


Early outcomes of short-course low intensity shockwave therapy (LiSWT) for erectile dysfunction: A prospective, randomized, double-blinded, sham-controlled study in Malaysia

William Lay Keat Ong¹  | Sivaneswaran Lechmiannandan^{1,2} | Yen Li Lim³ |
Devindran Manoharan¹ | Say Bob Lee¹

¹Department of Urology, Penang General Hospital, Penang, Malaysia

²Urology Unit, Hospital Raja Permaisuri Bainun, Ipoh, Perak, Malaysia

³Clinical Research Centre, Penang General Hospital, Penang, Malaysia

Correspondence

William Lay Keat Ong, Department of Urology, Penang General Hospital, Jalan Residensi, 10990 Georgetown, Penang, Malaysia.
Email: william_olk@hotmail.com

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Abstract

Low-intensity shockwave therapy (LiSWT) has emerged as a promising non-invasive treatment modality for erectile dysfunction (ED) yet the well-designed randomized clinical trials are still lacking to prove its claimed benefits. A randomized, prospective, double-blinded sham-controlled study was conducted to evaluate the effectiveness and safety profile of short course LiSWT on vasculogenic ED patients. The International Index of Erectile Function-5 (IIEF-5) and Erection Hardness Score (EHS) questionnaires were used for evaluation. Patients underwent weekly sessions for 4 weeks and were re-assessed at 1, 3 and 6 months post therapy. Fifty one patients were recruited and randomized into sham and treatment arms. The mean IIEF-5 scores were significantly improved in the treatment arm compared to worsening of scores in the sham arm after 1 month (14.1 vs. 9.3 $p < 0.001$), 3 months (14.9 vs. 8.6, $p < 0.001$) and 6 months (14.2 vs. 7.9, $p < 0.001$) post treatment. A significant improvement of EHS was demonstrated at 1 month (2.4 vs. 1.8, $p = 0.001$, 3 months 2.7 vs. 1.7, $p < 0.001$) and 6 months (2.7 vs. 1.6, $p < 0.001$) in the treatment arm compared to sham arm. The success rate based on IIEF score increment more than five points was 26% in treatment arm and 0% in sham arm. Improvement in EHS score ≥ 3 in the treatment versus sham arm was 63% and 4%, respectively. There was no adverse effect reported. This 4-week LiSWT protocol reflects better treatment compliance, and it prevents further deterioration of erectile function among this cohort of patients. This study proves that LiSWT is a well-tolerated treatment with modest improvements in erectile function and hardness, among patients with vasculogenic ED.

KEYWORDS

erectile dysfunction, erection hardness score, international index of erectile function-5, low-intensity shockwave therapy

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1 | INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance (NIH Consensus Conference, 1993). It is prevalent but under reported and treated in Malaysia. Many population-based prevalence studies have been conducted throughout the world, including Malaysia. Ab Rahman et al. (2011) demonstrated that 69.5% of men aged 40 years and above in primary care clinics reported ED to some extent (Ab Rahman et al., 2011). Increasing age, diabetes mellitus (DM), hypertension and ischemic heart disease have been associated with ED among men (Lewis et al., 2004). Non-surgical treatment by means of pharmacological or device intervention has proven to be safe, effective, and financially acceptable in treating ED (Mobley et al., 2017). However, treatment of the underlying pathology, particularly vascular changes among the diabetic patients, structural cause due to trauma or neurological injury secondary to prostatectomy, were not addressed. Low intensity extracorporeal shock wave therapy (LiSWT) deemed as a novel treatment modality, addresses the reversal of pathophysiological process in the course of vasculogenic ED (Ito et al., 2009). LiSWT is unique as it aims to restore the erectile mechanism in order to enable natural or spontaneous erections (Gruenwald et al., 2013; Lu et al., 2017).

While several published trials proving the efficacy of LiSWT, there have been no published Malaysian data on its efficacy and tolerability. We therefore decided to conduct a randomized controlled study of shockwave therapy for the treatment of ED to attain this information. We utilized a "short course" therapy (4 weeks session) protocol for this study as opposed to longer or repeated courses described in published clinical trials (Kalyvianakis et al., 2018). The objective of this trial was to assess the early outcome of LiSWT for erectile dysfunction in Malaysia and compare the results with similar trials done globally.

