

Protocol Title: Low Energy Shock Wave for the treatment of
interstitial cystitis/bladder pain syndrome
(IC/BPS) — a randomized, double-blind, placebo-
controlled, prospective study

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1. STUDY DESIGN

In this study we will evaluate the application of LESW for patients with IC/BPS. LESW with 2000 shocks, frequency of 3 pulses per second, and maximum total energy flow density 0.25 mJ/mm^2 or placebo (Shock Wave setting without shock wave energy transmission) will be applied to the suprapubic bladder region once a week for 4 weeks. Treatment parameters were modified from different urologic and non-urologic case studies and publications. The device used for the study was a standard electromagnetic shock wave unit with a focused shock wave source (LITEMED LM-ESWT-mini system, Taiwan). The focus zone penetration depth was in the range of 30–90 mm. This study was designed in a multicenter, randomized, double-blind, placebo-controlled trial to test the actual therapeutic effects of LESW on IC/BPS. The results of this study may provide clinical evidence for an alternative therapeutic regimen in the treatment of IC/BPS.

2. OBJECTIVE AND ENDPOINTS

The objective of this study is to evaluate the efficacy and safety of LESW for the treatment of IC/BPS.

The primary and secondary endpoints are described as shown below:

(1) Primary End-point (1 month)

The efficacy of LESW will be evaluated for:

Net changes of the O'Leary-Sant symptom score from baseline to 1 month after the treatment day.

(2) Secondary end-points

Efficacy

The efficacy of LESW will be evaluated for:

- (1) Net changes of the following parameters from baseline to 1 month after the treatment day: VAS, functional bladder capacity (FBC), voiding frequency at daytime and voiding frequency at night time as recorded in 3-day voiding diary.
- (2) Global response assessment (GRA) of therapeutic result by the patient (categorized from -3 to +3, indicating markedly worse to markedly improved) at 3 months after the treatment day.
- (3) Net changes of the maximum flow rate, voided volume, and PVR from baseline to 1 month after the treatment day.

(4) Changes of urinary nerve growth factor and cytokines level from baseline to 1 month after treatment day.

Effectiveness of treatment was considered if the patient has an improved GRA by 2 scales at the end-point assessments.

Safety

(1) Local adverse event incidences (hematuria, miction pain, UTI, urinary retention). The severity of adverse event is categorized as indicated below:

<i>Severity of AE</i>	<i>Description</i>
Mild	Transient and easily tolerable, not affecting usual daily activities
Moderate	Causes patient's discomfort, interrupting usual daily activities
Severe	Causes considerable interference with daily activities and may be incapacitating or life-threatening

(2) Systemic Adverse Events:

Any systemic adverse event occurring after LESW will be asked to report and patients will be properly investigated and treated. The cause for systemic adverse event may be not related with LESW.

(3) Changes in physical examinations.

(4) Changes in blood pressure and other laboratory test results will be examined if patients have severe adverse events or physical examinations reveal abnormalities.

(3) Follow-up (3 months)

Efficacy

The efficacy of LESW will be evaluated for:

- (1) Net changes of the following parameters from baseline to 1 month after the treatment day: VAS, functional bladder capacity (FBC), voiding frequency at daytime and voiding frequency at night time as recorded in 3-day voiding diary.
- (2) Global response assessment (GRA) of therapeutic result by the patient (categorized from -3 to +3, indicating markedly worse to markedly improved) at 2 months after the treatment day.
- (3) Net changes of the maximum flow rate, voided volume, and PVR from baseline to 2 months after the treatment day.
- (4) Changes of urinary nerve growth factor and cytokines level from baseline to 2 months after treatment day.

Effectiveness of treatment was considered if the patient has an improved GRA by 2 scales at the primary and secondary end-point assessments.

Patients who are not effective to the treatment at 2 months will receive repeated LESW treatment.

Safety

- (1) Local adverse event incidences (hematuria, miction pain, UTI, urinary retention) are reported.
- (2) Any systemic adverse event occurring after LESW will be asked to report and patients will be properly investigated and treated. The cause for systemic adverse event may be not related with LESW treatment.

