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A potential treatment of low intensity pulsed ultrasound on cavernous nerve injury for erectile dysfunction

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ABSTRACT

Erectile dysfunction after nerve injury is a common disease after radical prostatectomy. Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family, which plays an important role in the survival of existing neurons, the differentiation of new neurons, and synaptic plasticity. It has been demonstrated that low-intensity pulsed ultrasound (LIPUS) accelerates bone healing and axonal regeneration after injury. LIPUS may also be able to stimulate neuronal activity and enhance the levels of neurotrophic factors. Evidence suggests that elevated levels of BDNF in the brain have protective effects against neurodegenerative diseases. Previous studies have shown that the treatment on cavernous nerve injury repair, and protective effect plus neuro-regeneration effect by low-intensity pulsed ultrasound. They shared the similar mechanism including several trophic factors stimulation, Pl3K/akt pathway activation, and anti-fibrosis mechanism. We hypothesized that due to its combined neuroregenerative and protective effects, the non-invasive and easy-to-use method of LIPUS stimulation could have a therapeutic effect on erectile dysfunction stemming from cavernous nerve injury.

Background

Erectile dysfunction is a condition resulting from a multi-factorial disease process involving the brain, emotions, blood vessels, nerves, corpus cavernosum, and hormones. A normal erection requires adequate arterial inflow, relaxation of the cavernosal smooth muscles, and restricted venous outflow. The major molecular pathways and substances involved in achieving a normal erection include nitric oxide/cGMP signaling, RhoA/Rho-associated protein kinase, the renin-angiotensin system, and tumor necrosis factor-α [1]. Various treatment modalities were applied on treating erectile dysfunction, including oral phosphodiesterase 5 inhibitor, vacuum device, intra-cavernous injection, artificial prosthesis, and extracorporeal shock wave treatment. Though all the above treatments are focused on temporal improvement of erection, but lack in improving the pathogenic origin. Low intensity pulsed ultrasound has also been applied on animal studies with type 1 diabetes [2]. But most of the studies were applied on vasogenic erectile dysfunction, but rarely on neurogenic cause.

Radical prostatectomy is the gold standard of treatment for early stage prostate cancer, and it is the most common cause of neurogenic cause of erectile dysfunction. However, the prevalence of erectile dysfunction due to nerve injury after radical prostatectomy is about 14–90% [3]. In the latest studies, Jung Ki Jo et al showed that early penile rehabilitation with sildenafil immediately following nerve-sparing robot-assisted laparoscopic prostatectomy has significant improvement on erectile dysfunction compared to the delayed treatment [4]. But treatments on nerve injury after radical prostatectomy are still confined to the same treatment modalities as non-nerve causes [5], and have poor prognosis if delayed application. Meanwhile, previous studies have indicated that low-intensity pulsed ultrasound (LIPUS) has high potential to elicit nerve regeneration in cases of nerve injury stemming from radical prostatectomy due to its stimulation of neurotrophic factors [6,7] and reduction of neural inflammation [8,9]. Hence, we would like to review the effect of nerve regeneration by low intensity pulsed ultrasound and evaluating the possible molecular mechanism.

Medical hypothesis

Low intensity pulsed ultrasound for erectile dysfunction

The stimulation of peripheral nerve regeneration resulting from the

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use of oral medication was first reported in 2000 [10]. In 2004, low intensity ultrasound was applied to stimulate peripheral nerve regeneration via poly(DL-lactic acid-co-glycolic acid) conduits seeded with Schwann cells [11]. In 2005, lower intensity therapeutic ultrasound was reported to enhance nerve regeneration in a sciatic nerve injury rat model [12,13]. It is believed that LIPUS can promote cell proliferation and NT-3 gene expression in Schwann cells [14]. Various treatment modalities for erectile dysfunction due to nerve injury have been reported previously, including stem cell therapy [15], Rho-kinase inhibitor therapy [16], plant extracts such as icariin [17] and Ginkgo biloba [18], nerve conduits [19–21], nerve grafts [22], and gene therapy [23]. However, the long-term efficacy and adverse effects of such modalities have yet to be evaluated in large trials.