2 | MATERIALS AND METHODS

This was a prospective, randomized, double-blinded, sham controlled single centre trial conducted in Penang General Hospital, Malaysia. The study consisted of three phases, namely the screening phase, treatment phase and follow up phase at 1, 3 and 6 months. Study subjects were recruited by opportunistic screening from general outpatient and urology clinics. Others were directly referred by physicians for treatment of ED. The diagnosis of ED was made based on history and physical examination. Participants who were already on PDE5i medication, ceased their medication to allow a 2-week washout period before entering the study. They agreed not to take PDE5i until the end of 6 months period of study. All subjects completed the International Index of Erectile Function (IIEF-5) and Erection Hardness Score (EHS) response sheets by themselves at the stipulated interval pre and post therapy. Throughout the clinical study period, the subjects consented not to use any form of ED therapy. Detailed inclusion and exclusion criteria are listed in the Figure 1. A patient flow diagram is also presented in Figure 2.

All participants gave written informed consent before the study. The study was registered with National Medical Research Registry (No. NMRR-19-696-46324) and obtained ethical approval from the Medical Research Ethic Committee Malaysia (MREC) on 7th August 2019.

2.1 | Randomization and blinding

The study subjects were recruited between August 2019 till July 2020 and follow-up was carried out until December 2020. All eligible

Inclusion criteria:	
i.	Patients aged 18 years and older
ii.	Erectile dysfunctions symptoms which are present more than 1 month
iii.	Patients who voluntarily participated the study by signing an informed consent
iv.	Patients on ED medication who have withheld medications for a minimum of 2 weeks (drug washout period) prior to shock wave treatment
Exclusion criteria:	
i.	Uncorrected coagulation and bleeding disorders
ii.	active lesions or infections at the penis or pubic areas
iii.	Erectile dysfunction of psychological origin
iv.	Any psychiatric disorder
v.	Erectile dysfunction secondary to medications (use of corticosteroids, antipsychotic, antiandrogenic therapy, antidepressant, antiparkinsonians)
vi.	Spinal cord injury patients
vii.	Bladder cancer, prostate cancer, active colon cancer patients
viii.	Post radical prostatectomy or radical pelvic surgery patients
ix.	History of pelvic radiotherapy
x.	Penile implantation
xi.	Patients with sickle cell anemia
xii.	Endocrine diseases that occur with ED: acromegaly, gigantism, Addison's disease, hyperprolactinemia, androgenic deficiency, hypogonadism.
xiii.	Patients with neurological diseases (Parkinson's, CVD, dementia of any origin)

FIGURE 1 Inclusion and exclusion criteria

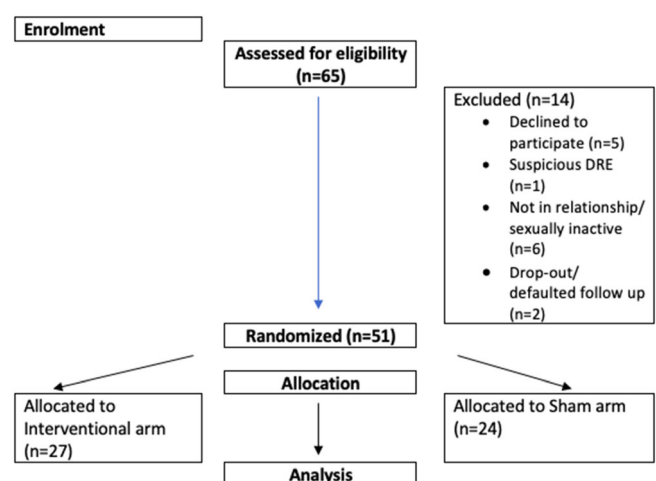


FIGURE 2 Low intensity shockwave therapy for ED consolidated standards of reporting trials flowchart

patients were randomized into Arm 1 or Arm 2 with an equal allocation ratio (1:1) (Figure 3). The randomization sequence was computer generated by the study coordinator. Treatment allocation was carried out in the proper manner for allocation concealment and bias minimization. The subjects and clinicians who were responsible for the data collection, were blinded to the treatment protocols of Arm 1 or Arm 2. The operators on the shockwave device, who were the assigned medical officer and assistants, maintained the generated randomization codes. COVID-19 precautions were strictly followed by patients and use of personal protective equipment by health care personnel as per hospital protocol was practised at all times.

