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**WITHDRAWN: Efficacy of thermobalancing therapy for chronic prostatitis/chronic pelvic pain syndrome, confirmed by clinical study, may suggest etiology and pathophysiology of this disease**

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## Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common condition that causes severe symptoms and worsens quality of life (QoL) in 8.2% of affected men [1], furthermore, the chronic inflammatory processes in the prostate may play role in the development of benign prostatic hyperplasia (BPH) [2]. CP/CPPS also takes a substantial toll on physical and mental health, and remains a major challenge and is a source of frustration to both the patient and physician since standard treatments often fail and a “panacea” is still lacking [3]. As there is no successful treatment for this common health problem, a treatment methodology for CP/CPPS is needed [4].

Different etiologies and mechanisms of CP/CPPS pathogenesis have been proposed with a suggested immunological, neurological, endocrine, or psychological basis [5]. For instance hypogonadism, a treatment of which is raise in the aging population [6] with the appropriate use of testosterone replacement therapy [7], today may be suggested as target in men with CP/CPPS [8]. However, in the last decade, pathogenesis of CP/CPPS has been also considered from the perspective of vascular dysfunction [9], chronic ischemic tissue [10], and increased prostatic pressure [11]. Color doppler investigation has shown that in CP/CPPS patients, there is a significant increase in blood circulation in the prostatic capsule and diffusion flow throughout the parenchyma [12].

Chronic prostatitis is often accompanied by erectile dysfunction (ED) or BPH. Therefore, there may be a strong link between the pathogenesis of both conditions. BPH, lower urinary tract symptoms (LUTS), and ED might be caused by microvascular dysfunction in the pelvic organs. A review of preclinical and clinical studies has confirmed that, indeed, the problems in the lower urinary tract are accompanied by endothelial and neurological dysfunction, leading to hypoxia, vasoconstriction, contractility changes of smooth muscles, and damage to autonomic neurons and ganglia [13]. These reports show that, in the etiology and pathogenesis of chronic prostatitis, the vascular factors play a significant role.

It has been suggested that all chronic internal diseases, including BPH and CP/CPPS, originate at the capillary level. This conclusion is based on 2 functional physiological properties of capillaries that are activated by a trigger, thereby leading to violation of the microcirculation along with emergence of a focus on hypothermia, which in itself becomes a continuous trigger leading to chronic disease. Thus it was proposed that continuous application of a natural thermoelement as source of energy could treat the chronic disorder and thermobalancing therapy (TT) with therapeutic device (DATD) were created [14]. The use TT with DATD for the treatment of LUTS and BPH led to a marked improvement and symptomatic relief [15, 16]. Furthermore, TT with DATD has shown to be effective for CP/CPPS [17, 18].

In this study, we are investigating the efficacy of DATD in treating CP/CPPS by assessing the dynamics of pain and QoL, PV, and  $Q_{max}$ .

## Methods

### *Study design*

We performed a clinical controlled study before and 6 months after treatment. The effectiveness of TT was studied by comparing men with CP/CPSP who received treatment with the physiotherapeutic device for 6 months with the control group, wherein men did not receive this therapy. It was an observational study as most men with CP and pelvic pain have serious psychological problems, and some experts believe that psychological problems are part of the cause of CP/CPSP [19]. So, men with CP/CPSP would typically not wear a device around their body for 6 months, for almost 22 h/day, if they do not feel convinced that it might help with the symptoms. Secondly, our goal was to identify if topically applied therapy can help and why it helps but not in finding the best material for thermoelement.

### *Participants*

45 men (age, <55 years) diagnosed with CP/CPSP were enrolled for the clinical trial at the Department of Urology of the Medical University. Ethics Committee of the Yerevan State Medical University has approved the study with Thermobalancing therapy. Inclusion criteria were as follows: confirmed diagnosis of chronic prostatitis and pain evaluation score  $\geq 1$ , according to the National Institute of Health-Chronic Prostatitis Symptom Index (NIH-CPSI); and serum prostatic specific antigen (PSA)  $>4$  ng/mL (with no histological evidence of cancer). Exclusion criteria were acute prostatitis; urethral stricture, neurogenic bladder, and other co-morbidities such as impaired renal function and diabetes mellitus. Ongoing medical treatments at the time of enrollment were not taken into consideration. The patient selection was carried out in a multidisciplinary manner in conjunction with a urologist, and written informed consent for participation in the study was obtained from all patients. The two study groups were statistically homogeneous.

### *Evaluation*

The effectiveness of TT was studied by comparing men with CP/CPSP who received monotherapy with DATD with the control group, who received no treatment. The baseline evaluations included complete physical examination; medical history; digital rectal examination; serum biochemical measurements including PSA, electrolytes, urinalysis; and renal function tests. Evaluations were made at baseline and 6 months after the treatment. At the baseline assessment, patients were evaluated for NIH-CPSI, NIH-CPSI-based pain and QoL scores, PV (mL), and uroflowmetry ( $Q_{max}$ ) mL/s. Dynamics of the symptoms and indicators in each group were assessed at the beginning and at the end of the treatment period by using NIH-CPSI. Uroflowmetry was used for the measurement of the rate of urine flow parameters, and ultrasound was used to determine the volume of the prostate gland.

