Study Title: **Investigation of Potential Therapeutic Effects of Pulsed Electromagnetic Field for the Treatment of Symptoms Associated with Interstitial Cystitis/Bladder Pain Syndrome**

IRB00068066

NCT04540887

Revised 08-13-2020

Study Title: Investigation of Potential Therapeutic Effects of Pulsed Electromagnetic Field for the Treatment of Symptoms Associated with Interstitial Cystitis/Bladder Pain Syndrome

Background, Rationale and Context

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a clinical diagnosis based primarily on chronic symptoms of pain perceived by the patient to emanate from the bladder and/or pelvis associated with urinary urgency or frequency in the absence of another identified cause for the symptoms[1]. Although it is not a life-threatening disease, the chronicity and severity of pain, along with urinary symptoms, causes great impairment in a patient's quality of life[2]. IC/BPS poses as a significant clinical challenge for many reasons. For one, the pathophysiology described in the literature is incompletely determined and likely multi-factorial, including factors such as inflammation, neurovascular dysfunction, ion imbalance, and impaired urothelial cell integrity[3,4,5]. Consequently, there are many options for IC/BPS therapy, many of which are driven primarily by patient-reported symptoms. In this regard, IC/BPS patients with moderate to severe pain typically require multi-modal therapy, often resulting in incomplete or no resolution of symptoms. Another clinical challenge is the heterogeneity of the symptoms. While pelvic pain is the distinguishing characteristic, patients with IC/BPS also routinely present with additional urological and non-urological medical symptoms and syndromes[6,7]. This has led to the description of two specific sub-phenotypes in IC/BPS based on anesthetized bladder capacity (BC), in which patients with BC < 400 cc are more likely to experience severe pain, urgency and frequency (bladder centric sub-phenotype), and patients with BC > 400 cc (non-bladder centric sub-phenotype) have a higher prevalence of non-urological associated syndromes (NUAS) such as fibromyalgia, chronic fatigue symptoms, irritable bowel syndrome, endometriosis and sicca syndrome[8,9].

The current landscape of IC/BPS therapies is vast and imperfect, with the level of invasiveness ranging broadly from lifestyle and behavioral changes to total cystectomy (for refractory end-stage disease). Current non-invasive treatments, including behavioral changes, dietary restrictions, and pelvic floor physical therapy have shown benefits in pain mitigation, but may not demonstrate consistent efficacy in more severe cases[10]. Pharmacologic strategies, such as NSAIDs and opiates, have also shown little evidence demonstrating consistent efficacy for treating the chronic pain state, and certainly are not without adverse effect profiles[11]. More invasive modalities such as cystoscopy with hydrodistention, botulinum toxin injections, or total cystectomies carry morbidity and procedural risk. Furthermore, there is a clear need for a new therapeutic strategy for IC/BPS management, as there is currently no standardized approach that provides relief for all, or even most, patients.

Pulsed Electromagnetic Field (PEMF) therapy may present a promising alternative therapy for IC/BPS. PEMF is a safe, non-invasive, and effective therapy currently used for wound healing,

bone-related diseases (osteoarthritis, RA), and chronic pain states (chronic lower back pain, fibromyalgia), the latter of which is frequently associated with IC/BPS as NUAS. Based on Faraday's law, electromagnetic interactions (e.g. PEMF) with biological processes and conditions (e.g. IC/BPS) will theoretically address many of the proposed pathophysiological causes of the condition. While the mechanism(s) of action are not fully understood, PEMF therapy has been shown in several studies (randomized, double-blinded, placebo-controlled trials) to decrease the output of pro-inflammatory proteins, improve oxygenation of blood and tissue, stabilize transmembrane action potential and ion channels, and stimulate tissue regeneration[12-15]. Thus, PEMF may provide a safe, non-invasive therapeutic option that would be complementary to, or serve as an alternative for, the treatments that are currently being administered in IC/BPS for pain reduction. Of note, PEMF has demonstrated an excellent safety profile with no associated systemic risks reported to date[16]. Additionally, the application of exogenous PEMF to stimulate the pelvic floor muscle has recently been introduced for treating urge and/or stress urinary incontinence and overactive bladder[17]. Furthermore, if patient safety and efficacy for pain reduction are demonstrated, these feasibility studies will provide the foundation for larger multi-site trials to determine additional parameters regarding the appropriate number of treatments as well as the duration of benefit (pain relief) following treatments.

Objectives

The objective of this pilot study is to test the idea that PEMF therapy will serve as a safe, non-invasive therapeutic modality that can effectively improve the chronic pain and/or associated symptoms of IC/BPS patients. We hypothesize that PEMF therapy will result in significant pain reduction in IC/BPS patients, specifically those with a non-bladder centric phenotype.