2.2 | Description of study design

Study subjects were randomly assigned to Arm 1 (Shock wave therapy) for which a weekly session of 4 consecutive weeks of shock waves were applied with the following parameters: penetration depth of 10–15 mm, frequency of 8 Hz and intensity of 15–20; 2000 impulses distributed in the dorsum penis (both corpus cavernosum) and 2000 impulses were delivered to the perineal area (both crus penis). A total of 4000 impulses were delivered for each session. Piezowave², a shockwave device manufactured by Richard Wolf GmbH, Pforzheimer StraBe 32 Knittlingen Germany was used in our study. The Piezowave² provides focused and linear shockwaves with good precision, with easy operating modes and independent adjustment of the penetration depth and the intensity setting. It offers superior treatment parameters and organ coverage using a new linear shockwave tissue coverage technique (LSTC-ED) (Motil et al., 2016). It has piezoelectric element to generate shockwaves and linear double layer technology to apply shockwaves to the target area. In linear shockwave therapy (LSWT), the treatment area is 46 mm long and 4 mm wide with a penetration depth into the target organ of 5–20 mm. Shocks are delivered at a maximum rate of 480 PPM (8 Hz), resulting in shorter treatment sessions than with other shockwave devices. These characteristics combined with the LSTC-ED technique allows sufficient energy to be applied to the whole penile area in a very short space of time.

Linear shockwave tissue coverage technique was used by slowly moving the PiezoWave² linear probe orientated transversely over the treatment areas, lubricated well with the shockwave gel. On the other hand, the subjects who were assigned to Arm 2 (Placebo therapy/

sham device) received a weekly session of 4 consecutive weeks of placebo wave therapy. The similar device was placed over penis as per distribution in Arm 1, however, no impulse was delivered to the subjects as the gel pad prevented the passage of energy. Duration of each session was about 20–25 min. Measurements using validated IIEF-5 questionnaire scores and erection hardness scores (EHS) and of the adverse events of the therapy, at the beginning and the end of the treatment (1 month) and 3, 6 months after therapies were recorded (Mulhall et al., 2007; Rosen et al., 2011).

2.3 | Statistical analysis

We included 27 and 24 patients in treatment and sham arm respectively to detect the improvement of IIEF-5 mean score. Standard deviation [SD] was estimated as 6.1 according to the original article published in 2014 with 80% certainty of power and alpha 0.05 using power and sample size calculator (DuPont & Plummer, 1997). We also expected 20% dropout rate in each arm. Patient's characteristics were summarized as mean and standard deviation for continuous normally distributed variables, as median and interquartile range for non-normally distributed variables and as frequencies and percentages for categorical variables. The characteristics of the patients in both intervention and sham group were compared using independent *t*-test or Mann–Whitney *U* test, Pearson's chi-square test or Fisher's Exact test. Student *t*-test or Mann–Whitney was used to analyse the univariate significance between the intervention and sham group. The threshold for statistical significance was set at $p < 0.05$. All analyses were performed using SPSS version 15.

3 | RESULTS

3.1 | Demographics

A total of 51 patients were recruited for this study of which 27 patients underwent a 4-week course of low intensity shockwave therapy (treatment arm), while 24 patients were not given shockwave therapy (sham therapy arm). The median age was 59 years old (Interquartile range = 11 years).

There was no significant difference for all the baseline demographics between the two groups except for age (55.5 vs. 61, $p = 0.049$) and

