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Principal Investigator: Tola Fashokun

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Title:

Use of Preemptive Pudendal Nerve Block Prior to Hydrodistention for the Treatment of Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS)

JHM IRB - eForm A – Protocol

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Interstitial cystitis/Painful bladder syndrome (IC/PBS) is a chronic debilitating condition that severely impacts between 2.7 and 6.5 percent of women in the United States. Despite its public health importance the pathogenesis of IC/PBS is not well understood and there is no consensus on the optimal treatment approach for this condition. Hydrodistention is the most commonly used therapy for this condition; but it is limited by severe immediate postoperative bladder pain and its short duration of action. It has been postulated that hydrodistention works by disrupting the sensory nerves within the bladder that may be contributing to bladder pain. Recent evidence has provided support for the use of preemptive pudendal nerve block as a way to blunt immediate postoperative pain. We hypothesize that preemptive pudendal nerve block prior to hydrodistention will result in lower postoperative pain after hydrodistention compared to placebo. This is a prospective double- blinded randomized study and patients will be randomized to receive preemptive bilateral pudendal nerve block with either 1% lidocaine or placebo. Bladder pain will be compared at baseline, 2 hours, 2 weeks, 6 weeks and 3 months using the Visual Analog Scale, O'Leary-Sant questionnaire and the Pelvic Pain Urgency and Frequency questionnaire.

2. Objectives (include all primary and secondary objectives)

Our overall goal is to determine the change in bladder symptoms after preemptive pudendal nerve block before hydrodistention in patients with IC/PBS. In order to effectively characterize our outcomes we have chosen different validated instruments to assess post-operative pain. First, in order to objectively quantify pain intensity we will determine the mean difference in postoperative pain at 2 hours in the treatment group (1% Lidocaine) compared to the placebo group (saline) using the Visual Analog Scale (VAS); this will serve as our primary endpoint (AIM 1). In order to capture the most important voiding and pain symptoms and to assess the degree of bother between the two groups we will measure mean difference in interstitial cystitis symptom index and the problem index (O'Leary-Sant) and in the Pelvic pain, Urgency and Frequency (PUF) questionnaire at baseline, 2 hours, 2 weeks, 6 weeks and 3 months after treatment with hydrodistention and preemptive pudendal nerve block compared to hydrodistention with placebo (AIM 2). Finally in an attempt to expand our knowledge about the change in bladder symptoms over time, we will measure the change in the interstitial cystitis symptom index and the problem index (O'Leary-Sant) and in the Pelvic pain, Urgency and Frequency (PUF) questionnaire at baseline, 2 hours, 2 weeks, 6 weeks and 3 months

after treatment (AIM3). With this project we propose a novel approach to decreasing the immediate postoperative pain and possibly prolonging the efficacy of this intervention for the management of IC/PBS.

