

# Low intensity extracorporeal shock wave therapy as a novel treatment for stress urinary incontinence: a randomized-controlled clinical study

**Kun-Ling Lin**

Kaohsiung Medical University

**Kuang-Shun Chueh**

Kaohsiung Medical University

**Jian-He Lu**

National Pingtung University of Science and Technology

**Shu-Mien Chuang**

Kaohsiung Medical University hospital

**Bin-Nan Wu**

Kaohsiung Medical University

**Yung-Chin Lee**

Kaohsiung Medical University hospital

**Yi-Hsuan Wu**

Kaohsiung Medical University

**Mei-Chen Shen**

Kaohsiung Medical University hospital

**Ting-Wei Sun**

Kaohsiung Medical University hospital

**Cheng-Yu Long**

Kaohsiung Medical University Hospital

**Yung-Shun Juan** (✉ [juanuro@gmail.com](mailto:juanuro@gmail.com))

Kaohsiung Medical University

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## Research Article

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# Abstract

**Aims:** To evaluate the effects of low intensity extracorporeal shock wave therapy (LiESWT) on stress urinary incontinence (SUI).

**Methods:** This investigation was a multicenter, single-blind, randomized controlled trial study. 60 female SUI patients were randomly assigned to receive LiESWT with 0.25 mJ/mm<sup>2</sup> intensity, 3000 pulses, and 3 pulses/second, once weekly for 4-week (W4) and 8-week (W8), or an identical sham LiESWT treatment without energy transmission. The primary endpoint was the changes in urine leakage as measured by pad test and validated standardized questionnaires. While the secondary endpoint was the changes in 3-day urinary diary among the baseline (W0), the W4 and the W8 of LiESWT, and 1-month (F1), 3-month (F3) and 6-month (F6) follow-up after LiESWT.

**Results:** The results showed that 4-week LiESWT could significantly decrease urine leakage based on pad test and validated standardized questionnaire scores, as compared to the sham group. Moreover, 4-week LiESWT could significantly reduce urine leakage, but increase urine volume and attenuate urgency symptom, which showed meaningful and persistent improvement at W8, F1, F3 and F6. Furthermore, validated standardized questionnaire scores were significantly improved at W4, W8, F1, F3 and F6 as compared to the baseline (W0).

**Conclusions:** 8-week LiESWT could attenuate SUI symptoms on physical activity, reduce urine leakage and ameliorate overactive bladder symptoms, which implied that LiESWT significantly improved the quality of life. Our findings suggested that LiESWT could serve as a potentially novel and non-invasive treatment for SUI.

## Introduction

Stress urinary incontinence (SUI), according to the International Continence Society, is the involuntary leakage of urine on physical exertion, effort, coughing or sneezing <sup>1</sup>. The global prevalence of urinary incontinence in female population is around 50% <sup>2</sup>, which is an significant problem, namely the impairment of the quality of life (QoL), such as reducing social interaction and physical activity, destroying sexual relationships, worsening emotional and mental health.

Excessive mobility of the urethra and/or bladder neck and internal sphincter deficiency are the two main mechanisms of SUI. Clinical managements of SUI are various, like lifestyle changes, pelvic floor muscle training (PFMT), medication, as well as surgery. PFMT is advocated as a valuable first choice with negligible complications and acceptable cure rate but requires patient long-term regular exercise to achieve satisfied results <sup>3</sup>. Mid-urethral sling (MUS) surgery is considered as the preferred surgical method because of the high cure rate <sup>4</sup> but with widely criticized for its early and late complications <sup>5</sup>. Moreover, sling operation and bulking agent injection only enhance the periurethral support and have

some anesthetic risks. Therefore, novel therapies that can restore normal urethra function are urgently needed.

The extracorporeal shock wave is a longitudinal acoustic wave, which propagates through human tissues at the speed of ultrasound wave in water<sup>6</sup>. Among them, low intensity extracorporeal shock wave therapy (LiESWT) could induce local inflammation reaction and promote angiogenesis, recruit mesenchymal stem cells and endothelial progenitor cells, stimulate cellular proliferation and regeneration<sup>7</sup>, and inhibit oxidative stress, thus improve blood circulation and enhance tissue repair<sup>8</sup>. In recent basic and clinical studies, the efficacy of LiESWT, in treating chronic injuries of soft tissues (e.g., erectile dysfunction (ED)<sup>9–11</sup> and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)<sup>12,13</sup>) has been well established. More importantly, the benefit of LiESWT is a non-invasive outpatient-based therapy featured with short treatment sessions, which helps patients to be free from anesthesia and multiple adverse effect of medication or surgery.