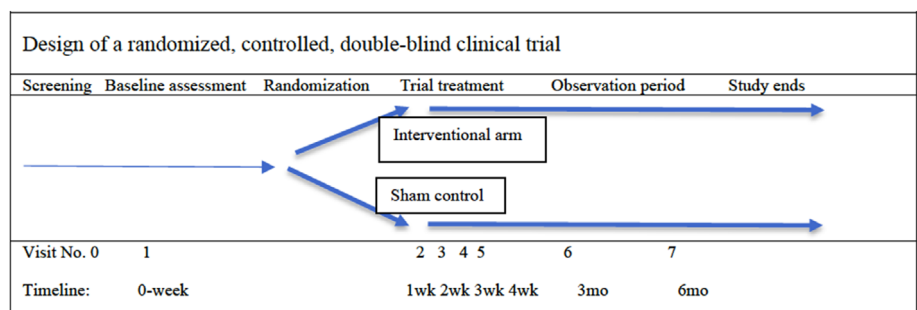


FIGURE 3 Schematic diagram of study design

Characteristics	Sham, n = 24	Intervention, n = 27	p Value
Age, median (IQR), years	55.5 (13)	61.0 (10)	0.049 ^a
Body mass index (BMI), median (IQR), kg m ²	25.5 (6.19)	25.6 (4.15)	0.992 ^a
Time to diagnosis, median (IQR), years	2.0 (3.50)	2.0 (3.00)	0.625 ^a
Race, n (%)			
Malay	8 (33.3)	10 (37.0)	0.803 ^b
Chinese	12 (50.0)	12 (44.4)	
Indian	3 (12.5)	5 (18.5)	
Others	1 (4.2)	0 (0)	
Smoking, n (%)			
Yes	8 (33.3)	6 (22.2)	0.531 ^b
No	16 (66.7)	21 (77.8)	
Co-morbid			
Yes	20 (83.3)	22 (81.5)	1.000 ^c
No	4 (16.7)	5 (18.5)	
Dyslipidemia			
Yes	3 (12.5)	14 (51.9)	0.006 ^b
No	21 (87.5)	13 (48.1)	
Hypertension			
Yes	15 (62.5)	14 (51.9)	0.573 ^b
No	9 (37.5)	13 (48.1)	
Diabetes mellitus			
Yes	13 (54.2)	13 (48.1)	0.781 ^b
No	11 (45.8)	14 (51.9)	
Ischaemic heart disease (IHD)			
Yes	7 (29.2)	3 (11.1)	0.160 ^c
No	17 (70.8)	24 (88.9)	
Benign prostatic hypertrophy (BPH)			
Yes	1 (4.2)	1 (3.7)	1.000 ^c
No	23 (95.8)	26 (96.3)	
Previous erectile dysfunction treatment			
Yes	10 (41.7)	14 (51.9)	0.577 ^b
No	14 (58.3)	13 (48.1)	
Severity of erectile dysfunction (ED)			
Severe	10 (41.7)	4 (14.8)	0.175 ^c
Moderate	4 (16.7)	7 (25.9)	
Mild moderate	9 (37.5)	15 (55.6)	
Mild	1 (4.2)	1 (3.7)	
No ED	0 (0)	0 (0)	
Baseline IIEF-5 Score, median (IQR)	10 (8)	12 (7)	0.129 ^a
Baseline Erection Hardness Score, mean (SD)	2.0 (0.69)	2.1 (0.83)	0.593 ^d

TABLE 1 Baseline demographics and disease characteristics between interventional group and sham group

Abbreviations: IQR, interquartile range; SD, standard deviation.

^aMann-Whitney *U* test.

^bPearson Chi-Square test.

^cFisher's exact test.

^dStudent *t*-test.

history of dyslipidemia (12.5% vs. 51.9%, $p = 0.006$). There was also no significant difference in baseline IIEF-5 score (10 vs. 12, $p = 0.129$) and

EHS score (1.96 vs. 2.07, 0.593) between both groups (Table 1). On subgroup classification of ED severity into mild, mild to moderate, moderate

and severe groups (mild: 17–21; mild to moderate: 12–16, moderate: 8–11, severe: 5–7), both treatment arm and sham therapy arm had similar compositions (p value = 0.175).

