

Evaluation of clinical efficacy, safety and patient satisfaction rate after low-intensity extracorporeal shockwave therapy for the treatment of male erectile dysfunction: an Australian first open-label single-arm prospective clinical trial

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Objective

To evaluate the efficacy, safety and patient satisfaction rate with low-intensity extracorporeal shockwave therapy (LiESWT) in Australian men with erectile dysfunction (ED), as LiESWT induces neovascularisation and potentially enhances penile perfusion and improves erectile function.

Patients and Methods

Open-label single-arm prospective study of patients with ED with five-item version of the International Index of Erectile Function (IIEF-5) scores of >12 at baseline were enrolled after informed consent. Patient demographics, change in IIEF-5 and Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) scores, and overall satisfaction score (on a 5-point scale) were recorded. Treatment consists of 3000 shockwaves (1000 shockwaves to the distal penis, base of penis and corporal bodies at the perineum) twice weekly for 6 weeks.

Results

All patients had tried and failed oral phosphodiesterase type 5 inhibitors and most of the patients had had ED for >18 months [mean (range) 21.8 (6–60) months]. No side-effects to LiESWT were reported. Most patients reported an improvement in IIEF-5 score by 5 points (60%) and EDITS Index score by >50% (70%). Most patients were satisfied (scoring 4 out of 5; 67%) and would recommend the therapy to their friends (80%).

Conclusion

LiESWT appears to improve erectile function, is safe and potential plays an important role in penile rehabilitation in men whom failed medical therapy.

Keywords

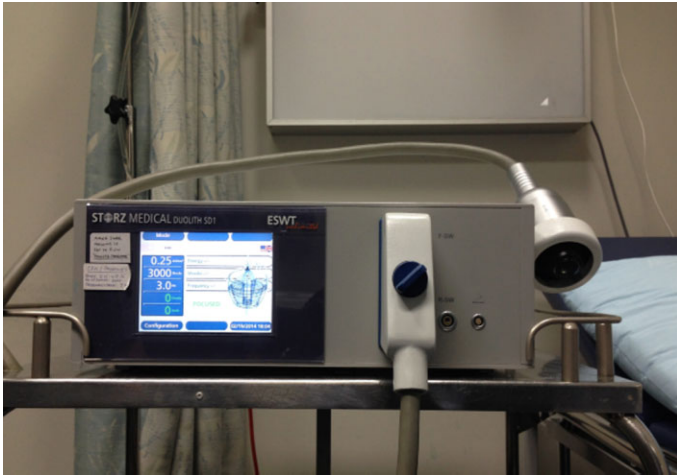
low-intensity extracorporeal shockwave therapy, erectile dysfunction, clinical outcomes, patient satisfaction, erectile function

Introduction

Erectile dysfunction (ED) is a common psychosexual condition affecting men across all ages and the current management strategies consist of a step-wise approach with modification of risk factors, optimisation of existing medical comorbidities followed by medical therapy, such as oral phosphodiesterase type 5 (PDE5) inhibitors and intracavernosal injection of vasoactive agents, with penile prosthesis implant reserved in the advanced stage [1]. While the efficacy of medical therapy is relatively high and the drugs are generally safe with minimal adverse effects, they treat the symptom of ED only and do not alter the underlying pathophysiology of the disease process.

The concept of penile rehabilitation is based on the premise that such therapy will eventually restore the erectile mechanism and allow men to regain spontaneous erection. Recent reports have indicated that low-intensity extracorporeal shockwave therapy (LiESWT) to the corpora cavernosa could play a role in penile rehabilitation [2,3]. Animal studies showed that LiESWT significantly improves penile haemodynamics and restores pathological changes in the penis of diabetic ED rat models [4,5]. Furthermore, LiESWT induces cellular microtrauma, and promotes angiogenesis by enhancing the expression of vascular endothelial growth factor [6,7] and recruitment of endothelial progenitor cells [8].

Fig. 1 The LiESWT was performed without local or systemic analgesia using Duolith SD1 ultra (Storz Medical AG, Tägerwilten, Switzerland) in the outpatient setting.



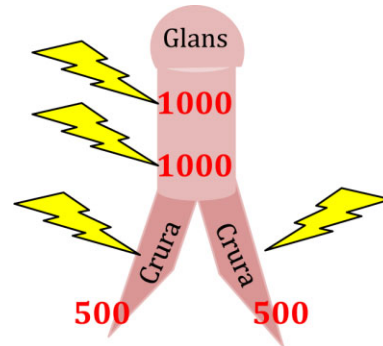
As a novel treatment method, LiESWT aims to restore natural and spontaneous erectile function and recent studies showed that LiESWT salvages men who were PDE5 inhibitor non-responders to become PDE5 inhibitor responsive [3]. To our knowledge this is the first Australian clinical study that evaluates efficacy, safety and patient satisfaction rate after LiESWT in men with ED.