A recent study using a SUI rat model induced by vaginal balloon dilation showed LiESWT ( 0.06 mJ/mm<sup>2</sup>, and 300 shocks at 3 Hz ) ameliorated SUI by promoting urethral sphincter regeneration, angiogenesis, and progenitor cell recruitment<sup>7</sup>. Recently, we published our preliminary results on human subjects to show that 8-week LiESWT attenuated SUI symptoms with short term follow up<sup>14</sup>. In the current study, we further evaluate the clinical application of LiESWT on SUI patients and its persistence efficacy, including attenuating bladder urine leaks, impacting on overactive bladder (OAB) symptoms, and promoting the quality of life.

## Results

### Diagnoses

From 2018 until January 2020, a total of 60 female participants aged 20–75 years were enrolled in this clinical trial study (NCT04059133). The designed timetable was shown in Fig. 1. The physical and serum parameters of metabolic syndrome may be associated with the symptoms of SUI. Therefore, we analyzed the baseline values and demographic features of patients. As presented in **Table 2**, all physical indicators and serum parameters were characterized for the normal range at W0. The results also revealed that there were no significant differences in these parameters between the sham group and the LiESWT group.

### Primary and Secondary End Points

A pad test is useful for detecting bladder involuntary leakage of urine during physical activity examination. The amount of bladder urine leakage in the sham group was no significantly different before or after 4-week treatment ( $p = 0.281$ ) (**Table 3 and Fig. 2A**). However, 4-week LiESWT noticeably decreased urine leakage as compared to the sham group ( $p = 0.004$ ). Moreover, LiESWT significantly decreased urine leakage from  $7.93 \pm 1.32$  (W0) to  $2.43 \pm 0.40$  grams (W4,  $p < 0.001$ ) and sustained until F6 (**Table 3 and Fig. 2B**). Further analysis found that 64.4 % of participants had moderate to better

improvement (> 50%) after 4-week LiESWT, and the proportion of improvement was increased to 68.8%, 77.8%, 82.3%, and 84.5% at W8, F1, F3, and F6, respectively (Fig. 2C).

The 3-day urinary diary was analyzed (**Table 3**). LiESWT significantly improved the average urine volume and the mean times of the urgency at W4, W8 and sustain the improvement until F6. The functional bladder capacity was noticeably raised at F3 and F6. Meanwhile, the urinary frequency was significantly decreased at F1. The mean time of the nocturia was meaningfully decreased at F1, F3 and F6. According to the 3-day voiding diary, 8 weeks of LiESWT significantly improved OAB symptoms in those SUI participants.

The effects of LiESWT on OAB symptom, physical activity induced involuntary urine leakage and QoL were examined. The results of questionnaire for QoL and social activity were shown in Fig. 3 and **Table 3**. In the sham group, there was no significant difference in OABSS, ICIQ-SF, UDI-6, and IIQ-7 questionnaire scores. However, 4-week LiESWT significantly improved ICIQ-SF ( $p = 0.034$ ), UDI-6 ( $p = 0.040$ ), and IIQ-7 ( $p = 0.048$ ) scores as compared to the sham group except OABSS ( $p = 0.520$ ). In the LiESWT group, all questionnaire also revealed significant improvement at W4, W8, F1, F3 and F6 (Fig. 3 and **Table 3**). Based on the questionnaires, the results showed that LiESWT treatment improved both bladder urine leakage and OAB symptoms, including urinary frequency, nocturia, urgency, and urgency incontinence, at W4 to F6 as compared to W0 (Fig. 3).

## Safety and adverse effects

All participants in this study were well tolerated with LiESWT. No significant adverse reactions related to LiESWT were detected, such as skin ecchymosis, hematuria or intolerable pain. There was no single patient withdrawn from the study due to any adverse effect.