Aim 1. To determine the mean difference in pain at 2 hours postoperatively in patients undergoing hydrodistention with preemptive pudendal nerve block (1% Lidocaine) compared to hydrodistention with placebo (saline) using the visual analog scale (VAS).
AIM 2. To determine the mean difference in interstitial cystitis symptom index and the problem index (O'Leary-Sant) and in the Pelvic pain, Urgency and Frequency (PUF) questionnaire at baseline, 2 hours, 2 weeks, 6 weeks and 3 months after hydrodistention with preemptive pudendal nerve block (1% Lidocaine) compared to hydrodistention with placebo (saline).
AIM 3. To measure the change in the interstitial cystitis symptom index and the problem index (O'Leary-Sant) and in the Pelvic pain, Urgency and Frequency (PUF) questionnaire at baseline, 2 hours, 2 weeks, 6 weeks and 3 months after treatment with hydrodistention with and without preemptive pudendal nerve block.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Painful bladder syndrome/interstitial cystitis (IC/PBS) is a disorder characterized by chronic bladder pain or discomfort[1]. The exact underlying etiology of IC/PBS is unknown however several theories exist which include epithelial dysfunction, mast cell activation, and neurogenic inflammation. Whatever the underlying inciting factor for IC/PBS, the resulting phenotype is one of urinary frequency, urgency and bladder pain improved after voiding[1]. Animal studies show that as the normal bladder fills, mechanoreceptors in the bladder wall respond to stretch through the discharge of afferent innervations or nerve firing [2,3]. In normal humans, there is no conscious perception that the bladder is filling until a threshold volume is reached[4]. Patients with PBS/IC are thought to have substantially lower cystometric bladder volumes and a heightened sensitivity to bladder filling[5]. Mechanoreceptors and chemoreceptors in the bladder may trigger myelinated A- delta or C-fibers found in the smooth muscle or in the submucosa in response to bladder distention. A- delta fibers are distributed mainly within the detrusor smooth muscle and are responsive to detrusor stretch that occurs during bladder filling. In contrast, C-type fibers seem to be more widespread and are distributed in the detrusor muscle, within the lamina propria and in close proximity to the urothelium[4, 5, 6]. There is considerable interest in mechanisms underlying sensitization of C-fiber afferents, as these nerves are thought to play a key role in symptoms of IC/PBS. It has been shown that the plexus of afferent nerves is most dense in the regions of the bladder neck and proximal urethra[4]. Lumbosacral afferent fibers in the pelvic and pudendal nerve, with cell bodies in the lumbosacral DRG, not only sense pain but also regulate continence and micturition [6,7,8]. In laboratory animals, the pelvic nerve supply contains more stretch-responsive afferent fibers and appears to be important in responses to bladder over-distention. Neurologic changes seen after the occurrence of cystitis or other bladder insult suggest reorganization of reflex connections in the spinal cord and changes to the bladder afferents, that may suggest a greater role for the influence of the pudendal nerve on bladder pain than had been previously thought [8,9].

The pudendal nerve is a peripheral nerve that is mainly composed of afferent sensory fibers from sacral nerve roots S1, S2, and S3 and consequently it is a major contributor to bladder afferent regulation and bladder function. Pudendal nerve entrapment often leads to significant voiding dysfunction including urinary incontinence and over active bladder syndrome [10,11] Furthermore, because the pudendal nerve carries such a large percentage of afferent fibers, it has been an attractive target for neuromodulation in treating refractory overactive bladder and may be useful for modulating pain experienced in IC/PBS[12,13, 14].

No treatment has been consistently shown to provide relief in the majority of patients with painful bladder syndrome[14]. Furthermore, combination treatment modalities are needed in the majority of patients. Cystoscopy with hydrodistention is thought to be a useful therapeutic tool in patients who are unresponsive to therapies like medication and pelvic floor physical therapy; however, its use has only been studied in a few observational studies and is currently listed as a third line treatment option for IC/PBS[1, 14,15]. According to the interstitial cystitis database

study experience cystoscopy with hydrodistention is reported to be the most commonly used treatment modality for IC/PBS and published studies have reported improvement in symptoms in 70 to 80 percent of patients while other studies have reported improvement in only 40 percent[14]. It has been postulated that hydrodistention works by disrupting the sensory nerves within the bladder that may be contributing to bladder pain and enabling the regeneration of afferent sensory nerves[16]. Though the exact mechanism of action is unclear, there is ample evidence to suggest the efficacy of cystoscopy with hydrodistention, in a recent study by Chien-Ying et al, therapeutic hydrdistension was associated with an increase in bladder capacity and significant reduction in average O'Leary-Sant symptom and problem scores after treatment[16]. In addition, Aihara et al who determined a positive therapeutic outcome in 71% of patients 1 month after hydrodistention have reported similar findings[17]. The disadvantages of hydrodistention are that some patients experience a temporary worsening of their symptoms immediately following the procedure and any beneficial effect often lasts between 2-6 weeks[18, 19,21,22]. The immediate worsening of bladder symptoms immediately after hydrodistention and its relatively short duration of effect are often deterrents to recommending this therapy to patients. Given the multimodal approach to managing patients with IC/PBS it is imperative that we investigate ways to prolong the efficacy of available options and one approach that has been recently suggested is the use of preemptive analgesia.