Patients and Methods

Following internal departmental ethics approval, patients with ED were prospectively enrolled from June 2013 to June 2014 in this open-label single-arm study at the Department of Urology, Princess Alexandra Hospital, Brisbane Australia. All patients received informed consent based on contemporary literature regarding LiESWT for the treatment of ED. Inclusion criteria included: patient age ≥ 18 years, failed or unsatisfactory outcome with oral PDE5 inhibitors and/or intracavernosal vasoactive agents, five-item version of the International Index of Erectile Function (IIEF-5) score of ≥ 12 and patient has been in a stable sexual relationship for >3 months. Exclusion criteria were: patients who had severe ED (IIEF-5 score < 12), history of coagulopathy, on anticoagulants or newer anti-platelet therapy, previously received pelvic radiotherapy or androgen-deprivation therapy, or had any anatomical, neurological or hormonal abnormalities. Patient demographics, change in IIEF-5 and Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) scores, and overall satisfaction rate (on a 5-point scale) were recorded at 6 weeks and 4 months after completion of LiESWT.

The LiESWT was performed without local or systemic analgesia using Duolith SD1 ultra (Storz Medical AG, Tägerwilten, Switzerland) in the outpatient setting (Fig. 1). The frames for the penis and transducer were fixed by a special

Fig. 2 LiESWT treatment template using 3000 shockwaves with energy density of 0.25 mJ/mm^2 and emission frequency of 6 Hz, delivered to the distal penis (1000 shockwaves), base of penis (1000 shockwaves), and corporal bodies on the perineum (500 shockwaves to each crura).



holding post provided by the manufacturer. All patients were treated twice weekly for 6 weeks, comprising of 3000 shockwaves delivered to the distal penis (1000 shockwaves), base of penis (1000 shockwaves), and corporal bodies on the perineum (500 shockwaves to each crura) (Fig. 2). As the depth of the shockwaves reaches both corpora, treatment was delivered on one side of the penile shaft only. The 3000 shocks at an energy density of 0.25 mJ/mm^2 and emission frequency of 6 Hz were delivered according to the manufacturer's guidelines. Each treatment session lasted 15 min. The shockwave generator implemented in our study has been used in the treatment of tenosynovitis and tendonitis. Adverse events such as penile pain, bruising and haematuria were recorded.

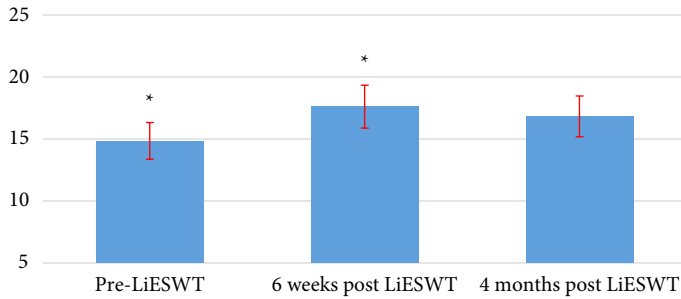
Statistical analysis was performed with SAS 9.1.3 (SAS Institute, Cary, NC, USA) computer software with values of the study variables compared using the Student *t*-test or Wilcoxon signed-rank test, as appropriate. A chi-square contingency analysis was used to examine the relationship between erectile function score and treatment satisfaction, with statistical significance set at 5%.

Results

Patient Demographics

In all, 30 patients were recruited into this trial. The mean (median, range) age was 55.8 (48, 42–68) years and most of the men (80%) had reported ED for >18 months [mean (range) 21.8 (6–60) months]. Cardiovascular risk factors were present in 26 patients with 10 patients reporting previous ischaemic heart disease and 10 patients had diabetes mellitus. The causes of ED were vasculogenic (27) and radical prostatectomy (3). The mean (range) IIEF-5 score was 14.8 (12–18) and most of the patients had a moderate ED classification (60%).

Fig. 3 Comparison of the mean IIEF-5 scores before and after LiESWT. * $P < 0.05$ and represents significance of difference between the two groups.



Efficacy, Safety and Patient Satisfaction Rate

At 6 weeks after completion of LiESWT, 18 (60%) patients reported a ≥ 5 points improvement in IIEF-5 score (Fig. 3). Of these men, 15 patients were able to achieve spontaneous erections sufficient for sexual penetration. An improvement in EDITS index score of $>50\%$ were reported in 21 (70%) patients. At the 4-month follow-up, these improvements persisted with no change in the IIEF-5 and EDITS index scores. Greater improvement in erectile function was reported in men with vasculogenic ED than those following radical prostatectomy ($P < 0.05$).