### *Statistical analysis*

As independent samples *t*-test and paired samples *t*-test are only suitable for interval and ratio data, we used the Wilcoxon signed-ranks test for analyses.  $P < 0.05$  was considered statistically significant. Statistical analyses were carried out using SPSS v22 (IBM, Armonk, NY, USA).

### **DATD**

Post screening, men in the treatment group were provided with DATD. This device facilitates treatment of the affected region by the topical application of a special mixture of waxes that can collect the naturally emitted body heat, thus turning into a source of energy itself. This wax mixture is called the thermoelement. DATD is an elastic neoprene belt that keeps the thermoelement in projection of prostate in close contact with the skin for a prolonged duration and the belt also prevents heat dissipation (**Figure 1**).

## **Results**

### ***Pain score and quality of life***

Figure 2 shows the changes in pain score in CP/CPSP patients at the beginning and at the end of the study. In the control group, the mean pain score decreased from 10.49 to 9.71 at the end of the study period, whereas in the treatment group the mean pain score decreased from 10.38 to 3.58. The z value of the control group was -2.243 at the significance level of 0.025 with a *P* value < 0.05, while for the treatment group, the z value was -5.725 at the significance level with a *P* value < 0.001. These data suggest that although the pain score decreased in both groups, the difference between scores was considerably higher (8.72:1) in the treatment group than the control group.

We assessed the QoL according to NIH-CPSI (Figure 2). In the control group, the mean QoL decreased slightly from 8.47 to 8.33, whereas in the treatment group, the mean QoL decreased from 8.11 to 2.98. The z value of the control group was -0.420 at the significance level of 0.675 with a *P* value > 0.05, while for the treatment group, the z value was -5.661 at the significance level with a *P* value < 0.001. These results indicate that treatment with the therapeutic device increased QoL significantly, while that in the control group only decreased slightly.

### ***Prostate volume and uroflowmetry $Q_{max}$***

Figure 3 shows the changes in PV in CP/CPSP patients at the beginning and end of the study. In the control group, the mean prostate volume increased from  $30.77 \pm 6.44$  to  $31.58 \pm 7.14$  mL at the end of the study period, whereas in the treatment group, the mean PV decreased from  $31.75 \pm 7.01$  to  $27.07 \pm 4.52$  mL. The z value of the control group was -2.574 at the significance level of 0.010 with a *P* value < 0.05, while for the treatment group, the z value was -5.392 at the significance level with a *P* value < 0.001. These data indicate that the therapeutic device significantly reduced PV, while the control group showed an increase in PV.

### ***Uroflowmetry $Q_{max}$ (mL/s)***

Figure 3 shows the results of the uroflowmetry  $Q_{max}$  mL/s in CP/CPSP patients. In the control group, the mean  $Q_{max}$  decreased from  $12.59 \pm 3.57$  to  $12.20 \pm 2.54$  mL/s, whereas in the treatment group the mean  $Q_{max}$  increased from  $11.93 \pm 4.34$  to  $16.45 \pm 3.50$  mL/s. The z value of the control group was -1.193 at the significance level of 0.233 with a *P* value > 0.05, while for the treatment group, the z value was -5.249 at the significance level with a *P* value < 0.001. Our results show that the therapeutic device increased the uroflowmetry  $Q_{max}$

significantly in CP/CPPS patients, with no significant difference in the  $Q_{\max}$  of the control group.

### Discussion

Our results allow us to conclude that TT dramatically reduces pain and significantly improves the QoL. The use of DATD considerably reduces PV and significantly increases the uroflowmetry  $Q_{\max}$ . We suggest that reduce in the prostate size is connected with improvement of blood circulation and termination of inflammation. Thus outcomes indicate that the thermobalancing technique is effective for CP/CPPS treatment by influencing its cause. Therefore, our data indicate that TT is effective for CP and it can have an important role in prevention of the development and progression of CP/CPPS. None of the patients who received TT presented with any adverse effects. Moreover, as the DATD is a one-time purchase, thermobalancing therapy is overall cost effective.

Clinical improvement and positive changes in the ultrasound and uroflowmetry parameters in patients with CP/CPPS who used DATD could be explained by positive changes in the prostate at the capillary level. This happened because the natural thermoelement in close contact with the body in the projection of the prostate gland helped maintain the accumulated temperature for a long period. We believe that the use of this device aids to spread the energy toward the prostate gland and acts on the micro-hypothermia and ischemia elements, thereby relieving continuous pressure from the prostate tissue and resolving CP/CPPS symptoms [22]. TT provides an alternative approach to classical chronic prostatitis treatments, by eliminating the pressure in the prostate; this is in agreement with previous research that showed patients with CP/CPPS have significantly higher pressure in the prostatic tissues than the control group subjects [23].

