A PROSPECTIVE, RANDOMIZED, PLACEBO CONTROLLED, DOUBLE-BLIND STUDY OF PELVIC ELECTROMAGNETIC THERAPY FOR THE TREATMENT OF CHRONIC PELVIC PAIN SYNDROME WITH 1 YEAR OF FOLLOWUP

E. ROWE, C. SMITH, L. LAVERICK, J. ELKABIR, R. O'N WITHEROW AND A. PATEL

From the Department of Urology, St. Mary’s Hospital, London, United Kingdom

ABSTRACT

Purpose: Male chronic pelvic pain syndrome is a condition of uncertain etiology and treatment is often unsatisfactory. There is evidence that the symptom complex may result from pelvic floor muscular dysfunction and/or neural hypersensitivity/inflammation. We hypothesized that the application of electromagnetic therapy may have a neuromodulating effect on pelvic floor spasm and neural hypersensitivity.

Materials and Methods: Following full Stamey localization men with National Institute of Diabetes and Digestive and Kidney Diseases category III prostatitis were prospectively randomized to receive active electromagnetic or placebo therapy. Active therapy consisted of 15 minutes of pelvic floor stimulation at a frequency of 10 Hz, followed by a further 15 minutes at 50 Hz, twice weekly for 4 weeks. Patients were evaluated at baseline, 3 months and 1 year after treatment using validated visual analog scores.

Results: A total of 21 men with a mean age of 47.8 years (range 25 to 67) were analyzed. Mean symptom scores decreased significantly in the actively treated group at 3 months and 1 year (p<0.05), unlike the placebo group, which showed no significant change (p>0.05). Subanalysis of those receiving active treatment showed that the greatest improvement was in pain related symptoms.

Conclusions: The novel use of pelvic floor electromagnetic therapy may be a promising new noninvasive option for chronic pelvic pain syndrome in men.

Key Words: pelvic pain, electromagnetics, prostate, pain, prostatitis

The uncertain etiology and variable response to treatment has made prostatitis a challenging entity. In a national survey of physician visits in the United States a diagnosis of prostatitis was made in 8% of urological and 1% of primary care physician visits, respectively.1 This confirmed it as a significant health problem, supporting previous estimates of approximately 2 million prostatitis related outpatient visits yearly nationwide.2 Globally the reported incidence of prostatitis-like symptoms has been shown to be 2.7% in the Far East to 14.2% in Northern Europe.3, 4 In 1995 the National Institutes of Health-National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) workshop reached a consensus on the definition and classification of prostatitis syndromes.5 This has formed the basis for subsequent research on the pathophysiology of the disease and the efficacy of therapeutic measures.

The commonest and yet most poorly understood of these prostatitis syndromes is category III or chronic pelvic pain syndrome (CPPS). It has been shown that, while men with CPPS have significantly higher leukocyte counts in urine and expressed prostatic secretions compared with age matched controls, inflammation and infection do not necessarily correlate with symptom severity.6, 7 The lack of a direct relationship between inflammation and symptoms is supported through studies of prostate histopathology, in which moderate or severe inflammation was identified in only 5% of men with CPPS.8

Contributory factors in the pathophysiology of CPPS may include obstruction to bladder emptying. Symptomatic relief has been demonstrated with the use of α-blocking pharmaco-therapy, particularly with regard to decreasing pain.9 Therefore muscle tone in the urethra/sphincter mechanism may contribute to the pain experienced by men with CPPS.