3.2 | IIEF-5 score improvement

A mixed between-within subjects analysis of variance (ANOVA) was then conducted to assess the impact of LiSWT on patients with ED across four treatment periods (Pre-treatment, post 1 month, post 3 months and post 6 months follow-up). Mauchly's test indicated that the assumption of sphericity had been violated ($\chi^2(5) = 16.87$, $p < 0.001$), therefore degrees of freedom were corrected using Greenhouse–Geisser estimates of sphericity. Overall, there was a significant interaction between shockwave intervention and time in terms of IIEF-5 score, ($F[2.389, 117.078] = 20.325$, $p < 0.001$, ηp^2 0.293) where the intervention group showed a significant increase in mean score from baseline to 1 month (baseline mean = 11.85; SD = 3.769, post 1 month mean = 14.07; SD = 4.132, $p < 0.001$, Cohen's $d = 0.562$), baseline to 3 months (baseline mean = 11.85; SD = 3.769, post 3 months mean = 14.93; SD = 14.150, $p < 0.001$, Cohen's $d = 0.775$), and up to 6 months post treatment (baseline mean = 11.85; SD = 3.769, post 6 months mean = 14.19; SD = 4.386, $p = 0.011$, Cohen's $d = 0.571$). In comparison, sham group showed a significant reduction in mean score only after 3 months post sham treatment (baseline mean = 10.00; SD = 4.222, post 3 months mean = 8.63; SD = 3.187, $p = 0.02$, Cohen's $d = -0.368$), after 6 months post sham treatment (baseline mean = 10.00; SD = 4.222, post 6 months mean = 7.88; SD = 2.643, $p = 0.001$, Cohen's $d = -0.603$). There was no statistically significant reduction in mean IIEF-5 score from baseline to 1 month post sham treatment.

It was noted that the two simple main effect analysis results were in the opposite direction (both significant statistically) and shows that

IIEF5 score increased significantly in patients who received the shockwave treatment from baseline up to 6 months post treatment, however, by contrast, those who received the sham treatment experienced a reduction in IIEF-5 score significantly post 3 and 6 months (Figures 4 and 5). The between subject effect comparing the two types of intervention was significant, ($F[1, 49] = 23.376$, $p < 0.001$, ηp^2 0.323) suggesting a significant difference in mean IIEF-5 score between the intervention and sham group.

Since there was significant difference in baseline characteristics with regards to age and history of dyslipidemia between the two groups, analysis was conducted to adjust for this. The final result still indicates a significant interaction between intervention with shockwave and time in terms of IIEF-5 score ($F[2.37, 111.4] = 15.339$, $p < 0.001$). The main effect comparing the intervention and sham group was still significant ($F[1, 47] = 21.828$, $p < 0.001$) suggesting a significant difference in mean IIEF-5 score between intervention and sham group.

When evaluating for success of treatment, defined as IIEF score improvement of more than five points, only 15%, 22% and 26% of patients in the treatment arm achieved such results at 1, 3 and 6 months, respectively. None of the patients in the sham arm had a 5-point increment (Table 2).

3.3 | Erection hardness score

A mixed between-within subjects analysis of variance (ANOVA) was then conducted to assess the impact of low intensity shockwave therapy on patients with erectile dysfunction across four time periods (Pre-treatment, post 1 month, post 3 months and post 6 months follow-up). Mauchly's test indicated that the assumption of sphericity had been violated ($\chi^2(5) = 29.142$, $p < 0.001$), therefore degrees of freedom were corrected using Greenhouse–Geisser estimates of sphericity. Overall, there was a significant interaction

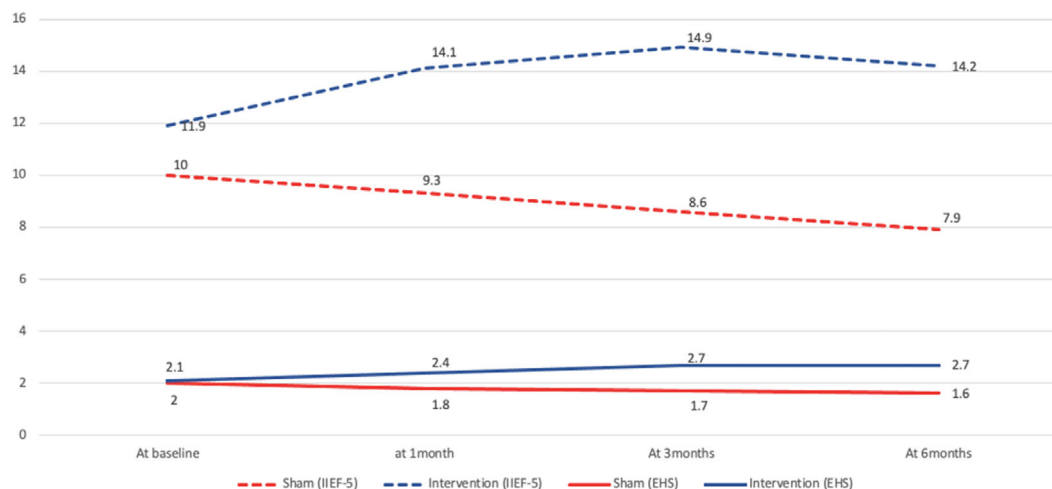


FIGURE 4 Graph showing the changes in mean IIEF-5 score and EHS between the patients in intervention and Sham group at baseline, 1, 3 and 6 months.

