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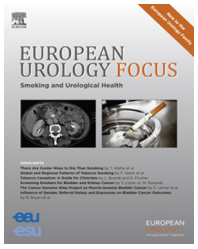

Clinical Case Discussion

A Phase 2 Randomized Trial To Evaluate Different Dose Regimens of Low-intensity Extracorporeal Shockwave Therapy for Erectile Dysfunction: Clinical Trial Update

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Internationally, several trials have investigated the efficacy of low-intensity extracorporeal shockwave therapy (LI-ESWT) for the treatment of erectile dysfunction (ED). These trials have included varying treatment protocols, with the delivery of between 6000 and 18 000 therapeutic shockwaves over a period of 6–10 wk. However, the results have thus far been equivocal [1–4]. It is noteworthy that multiple meta-analyses have demonstrated a significant improvement in ED with LI-ESWT, as measured via International Index of Erectile Function (IIEF) scores [5,6]. Nonetheless, the US Food and Drug Administration (FDA) has not approved LI-ESWT for ED in the USA.

In this clinical trial update, we report the results from a phase 2 clinical trial at the University of Miami investigating LI-ESWT using the MoreNova shockwave generator developed by DirexGroup (Canton, MA, USA). We are specifically investigating treatment protocols requiring fewer shockwaves over a shorter duration of time. The study is listed on ClinicalTrials.gov as NCT03067987. In brief, we recruited 80 men with ED. Our inclusion criteria were: men aged 30–80 yr with a baseline IIEF-EF score of 11–25, total testosterone 300–1000 ng/dl, no history of neurologic or psychiatric disease or pelvic surgery or radiation, no anatomic malformations, and hemoglobin A1c $\leq$7.0%. We did not exclude patients suspected of having psychogenic ED. We used RedCap software to register patients according to an embedded randomization schema developed by Stata (StataCorp, College Station, TX, USA), in which a block design was used to randomize the patients in a 1:1 allocation ratio to receive one of two treatment protocols. Importantly, men already taking a phosphodiesterase-5 inhibitor (PDE5i) were assigned a washout period of 4 wk before beginning the study and remained without PDE5i for the duration of the study.

Group A is undergoing five treatments of 720 shockwaves given over five consecutive days. Group B receives six treatments of 600 shockwaves given every other day over 2 wk. Each group receives a total of 3600 shockwaves. The device delivers electromagnetic shockwaves in linear segments, circumferentially around the penis, with an energy intensity of ~0.09 mJ/mm (Fig. 1). Subjects are assessed using both the IIEF and Erection Hardness Score (EHS) questionnaires at baseline and at 1, 3, and 6 mo after treatment. One-way repeated-measures analysis of variance (ANOVA) is used to calculate within-group differences in response to treatment. We also calculate the percentage of patients who reach the minimal clinically importance difference (MCID), which is an increase in IIEF of $\geq$2 for patients with baseline mild ED (IIEF score of 17–25), and $\geq$5 for patients with baseline moderate ED (IIEF score of 11–16) at the end of 6 mo [7]. Two-way repeated-measures ANOVA is used to determine whether there was a significant difference between groups A and B.

Thus far, 78/80 patients have begun the trial, of whom 21 have completed their treatment, eight in group A and

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https://doi.org/10.1016/j.euf.2018.07.011

Fig. 1 – The MoreNova shockwave generator used for this trial.

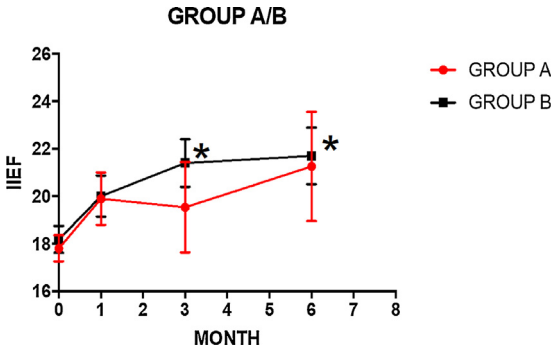

Fig. 2 – International Index of Erectile Function (IIEF) scores for groups A and B at baseline and at 1, 3, and 6 mo after treatment. * Statistically significant change from baseline.

Table 1 – Baseline characteristics for the two study groups.

Parameter	Group A	Group B
Age (yr)	60.8 ± 4.1	48.3 ± 4.3
Testosterone (ng/dl)	514.5 ± 52.0	466.8 ± 34.6
Hemoglobin A1c (%)	5.3 ± 0.1	5.6 ± 0.2
International Index of Erectile Function score	18.3 ± 1.2	17.6 ± 1.0
Erection Hardness Score	2.6 ± 0.3	2.7 ± 0.1

13 in group B. No side effects arising from the treatment were reported. Baseline characteristics are reported in Table 1. For group A there was no significant difference in mean IIEF or EHS scores at the different time points (Fig. 2). Nevertheless, 62.5% of the men achieved MCID according to IIEF scores. For group B, mean IIEF scores differed significantly between the time points. Post hoc tests using Bonferroni correction revealed that LI-ESWT elicited an increase in IIEF scores from baseline beginning at 3 mo (21.4 ± 1.3 vs 17.6 ± 1.0; $p = 0.009$) and continuing at 6 mo (21.8 ± 1.2 vs 17.6 ± 1.0; $p = 0.028$; Fig. 2). Furthermore, mean EHS scores differed significantly between all time points. However, post hoc tests using the Bonferroni correction revealed no statistically significant increases between specific time points. Similar to group A, 61.5% of men in group B achieved MCID. In addition, there was no statistically significant difference between groups A and B.

Preliminary results from our study provide further evidence that LI-ESWT is an effective and durable noninvasive treatment modality for ED. It is important to note that the findings were only significant for the group B treatment protocol; however, this is probably secondary to a greater number of group B patients having completed the trial at the time of this update. Therefore, our preliminary data demonstrate that a reduced treatment protocol with 3600 shockwaves delivered over 2 wk is effective for the treatment of mild to moderate ED. As more patients complete the trial, we will determine whether 1 wk of therapy is equally effective. In addition, since there is no sham group, we are unable to control for any placebo effect. Nonetheless our results are consistent with research in other countries, demonstrating a moderate clinically significant improvement in ED with LI-ESWT.

In conclusion, it has been shown that LI-ESWT is safe and effective as a treatment modality for ED. It has not been approved by the FDA as more studies in the USA are needed. LI-ESWT is best used for mild to moderate ED, is potentially more durable than PDE5i and less invasive than IPPs, and may play a major role in the future of ED treatment.

Conflicts of interest: Ranjith Ramasamy was provided with a MoreNova shockwave device by DirexGroup (the product manufacturer) and received support from the Barton Weiss Men's Health Initiative. The remaining authors have nothing to disclose.

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Please cite this article in press as: Katz JE, et al. 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), https://doi.org/10.1016/j.euf.2018.07.011