Despite these findings the pathophysiology remains elusive and the role of neurogenic inflammation may offer a possible explanation. It results from a complex interaction between the central/peripheral nervous system and the immune system, causing the release of neuropeptides that activate receptors on specific cells, including mast cells, Langerhans' cells, microvascular endothelial cells, fibroblasts and infiltrating immune cells. The concept of neurogenic inflammation and its effect on mast cell function, vasoconstriction and leukocyte recruitment in the pathophysiology of CPPS represents a new and interesting avenue for further research.10, 11 Also, the role of purinergic signaling through the release of urothelial adenosine triphosphate and the stimulation of subepithelial nerve plexuses via the purinergic P2X3 receptor, resulting in pain, may provide an explanation for the symptom profile seen in CPPS.12

Conventional treatment has focused on long, empirical courses of expensive broad-spectrum antibiotics, mostly of the quinolone class, with or without the concomitant use of an α-blocker and anti-inflammatory agents. Stepwise introduction of these therapies has also been shown to be of benefit.13 There is also emerging evidence of the benefits of finasteride in the management of CPPS.14

At the turn of the 19th century stimulation with electrical current and changing magnetic fields was used to treat surface conditions associated with intractable pain, such as painful malignant ulcers. The analgesic benefits of pulsed electromagnetic fields for relieving pelvic pain has been investigated in women with tissue trauma and chronic refractory pelvic pain.15, 16 However, in the application of electro-
magnetic stimulation to the pelvis most research has been in the management of female stress and urge incontinence. Despite its uncertain etiology there is some evidence that the symptom complex found in CPPS may be founded at least in part in pelvic floor muscular dysfunction and/or neurogenic hypersensitivity/inflammation. We hypothesized that the application of a rapidly changing electromagnetic field applied noninvasively to the perineum of the subject may result in neural excitation and pelvic floor muscle stimulation to a degree that breaks the cycle of tonic muscular spasm and neural hypersensitivity/inflammation, thereby, restoring more normal pelvic floor muscular activity.

MATERIALS AND METHODS

A total of 21 men attending the urology outpatient clinic with a diagnosis of NIDDK category IIIA or IIIB prostatitis syndrome were invited to take part in a trial of electromagnetic pelvic floor therapy. Entry criteria were age 70 years or less and a full Stamey procedure to exclude urinary microorganisms. Prostate cancer had been excluded by normal serum prostate specific antigen, clinically benign digital rectal examination or negative previous biopsy. Patients with previous pelvic radiotherapy were also excluded.

Each man had previously undergone several types of failed medical therapy for the condition, which typically included multiple antibiotic courses, α-blockers and occasionally antidepressants. After obtaining informed consent eligible subjects were randomized to active and placebo groups using computer generated, blocked randomization numbers. Patients were informed about the nature of the treatment, the treatment schedule and the possibility that they might be randomized to placebo but they were not given a detailed description of what local pelvic sensations, if any, to expect during treatment, so as not to bias blinding.

All men were asked to complete a baseline symptom visual analog score (VAS) questionnaire that included 5 items of pain related questions and 4 covering urinary symptoms (see Appendix). The VAS questionnaire was adopted from the validated symptom severity index designed by Nickel and Sorensen. The question regarding painful digital rectal examination was omitted because the questionnaire was mailed and, hence, clinical evaluation was not possible. Each individual question was scored from 0—asymptomatic to 10—severely symptomatic, providing a total score of 0 to 90. The symptom score questionnaire was re-administered 3 months and again 1 year following treatment in a double-blind manner with patients and the individual analyzing the data blinded to the identity of those who had received active treatment.

The active treatment regime was empirical and consisted of 2 sessions weekly for 4 weeks (total 8 sessions). During each half-hour session the patient would sit centrally on the Neotonus™ electromagnetic chair for 2 consecutive 15-minute periods (fig. 1). The frequency was set low at 10 Hz for the first 15-minute period and increased to 50 Hz for the second 15-minute period. The gain was set low initially and gradually increased, as tolerated by the patient. Patients who received placebo were treated in a manner identical to that in the active treatment group in all respects except no active stimulation was applied from the device. Instead, the chair was switched on so that the fan could be heard and a hidden speaker under the stimulation device replicated the sounds created during active treatment. Men receiving active and placebo therapy were treated on alternate days to prevent cross-talk between groups, which may have compromised study blinding. Statistical analysis was performed using Student’s t test.