Proportion of ED severity groups in intervention and sham groups at baseline, 1 month, 3 months, and 6 months

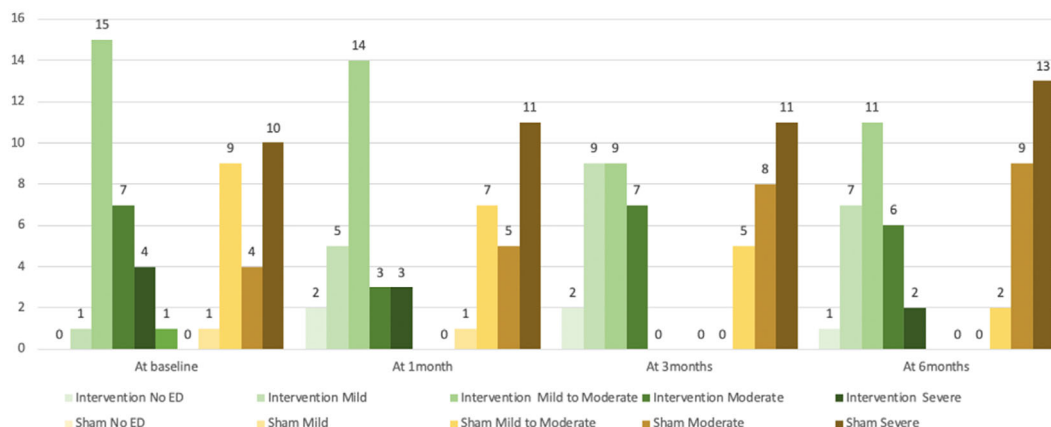


FIGURE 5 Proportion of ED severity groups in intervention and sham groups at baseline, 1, 3 and 6 months

IIEF-5 at least five points increased	Sham (n = 24)	Intervention (n = 27)	p Value
At 1 month			
Yes	0 (0)	4 (14.8)	0.113
No	24 (100)	23 (85.2)	
At 3 months			
Yes	0 (0)	6 (22.2)	0.024
No	24 (100)	21 (77.8)	
At 6 months			
Yes	0 (0)	7 (25.9)	0.011
No	24 (100)	20 (74.1)	

TABLE 2 Proportion of patients achieving at least five points increase in IIEF-5 score at 1, 3 and 6 months after treatment compared to baseline between intervention and sham group (using fishers exact test).

between intervention with shockwave and time in terms of EHS, ($F [2.129,104.329] = 22.061, p < 0.001, \eta p^2 0.310$) where the intervention group showed a significant increase in mean score from baseline to 1 month (baseline mean = 2.07; SD = 0.829, post 1 month mean = 2.44; SD = 0.751, $p = 0.004$, Cohen's $d = 0.468$), baseline to 3 months (Baseline mean = 2.07; SD = 0.829, post 3 months mean = 2.70; SD = 0.609, $p < 0.001$, Cohen's $d = 0.866$), and up to 6 months post treatment (Baseline mean = 2.07; SD = 0.829, post 6 months mean = 2.67; SD = 0.679, $p = 0.001$, Cohen's $d = 0.783$). In comparison, sham group showed a significant reduction in mean score only after 3 months post sham treatment (Baseline mean = 1.96; SD = 0.690, post 3 months mean = 1.67; SD = 0.637, $p = 0.032$, Cohen's $d = -0.440$), after 6 months post sham treatment (Baseline mean = 1.96; SD = 0.690, post 6 months mean = 1.58; SD = 0.584, $p = 0.007$, Cohen's $d = -0.587$). There was no significant reduction in mean EHS score from baseline to 1 month post sham treatment. Similarly, it was noted that the two simple main effect analysis results were in the opposite direction (both significant statistically) and showed that mean EHS score

increased significantly in patients who received the shockwave treatment from baseline up to 6 months post treatment, however, by contrast those who received the sham treatment experienced a reduction in mean EHS score significantly post 3 months and 6 months (see Figure 4). The between subject effect comparing the two types of intervention was significant, ($F[1, 49] = 18.087, p < 0.001, \eta p^2 0.270$) suggesting a difference in mean EHS between the intervention and sham group.