## Discussion

This investigation was a multicenter, single-blind, randomized controlled trial study. The results showed that 4-week LiESWT decreased urine leakage by pad test and attenuate urgency symptom by 3-day urinary diary. There was significant and persistent improvement as long as 6 months of follow up. Besides, validated standardized questionnaire scores were also significantly improved at W4, W8, F1, F3 and F6 as compared to the baseline. These findings indicated that 8-week LiESWT significantly attenuated SUI symptoms on reducing urine leakage, ameliorated overactive bladder symptoms and improved the QoL, which implied that LiESWT could serve as a novel, non-invasive treatment for SUI (Fig. 4).

Clinically, the applications of LiESWT in urological disorders includes ED<sup>9-11</sup> and CP/CPPS<sup>12,13</sup>, but the safety and the effectiveness of treating female SUI are still under investigation. LiESWT (0.09–0.25 mJ/mm<sup>2</sup>, 1500–6000 pulses, 1–2 times per week, 4–12 sessions) was found to significantly increase penile hemodynamics and induce penile tissue regeneration in ED patients<sup>9,11</sup>, and 50% of these patients maintained such therapeutic effect after 2 years<sup>10</sup>. In addition, LiESWT with 0.25 mJ/mm<sup>2</sup> intensity,

2500–3000 pulses, and 3–4 Hz, 1 times per week for 4 weeks can noticeably relieve perineum pain, improve bladder voiding symptoms and QoL and its significant therapeutic effects lasted for 4 months to 1 year post treatment <sup>12,13,18</sup>. Our results showed that 8-week LiESWT with 0.25 mJ/mm<sup>2</sup> intensity, 3000 pulses, 3 pulses/second and once weekly could significantly decrease urine leakage, attenuate urgency symptom of overactive bladder and improve the QoL, which showed persistent improvement as long as 6-month follow up. In summary, the application of LiESWT is helpful not only for the treatment of CPPS and ED, but also SUI. Further application of LiESWT on other urologic diseases, such as OAB is under investigation.

SUI is a common and disturbing disease with a variety of management modalities, including PFMT, biofeedback training, electrostimulation, vaginal laser therapy, and surgery. PFMT is promoted as a valuable first choice physical therapy for SUI women, with a reported cure rate of 56%, and the therapeutic effect can be maintained up to one year after treatment <sup>3</sup>. However, there were no standard parameters of muscle contraction and relaxation for PFMT, and it required more than six months to achieve significant improvement, the patients are prone to give up PFMT <sup>19</sup>. Moreover, the effect of PFMT on patients with moderate to severe urinary incontinence is also poor. MUS surgery seemed to work well for short term follow up (up to one year) in SUI patients with over 80% of cure rate <sup>4</sup>. However, while few in number, implanted slings have surgical risks and adverse consequences. Souders et al analyzed more than 70,000 legal statements on the use of artificial mesh or sling from 2000 to 2014, and found that most (63%) of them were related to the retropubic or transobturator sling procedures for the treatment of SUI <sup>20</sup>. Reported complications included bladder injury, hemorrhage, urinary tract infections, bowel injury, and mesh erosion, with an incidence of 4.3–75.1% <sup>5,21</sup>. According to FDA recommendations, clinically meaningful improvement in SUI symptoms is defined as improvement in pad weight or the number of incontinence episodes with a reduction from baseline greater than 50%. Our investigation demonstrated that 64.4% of women had moderate to better improvement (> 50%) after 4-week LiESWT therapy, and sustained until F6 (Fig. 2C). In addition, no side effects were observed in all participants during LiESWT treatment and follow-up.

Interestingly, the results also showed that 8-week LiESWT with 0.25 mJ/mm<sup>2</sup> intensity, 3000 pulses, 3 pulses/second and once/week, once weekly could not only significantly decrease urine leakage, but also attenuate urgency symptom of overactive bladder and improve the QoL, which showed persistent improvement as long as 6-month follow up. The actual mechanism of the beneficial effect of LiESWT on OAB is still unclear. In previous study, the contraction of urethral sphincter could lead to suppression of detrusor pressure. By this mechanism, voluntary urinary inhibition reflex can be mediated <sup>22,23</sup>. Several studies also raised the “integral theory”, which point out that the instability and stretch of pelvic floor muscle would induce inadequate micturition reflex and result into OAB symptoms <sup>24</sup>. Moreover, other study also proved that pelvic floor reconstruction could also ameliorate OAB symptoms <sup>25</sup>. From these points of view, LiESWT can consolidates pelvic floor muscle, reduces micturition reflex and finally have benefit on OAB symptoms.