RESULTS

A total of 21 men with a mean age of 47.8 years (range 25 to 67) were entered into the study. Of the 21 men 11 were randomized to the active treatment group and 10 were randomized to the placebo treatment group. Four men failed to complete the 4-week treatment, including 1 in the active treatment group and 3 in the placebo group. They were excluded from further analysis. Followup data were obtained on 17 men at 3 months (10 in the active and 7 in the placebo group) and 13 at 1 year (8 and 5, respectively).

A significant difference was observed when mean symptom scores in the active and placebo groups were analyzed. There was a statistically significant decrease in mean symptom scores in the active treatment arm from 38.8 of 90 at baseline to 26.4 of 90 at 3 months (95% CI 0.9 to 21.9, p < 0.05) and to 24.0 of 90 at 1 year (95% CI 0.15 to 30.85, p < 0.05). There was no statistically significant change in symptom scores in the placebo group, which remained relatively unchanged at mean of 39.3 of 90 at baseline, 42.4 of 90 at 3 months (95% CI 1.7 to 22.37, p > 0.05) and 33.6 of 90 at 1 year (95% CI –2.66 to 28.26, p > 0.05, fig. 2).

On differential analysis separating pain scores from urinary scores similar improvement was seen in the active treatment group. The pain score decreased significantly in those receiving active treatment from a mean baseline of 21.7 of 50 to 14.7 of 50 at 3 months (95% CI 2.7 to 12.49, p < 0.05) and to 11.9 of 50 at 1 year (95% CI 2.5 to 18.7, p < 0.05). The mean pain score in the placebo group remained relatively unchanged for the same periods, that is 22.4 of 50 at baseline, 22.4 of 50 at 3 months (95% CI –6.38 to 13.8, p > 0.05) and 18 of 50 at 1 year (95% CI –22.6 to 19.8, p > 0.05, fig. 3).

Mean urinary symptom scores showed a significant decrease from 17.1 of 40 at baseline to 11.7 of 40 at 3 months in those receiving active treatment (95% CI 1.2 to 12.4, p < 0.05). While mean urinary symptom scores remained below baseline at the 1-year followup, improvement in the actively treated group no longer achieved statistical significance. There was no corresponding improvement in urinary symptoms in the placebo group, which changed little from the baseline of 18.9 of 40 to 19.3 of 40 at 3 months (95% CI –6.5 to 0.8, p > 0.05, fig. 4).
No significant side effects were observed. One patient in the active group experienced transient paresthesia 48 hours in duration with subsequent complete resolution.

**DISCUSSION**

In this pilot study we prospectively tested the hypothesis that pelvic floor neuromuscular dysfunction/neurogenic inflammation may account for some symptoms of CPPS (NIDDK IIIA and IIIB) and this dysfunction could be decreased by the noninvasive application of local electromagnetic therapy. Sustained improvement was observed in the symptom scores of men in the active group compared with scores those who received sham treatment.

When mean symptom scores were compared at 3 months and 1 year, there was a statistically significant decrease of approximately 40% in men in the active group, which was not observed in the placebo group. Further subanalysis of VAS pain and urinary symptom scores showed that the greatest improvement in the symptom profile was seen in the pain categories of men receiving active treatment, which was sustained at 1 year. There was also a significant improvement in urinary symptoms at 3 months of followup in the active group, although this decrease was of lower magnitude than the improvement in pain symptoms (approximately 30%) and it was no longer significantly different from baseline at 1 year. Nevertheless, no equivalent improvement was seen in the placebo group. Although we did not test the effectiveness of blinding the sham treatment group, we believe that the differences that we observed represent a real effect through mechanisms that have yet to be elucidated. Since this was a pilot study, quantitative analysis of the effectiveness of blinding to active or placebo treatment was not done and this should be part of any future study. However, because men in each arm wrote to ask if they had received active treatment at the 1-year followup, this anecdotal evidence reassured us as to the effectiveness of blinding. The failure to obtain followup data on all of those who participated in the study is at least in part a reflection of the transient nature of the urban population in which this study was performed.

