

Novel Low Intensity Shockwave Therapy Sham Delivery Method (Zero Energy) Assessed Objectively by Grayscale and Doppler Ultrasound Results

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Introduction: Most ED LiSWT studies use the IIEF as a primary outcome. While clinically relevant, the IIEF does not directly assess erectile tissue structure. To establish a more objective parameter, we investigated the estimation of hypoechoic area in grayscale ultrasound images of erectile tissue as an objective primary outcome for clinical trials assessing the efficacy of LiSWT. During erection, grayscale imaging of the penis demonstrates corpora cavernosa (CC) that is homogenous in healthy men and heterogeneous to varying degrees in men with ED. A critical aspect of using grayscale ultrasound is to determine that sham treatment reliably results in no significant improvement in erectile tissue structure. Other studies have used sham probes with cotton wadding or non-penetrable gel pads to dampen delivery of shockwave energy flux density, however a small amount of energy may still be delivered. We report a novel sham-controlled methodology in LiSWT RCT for ED.

Objective: To evaluate erectile tissue heterogeneity as an endpoint in LiSWT sham-controlled trials using grayscale analysis of percent hypoechoic regions in CC after sham delivery of zero energy flux density.

Methods: A single-blind, sham-controlled, randomized prospective study was performed in men with ED naïve to any kind of acoustic wave therapy. Those meeting inclusion/exclusion completed baseline assessments and were randomized to active or sham within each treatment arm. This interim sub-analysis only examined the sham group (n = 7). For each treatment, the shockwave device was already on in the exam room. When the subject was ready a curtain was suspended above his mid-section blocking the device, and noise cancelling headphones provided. When the probe was placed on the penis, a high-quality recording of shockwave sounds was activated for sham treatment. Twenty weeks after zero energy sham treatment, grayscale and DUS imaging using a 15.4 MHz probe under pharmacologic erection 3-4/4 hardness was performed before unblinding. Grayscale percent hypoechoic regions within the CC were assessed by computer-assisted histometry using Image J.(Fig 1) The IIEF was also administered to all

patients at baseline and week 20. Grayscale data were analyzed by two-way repeated measures ANOVA. IIEF-EF scores and bloodflow values (PSV and EDV) were compared using the Wilcoxon matched-pairs signed rank test.

Results: Compared to baseline, there were no significant changes ($p>0.7$; see figure) at week 20 in hypoechoic area in the proximal, middle, and distal erect penile shaft. (Fig 2) Furthermore, there were no significant changes in PSV ($p>0.15$), EDV ($p>0.2$), or IIEF-EF ($p>0.6$) from baseline to week 20.

Conclusion: Using computer-assisted histometry to determine hypoechoic area in grayscale ultrasound images to assess penile erectile tissue heterogeneity, we demonstrated that a novel sham treatment protocol that ensures zero energy delivery does not change erectile tissue integrity. The lack of improvement in PSV, EDV, and IIEF-EF further support our findings with grayscale ultrasound. Future studies will assess the appropriateness of grayscale ultrasound image analysis as a primary endpoint in LiSWT clinical trials.

Keypoints:

We evaluated sham delivery (zero energy flux density) on erectile tissue heterogeneity as an endpoint in low intensity shockwave therapy (LiSWT) trials using grayscale analysis of percent hypoechoic regions in corpora cavernosa (CC). Most ED LiSWT studies use IIEF as primary outcome, not directly assessing erectile tissue structure. Grayscale imaging of the penis during erection demonstrates CC homogeneity in healthy men and heterogeneity to varying degrees in men with ED. This single-blind, sham-controlled, randomized prospective studied men with ED naïve to acoustic wave therapy. Using computer-assisted histometry Image J, we calculated percent hypoechoic regions in CC at baseline and week 20 in the sham group ($n = 7$). Compared to baseline, there were no significant changes at week 20 in hypoechoic area in the proximal, middle, and distal erect penile shaft, or PSV, EDV, or IIEF-EF with zero energy delivery.