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2023

Background

At present, treatment of erectile dysfunction (ED) mainly includes a step-wise method to modify risk factors, optimise the medical comorbidities, and to carry out medical treatments like vasoactive agents given through cavernous body and phosphodiesterase type 5 inhibitors (PDE5i) administered orally; besides, a penile prosthesis may also be implanted in advanced cases. While many patients are satisfied with these treatments, others are not due to the poor efficacy or inability to use them. Furthermore, the above therapeutic means mainly aim to enhance erectile function but do not address the pathophysiological factors. Hence, shockwave therapy has been suggested as an alternative. The clinical term for this treatment used by urologists is low-intensity extracorporeal shockwave therapy (LI-ESWT). This therapy involves applying shockwaves to the penile shaft at a specified energy setting for a predetermined number of shocks per minute and for a set treatment duration and number of treatments. While its mechanism of action is still not completely elucidated, the low-intensity energy from shockwave therapy stimulates new blood vessel growth through a process called angiogenesis. This increases penile blood flow, which may improve erectile function. Although the number of systematic reviews/ meta-analyses is increasing, results were somewhat varied and there were inherent challenges in deciphering treatment outcomes due to variations in treatment protocols and patient populations. Given the controversy and lack of clarity surrounding LI-ESWT, as well as the increasing number of clinicians who are offering the treatment, this technology review was requested by the Director of Medical Practise Division, Ministry of Health Malaysia (MOH) to evaluate whether LI-ESWT can be used as an alternative to standard treatment for ED in Malaysia.

Objective

To assess the effectiveness, safety, and economic implication of LI-ESWT as a treatment option for men with ED.

Methods

The following electronic databases were searched through the Ovid interface: MEDLINE (R) ALL 1946 to 31st March 2023, EBM Reviews - Health Technology Assessment 4th Quarter 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to 28th March 2023, EBM Reviews - Cochrane Central Registered of Controlled Trials February 2023, EBM Reviews - Database of Abstracts of Review of Effects 1st Quarter 2016, and EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016. Parallel searches were run in PubMed, US FDA and INAHTA database while additional articles were retrieved from reviewing the bibliographies of retrieved articles. The search was limited to articles on human. There was no language limitation in the search. The last search was conducted on 4th April 2023.

Results and conclusion:

Efficacy/ effectiveness

There was substantial fair level of retrievable evidence to suggest that LI-ESWT improved erectile function regarding patient-subjective outcomes relative to those who received placebo/ sham control treatment for ED. Findings in general indicated that:

i. LI-ESWT increased the International Index of Erectile Function-Erectile Function domain (IIEF-EF) score with a mean difference (MD) between 2.00 and 3.20 points ($p<0.0001$).
ii. LI-ESWT improved the Erection Hardness Score (EHS ≥3) with odds ratio (OR) between 4.35 and 10.40 points ($p<0.0001$).

iii. Patients treated by LI-ESWT developed a good therapeutic effect that lasts for at least 3 to 6 months.
iv. Patients who had mild or moderate ED and without comorbidities ($p<0.001$) had better therapeutic efficacy after treatment than patients with more severe ED ($p=0.30$) or comorbidities ($p=0.33$).

v. LI-ESWT showed a significant effect (improved IIEF score) on early recovery in penile rehabilitation of ED following radical prostatectomy (weighted mean difference [WMD] -2.04; 95% CI: -3.72 to -0.35; $p=0.02$).
vi. The combination of LI-ESWT and pelvic floor muscle exercise improved IIEF-EF score for the treatment of diabetic patients with ED (17.5 ± 2.72 versus 13.40 ± 2.85; $p<0.001$).

vii. In patients with ED unresponsive to PDE5i, LI-ESWT showed improvement in efficacy parameters (IIEF-EF, EHS, Sexual Encounter Profile diaries) and responded positively to the Global Assessment Question (GAQ) in 60% of patients treated.
viii. LI-ESWT versus on-demand 20 mg tadalafil has a comparable therapeutic efficacy at 12 weeks when comparing the baseline values to the follow-up variables for IIEF-5 (17.64 ± 4.01; $p<0.001$ within the Li-ESWT group and 15.72 ± 3.6; $p<0.001$ within the tadalafil group) and EHS (3.2 ± 0.76; $p<0.001$ within the LI-ESWT group and 3.1 ± 0.69; $p<0.001$ within the tadalafil group).

ix. LI-ESWT had similar efficacy as on-demand 100 mg sildenafil for general ED patients as measured by IIEF-5 and EHS scores ($p>0.05$ at baseline and third month).

x. Adjuvant daily therapy with L-arginine 2,500 mg and tadalafil 5 mg improved erectile function in terms of IIEF-EF and EHS scores ($p<0.0001$). The increase in both scores was statistically significant at all follow-up visits at 1, 6, and 12 months ($p<0.0001$).

Safety

There was substantial fair level of retrievable evidence to suggest that LI-ESWT was generally safe with low incidence of minor adverse effects (AEs) and well-tolerated by patients during the treatment of ED. Overall, studies reported that LI-ESWT was not associated with any chronic pain, discomfort or treatment-related AEs (minor skin bruises, haematoma, haematuria, urinary retention) during the sessions or the follow-up. The most common mild side effects were headache and dizziness, dyspepsia, stinging sensation, and local penile pain. There was no participant discontinuation due to AEs. However, the United States Food and Drug Administration (US FDA) has not yet approved shockwave therapy as a treatment for ED.

Organisational issues

There was no retrievable evidence in the context of procedural time points and training or learning curve related to LI-ESWT for ED. However, different LI-ESWT setup parameters such as energy flux density (EFD) and number of pulses, and different treatment protocols including treatment frequency and length of course resulted in differences in reported efficacy. Given this information, recent evidence has demonstrated that the improvement in IIEF was better in the group with lower energy density (EFD 0.09 mJ/mm2 versus EFD 0.1-0.2 mJ/mm2; MD 3.81; 95% CI: 2.07 to 5.55; p<0.0001) while administering more shockwaves reported a significant increase in IIEF compared with delivering fewer shockwaves (number of pulses 3,000: MD 2.86; 95% CI: 1.54 to 4.19; p<0.0001). Shorter course of <6 weeks reported a significant increase in the IIEF (MD: 2.11; 95% CI: 0.98-3.25; p=0.0003).

With regard to treatment satisfaction, patients and their partners in the LI-ESWT group had similar total Erectile Dysfunction Inventory of Treatment Satisfaction questionnaires (EDITS) and EDITS Index scores as those in the sildenafil group. However, more patients and their partners in the LI-ESWT group were very satisfied and somewhat satisfied with the duration of intercourse compared with those in the sildenafil group. The improvement effect sustained 1-month after treatment without any additional active intervention, implying that LI-ESWT exerted a genuine physiologic effect on cavernosal tissue.

There are several international organisations that have published guideline recommendations surrounding LI-ESWT including the American Urological Association (AUA; 2018), Asia-Pacific Society for Sexual Medicine (APSSM; 2020), European Society of Sexual Medicine (ESSM; 2019), and European Association of Urology (EAU; 2020). All organisations acknowledge LI-ESWT as a potential treatment for ED with promising early clinical studies.

Economic implication

The cost-effectiveness of LI-ESWT for the treatment of ED has not yet been formally evaluated. However, cost associated to use this treatment is higher than self-administered 20 mg tadalafil on-demand, as reported in one prospective study. For each participant (n=51), the average number of sessions in the shockwave group was six sessions with an average total cost of USD 500.00, while the average of the medical treatment group was 30 tablets throughout the study costing about USD 62.50 (p<0.001).