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COMMENT

Clinical trial update on shockwave therapy and future of erectile function restoration

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Abstract

Our interim analysis of a phase II clinical trial on low-intensity extracorporeal shockwave therapy (Li-ESWT) for men with erectile dysfunction (ED) has demonstrated it is safe with no reported adverse outcomes. Interim analysis has demonstrated Sexual Encounter Profile 3 (ability to maintain erection till completion) was achieved in 60% of men prior to Li-ESWT, which increased to 90% after treatment. Nevertheless, limitations of our clinical trial include the lack of a sham arm and our inability to exclude men with psychogenic ED. We have begun recruitment of our phase III clinical trial that will allow assessment of treatment efficacy against a sham control arm. There exists substantial interest in the use of restorative therapies (i.e., Li-ESWT, stem cells, and platelet rich plasma) for men with ED with the potential to combine therapies to potentially lead to an augmented response.

Commentary

Erectile dysfunction (ED) is very common with 1 in 5 US men being afflicted by this condition. ED can have deleterious effects on the quality of life of both the man and his partner [1]. Fortunately, there exists several well-established treatment options for ED which range from oral medications (i.e., phosphodiesterase-5 inhibitors) to more invasive interventions (penile prosthesis). However, these treatments, although highly effective in many men, fail to reverse the underlying pathophysiology of the condition [2]. Further, these treatments carry with them adverse events and contraindications that must be discussed and identified prior to initiating therapy. ED therapy also limits the spontaneity of a sexual encounter as it may require planning and therefore a treatment that aims to reverse the underlying cause is strongly desired [2]. Since the initial study by Vardi et al. in 2010 for the use of low-intensity extracorporeal shockwave therapy (Li-ESWT) for ED, there has been widespread media attention and excitement at the prospect of a non-invasive cure for ED [3]. Nonetheless, large well-designed randomized trials are required to confirm the effectiveness of therapy. Currently Li-ESWT is not approved by the Federal Drug Administration (FDA) for the treatment of ED and both the American Urological Association and Sexual Medicine Society of North America do not recommend its use outside of an investigational setting [4, 5].

The use of Li-ESWT within urology is not new with its application initially for the treatment of renal and ureteral calculi. Given its non-invasive technique and limited anesthetic requirements its use has branched substantially to other specialties with studies having been published within the cardiac and orthopedic literature [6, 7]. The full mechanism of how Li-ESWT has yet to be fully understood but numerous well-conducted rodent studies have provided the framework to the mechanism of action. Primarily, the main mechanism is stimulation of angiogenesis and restoration of blood flow. Prior studies have reported upregulation of various proangiogenic factors, such as vascular endothelial growth factor and endothelial nitric oxide synthase [8]. Other mechanisms include promotion of recruitment of endogenous progenitor cells and activation of Schwann cells, which has the ability for nerve generation which has been demonstrated in rat models with pelvic neurovascular injuries [9].

We are currently in the midst of completing a phase II clinical trial at the University of Miami (NCT03067987)

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using the MoreNova shockwave generator developed by DirexGroup (Canton, MA, USA) [10]. We have recruited 80 men with the following inclusion criteria: men aged 30–80 years old with a baseline IIEF-EF score of 11–25 (mild to moderate), total testosterone 300–1000 ng/dl, no history of neurologic or psychiatric disease or pelvic surgery or radiation, no anatomic malformations, and hemoglobin A1c ≤ 7.0%. Importantly, men already taking a phosphodiesterase-5 inhibitor (PDE5i) were assigned a washout period of 4 weeks before beginning the study and remained without PDE5i for the duration of the study. Patients were randomized in a 1:1 allocation ratio to receive one of two treatment protocols. Group A underwent five treatments of 720 shockwaves given over five consecutive days. Group B received six treatments of 600 shockwaves given every other day over two weeks. Each group received a total of 3600 shockwaves. The device delivered electromagnetic shockwaves in linear segments, circumferentially around the penis, with an energy intensity of ~0.09 mJ/mm. Minimal clinically importance difference (MCID) was defined as an increase in IIEF of ≥ 2 for patients with baseline mild ED (IIEF score of 17–25), and ≥ 5 for patients with baseline moderate ED (IIEF score of 11–16) at the end of six months. Our interim analysis has demonstrated MCID for the IIEF-EF was achieved in 66% of group A and 75% of group B, and the percentage of yes responses to Sexual Encounter Profile 3 went from 63 to 88% in group A and 58 to 92% in group B (Figs. 1 and 2). No treatment-related side effects were reported. The results are encouraging and will hopefully provide valuable data for the clinical efficacy of Li-ESWT. We have begun recruitment for our phase III clinical trial to assess the efficacy of Li-ESWT against a sham control group with an extended follow-up of 12 months (NCT03670628).