In 1983, Woolf proposed that persistent pain experienced after trauma or surgery is due to posttraumatic functional changes not only in the peripheral pain receptors but also in the dorsal horn of the spinal cord a property known as hyperexcitability[23]. The hyperexcitable state persists long after such stimuli cease, causing the patient to perceive pain from stimuli normally believed to be painless a common occurrence thought to be seen in patients with IC/PBS. Therefore, prevention of spinal hyperexcitability by blockade of the afferent nerve pathway from surgical site to spinal cord may therefore decrease the amount and duration of postoperative pain perception[24]. This theory has been tested in various animal studies and was first described by Wall in 1988. In addition, the current literature on preemptive analgesia in gynecology is supportive of this approach[25, 26]. In a study by Ismail et al, 130 patients undergoing posterior colporrhaphy were randomized to receive preemptive pudendal nerve block with either .25% bupivacaine or normal saline. Study findings demonstrated an average postoperative VAS score of 51.1 for the bupivacaine group compared to 23.5 in the placebo group. We postulate that since the pudendal nerve is an important contributor to bladder afferent regulation, preemptive nerve block prior to hydrodistention may block afferent impulse transmission to the spinal cord and decrease the initial increase in postoperative bladder pain.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

This study is a prospective double-blinded randomized controlled study that will be done at two sites: Johns Hopkins Bayview Medical Center and Greater Baltimore Medical Center. Female patients over 18 years of age, who present for treatment of painful bladder syndrome (IC/PBS) at the Pelvic Floor Center at the Johns Hopkins Bayview Medical Center, will be considered for inclusion in the study (please see below for inclusion and exclusion criteria). The primary investigator and co-investigators will determine patient eligibility. The patients will be asked to participate in the study if they are undergoing cystoscopy with hydrodistention for a presumed diagnosis of IC/PBS. When the patient presents to the operating room on the day of their scheduled surgery they will be asked to complete the PUF questionnaire, the interstitial cystitis symptom and problem index, and the Visual Analog Scale (VAS). This time point has been chosen to minimize the temporal variation seen in pain. Patients will be randomized to either preemptive bilateral pudendal nerve block with either 20 cubic centimeters 1% lidocaine or 20 cubic centimeters normal saline after anesthesia induction, participants will be stratified by type of anesthesia. The circulating nurse will be provided with a sealed opaque envelope with the patient group allocation and he/she will provide the operating surgeon with the study drug in a syringe labeled "pudendal nerve block". The placement of the pudendal nerve block will be performed in a standardized fashion per protocol. The patients will receive their standardized anesthetic regiment per anesthesiology guidelines. At the conclusion of the case the patients will be monitored in the postoperative anesthesia unit for recovery per nursing guidelines. The patients will be asked to rate their pain on a 100mm VAS, the O'Leary Sant, and the PUF at 2 hours postoperatively.

b. Study duration and number of study visits required of research participants.

The interstitial cystitis symptom index and the problem index and PUF questionnaire and VAS will be repeated at 2 hours, 2 weeks, 6 weeks and 3 months postoperatively via a telephone interview. These time points have been specifically chosen due to their common use as intervals for assessing pain. Additionally, the expected difference in pain intensity for these time intervals is well described in the literature[17]. Furthermore, the mean duration of action of cystoscopy with hydrodistention is reported to last between 2 and 6 weeks, and we will be certain to capture evidence of prolonged efficacy if study follow up is extended to 3 months post operatively[17, 18, 19].

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Randomization to 1% Lidocaine versus placebo will be performed using computer or hand generated 1:1 block permutations and stratified by anesthesia type. Assignment will be revealed in the operating room after the patient receives anesthesia. We will randomize 120 patients total (60 at each site, 30 for placebo and 30 for treatment).