The final result still indicates a significant interaction between intervention with shockwave and time in terms of EHS ($F [2.109,99.115] = 14.975, p < 0.001, \eta p^2 0.242$). The between subject effect comparing the intervention and sham group was still significant ($F[1,47] = 15.863, p < 0.001, \eta p^2 0.252$) suggesting a difference in mean EHS between intervention and sham group.

With regards to significant improvement in erection hardness score, defined as EHS of 3 or more, 44%, 63% and 63% of patients in the treatment arm achieved significant erection hardness, at 1, 3 and 6 months, respectively. In the sham arm, only 8%, 8% and 4% of patients achieved this at similar time intervals (Table 3).

TABLE 3 Proportion of patients with EHS of at least 3 at 1, 3 and 6 months after treatment compared to baseline between intervention and sham group (using Pearson Chi Square test).

EHS ≥ 3	Sham (n = 24)	Intervention (n = 27)	p Value
At 1 month			
Yes	2 (8.3)	12 (44.4)	0.004
No	22 (91.7)	15 (55.6)	
At 3 months			
Yes	2 (8.3)	17 (63.0)	<0.001
No	22 (91.7)	10 (37.0)	
At 6 months			
Yes	1 (4.2)	17 (63.0)	<0.001
No	23 (95.8)	10 (37.0)	

3.4 | Adverse events

No adverse events such as minor skin bruises, hematoma, hematuria, urinary retention and chronic pain were reported during the course of our study. 9.8% (n = 5) of patients were on regular low-dose acetylsalicylic acid therapy (75–150 mg/day), but no adverse effects were demonstrated.

4 | DISCUSSION

Low intensity shockwave therapy (LiSWT) has recently emerged as a novel and promising modality in the treatment of vasculogenic ED. It is unique as it aims to restore the erectile mechanism for natural or spontaneous erections. The working theory behind this is that the applied shockwave will interact with the human tissues and subsequently induce a cascade of biological reactions, resulting in release of growth factors. This will in turn stimulate the neovascularization of tissue to improve the penile blood supply (Leu et al., 2021; Pan et al., 2016; Wang et al., 2003). Vardi et al. in 2012 conducted the first randomized, double-blind, sham-controlled study that showed LiSWT had a positive clinical and physiological effect on the erection of men who were PDE5i responders (Vardi et al., 2012). They found significant increase in the IIEF-EF domain score and improved penile hemodynamic after 1 month in the LiSWT group than in the sham-treated group. Since then, there have been many published studies that range from retrospective single arm observational study, to prospective double blinded RCTs, reporting positive short term and long term outcomes (Sokolakis & Hatzichristodoulou, 2019). Interestingly, a few meta-analyses have suggested that regardless of variation in setup parameters or treatment protocols, LiSWT can significantly improve the IIEF and EHS of ED patients (Campbell et al., 2019; Clavijo et al., 2017; Dong et al., 2019; Sokolakis & Hatzichristodoulou, 2019). However, the RCTs analysed in these meta-analyses had questionable results as those with multiple sessions on long term follow up had a high-dropout rate in both treatment and placebo arms. (Clavijo et al., 2017; Dong et al., 2019).

Srini et al conducted a double blind RCT comparing treatment arm with LiSWT of 12 sessions in 9 weeks against a sham placebo arm and followed up patients for 12 months. They found sustained improvements in IIEF, EHS and penile hemodynamic scores as early as 4 weeks but the dropout rates were high in both groups (Srini et al., 2015). The authors attributed these to lack of patient compliance due to long length of the treatment (12 sessions), early sufficient improvement in the treatment group and lack of improvement in the placebo group. They concluded that shorter protocols with perhaps fewer treatment sessions are to be evaluated to avoid the high-dropout rate. Fojecki and colleagues, on the other hand found no significant improvement on long term follow up in a similar RCT. In their study though, patients in the placebo arm were treated with LiSWT after 4 weeks and followed up for 12 months. The placebo arm had a non-significant improvement of ED compared to the treatment arm of 10 sessions. They too faced similar selection bias due to high dropout rate (Fojecki et al., 2017).

