Low Intensity Shockwave Therapy (LiSWT) for Improvement of Erectile Function: Prospective Study and Engineering Studies (Goldstein et al., 2023)

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Introduction: The Softwave electrohydraulic shockwave device is FDA cleared for improved blood flow and connective tissue activation; retrospective studies in ED patients have shown positive outcome. There are limited engineering studies of energy absorption during shockwave treatment for ED.

Objective: To perform an analysis of sham/active treatment changes in primary outcome measures of grayscale ultrasound and DUS. To perform shockwave modeling to better assess energy absorption during shockwave treatment for ED.

Methods: A: A single-blind, sham-controlled, randomized, prospective study in men with ED naïve to acoustic wave therapy was performed. Those meeting inclusion/exclusion were randomized to one of two treatment arms and assigned to active or sham, 2:1 within each arm. Arm 1 consisted of three treatments of 5000 shocks every three weeks, 4 Hz, 0.12 mJ/mm2; arm 2 consisted of 5000, 3000 and 3000 shocks, 4 Hz, 0.12 mJ/mm2; weeks one, two and three respectively, three weeks without treatment, then repeat treatments every three weeks. First follow-up was 20 weeks after initial treatment; DUS and grayscale imaging using a 15.4 MHz probe were repeated under pharmacologic erection 3-4/4 hardness. Post-treatment grayscale percent hypoechoic regions within the corpora cavernosa were assessed: none (0), mild (1), moderate (2) and severe (3) and compared to baseline. Post-treatment EDV and PSV were compared to baseline. Upon completion subjects were unblinded. Subjects assigned to sham were crossed over to the opposite arm for active treatment. Subjects initially in active treatment underwent a second follow-up 32 weeks after initial treatment. Data from each treatment arm were analyzed by two-way repeated measures ANOVA with Geisser-Greenhouse correction. Follow-up pairwise comparisons to baseline were performed using Dunnett's multiple comparison test. In subjects with one on-treatment assessment, missing data due to early discontinuation from the study were imputed by the "last observation carried forward" method.

Methods B: This research used the Softwave TRT (MTS UroGold) electrohydraulic shockwave device. When sound waves pass through an interface between 2 media with different impedances, sound propagation can be significantly altered. If impedances of the media are different, part of the sound energy is reflected into the incident medium; the rest of the sound energy is transferred to the second medium. Sound propagation in tissue can be illustrated via computer simulation by mathematically calculating the damping and deflection of the sound wave by different tissue structures. Finite Element Method (FEM) simulation models are particularly suitable for the mathematical description of complex processes of shockwave propagation, such as in the flaccid and erect penis. Based on results, a "prediction" of propagation of LiSWT in tissue is possible. This patient-specific procedure is based on consideration of individual anatomical structures: corporal lacunar spaces and physical-acoustic laws. For FEM modelling of LiSWT propagation, program systems ANSYS, MATLAB and PZFLEX/ONSCALE were used.

Methods: C) 3-dimensional numerical non-linear shockwave modeling is used to evaluate the pressure field distributions during the application of low intensity shockwaves therapy to the penis for erectile dysfunction (Figure 1). Using water bath reference and phantom-based in-situ hydrophone sound pressure measurements, a systematic evaluation of a therapeutic application may be performed. A detailed knowledge of the soundwave propagation allows for evolutionary strategy-based optimization of ideal reflector geometries.

Results A: Powered for 60 subjects, recruitment was stopped (COVID) after randomizing 36 subjects (22 active, 14 sham). The proximal penis exhibited greatest improvement (decreased heterogeneity score) on grayscale. The number of subjects with improved erectile tissue grayscale ratings in the proximal region was consistently higher in active treatment versus sham groups (Arm 1 = 88.9% vs. 11.1%; Arm 2 = 40.0% vs. 20.0%, respectively). Sham subjects rolled over to active LiSWT also had improved grayscale ratings (Arm 1 = 33.3% vs. 11.1%; Arm 2 = 40.0% vs. 20.0%). Change in heterogeneity was statistically significant for the proximal region in active treatment Arm 1 at both Week 20 (p=0.005) and Week 32 (p=0.001). Mean IIEF-EF scores were nominally higher in subjects in active treatment with improved grayscale ratings versus those with no improvement on grayscale. Concerning penile blood flow, improvement after LiSWT greater numbers of patients had higher PSV or lower EDV relative to baseline; greater numbers of patients had no worsening in blood flow parameters. Decrease in EDV reached statistical significance in active treatment Arm 2 at Week 32 (p=0.003). Adverse events were transient.

Results B: Using the FEM calculation model of the simulation analyses, the shockwave pulse is applied at the bottom edge of the model (Fig 2-1) and propagates through the erect (Fig2- 2a) and flaccid (Fig 2-2b) states, with the most energy absorption in the erect penis, shown in red. Fig 2-3 shows the effect of increased penile pressure on energy absorption when the volume is constant.