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Currently, hydrodistention is routinely done without pudendal nerve block. This study will introduce an addition to standard care that may alleviate postoperative pain.

e. Justification for inclusion of a placebo or non-treatment group.

This study requires a placebo as this will allow for a comparison group, will enable us to account for a placebo effect and potential bias. However, both groups will be receiving standard treatment, which is hydrodistention.

f. Definition of treatment failure or participant removal criteria.

Participants may be removed from the study if they are diagnosed/newly recognized to meet any of the exclusion criteria, including intolerance of local anesthesia, new bleeding disorder, or new onset mental status change that precludes the patient from being be able to follow instructions or accurately assess pain control.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

At the completion of the study if patients receive a significant improvement in their symptoms after hydrodistention and pudendal nerve block then they will continue to be managed with this therapy in the future. If they do not receive benefit or their participation ends prematurely they will be offered alternative therapies to treat their IC/PBS symptoms.

5. Inclusion/Exclusion Criteria

Inclusion Criteria: All women aged greater than 18 years of age scheduled to undergo cystoscopy with hydrodistention who are literate, English speaking and can provide written informed consent will be included in this study.
Exclusion Criteria: Patients who have intolerance or known allergies to local analgesia will be excluded. In addition, patients who have coagulation disorders will also be excluded as this may increase their risks of complication from bleeding. Patient will also be excluded if they have a history of dementia as this may impair their ability to follow instructions. Patients who are non-ambulatory and who have an inability to fully assess pain will

also be excluded. Patients receiving additional surgical procedures will be excluded from the study, as the source of their pain may be difficult to decipher in the immediate post-operative period.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Total 20cc (10cc bilateral) of 1% Lidocaine: Lidocaine is a commonly used anesthetic agent suitable for infiltration, block and surface anesthesia, It is characterized by a rapid onset of action, intermediate duration of efficacy, and its elimination half-life is 90-120 minutes. Lidocaine alters signal conduction in neurons by blocking the fast voltage gated sodium (Na) channels in the neuronal cell membrane that are responsible for signal propagation[31]. With sufficient blockage the membrane of the postsynaptic neuron will not depolarize and will thus fail to transmit an action potential. This creates the anesthetic effect by not merely preventing pain signals from propagating to the brain but by stopping them before they begin. Adverse drug reactions are rare when lidocaine is used as a local anesthetic and when administered correctly[27].

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed. n/a

c. Justification and safety information if non-FDA approved drugs without an IND will be administered. n/a

7. Study Statistics

a. Primary outcome variable.

Visual Analog Scale (VAS): The most common VAS consists of a 100mm horizontal or vertical line with the two endpoints labeled "no pain" and "worst pain ever" (or similar verbal descriptors). Patients are required to place a mark on the 100mm line at a point that corresponds to the level of pain intensity they feel. The distance in centimeters from the low end of the VAS to the patient's mark is used as a numerical index of the severity of pain[28]. Pain scores of 30–54 mm are regarded as moderate while a score over 54 indicates severe pain[28,29].
Visual analog scales are sensitive to pharmacologic and non-pharmacologic procedures that alter the experience of pain and correlate highly with pain measured on verbal and numeric rating scales. A major advantage of the VAS as a measure of sensory pain intensity is its ratio scale properties. In contrast to many other pain-measurement tools, equality of ratios is implied, making it appropriate to speak meaningfully about percentage differences between VAS measurements obtained at multiple points in time or from independent samples of subjects. Other advantages of the VAS include its ease and brevity of administration, scoring and minimal intrusiveness; and, providing that adequately clear instructions are given to patients, its conceptual simplicity[30,].

b. Secondary outcome variables.

The interstitial cystitis symptom index and the problem index (O'Leary-Sant):
The interstitial cystitis symptom index and the problem index have been designed to capture the most important voiding and pain symptoms and to assess how problematic patients find them in the clearest and most concise manner possible[31]. Both instruments have been designed and validated for self-administration, so that trained interviewers are not needed to use them. This is a unique tool that will enable us to monitor symptom regression and efficacy of our treatment.