The status of pelvic floor muscles plays an important role of pelvic organ steady. The main cause of SUI is related to pelvic floor malfunction, which result into pelvic organ over-mobilization. Previous studies of animal models suggested that LiESWT could induce local inflammation reaction and promote angiogenesis by enhancing the expression of VEGF and recruitment of mesenchymal stem cells and endothelial progenitor cells to the injured site<sup>7</sup>. LiESWT was also shown to stimulate cellular proliferation and regeneration<sup>7</sup>, inhibit oxidative stress production<sup>8</sup>, anti-apoptotic cells<sup>8</sup>, thus improving blood circulation<sup>7,8</sup>, increasing urethral muscle regeneration<sup>7</sup>, and enhancing tissue repair<sup>8</sup>. Theoretically, by the effect of LiESWT, pelvic floor muscles can repair gradually, and the over mobilization of bladder can attenuate, which result into the improvement of stress urinary incontinence.

Our study had several limitations. First, patients were limited in small numbers. People benefiting from LiESWT treatment have yet to be confirmed in larger prospective studies. Second, the inability to obtain bladder tissue in clinical trials, leading to biomarker analysis (such as inflammation, angiogenesis, tissue repair and regeneration-related genes) was not comprehensive in this study. Animal experiments are needed in the future to investigate the potential molecular mechanism underlying LiESWT treatment for SUI. Another important limitation of this study is the lack of follow-up for the sham-treated participants who dropped out and refused to follow up for reasons of ineffectiveness. Although it was explained at the time of recruitment that the LiESWT treatment might not be effective immediately, however, some participants in the sham group due to over expected the efficacy of LiESWT, dropped out and refused to follow up for the reasons of ineffectiveness after 5–6 treatments with LiESWT, which resulted in the lack of W8, F1, F3 and F6 data.

## Conclusion

The present study demonstrated that 8-week LiESWT could improve the SUI symptoms on physical activity, reduce urine leakage, lessen OAB symptoms, and promote QoL. The effects of LiESWT might restore the pathophysiology of SUI and sustain it for 6 months. These findings suggested that LiESWT could serve as a potentially promising and alternative method for treating SUI patients.

## Methods

### Design

This single blind, prospective, randomized controlled trials was performed of a tertiary medical center in Taiwan from December 2018 through January 2020. The investigation was approved by the Kaohsiung Medical University Hospital Institutional Review Board (IRB No. KMUHIRB-F(II)-20180010) and was registered at clinicaltrials.gov (NCT04059133) on August 16, 2019. The study enrolled 60 female participants aged 20–75 years who were diagnosed with SUI or mixed urinary incontinence (MUI) but SUI predominant patients for more than 3 months in this investigation (sham, n = 15; LiESWT, n = 45). The major inclusion and exclusion criteria were shown in **Table 1**. Based on the limitations regarding the feasibility of the project at our center, as well as a type I error ( $\alpha$ ) of 0.05 and type II error ( $\beta$ ) of 0.2, we

aim to enroll total of 60 patients in this study. Considering that patients may more likely to join a trial if they have a good chance of getting active treatment, participants were randomly assigned in a 3:1 ratio with blinded computer-assisted allocation to the study groups. All participants were provided with informed consent before entering the study and randomly allocated to the sham group or to the LiESWT group by computer generated random numbers. All experiments and methods were performed in accordance with relevant guidelines and regulations.

## **Physical indicators and biochemical parameters of studied participants**

The physical and serum parameters of metabolic syndrome were associated with the symptoms of SUI<sup>15</sup>. In order to investigate the baseline characteristics of SUI population, the physical indicators (age, height, weight, waistline, body mass index, systolic pressure, diastolic pressure, and mean arterial pressure) and biochemical parameters (hemoglobin A1c (glycated hemoglobin), blood sugar, glutamate oxaloacetate transaminase and glutamate pyruvate transaminase for liver function index, blood urea nitrogen and creatinine for renal function index, lipid profile on triglycerides, cholesterol, high-density lipoprotein, and low-density lipoprotein) were analyzed.