3. SHOCK WAVE MACHINE AND PROCEDURES

The shock wave applicator (“LITEMED” LM-ESWT-mini system, Taiwan) will be gently placed directly on the ultrasound transmission gel over the skin surface of suprapubic region above the urinary bladder during once a week for 4 weeks, with 2000 shocks, frequency of 3 pulses per second, and maximum total energy flow density 0.25 mJ/mm^2 . The current shock wave intensity and number used was modified from previous report [1, 2].

Eligible patients will be assigned a randomization number in sequential order and each of the randomization will determine the allocation of one of the two treatment groups (LESW and Placebo) in 1: 1 ratio as shown below. The LESW and placebo will be controlled by a research assistance who will not evaluate the therapeutic outcome to ensure the double-blind method.

Vital signs (body temperature, blood pressure, heart rate and respiration rate) will be recorded at pre-treatment and 30 minutes following treatment.

The treatment will be carried out in the out-patient clinic. Patient will be stayed in a treatment room and accompanied by a research assistant.

3.1. Randomization

Permuted block randomization method will be applied to generate randomization codes. Each randomization number will be assigned to individual patient according to the time-sequence for screened patient become eligible.

3.2. Blinding

The blinding of the study is double blind to the investigator and patients. The placebo treatment was performed with the same therapy head, which was also fitted with a placebo stand-off. This stand-off contained shock wave-absorbing material, a layer of air, and air-filled microspheres [1].Performance of the placebo stand-off was validated by measuring the output pressure in a laboratory setup. The setting was identical to the verum treatment. The blinding included the specification that neither the patient nor the investigator/follow-up observer was aware of placebo or verum assignment.

4. SUBJECTS

4.1. Number and Source

Approximately 96 patients will be enrolled and a total of 76 evaluable patients will be completed within the two-year study period.

4.2. Inclusion Criteria

Patients must meet all the following criteria to be eligible to enter the trial:

- 4.2.1. Adults with age of 20 years old or above.
- 4.2.2. Patients with symptoms of unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six months duration, in the absence of infection or other identifiable causes.
- 4.2.3. Patients has received cystoscopy and ruled out other bladder lesion.
- 4.2.4. Free of active urinary tract infection.
- 4.2.5. Free of bladder outlet obstruction on enrollment.
- 4.2.6. Free of overt neurogenic bladder dysfunction and limitation of ambulation.
- 4.2.7. Patient or his/her legally acceptable representative has signed the written informed consent form.

4.3. Exclusion Criteria

- 4.3.1. Patients had received intravesical hyaluronic acid treatment in recent 3 months, or intravesical Botox injection in recent 12 months. Patients with severe cardiopulmonary disease and such as congestive heart failure, arrhythmia, poorly controlled hypertension, not able to receive regular follow-up.
- 4.3.2. Patients with bladder outlet obstruction on enrollment.
- 4.3.3. Patients with PVR >100 ml.
- 4.3.4. Patients with uncontrolled confirmed diagnosis of acute urinary tract infection.
- 4.3.5. Patients have laboratory abnormalities at screening including:
 - ALT > 3 x upper limit of normal range.
 - AST > 3 x upper limit of normal range.
- 4.3.6. Patients have abnormal serum creatinine level > 2 x upper limit of normal range.

- 4.3.7. Female patients who is pregnant, lactating, or with child-bearing potential without contraception.
- 4.3.8. Patients with any other serious disease considered by the investigator not in the condition to enter the trial.
- 4.3.9. Patients had received intravesical treatment for IC within recent 1 month.
- 4.3.10. Patients had participated investigational drug trial within 1 month before entering this study.
- 4.3.11. Patients with coagulopathy.

5. STUDY PROCEDURE

5.1. General Study Design

This study is designed as a double-blind, randomized, paralleled, controlled trial. The IC/BPS confirmed patients will be randomly assigned to receive (1) LESW or (2) placebo control group. The treatments will be evaluated at baseline screening and at least 2 study required visits (treatment visit and primary end-point evaluation visit) will be performed for symptom score recording, VAS, uroflometry studies, adverse event recording and global satisfaction assessments. Urine samples (30 ml) will also be collected at each visit for analysis of the urinary NGF and cytokines levels.

Procedures of LESW

Studied patients are requested to void completely before treatment. Urine samples (30 ml) will be collected for analysis of the urinary NGF and cytokines levels. The patients are placed in supine position in an examination room at out-patient clinic.