Published results from randomized, double-blinded, placebo-controlled clinical trials that have evaluated the efficacy of PEMF for pain management in conditions such as lower back pain, osteoarthritis, rheumatoid arthritis, and fibromyalgia have all reported significant pain reduction following PEMF therapy. Chronic pelvic pain and widespread, non-localized pain (beyond the bladder) are common findings in many IC/BPS patients. The proposed mechanism of action of PEMF therapy (increased microcirculation and tissue regenerative capacity through modulation of inflammatory processes) provides a compelling rationale for evaluating the efficacy of PEMF in IC/BPS patient pain relief.

Methods and Measures

Design

This is a single center clinical series evaluating symptom relief following a 4-week trial of PEMF therapy. From our registry of IC/BPS patients we will recruit women, ages 18-80, who

have met all inclusion and exclusion criteria, which includes demonstration of an anesthetic BC > 400 cc (non-bladder-centric phenotype) and a current numeric rating scale (NRS) pain score for pelvic pain ≥ 6. Upon enrollment, each patient will be taught how to administer home treatment with the BEMER **(**Bio Electro Magnetic Energy Regulation) PEMF devices which consist of a total body mat (B.Body) plus a targeted pelvic mat (B.Pad). Following the brief in-clinic training, participants will be sent home with the PEMF devices (pre-set to deliver the same level of energy each time) and will self-administer 8 minute PEMF therapy sessions, twice daily (once in the morning, once in the evening).

Patient assessments will occur at three time points: (1) enrollment, (2) after four weeks of treatment, and (3) at twelve weeks post-enrollment. The primary outcome measure will be the change in NRS pain score for pelvic pain. A decrease of at least 2 points on the NRS pain scale will be considered as representative of a significant decrease in pelvic (and/or widespread) pain. Secondary outcomes will be assessed by validated IC/BPS questionnaires (O'Leary-Sant indices), voiding characteristics (patient recorded voiding diary), change in perceived pain as determined by pain body maps, and the patient's overall impression of change (Global Response Assessment). Follow-up assessments will be completed remotely through phone or email surveys. During the twelve-week study, patients will not undergo any of the following IC/BPS therapies: cystoscopy with hydrodistention, bladder instillations, or trigger point injections. Patients that were prescribed a stable dose of pro re nata (PRN) narcotic medication at least three months prior to enrollment will be included in the study. Patients will be expected to report which, if any, pain medications they have been taking prior to enrollment and what additional medications they plan to use throughout the duration of the study. The following IC/BPS oral medications will be allowed during this time: amitriptyline, cimetidine, hydroxyzine, and pentosan polysulfate.

The demographic data will be extracted from patient's electronic medical record. The basic office evaluation will be composed of detailed medical history, physical exam, urinalysis, urine culture, 7-daysvoiding diary, O'Leary-Sant symptom and problem index (ICPI/ICSI), Pelvic Pain and Urgency/Frequency Patient Symptom (PUF) scale, Genitourinary Pain Index (GUPI), SF-36 quality of life questionnaires, and numeric rating scale for pain in the last 24 hours.

In this proof of concept study, *all* participants will receive the full therapy (i.e. there will not be a control group). In the double-blind placebo-controlled crossover trial that will follow this proof-of-concept study, we will have access to placebo (sham) mats for use as a control.

Subject Selection Criteria

Participants will be recruited from the Urology Clinic at Wake Forest Baptist Hospital and all study participants will provide written informed consent.

- **Inclusion Criteria**
  Female patients between 18 to 80 years with a previously established clinical diagnosis of IC/BPS. Participants must have an anesthetic BC > 400 cc, a current NRS score ≥ 6, and have no cognitive deficits. Patients will be required to attest that they will not receive a new prescription and/or an increased dose of narcotic medication while participating in the study.

- **Exclusion Criteria**
  Any history of bladder, uterine, ovarian, or vaginal cancer, urethral diverticulum, spinal cord injury, stroke, Parkinson's disease, multiple sclerosis, spina bifida, radiation cystitis, cyclophosphamide treatment, immunosuppressive therapy in consequence of transplantation, allogeneic cellular transplantation, or bone marrow or stem cell transplantations, deep vein thrombosis, or genital herpes. Patients will be excluded from this study if they have an implanted pace-maker, metal prosthesis, urinary tract infection, BMI > 40, or are currently pregnant.

- **Sample Size**
  For this small pilot study, we will enroll up to 10 study patients with the goal of achieving a full dataset from at least 6 patients.

Human Subjects Protection

Informed Consent: An IRB-approved written informed consent will be obtained from each subject. Patients will initially be contacted and introduced to the study via phone call from a study team member to discuss study details and answer questions. If they agree, an electronic copy of the IRB-approved consent form will be e-mailed to the patient. Informed consent and signature will be acquired in the Wake Forest University Urology Outpatient Clinic prior to training on the PEMF device.