## **Procedure and medical information of LiESWT**

Participants were informed of treatment modalities, including the required consent to join this study and once weekly LiESWT for 8 weeks and follow-up at 6-month after completing the course of treatment (Fig. 1). Our instrumentation was the DUOLITH SD1-TOP focused shock wave system (STORZ MEDICAL AG). The LiESWT was applied with 0.25 mJ/mm<sup>2</sup> of intensity, 3000 pulses of shock, and of 3 pulses/second of frequency on the middle urethra, including middle, left, and right side of the participant's labia<sup>14</sup>. The sham group used identical treatment without energy transmission to the tissue.

## **Pad test for the evaluation of SUI**

The pad test was applied as a non-invasive diagnosis for quantifying the severity of urine leakage in SUI participants<sup>16,17</sup>. The purpose of pad test in this study was to evaluate the effect of LiESWT on reducing urinary incontinence. The detailed steps were performed according to our previous study<sup>14</sup>. The percentage (%) of improvement was evaluated at 4-week (W4), 8-week (W8), and 1-month follow up (F1), 3-month follow up (F3), 6-month follow up (F6) after LiESWT treatment, and the results were normalized with pre-treatment baseline data (W0).

## **Outcomes Measures and therapeutic efficacy assessment for LiESWT**

To analyze the effects of LiESWT, the primary endpoints were the changes in pad test and questionnaires (Overactive Bladder Symptom Score (OABSS), International Consultation on Incontinence Questionnaire short form (ICIQ-SF), Urinary Distress Inventory, Short Form (UDI-6), and Incontinence Impact Questionnaire, Short Form (IIQ-7))<sup>14</sup>, and the secondary endpoints were the changes in 3-day urinary

diary (bedtime and wake up time, fluid Intake, amount of urine drained and leaks) at the baseline (W0), 4-week (W4), 8-week (W8), and 1-month follow up (F1), 3-month follow up (F3), 6-month follow up (F6) .

## Statistical analysis

Data were analyzed using SAS 9.3 (SAS Institute, Cary, NC, USA). Quantitative data were represented as the mean  $\pm$  standard error of mean (SEM). Paired t-test was used to perform a repeated measurement analysis for intragroup before/after treatment <sup>14</sup> and the student t-test was performed for the intergroup comparison (the sham group vs. the LiESWT group). For all statistical analyses,  $p < 0.05$  was considered to be statistically significant.

## Declarations

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## Tables

Due to technical limitations, Table 1, Table 2, and Table 3 are only available as a download in the supplementary files section.