The shock wave applicator (“LITEMED” LM-ESWT-mini system, Taiwan) will be gently placed directly on the ultrasound transmission gel over the skin surface of suprapubic region above the urinary bladder weekly for 4 weeks, with 2000 shocks, frequency of 3 pulses per second, and maximum total energy flow density 0.25 mJ/mm^2 . The current shock wave intensity and number used was modified from previous report [1, 2].

Patients will be asked about any painful sensation that they experience during the treatment. Vital signs (body temperature, blood pressure, heart rate and respiration rate) will be recorded at pre-treatment, and 30 mins following treatment. During the treatment, patient will be stayed in a treatment room and accompanied by a research assistant.

5.2. Study Visits and Evaluations

5.2.1. Screening Visit (2 weeks before the treatment day)

5.2.1.1 Explain the nature of the study and have patients to read and sign an Informed Consent Form.

5.2.1.2 Screen patients for inclusion/exclusion criteria (section 4.2 and 4.3).

5.2.1.3 Medical History of IC/BPS and previous treatment modalities.

5.2.1.4 Vital signs monitoring and general physical examinations of all systems, EKG examination to rule out abnormal cardiac diseases, and biochemistry examinations including CBC, PT, APTT, ALT, AST and Cr.

5.2.1.5 Check Uroflowmetry and record, maximum flow rate, voided volume and PVR volume.

5.2.1.6 Urinalysis for WBC, RBC, PH, Protein, Glucose, Bacteria if patient has symptoms suggestive of urinary tract infection.

5.2.1.7 Physical assessments to exclude bladder outlet obstruction or bladder pathology.

5.2.1.8 Record concomitant medication.

5.2.1.9 Dispense three-day voiding diary to record for 3 days before the treatment day.

5.2.1.10 Record O'Leary-Sant symptom score, VAS.

5.2.1.11 Discontinue all previous IC-related medication.

5.2.2. Randomization and Treatment Visit (V1, Week 0)

5.2.2.1 Vital signs monitoring, check EKG and biochemistry results and confirm eligibility of patients.

5.2.2.2 A randomization number is given to eligible patient.

5.2.2.3 Inform patient of the possible adverse events.

5.2.2.4 Review three-day voiding diary.

5.2.2.5 Collect 30 ml urine for analysis of the urinary NGF and cytokines levels.

5.2.2.6 LESW given.

5.2.3. Treatment Visit (V2, Week 1, 1 week \pm 3 days after the V1 treatment day)

5.2.3.1 Vital signs monitoring, and confirm eligibility of patients.

5.2.3.2 LESW given.

5.2.4. Treatment Visit (V3, Week 2, 1 week \pm 3 days after the V2 treatment day)

5.2.4.1 Vital signs monitoring, and confirm eligibility of patients.

5.2.4.2 LESW given.

5.2.5. Treatment Visit (V4, Week 3, 1 week \pm 3 days after the V3 treatment day)

5.2.5.1 Vital signs monitoring, and confirm eligibility of patients.

5.2.5.2 LESW given.

5.2.5.3 Dispense three-day voiding diary to record for 3 days before the next visit day.

5.2.6 Evaluation Visit I (V5, 1 week \pm 3 days after the V4 treatment day)

5.2.6.1 Review patients voiding diary for urinary frequency, functional bladder capacity, and record reported VAS, O'Leary-Sant symptom score, and GRA.

5.2.6.2 Vital signs monitoring and record adverse events.

5.2.6.3 Check urinalysis for urinary tract infection if patient has symptoms.

5.2.6.4 Check uroflometry for maximum flow rate, voided volume, and PVR volume.

5.2.6.5 Appointment for the next visit at 1 month \pm 3 days after the V4.

5.2.6.6 Dispense three-day voiding diary to record for 3 days before the next visit day.

5.2.6.7 Collect 30 ml urine for analysis of the urinary NGF and cytokines levels.

5.2.7 Evaluation Visit II (Primary end-point, V6, 1 month \pm 7 days after the V4)

5.2.7.1 Review patients voiding diary for urinary frequency, functional bladder capacity, and record reported VAS, O'Leary-Sant symptom score, and GRA.