Other restorative therapies which are currently being investigated is the use of plasma rich proteins and mesenchymal stem cell (MSC) therapy. MSC therapy are thought to stimulate endothelial cell proliferation and lead to inhibition of endothelial cell apoptosis mediated by a paracrine mechanism. Unfortunately, survival rates of MSC is quite dismal when

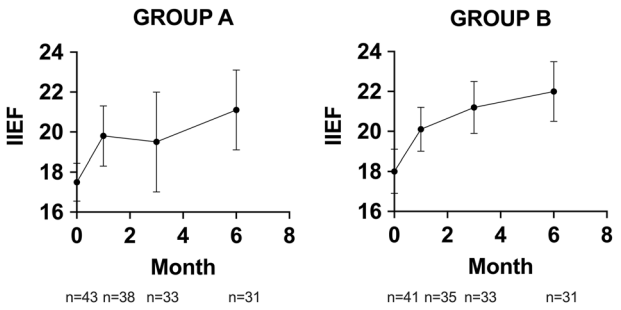

Fig. 1 IIEF scores at baseline, 1, 3, and 6 months for both treatment groups

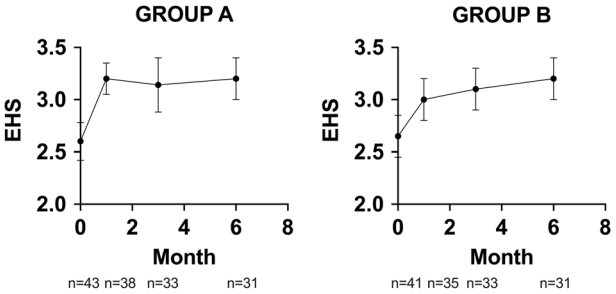

Fig. 2 EHS scores at baseline, 1, 3, and 6 months for both treatment groups

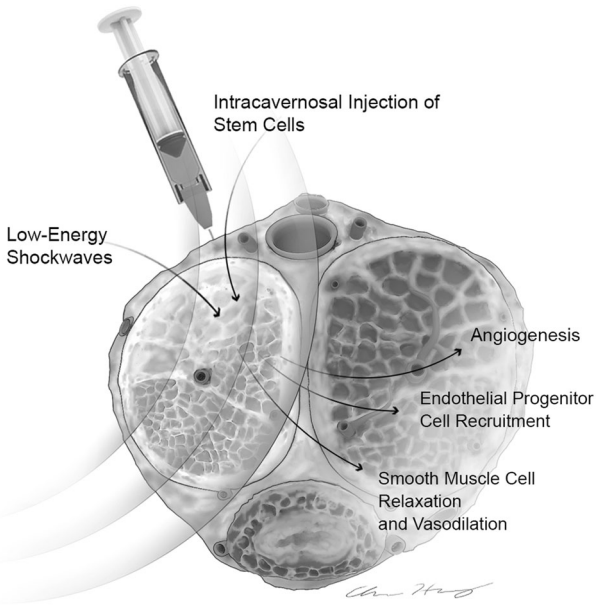

Fig. 3 Combination of shockwave and stem cells for erectile dysfunction may potentially lead to augmented therapeutic response

injected into the cavernosal tissue [8]. There has been evidence to suggest concomitant Li-ESWT and stem cell therapy leads to an increased proliferation rate of the stem cells which could have beneficial effects on the target tissue [11]. Fig. 3 illustrates the potential augmented response by dual therapy. A recent animal study found combination of Li-ESWT and adipose-derived mesenchymal stem cells lead to superior outcomes than either treatment modality alone in protecting against ischemia-reperfusion induced thigh injury [12]. This study has limitations in that it assessed acute ischemic injury which is unlike the pathophysiology of ED but demonstrates a potential augmented response by combined both Li-ESWT and stem cell therapy. Another study within the orthopedic literature found radial shockwaves lead to greater proliferation of MSCs as well as self-renewal in vitro and were found to accelerate cartilage repair in a rabbit model [7]. With respect to using Li-ESWT and MSCs for the treatment of ED, one study of 8-week old rats treated with a combination of both modalities found Li-ESWT stimulated MSCs to express more

VEGF than either treatment alone. Li-ESWT also increased the quantity of MSCs within the corpus cavernosum and has the potential to augment tissue repair [6].