## Figures

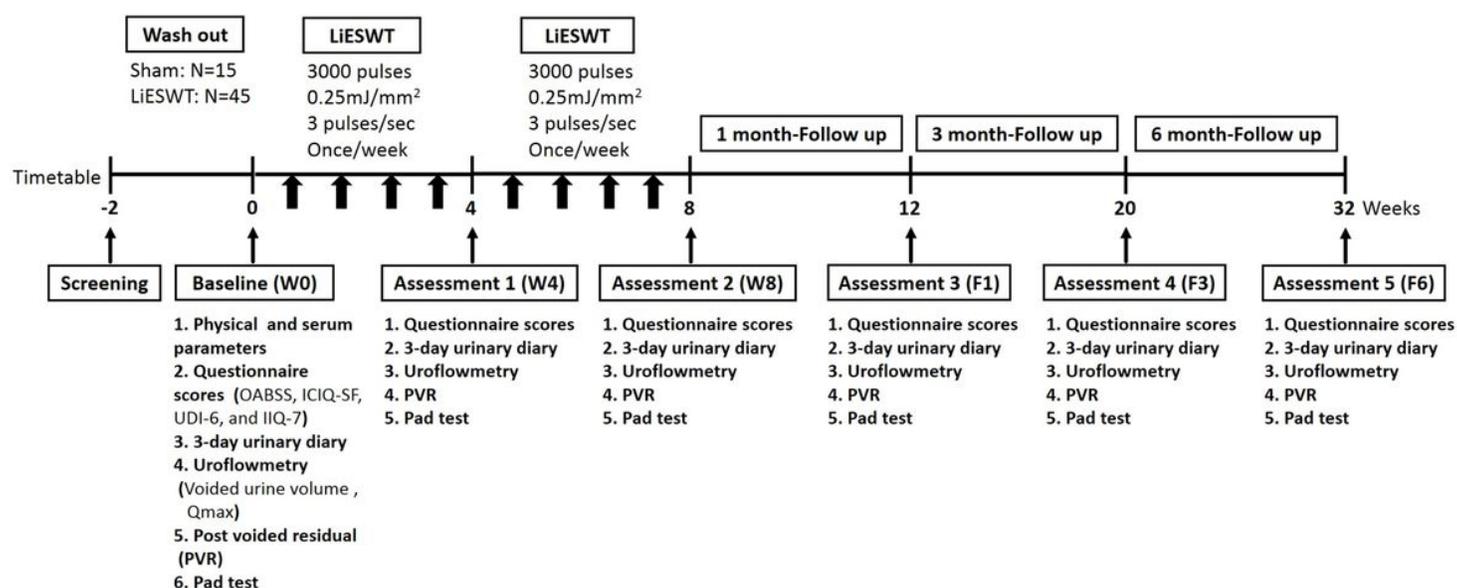
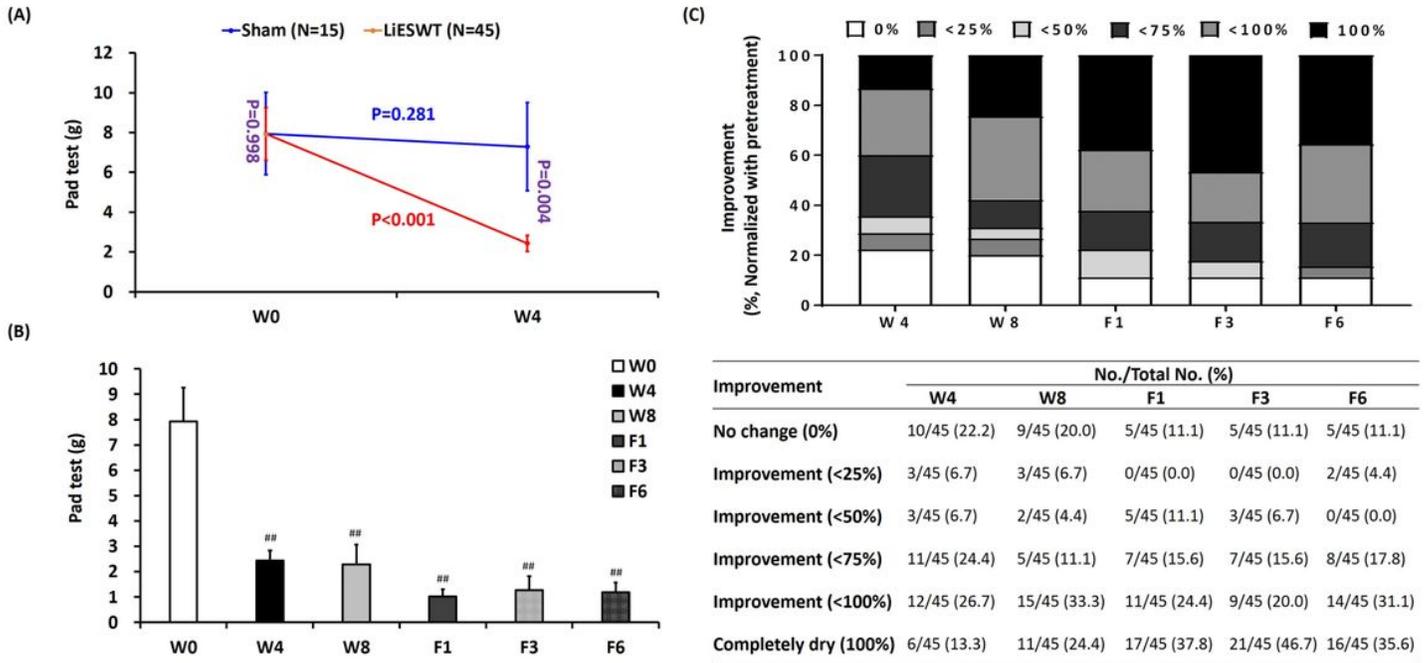


Figure 1

Time table designed for the clinical trial of stress urinary incontinence (SUI).