While the precise etiology of CPPS continues to be obscure, there is growing evidence that it may result from muscular/neural dysfunction of the lower urinary tract rather than an inflammatory process in the prostate gland, which is supported by histological evidence and the failure of antibiotic treatment in a randomized, placebo controlled, multicenter trial. Support for the theory that it may result from a spasm in the proximal sphincter mechanism may derive from the decrease in symptoms in men treated with α-blockers. However, the pathways in neurogenic inflammation and in particular the complex interaction between central and peripheral nervous and the endocrine system, and their effects on immunomodulatory mechanisms may provide an explanation for the symptom pattern seen in men with CPPS. The modification/interruption of this pathway through electromagnetic stimulation may explain the improved symptom profile in those who received active treatment. By breaking the cycle of tonic muscular spasm and neural hypersensitivity/inflammation normal pelvic floor muscular activity is restored. This may account for the durability of the response. Another possible explanation is that purinergic P2X3 receptor subunits are up-regulated in CPPS, as reported in interstitial cystitis, and this up-regulation is reversed or there is desensitization of purinergic receptors.
following treatment. Interference of this pathway could explain why pain symptoms showed the greatest response.

To date electromagnetic stimulation therapy has generally been reserved for stress and urge female urinary incontinence. The frequencies used for this purpose were 10 and 50 Hz. Hence, these frequencies were applied in our phase II study. It may be that a single frequency will suffice and shorten treatment time, leading to cost savings. Frequencies of 20 Hz have been used successfully in the treatment of detrusor hyperreflexia, showing functional responses in the pelvic sphincter muscles together with an inhibition of detrusor hyperreflexia, possibly via the activation of pudendal nerve afferents blocking parasympathetic detrusor motor fibers at the spinal reflex arc. If the changing electromagnetic field exerts its effect in CPPS by decreasing tone in the proximal sphincter mechanism, frequencies with a maximal effect at this site may prove more effective.

The electromagnetic chair is unlikely to exert its effect on pain pathways similar to a transcutaneous electrical nerve stimulation machine. 1) This would not account for the improvement in urinary symptoms. 2) The transcutaneous electrical nerve stimulation machine operates at a much higher frequency of 120 Hz. The noninvasive nature of electromagnetic stimulation treatment and the ease of repeating it if necessary makes it attractive to patients and physicians alike since it can be easily performed in the office environment.

CONCLUSIONS

In this study we noted the safe, effective and novel use of a noninvasive pelvic floor stimulation device, that is the electromagnetic chair, for treating CPPS symptoms in a prospective, double-blind, placebo controlled study. These subjective improvements at 3 months of followup in patients in whom many other treatment regimens have previously failed were durable in the majority at 1 year. Further large-scale multicenter studies are required fully to evaluate the efficacy of this treatment and establish the optimal stimulation frequency as well as the usefulness of repeating treatment in those in whom initial therapy fails. These studies should incorporate the National Institute of Health CPPS index as a primary outcome measure, which was unfortunately not published at the time of initiation of this study.

Robert Redfern assisted with statistical data analysis. Neotonus™ provided the electromagnetic chair.

APPENDIX: VAS SCORES

Each symptom category was scored from 0 (asymptomatic) to 10 (severe symptoms)

1) Pain or discomfort in the penis, testicles or scrotum
2) Pain or discomfort in the perineum (area where you sit, between the testicles and anus
3) Pain or discomfort in the suprapubic or bladder area
4) Pain or discomfort during ejaculation
5) Pain or discomfort in the low back, upper leg or groin area
6) Uncomfortable and difficult urination (stranguria)
7) Voiding often (frequency)
8) Difficulty postponing urination (urgency)
9) Burning feeling during urination (dysuria)

REFERENCES


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