The notion of restorative therapy that has the potential to reverse the underlying pathophysiology of ED is very exciting and has gained widespread media attention with numerous clinics offering Li-ESWT and stem cell therapy for the treatment of ED. Unfortunately, ongoing trials (NCT03670628) and future research is still required to truly determine the clinical efficacy of these restorative therapies. Until mature data become available, Li-ESWT and stem cell therapy are not FDA approved therapies for ED and not recommended by both the AUA and SMSNA outside of an investigational setting. Although highly enticing, we as physicians should continue to counsel patients to seek treatment options which have demonstrated clinical and long-standing efficacy.

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Compliance with ethical standards

Conflict of interest RR is the Principal Investigator for the Phase II & III Shockwave Clinical Trial. Remaining authors declare that they have no conflict of interest.

References

1. Rizk PJ, Krieger JR, Kohn TP, Pastuszak AW. Low-intensity shockwave therapy for erectile dysfunction. Sex Med Rev. 2018;6:624–30.
2. Young Academic Urologists Men's Health Group, Fode M, Hatzichristodoulou H, Serefoglu EC, Verze P, Albersen M. Low-intensity shockwave therapy for erectile dysfunction: is the evidence strong enough? Nat Rev Urol. 2017;14:595–606.
3. Vardi Y, Appel B, Jacob G, Massarwi O, Gruenwald I. Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. Eur Urol. 2010;58:243–8.
4. Burnett AL, Nehra A, Breau RH, Culkin DJ, Faraday MM, Hakim LS, et al. Erectile dysfunction: AUA guideline. J Urol. 2018;200:633–41.
5. SMSNA Position Statement On Restorative Therapies for ED. Accessed 10 December 2018. http://www.smsna.org/V1/news/433-smsna-position-statement-on-restorative-therapies-for-ed.
6. Wang J, Zhou C, Liu L, Pan X, Guo T. Clinical effect of cardiac shock wave therapy on patients with ischaemic heart disease: a systematic review and meta-analysis. Eur J Clin Invest. 2015;45:1270–85.
7. Zhang H, Li ZL, Yang F, Zhang Q, Su XZ, Li J et al. Radial shockwave treatment promotes human mesenchymal stem cell self-renewal and enhances cartilage healing. Stem Cell Res Ther. 2018; e-pub ahead of print 9 March 2018; https://doi.org/10.1186/s13287-018-0805-5.
8. Zhu GQ, Jeon SH, Bae WJ, Choi SW, Jeong HC, Kim SJ et al. Efficient Promotion of Autophagy and Angiogenesis Using Mesenchymal Stem Cell Therapy Enhanced by the Low-Energy Shock Waves in the Treatment of Erectile Dysfunction. Stem Cells Int. 2018; e-pub ahead of print 29 August 2018; https://doi.org/10.1155/2018/1302672.
9. Li J, Matheu MP, Sun F, Wang L, Sanford MT, Ning H, et al. Low-energy shock wave therapy ameliorates erectile dysfunction in a pelvic neurovascular injuries rat model. J Sex Med. 2016;13:22–32.
10. Katz JE, Molina ML, Clavijo R, Prakesh NS, Ramasamy R. A phase 2 randomized trial to evaluate different dose regimens of low-intensity extracorporeal shockwave therapy for erectile dysfunction: clinical trial update. Eur Urol Focus. 2018;4:336–7.
11. Raabe O, Shell K, Joessi A, Crispens C, Delhasse Y, Eva A, et al. Effect of extracorporeal shock wave on proliferation and differentiation of equine adipose tissue-derived mesenchymal stem cells in vitro. Am J Stem Cells. 2013;2:62–73.
12. Yin TC, Wu RW, Sheu JJ, Sung PH, Chen KH, Chiang JY et al. Reperfusion Injury of Quadriceps Muscle. Oxid Med Cell Longev. 2018; e-pub ahead of print 2 April 2018; https://doi.org/10.1155/2018/6012636.