**Figure 2**

LiESWT decreased bladder leaks by pad test. (A) Pad test of the studied population for stress urinary incontinence (SUI) at 4-week (W4) in the sham-treated group (N=15) and the LiESWT-treated group (N=45). The blue font or red font denotes the p-value before and after 4 weeks of treatment in the sham group or in the LiESWT-treated group. The purple font indicates the p-value between the sham-treated group and the LiESWT-treated group at baseline (W0) and W4. Values are reported as means ± SE. (B) Pad test of the studied population for SUI at W4, 8-week (W8), 1-month follow-up (F1), 3-month follow-up (F3), and 6-month follow-up (F6). Values are reported as means ± SE. N=45. ##p < 0.01 compared to the W0. (C) The percentage of improvement at W4, W8, F1, F3 and F6 after the LiESWT treatment, as normalized with the W0. N=45.

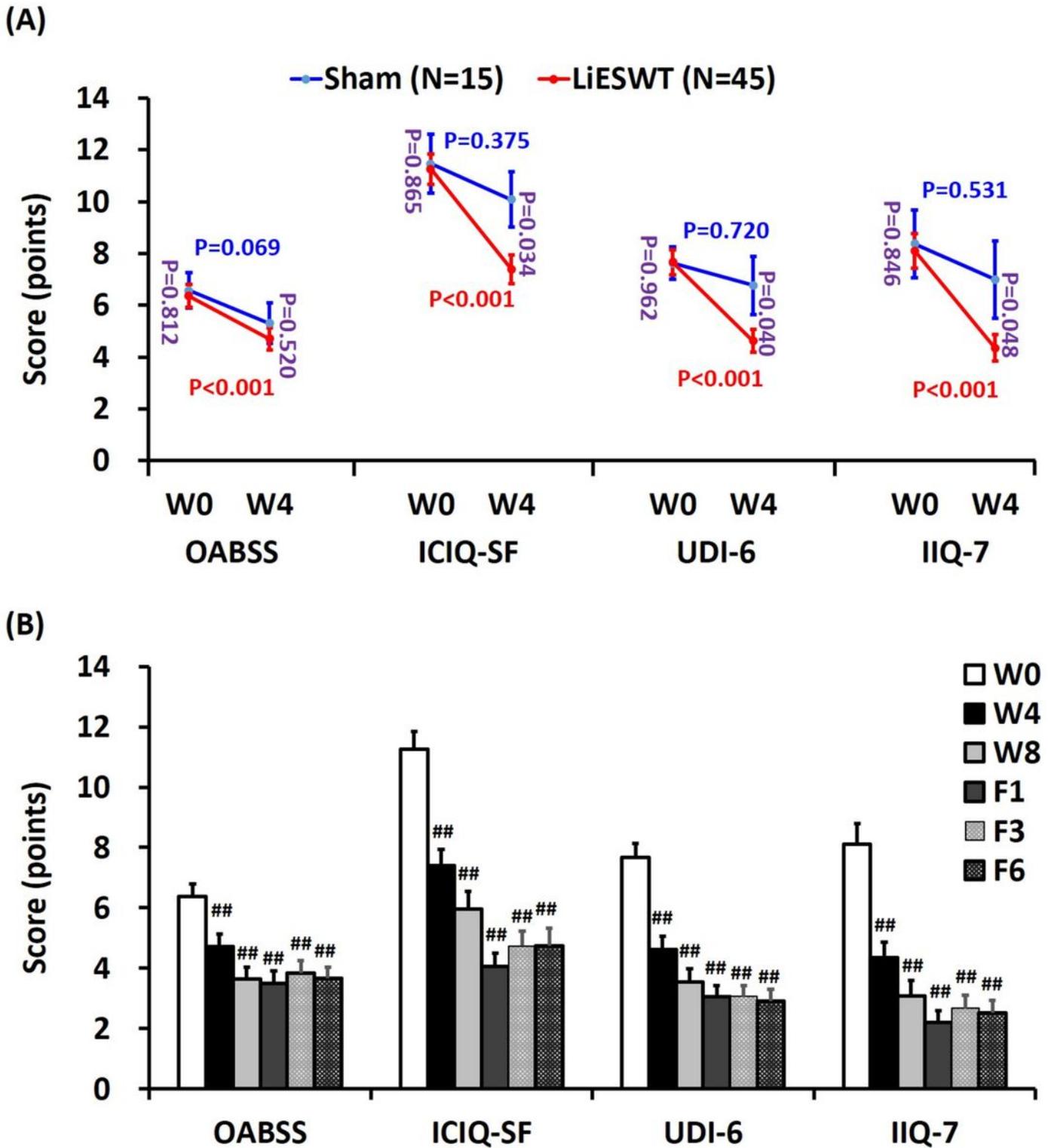


Figure 3

Changes in stress urinary incontinence (SUI) symptoms and validated standardized questionnaire scores after the LiESWT treatment. (A) The validated standardized questionnaire scores included overactive bladder Symptom Scores (OABSS), International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF), Urogenital Distress Inventory (UDI-6)-Short Form, and Incontinence Impact Questionnaire-7 (IIQ-7) score at 4-week (W4) in the sham group (N=15) and the LiESWT-treated group (N=45). The blue font or