Results C: Therapeutic longitudinal shockwaves reflected at the lateral end of application undergo phase-inversion at the air interface resulting in the local creation of an enhanced tensile wave about the boundary. The geometry of the genitalia creates a collecting reflection but due to the symmetry and phase mismatches no significant refocusing occurs at this secondary reflector. The addition of an applicator-matched reflector removes the enhanced tensile wave inside the treatment zone and provides a successive tertiary pulse of intensity between that of the insignificant primary and strongest secondary wave pulse. Figures A and B show tensile pressures of 3-dimensional numerical non-linear shockwaves. Fig A shows the traditional treatment method, while Fig B displays a reflector placed behind the penis with a layer of water acting as a buffer zone for potentially damaging tensile waves. The tensile pressure content inside the penis is significantly lower in B than A.

Conclusion A: Flaccid penile LiSWT appears to be safe and efficacious for treating ED based on statistically significant changes between sham and active treatments in primary outcome measures grayscale ultrasound and DUS.

Conclusion B: More energy is absorbed in cavernosal tissue during erection than in the flaccid state, with greater opportunity for beneficial mechanotransduction regenerative mechanisms. This is due, in part, to increased intracavernosal pressure and tissue volume with larger blood- filled lacunar spaces during erection. LiSWT to treat erectile dysfunction should be more effective when performed in the erect state.

Conclusion: In low-intensity shockwave therapy treatment of the penis much of the applicator's focal zone may extend past the body. The targeted use of a reflector may potentially improve clinical outcomes by i) reducing tissue stress due to tensile forces and potential damaging cavitation effects, and ii) enhancing the size of the treatment volume of a single pulse by refocusing the tertiary wave in rapid succession of the main treatment pulse, resulting in a potentially enhanced therapeutic efficacy.

Figure 1

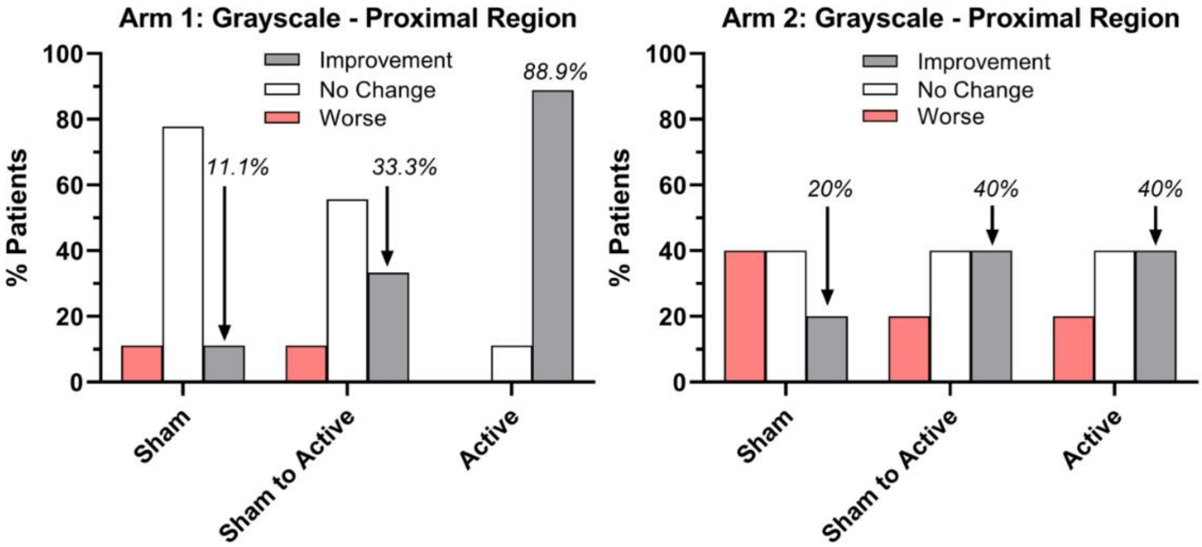

Figure 2

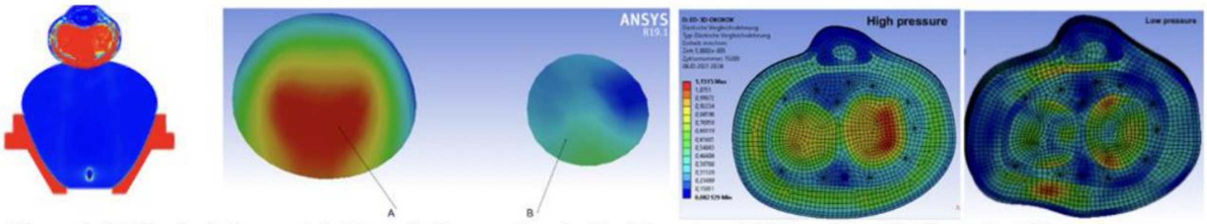

Figure 1. FEM calculation model. Figure 2. Energy absorbed in (a) erect and (b) flaccid penis. Figure 3. Effect of pressure.

Figure 3

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Study Performance: urogold100 applicator OP155