Editorial

Low-energy shock wave therapy ameliorates erectile dysfunction in a pelvic neurovascular injuries rat model

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Currently available pharmacological erectile dysfunction (ED) treatments improve erectile function when impaired, yet none are curative. The search for a disease-modifying treatment for ED is the goal of this coming decade, with the advent of promising therapeutic strategies such as gene therapy and stem cell regeneration, while attempts for rehabilitation treatment protocols in men with ED using chronic phosphodiesterase-5-inhibitors (PDE5-Is) i.e., after radical prostatectomy have failed. However, data on the therapeutic benefits of these treatments to restore erectile function are still scarce. Pioneer clinical studies reporting the use of low-intensity extracorporeal shock wave therapy (Li-ESWT) have shown that Li-ESWT could improve erectile function and penile hemodynamics in men with ED who respond to pharmacotherapy and convert PDE5-I non-responders to responders (1-4). More clinical studies have been conducted since then revealing encouraging results, such as the improvement of International Index of Erectile Function score and/or Erectile Hardness Score and an effect that lasts up to 1 year (5-10). Therefore, it seems that Li-ESWT has the potential to become the first non-invasive curative treatment for ED patients (11-13).

These exciting clinical proof-of-concept studies trigger many questions, among which the mechanism of action of Li-ESWT responsible for this beneficial effect on erectile function. To date, however, very few preclinical studies have been led to investigate these aspects (14-16). Of note, all these studies report positive effects of Li-ESWT on erectile function whatever the experimental ED model used. Moreover, several hypotheses for Li-ESWT's mechanisms of action in erectile function recovery have been inspired by previous studies conducted in other basic science fields. It was thus shown that Li-ESWT triggers the activation of various intracellular signaling pathways causing upregulation of numerous angiogenic factors (i.e., VEGF…) to promote neovascularization and mobilizes the recruitment of endogenous progenitor cells thereby favoring angiogenesis and tissue regeneration in cardiovascular medicine and wound healing (17-21). These pro-angiogenic signaling pathways and recruitment of endogenous progenitor cells have also been shown to be activated in the penile tissue following Li-ESWT treatment in diabetic ED models (15,16), despite the fact that it does not upregulate the NO/cGMP pathway (14). Moreover, the role of Li-ESWT in the regeneration of peripheral nerves has also been previously suggested after nerve compression or in a model of autologous nerve graft (22,23) and later investigated in the context of erectile function recovery in diabetic ED models (15,16).

In this study (24), Tom Lue and his colleagues investigated the effects of two different treatment regimen using Li-ESWT (low energy: 0.06 mJ/mm^2, 300 pulses, 3 Hz during 4 weeks and 1 week wash-out or high energy: 0.09 mJ/mm^2, 1,000 pulses, 3 Hz during 4 weeks and 1 week

wash-out) in a new experimental model of neurovascular ED produced by both bilateral cavernous nerve injury (CNI) and internal pudendal bundle (IPB) injury. This model is meant to mimic trauma-related ED that "*commonly occurs in the setting of pelvic surgery or as a result of local injuries such as improvised explosive device in battlefield […]*". Patients suffering from this form of ED are often not responsive to standard of care such as PDE5-Is and represent difficult-to-treat patients. In this study, Li-ESWT at both "low energy" and "high energy" is successful at improving erectile response to cavernous nerve stimulation. Demonstration of penile angiogenesis, tissue restoration, and penile nerve regeneration including nNOS-positive nerve fibers coinciding with recruitment of endogenous progenitor cells to the damaged area was obtained. Moreover, both dedifferentiation and proliferation of Schwann cells at the site of pelvic injury was evidenced, further supporting the concept of nerve regeneration.

Shock waves are acoustic waves characterized by high pressure amplitudes and an abrupt increase in pressure in comparison to the ambient pressure. There are various medical devices delivering shock waves, using various techniques [Radial pressure wave (RSWT), electrohydraulic, electromagnetic or piezoelectric shockwave] and equipped with a focused, soft-focused and/or unfocused reflector depending on the indication and the tissue that shall be treated. Thus, these technologies differ in the manner in which the shockwaves are produced, the ability of the shockwave to be controlled and focused, the depth to which the shockwaves can penetrate, and the overall amount of energy being produced.

Therefore, results obtained in a study with a specific device/protocol do not allow for extrapolation on different devices or setups. It is particularly the case when investigating Li-ESWT in a preclinical setting, since particular care is needed to adapt the equipment to the size of the experimental model used. Thus, care to reduce the loss of energy between the shockwave electrode and the targeted tissue is mandatory. Intensity, duration of each session and total number of sessions may need to be determined according to the kind of equipment, and it is of paramount importance that measurement of the actual amount of energy delivered to the targeted site is performed, in order to mimic as closely as possible the amount of energy which is delivered to patients.

In this study, it is inferred that these treatments were applied once a week although this information was not provided. Moreover, the focused shockwave source was delivered to the "pelvic region" of the rat. Has the actual amount of energy been measured on the targeted site and how does this setting compare to the delivery of Li-ESWT to the penile shaft of ED patients receiving Li-ESWT treatment?

In any case, it should be emphasized that such experimental studies on the use of Li-ESWT are very rare and time-consuming. As such, these data are a very valuable contribution in the understanding of the mechanistic actions of Li-ESWT in an experimental setting of ED. Thus, Li and co-workers (24) should be both congratulated for this work and encouraged to pursue this line of much-needed basic science research.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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