All patients completed the treatment study and there was no adverse events reported.

Most patients were satisfied and scored 4 out of 5 (20 patients; 67%) for LiESWT and would recommend this therapy to their friends (24 patients, 80%). There was a positive correlation between men who reported improvement in erectile function and treatment satisfaction level with LiESWT ($P < 0.05$).

Discussion

The current treatment strategies for ED consists predominantly of treatment options that do not address and/or restore underlying pathological changes in the penis and are often associated with various treatment-related side-effects. A treatment regimen that offers men a safe rehabilitative or even curative intent to regain spontaneous erection is an ideal goal. Recent publications show that LiESWT can restore natural and spontaneous erectile function by improving penile haemodynamics and underlying pathological changes through its angiogenic properties [2,3,8,9].

Vardi et al. [10] first reported the use of LiESWT in the treatment of ED. In that study, 10 of the 20 patients recovered good erectile function without the need for further oral therapy at 6 months. A follow-up randomised, double-blind, sham-controlled study from the same group 2 years later showed that LiESWT had a positive short-term clinical and

physiological effect on erectile function, and $\approx 50\%$ of patients recovered spontaneous erection sufficient for sexual penetration [11]. Similarly in our present study, 60% of patients reported ≥ 5 -point improvement in IIEF-5 score and 50% of patients were able to achieve spontaneous erections sufficient for sexual penetration.

In our present study, men with vasculogenic ED responded better to LiESWT than men who developed ED after radical prostatectomy ($P < 0.05$). It is likely that the underlying postoperative cavernosal nerve injury was associated with greater expression of pro-fibrotic factors and therefore limited the effects of LiESWT in cavernosal neovascularisation and neuro-regeneration. Hence current publications only support the role of LiESWT in men with vasculogenic ED [2,3].

As expected and akin to published data, LiESWT appears to be safe and highly tolerable in our present study. All of our present patients completed the treatment course with no discontinuations and no patient reported penile pain, bruising or haematuria during or at subsequent follow-up visits. It is possible that the high patient satisfaction rate in our present study may be due to a positive experience with LiESWT, and that most patients valued the potential to regain spontaneous erection without the need for medical therapy after LiESWT.

In contrast to the LiESWT machine used by Vardi et al. [10,11], the Omnispec ED1000 (Medispec Ltd, Yehud, Israel) that utilised electrohydraulic principle, the Duolith SD1 machine used in the present study employed electromagnetic source to deliver low-energy shockwaves to the cavernosal tissues. The electromagnetic shockwave can be delivered at the maximal energy density of 1.25 mJ/mm^2 at 65 mm penetration depth and it delivers a constant energy across the penetration depths. At present there is no study that directly compares the efficacy between these two modalities of LiESWT technology. Nonetheless we think the efficacy, safety and tolerability between these two machines should be similar based on the therapeutic effect of shockwaves.

We acknowledge the various limitations in our present study, such as the lack of a sham (control) arm, objective penile haemodynamic measurements, small number of participants and short-term follow-up. Furthermore, our treatment protocol is based on manufacturer's guidelines, which is probably derived from orthopaedic and cardiology research. Nonetheless, our present study outcomes concurred with the limited published data on LiESWT. We agree that further basic research is required to explore the various pathophysiological mechanisms of LiESWT on erectile tissue including long-term efficacy, safety and histological changes. While current data appears promising, several important factors pertaining to LiESWT, such as the modalities of shockwave energy, treatment templates and protocols, patient characteristics, actual physiological changes in the penile tissues and longer term success and safety have yet to be fully elucidated.

In conclusion, the potential appeal of LiESWT to provide sustained improvement in the erectile mechanism and cure ED, unlike current ED treatments, which are symptomatic and used on an on-demand basis, is exciting and novel. This proof-of-concept study shows LiESWT to be effective, safe and tolerable in Australian men in the short term. Additional studies with large multicentre, longer term, randomised and sham-controlled studies are required before LiESWT can be adopted as a standard therapy and indeed a treatment that can 'cure' ED.

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Conflicts of Interest

There is no conflict of interest or disclosure.

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Abbreviations: ED, erectile dysfunction; EDITS, Erectile Dysfunction Inventory of Treatment Satisfaction; IIEF-5, five-item version of the International Index of Erectile Function; LiESWT, low-intensity extracorporeal shockwave therapy; PDE5, phosphodiesterase type 5.