5.2.7.2 Vital signs monitoring and record adverse events.

5.2.7.3 Check urinalysis for urinary tract infection if patient has symptoms suggestive of urinary tract infection.

5.2.7.4 Perform Uroflowmetry study for maximum flow rate, voided volume and PVR volume.

5.2.7.5 Collect 30 ml urine for analysis of the urinary NGF and cytokines levels.

5.2.8 Evaluation Visit III (V7, 3 month \pm 7 days after the V4)

5.2.8.1 Review patients voiding diary for urinary frequency, functional bladder capacity, and record reported VAS, O'Leary-Sant symptom score, and GRA.

5.2.8.2 Vital signs monitoring and record adverse events.

5.2.8.3 Check urinalysis for urinary tract infection if patient has symptoms suggestive of urinary tract infection.

5.2.8.4 Perform Uroflowmetry study for maximum flow rate, voided volume and PVR volume.

5.2.8.5 Collect 30 ml urine for analysis of the urinary NGF and cytokines levels.

5.2.8.6 Patients who do not respond to treatment will be provided with repeat LESW treatment optionally.

5.3. Withdrawal Criteria

Patients with any of the following conditions may be withdrawn from the trial:

- 5.3.1. Patients decide to withdraw their consent at any time-point.
- 5.3.2. Patients indicate the status of lack of efficacy which is of clinical significance judged by the investigators that may lead to permanent damage to the patients.
- 5.3.3. Investigators consider that there is of safety concerns for the patients to remain in the trial (such as development severe medical disease).
- 5.3.4. Lost of follow-up or death.

5.4. Concomitant Treatments

Investigator will try to minimize the concomitant medications for the patients during the trial duration.

Patients are not allowed to take any of the following medications during the study:

1. Intravesical instillation of hyaluronic acid, heparin, or GAG replacement therapy.
2. Anticholinergics: oxybutynine, tolterodine, solifenacin, propiverine.
3. β 3 agonist: mirabegron.
4. Tricyclic anti-depressants: imipramine, amitriptyline.
5. COX-2 inhibitor: such as celecoxib.
6. Narcotics or pain killers: such as morphine, codeine, tramadol.

6. ADVERSE EVENTS

6.1. Introduction

An adverse event is defined as a new medical condition or worsening of the existing condition following or during the trial medicinal exposure (including placebo). However, a deterioration of

medical condition can be in doubt of either an adverse event or being due to the lack of efficacy of the treatment. Situations as such should be considered as a lack of efficacy unless the sponsor or the investigators or the regulatory authorities state to the contrary.

All adverse events occurring during the study should be documented on Adverse Event Forms. One Adverse Event Form should be filled out for each adverse event. All items on the form should be completed and feedback to National Reporting System of Adverse Drug Reaction in Taiwan (ADR) as soon as possible. For serious adverse events, a preliminary Adverse Event Form must be returned to the ADR immediately (within 24 hours), with complete and/or new information submitted to the ADR as soon as it becomes known.

6.2. Nonserious Adverse Event

A nonserious adverse event is defined as a change in a patient's medical health which does not fulfill the definition of Serious Adverse Event. Nonserious AEs should be reported to ADR by use of an Adverse Event Form.

6.3. Serious Adverse Event

Serious adverse events are defined as any finding which suggests a significant hazard, contraindication, side effect, or precaution.

Additionally, any adverse event which the consequence is:

Fatal

Life threatening

Permanently disability or incapacity

Requiring hospitalization or prolonging a current hospitalization

A congenital abnormality

Serious, alarming and/or unusual adverse events must be reported to the following individual within 24 hours of the investigator's knowledge of the event.

An Adverse Event Form should be completed for all serious adverse events and forwarded to the ADR within 24 hours. When new significant information is obtained as well as when outcome of an event is known, the investigator should inform the ADR. In applicable cases, ADR may request a letter from the investigator summarizing events related to the case. Investigators should follow patients as far as possible until an outcome to the events is known.

The investigator is responsible to communicate details of medical emergencies in trial patients to the ethics Committee.

REFERENCES

1. Wang HJ, Lee WC, Tyagi P, Huang CC, Chuang YC*. Effects of Low Energy Shock Wave Therapy on Inflammatory Molecules, Bladder Pain, and Bladder function in a Rat Cystitis Model. *NeurourolUrodyn.* 2017; 36: 1440-1447.
2. Zimmermann R, Cumanas A, Miclea F, Janetschek G. Extracorporeal shock wave therapy for the treatment of chronic pelvic pain syndrome in males: a randomised, double-blind, placebo-controlled study. *European urology.* 2009;56(3):418-24.