We therefore decided to implement a short treatment protocol of 4 weeks since improvement in ED was seen as early as 4 weeks and also to improve patient compliance and avoid high-dropout rates, as seen in the above-mentioned studies. This proved to be effective as we only had a 5% dropout rate, the lowest in any reported RCTs on shockwave therapy, thus strengthening the validity of our outcomes without selection bias.

While the results of our study showed significant improvements in EHS and modest increases in IIEF scores, it drew attention to a finding not seen in other studies. The sham arm (placebo group), showed some degree of deterioration in IIEF and EHS scores, particularly after 3 months from baseline. This may be due to strict compliance of not undergoing any ED treatment, observed among sham group patients throughout the study period. Unlike in other studies where sham group were given LiSWT treatment after 4 weeks, our study was designed to avoid this, to truly differentiate the treatment effect between both groups. The patients in both groups were aware of this and accepted the risk of having no treatment for 6 months. These results signify a time related progression in vasculogenic ED that requires early treatment intervention to avoid further deterioration in erectile function.

With regards to sustainability of treatment efficacy, the intervention group showed a sustained increase of mean score from baseline up to 6 months post treatment, enabling them to have substantial erections for sexual intercourse over a prolonged period of time. The lasting effect of LiSWT was evaluated in several clinical trials. Bechara et al reported that LiSWT treatment was effective in 60% of their PDE5i non-responders ED patients and the efficacy response was maintained for 12 months in 91.7% of these patients (Bechara et al., 2016).

Overall, we reported no serious adverse events related to LiSWT. 9.8% of patients were on regular low-dose acetylsalicylic acid (aspirin) therapy (75–150 mg/day) throughout the study period, with none developing hematoma or bleeding complications post therapy. We thus concluded that LiSWT is a safe treatment therapy. This outcome reverberates the results of similar clinical trials that also looked into

its safety profile. Future trials on LiSWT could thus safely explore the effect of increasing number of shockwaves and changing the penetration depth that could further enhance erectile function and hardness for penetration.

4.1 | Limitations

Our study was limited by several factors, one of which was the small sample size. However, we managed to achieve the minimum required number of subjects to power the study, particularly during this unprecedented COVID-19 pandemic as most of the urology outpatient appointments were significantly cut down (Ong et al., 2020). Despite there was a significant difference in baseline characteristics with regards to history of dyslipidemia between the two groups, additional sub-analysis will be required in future to determine whether LiSWT provides the same advantages regardless of independent comorbidities. We did not use duplex ultrasonogram to objectively diagnose vasculogenic erectile dysfunction as part of the selection criteria. Doing so, may have improved treatment outcome as evident in the studies by Vardi et al and Kitrey et al (Kalyvianakis & Hatzichristou, 2017; Kitrey et al., 2016; Vardi et al., 2010, 2012). Our trial was also not specifically powered to make distinctions between PDE5i responders and non-responders though some of the previous clinical trials suggested PDE5i responders showed significantly improved erectile function (Kitrey et al., 2016). We entirely relied on the patients' assessment based on IIEF-5 and EHS questionnaire as we felt this was more reflective of the real world scenario, where application of advanced diagnostics such as penile hemodynamics would not have been a practical investigation to be carried out in all urology centres. It can be argued that this diagnostic tool may stream down treatment benefit to those who are truly suffering from vasculogenic ED. Perhaps in the near future when such investigative devices are readily available to all, it can be incorporated as a routine pre-treatment assessment tool.

5 | CONCLUSION

In conclusion, this double blinded randomized study proves that LiSWT is a well-tolerated treatment modality that improves erectile function and hardness for penetration among our clinically diagnosed ED patients. The short 4-week protocol reflects better treatment compliance as opposed to protocols with longer duration and repeated sessions with higher dropout rates. While the improvement seen is modest, this study certainly demonstrates that LiSWT has an added benefit of preventing further deterioration of erectile function among this cohort of patients.

CONFLICT OF INTEREST

We declare that there is no conflict of interest in this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

State study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. The study protocol and any other documents that the Independent Ethics Committee (IEC) fulfilled its responsibilities including the Patient Information Sheet, Consent Form, subject requirement procedures to be used, were submitted to a properly constituted Independent Ethics Committee (IEC).

ORCID

William Lay Keat Ong  <https://orcid.org/0000-0002-3048-1170>

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