7.2, respectively ($p = 0.003$ for 6 vs 12; $p = 0.01$ for 12 vs 18). The MCID in IIEF–EF, SEP-3 score, and hemodynamic parameters all trended towards significance with 18 treatment sessions providing the greatest improvement. The side effects of all three groups were similar and very mild, suggesting that 18 sessions can be given with minimal consequences.

In summary, more shocks and stronger shocks typically lead to greater improvements in ED with minimal side effects. However, it is unclear when this effect plateaus. A cost-benefit analysis of additional treatment has not been done.

It is currently unclear whether a break between treatment sessions is beneficial for optimal tissue remodeling. The most prevalent practice is to split treatments into two batches with a 3 to 4 week break in between. The commonly used "twice 3 weeks" protocol (6 treatment sessions over 3 weeks followed by a period of rest and then another 6 treatments over 3 weeks) has been shown to be effective in several studies [3, 11, 12, 14, 18]. Alternatively, Kalyvianakis et al. [12] was also able to demonstrate that 12 consecutive sessions over 6 weeks provides good outcomes. There are currently no study directly comparing these two treatment protocols.

Other treatment-related details that are not adequately investigated include shocks per session, intensity of shockwave, type of probe used, and optimal location of shock coverage.

Sustainability of benefit

A major concern regarding Li-ESWT is the sustainability of the treatment. While the ESWT theoretically does address the etiology of ED at a local level, it does not correct systemic risk factors such as diabetes and atherosclerosis. Another concern is that the induced changes at the tissue level may regress over time. Since most of the published randomized trials have follow-up that is limited to less than 6 months (Table 1), the long-term efficacy is unknown. To date, the longest RCT conducted [12] followed 30 patients who had Li-ESWT and 16 patients with sham procedures for a 12-month period. They found that the mean IIEF–EF score, percent with MCID, and peak systolic velocity on triplex US was significantly improved in the treatment group at 12 months. However, other studies demonstrate a less durable effect. Olson et al. [19] demonstrated a significant improvement in patients achieving EHS > 3 at 1 month (57% vs. 9%, $p < 0.0001$). At their 6-month evaluation, only 19% of the treatment group (vs. 23% in placebo group) had EHS > 3. Kitrey et al. [15] followed 156 patients who were previously enrolled in two separate studies after the trials concluded. In this cohort, 63.5% of patients had an initial benefit in IIEF–EF score above MCID. This number decreased to 42.9% at 12 months and 34% at 24 months. Severe ED, history of diabetes, and previous response to PDE-

5 inhibitors all predicted decreased durability; of the initial responders with severe ED, only 23.3% had a sustained response at 24 months.

Cost analysis

To date, there has been no cost-benefit analysis done on Li-ESWT. What is known is that this treatment requires multiple sessions: the studies that have shown a significant benefit gave patients at least 12 treatment sessions over the course of 6 to 12 weeks. Each session, depending on the rate and number of shocks, can take up to 25 minutes plus setup time, patient travel time, and waiting time. This is time-intensive for both the patient and the physician's office, especially if repeat treatment sessions are warranted to maintain the therapeutic effects.

Conclusion

Despite the important progress made by various groups in investigating the utility of Li-ESWT as a minimally invasive treatment for vasculogenic ED, many questions remain unanswered. The sustainability of Li-ESWT is still unknown, as most of the evidence is limited to 6 months of follow-up. The optimal treatment protocol and patient population is also unknown. The AUA 2018 ED guidelines currently rated penile ESWT as conditional with Grade C evidence [1] and states that its use should only be in an experimental setting. Until these pressing questions discussed above can be answered this recommendation will likely remain in effect.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Burnett ArthurL, Nehra Ajay, Breau RodneyH, Culkin DanielJ, Faraday MarthaM, Hakim LawrenceS, et al. Dysfunction: AUA Guideline. J Urol. 2018;200:633–41.
2. Wood AJ, Lue TF. Erectile dysfunction. N Engl J Med. 2000;342:1802–13.
3. Vardi Y, Appel B, Kilchevsky A, Gruenwald I. Does low intensity extracorporeal shockwave 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.
4. 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.
5. Khattab AA, Brodersen B, Schuermann-Kuchenbrandt D, Beurich H, Tölg R, Geist V. et al. Extracorporeal cardiac shock wave therapy: first experience in the everyday practice for treatment of chronic refractory angina pectoris. Int J Cardiol. 2007;121:84–5.
6. Dumfarth J, Zimpfer D, Vögele-Kadletz M, Holfeld J, Sihorsch F, Schaden W. et al. Prophylactic low-energy shock wave therapy improves wound healing after vein harvesting for coronary artery bypass graft surgery: a prospective, randomized trial. Ann Thorac Surg. 2008;86:1909–13.
7. Young SR, Dyson M. The effect of therapeutic ultrasound on angiogenesis. Ultrasound Med Biol. 1990;16:261.
8. Lin G, Reed-Maldonado AB, Wang B, Lee YC, Zhou J, Lu Z. et al. In situ activation of penile progenitor cells with low-intensity extracorporeal shockwave therapy. J Sex Med. 2017;14:493–501.
9. Andersson K-E. Mechanisms of penile erection and basis for pharmacological treatment of erectile dysfunction. Pharmacol Rev.2011;63:811–59.
10. Gotte G, Amelio E, Russo S, Marlinghaus E, Musci G, Suzuki H. Short-time non-enzymatic nitric oxide synthesis from L-arginine and hydrogen peroxide induced by shock waves treatment. FEBS Lett. 2002;520:153–5.
11. Kitrey ND, Gruenwald I, Appel B, Schechter A, Massarwa O, Vardi Y. Penile low intensity shockwave treatment is able to shift PDE5i non-responders to responders: a double-blind, sham controlled study. J Urol. 2016;185:1550–5.
12. Kalyvianakis D, Hatzichristou D. Low-intensity shockwave therapy improves hemodynamic parameters in patients with vasculogenic erectile dysfunction: a triplex ultrasonography-based sham-controlled trial. J Sex Med. 2017;14:891–7.
13. Kalyvianakis D, Memmos E, Mykoniatis I, Kapoteli P, Memmos D, Hatzichristou D. Low-intensity shockwaves therapy for erectile dysfunction: a randomized clinical trial comparing 2 treatment protocols and the impact of repeating treatment. J Sex Med. 2018;15:334–45.
14. 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.
15. Kitrey ND, Vardi Y, Appel B, Shechter A, Massarwi O, Abu-Ghanem Y. et al. Low intensity shockwave treatment for erectile dysfunction – how long does the effect last?. J Urol. 2018;200:167–70.
16. Fojecki GL, Tiessen S, Osther PJS. Effect of low-energy linear shockwave therapy on erectile dysfunction—a double-blinded, sham-controlled, randomized clinical trial. J Sex Med. 2017;14:106–12.
17. Fojecki GL, Tiessen S, Osther PJ. Effect of linear low-intensity extracorporeal sohckwave therapy for erectile dysfunction—12 month follow-up on a randomized, double-blinded, sham-controlled study. J Sex Med. 2018;6:1–7.
18. 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;22:7614–22.
19. Olsen AB, Persiani M, Boie S, Hanna M, Lund L. Can Low-intensity extracorporeal shockwave therapy improve erectile dysfunction. A prospective, randomized, double-blinded, placebo-controlled study. Scand J Urol. 2014;49:329–33.