In previous studies, effects on several molecular mechanisms involved in erectile dysfunction after nerve injury have been reported. Corporal fibrosis and apoptosis were improved after inhibition of Rho-kinase pathway inhibition via downregulation of the TGF-b1/S1P/Rho-kinase/LIMK2/cofilin pathway and modulation of the Rho-kinase/Akt/Bad/Bax/caspase-3 pathway [24,25]. Previous studies have also suggested that phosphatidylinositol-3 kinase (PI3K) regulates axonal cytoskeleton via glycogen synthase kinase 3b (GSK-3b) and multiple microtubule binding proteins [26]. Yue et al. showed that the mRNA and protein expression of ErbB3, NRG1, and Krox20 were increased together by LIPUS and co-culturing with adipose-derived stem cells or independently by LIPUS alone [27], and they further noted that the NRG1/ErbB3 signaling pathway activates a variety of signaling pathways (PI3K/Akt, Erk1/2, FAK, Rac/Cdc42) of Schwann cell biology, including pathways involved in myelination, proliferation, and migration. Furthermore, Pozniak et al. showed that TNF-alpha-induced neurite regrowth occurs primarily through EphB2 signaling via the stimulation of NF-kappaB [28], while Lin et al. demonstrated that brain-derived neurotrophic factor (BDNF) enhances nerve regeneration via the indirect mechanism of activation of the JAK/STAT pathway in Schwann cells, rather than via direct effects on neurons themselves [29].

Su et al. reported that LIPUS treatment significantly promoted BDNF and vascular endothelial growth factor (VEGF) at day 4 after TBI. Meanwhile, LIPUS was also reported to enhance the phosphorylation of tropomyosin-related kinase B (TrkB), Akt, and cAMP-response element binding protein (CREB) [30]. Meanwhile, Liu et al. showed that the regulation of BDNF regulation occurs through the activation of NF-kappaB via the TrkB/PI3K/Akt and calcium/CaMK signaling pathways [7]. Given the effect of LIPUS in terms of stimulating neurotrophic factors and the findings of previous studies regarding the treatment of erectile dysfunction due to nerve injury following radical prostatectomy, we believe that LIPUS has high potential to serve as an effective treatment for nerve injury-induced erectile dysfunction by stimulating nerve regeneration and decreasing neural inflammation.

Evaluation of the hypothesis

Several experiments could be conducted to evaluate the efficacy of LIPUS in treating erectile dysfunction after radical prostatectomy. First, we would use a cavernous nerve crush rat model to simulate the state of human patients after radical prostatectomy [31]. Our study will include 24 Sprague-Dawley rats (3 months old, 250–300 g) and divide into four groups: group 1 contains 6 rats receiving sham operation with a midline incision and dissection of the cavernosal nerves with no manipulation; group 2 contains 6 rats receiving cavernosal nerves intentional 2-min crush injury by a hemostatic clamp; group 3 contains 6 rats receiving same operation as group 2 with LIPUS treatment 15 min per day for 7 days; group 4 containing 6 rats receiving same operation as group 2, but LIPUS treatment delayed for 2 weeks.

At group 1, 2 and 3, we will perform electrical stimulation on the proximal injured cavernous nerve and record the intra-cavernous pressure indicating erection degree on the day after the final LIPUS treatment (Day 8). At group 4, we will perform the above procedure on the day after the delayed LIPUS treatment (Day 22).

After sacrifice of the animals, the penis micro-structure of these rats would be examined to confirm the pathological changes and the serum molecular pathway changes, including brain-derived neurotrophic factor (BDNF), nitric oxide (NO), inflammatory cytokines such as IL-1, IL-6, NF-κB, and Phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) and AKT. Then the erectile function test and the serum factors of the sham group, injury group and LIPUS treated group of rats would be examined and compared.

To verify the treatment effect of erectile dysfunction, we will make a midline incision and identify the previously injured cavernous nerve at the end of the protocol, and then apply electrical stimulation to observe the response of intra-cavernous pressure, which is indicating the erection degree. Then we will harvest the tissues including the injuries cavernous nerve, and then exam them by certified pathologist to evaluate nerve regeneration degree.

In the second stage, if erectile function is found to be improved after LIPUS treatment, then cellular experiments would be conducted to identify the molecular pathway mechanisms involved in the improvement resulting from LIPUS treatment. According to the relevant previous studies, LIPUS treatment for erectile dysfunction could constitute a noninvasive and easy-to-perform procedure.

Conclusions

LIPUS is a noninvasive procedure that is easy to perform. It can stimulate increased levels of neurotrophic factors and decreased inflammation in neural tissues. We believe that it could serve as an effective treatment for erectile dysfunction not only via vascular mechanisms but also via its effects on direct and indirect nerve injuries caused by surgical procedures such as radical prostatectomy.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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