Pelvic Pain, Urgency and Frequency (PUF) questionnaire:
The PUF questionnaire is a commonly used measure for evaluating patients suspected of having IC/PBS. Its domains address what are considered the hallmarks of the disease, namely pain, urinary urgency, and frequency of urination[32]. Parsons et al. initially examined the value of the PUF questionnaire as a predictive diagnostic tool in 2002. In this study, a direct correlation was found between greater PUF scores and the likelihood of a positive PST in patients with suspected IC/PBS and gynecologic pain[33]. Since then the PUF questionnaire has been considered a valid diagnostic screening tool for patients with possible IC/PBS and will be the tool used in this study for that purpose.

c. Statistical plan including sample size justification and interim data analysis.

Recent evidence suggests a significant difference in 2-hour postoperative mean VAS scores after preemptive analgesia with 1% lidocaine (50.1±27.9) compared to placebo (70.6 ± 22.6) [34]. Based on this estimated mean difference we are planning this study with 50 participants (n= 50). The Type I error probability associated with the test of this null hypothesis is 0.05, with a power of 80%. Demographic, surgical, and clinical outcomes will be assessed using t-test, chi squared, and Fisher exact tests where appropriate. For continuous measures, normally distributed data will be compared with Students t test; non-normally distributed data will be compared with Wilcoxon test. Visual analog pain scores will be compared using repeated measures of variance. Furthermore, an intention to treat analysis will be performed for the participants who drop out prior to study completion.

d. Early stopping rules.

e. Participants who no longer wish to be a part of the study may stop without penalty at any time during the study.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

There is minimal risk involved in performing pudendal nerve blocks, these risk include a less than 1% chance of additional pain, bleeding, hematoma or lidocaine systemic toxicity.

b. Steps taken to minimize the risks.

In order to minimize risk the pudendal nerve block will be performed by a trained urogynecologist in the operating room, additionally the patients will be monitored by an anesthesiologist during the procedure for any signs of systemic toxicity.
The participants will also be monitored in the postoperative recovery area for 2 hours after their procedure.

c. Plan for reporting unanticipated problems or study deviations.

All unanticipated problems and study deviations will be reported to the IRB at regular intervals.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

The legal risks of this procedure are similar to other surgical interventions: there is a risk of bleeding, infection, damage to surrounding structures, or failure to obtain desired result. There are also risks associated with confidentiality if patient information were not to be appropriately transferred during the course of the procedure.

e. Financial risks to the participants.

Financial risks to participants are significant for lost work time, including recuperation. These are not considered to be significantly different compared to the current standard of care for execution of pudendal nerve block.

9. Benefits

a. Description of the probable benefits for the participant and for society.

Pudendal nerve blocks are widely performed in Obstetrics and Gynecology. The procedure involves injecting local anesthetic around the trunk of the pudendal nerve located behind the sacrospinous ligament. Infiltration of local anesthesia at the site of the pudendal nerve leads to analgesia at the areas being innervated by sacral nerve roots two, three and four. Recent improvement in our understanding of pain management in other specialties have provided us with insight on how to blunt the immediate increase in bladder pain seen after hydrodistention and prolong the effect of this therapy on patients with IC/PBS. Following surgery, afferent impulses centrally processed can increase postsurgical pain[26]. Preemptive analgesia is an intervention provided prior to the initiation of painful stimuli, which may reduce or blunt subsequent pain in the postoperative period [35,36 ,37,38].The use of pudendal nerve blocks in combination with hydrodistention may allow us to improve the immediate efficacy of this treatment modality and also prolong the duration of action of this therapy. Currently there are no studies evaluating the use of pudendal nerve blocks with hydrodistention for the treatment of painful bladder syndrome.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

We will not be offering compensation to patients participating in this protocol.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will not be cost associated with participation from our participants.

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