Confidentiality and Privacy: Confidentiality will be protected by collecting only information needed to accomplish future demographic matching (i.e. patient's age, ethnicity, BMI, etc.), minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a separate master log. The master log will be kept secure, with access limited to designated study personnel. Following data collection, subject identifying information will be destroyed at the earliest opportunity consistent with data validation and study design,

producing an anonymous analytical data set. Data and records will be kept locked and secured, with access limited to study staff and password protection on all data stored electronically. No reference to any individual participant will appear in reports, presentations, or publications that may arise from this study.

Every effort will be made to maintain participant privacy. Data will only be released to scientists who are qualified and prepared to conduct a research study. If publications or presentations result from this research, participants will not be identified by name or any other personal identifier.

Data and Safety Monitoring

The principal investigator and study coordinator will be responsible for the overall monitoring of the data and safety of study participants and will ensure that the subjects' information is not revealed. The principal investigator will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations, or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

References

1. Van de Merwe JP NJ, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, Elneil S, Fall M, Hohlbrugger G, Irwin P, Mortensen S, van Ophoven A, Osborne JL, Peeker R, Richter B, Riedl C, Sairanen J, Tinzl M, Wyndaele JJ. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol. 2008;53(1):60-67.
2. Vasudevan V, Moldwin R. Addressing quality of life in the patient with interstitial cystitis/bladder pain syndrome. Asian J Urol. 2017; 4(1): 50-54.
3. Keay SK, Birder LA, Chai TC. Evidence for bladder urothelial pathophysiology in functional bladder disorders. *Biomed Res Int*. 2014;2014:865463. doi:10.1155/2014/865463
4. Parsons CL. "The role of leaky epithelium and potassium in the generation of bladder symptoms in interstitial cystitis/overactive bladder, urethral syndrome, prostatitis and gynaecological chronic pelvic pain." *BJUI*. 2010 (107): 370-375.
5. Christmas TJ, Rode J, Chapple CR, et al. "Nerve fibre proliferation in interstitial cystitis." *Virchows Arch A Pathol Anat Histopathol.* 1990 (416): 447-451.
6. Warren JW, van de Merwe JP and Nickel JC: Interstitial cystitis/bladder pain syndrome and nonbladder syndromes: facts and hypotheses. Urology 2011; 78: 727.

7. Nickel JC, Irvine-Bird K, Jianbo L et al: Phenotype-directed management of interstitial cystitis/bladder pain syndrome. Urology 2014; 84: 175.
8. Walker S, Zambon, JP, Andersson, KE, Langefeld, CD, Matthews CA, Badlani, G, Bowman, H, Evans, RJ. Bladder capacity is a biomarker for abladder centeric versus systemic manifestation in interstitial cystitis/bladder pain syndrome. *J Urol.* 2017;198(2):369-375.
9. Jhang J, Kuo, HC. Pathomechanism of interstitial cystitis/bladder pain syndrome and mapping the heterogeneity of disease. *Intl Neurol J.* 2016;20(Suppl 2):S95-S104.
10. Adamian L, Urits I, Orhurhu V, et al. A Comprehensive Review of the Diagnosis, Treatment, and Management of Urologic Chronic Pelvic Pain Syndrome. *Curr Pain Headache Rep*. 2020;24(6):27. Published 2020 May 6. doi:10.1007/s11916-020-00857-9
11. Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain--Misconceptions and Mitigation Strategies. *N Engl J Med*. 2016;374(13):1253-1263. doi:10.1056/NEJMra1507771
12. Benedetti M, Cavazzuti, L, Mosca, M, Fusaro, I, Zati, A. Bio-Electro-Magnetic-Energy-Regulation (BEMER) for the treatment of type I complex regional pain syndrome: A pilot study. *Physiother Theory Pract.* 2018;9(doi: 10.1080/09593985.2018.1491661.):1-9.
13. Strauch B, Herman, C, Dabb, R, Ignarro, LJ, Pilla, AA. Evidence-Based Use of Pulsed Electromagnetic Field Therapy in Clinical Plastic Surgery. *Aesthet Surg J.* 2009;29(2):135-143.
14. Ross C, Harrison, BS. The use of magnetic field for the reduction of inflammation: a review of the history and therapeutic results. *Altern Ther Health Med*. 2013a;19(2):47-54.
15. 10. Ikehara T, Yamaguchi, H, Miyamoto, H. Effects of electromagnetic fields on membrane ion transport of cultured cells. *J Med Invest.* 1998;45(1-4):47-56.
16. Ross C, Harrison, BS. The use of magnetic field for the reduction of inflammation: a review of the history and therapeutic results. *Altern Ther Health Med*. 2013a;19(2):47-54
17. Jorgensen W, Frome, BM, Wallach, C. Electrochemical therapy of pelvic pain: effects of pulsed electromagnetic fields (PEMF) on tissue trauma. *Eur J Surg Suppl.* 1994;574:83-86.