red font denotes the p-value before and after 4 weeks treatment in the sham group or in the LiESWT-treated group, respectively. The purple font indicates the p-value between the sham group and the LiESWT-treated group at the baseline (W0) and W4. Values are the means  $\pm$  SE. (B) The OABSS, ICIQ-SF, UDI-6, and IIQ-7 questionnaire scores analyzed at W4, 8-week (W8), 1-month follow-up (F1), 3-month follow-up (F3), and 6-month follow-up (F6). Values are the means  $\pm$  SE. N=45. ##p < 0.01 compared to the W0.

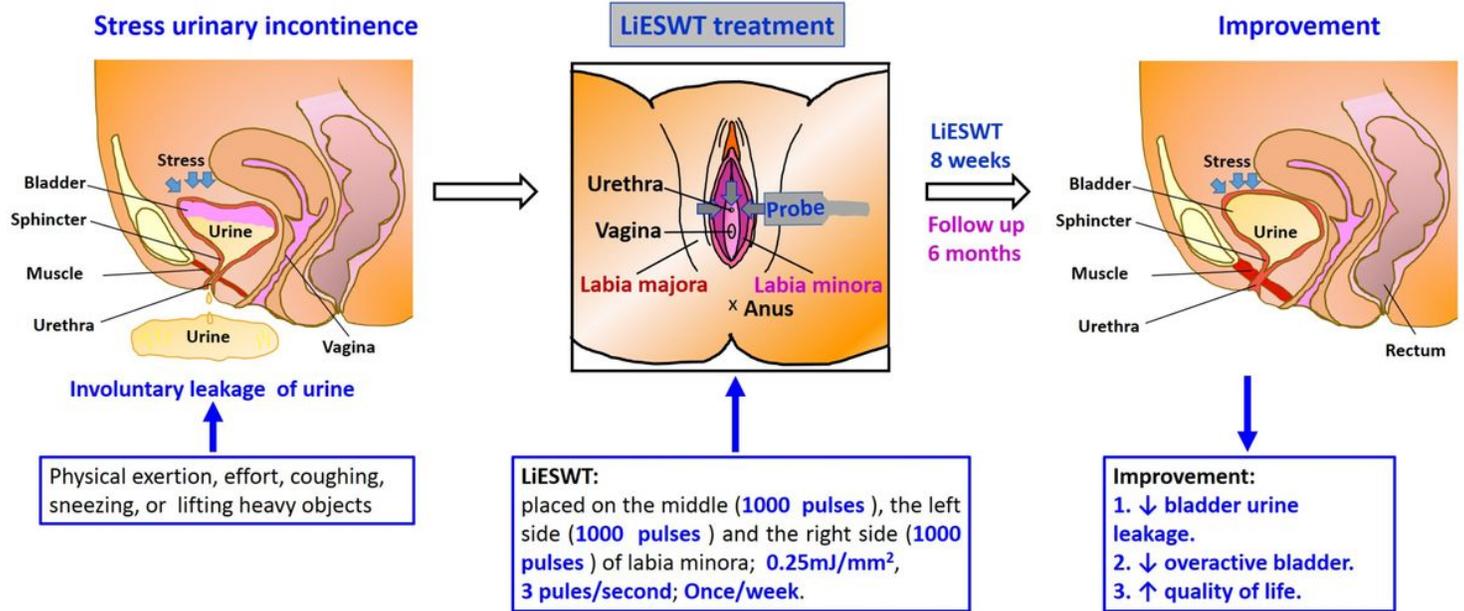


Figure 4

Short graphic abstract of studying the proposed potential effect of LiESWT. SUI, stress urinary incontinence; LiESWT, low intensity extracorporeal low energy shock wave therapy.

## Supplementary Files

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