A recent review on pathophysiology of CP/CPPS has stated that many factors, such as infectious agents, hormonal changes, physical trauma, urine reflux, and dietary habits initiate the process of CP/CPPS. However, development of this condition is hard to understand, thus future research the psychoneurologic dysfunctions responsible for chronic pain may be identified and lead to definitive, curative treatments [24]. Uncertainty in the etiology of CP/CPPS led to investigation of some diet and lifestyle factors that were thought to correlate with this problem [25]. However, no associations were observed between major lifestyle factors (obesity, smoking, and hypertension) and CP/CPPS [26].

We consider our study is important and makes significant contributions. For instance, a meta-analysis conducted by the Harvard Medical School on different types of treatment for CP from 1947 to 2011 concludes, “Our current understanding of CP/CPPS is not complete enough to allow us to employ appropriate interventions for all patients and it is important to continue to conduct research to improve our understanding of the mechanism and treatment of the disease” [27].

Many new drugs for CP treatment do not show sufficient efficacy [28, 29], and most commonly used drugs have adverse effects, especially when used long-term [30]. Today it is important for clinicians managing patients with CP/CPPS to be skilled and knowledgeable about the principles of pain management. The new pelvic pain management program was developed in the United Kingdom [31]. However TT, based on the positive dynamics in the

clinic and parameters, should be considered as first-line treatment option for men CP/CPPS [32].

The initiating factors for prostatitis may differ but the trigger for the development of chronic disease hides at the capillary level, i.e., constriction with an emergent focus of hypothermia in the prostate tissue. This phenomenon leads to spontaneous expansion of capillaries that increases pressure in the prostate gland provoking repeated constrictions. This “micro-focus” of hypothermia and, consequently, ischemia, sets up a vicious cycle of spontaneous growth of capillaries and continuous pressure in prostate-gland tissue that leads to CP/CPPS. By terminating “micro-focus” of hypothermia with DATD microcirculation within the prostate improves. Thus TT acts on the etiology of patients with CP/CPPS.

### **Conclusion**

The use of TT with DATD for a prolonged duration has resulted in improvement of QoL in men with CP/CPPS. We believe that reduced pain, PV and increased  $Q_{max}$  are related to termination “micro-focus” of hypothermia that triggers the development of CP/CPPS. More studies with TT are needed to investigate changes in the prostate gland in details.

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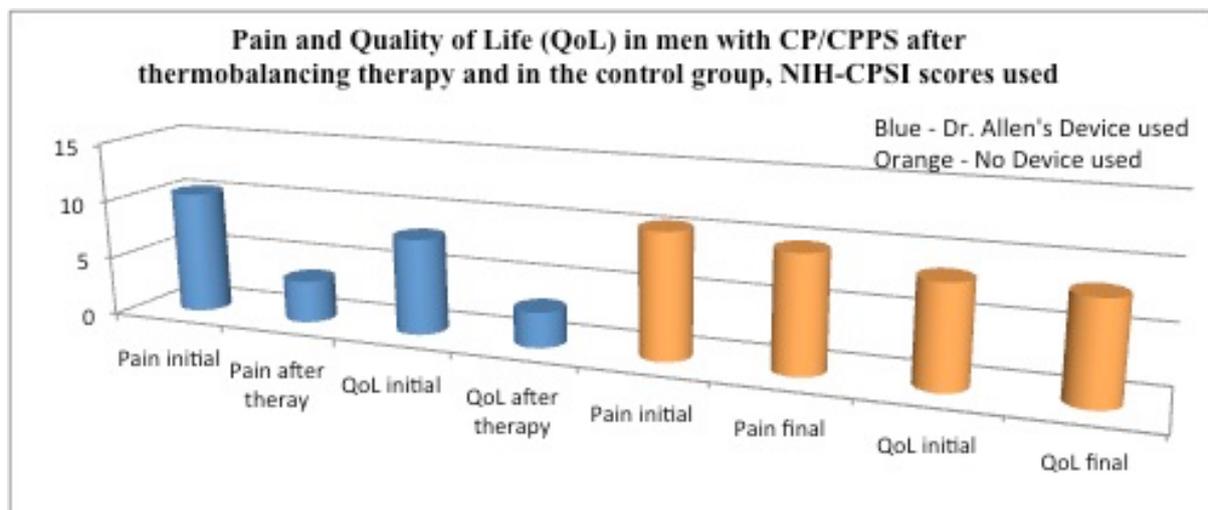
## Figures and Tables

**Fig. 1.** DATD tightly attaches thermoelement to the skin in the coccyx area.

The production of the therapeutic device started in 2010 in England, when the device was registered at the Medicines and Healthcare Products Regulatory Agency (MHRA) as a class-1 medical device [20]. A class-I medical device without a measuring function and supplied in non-sterile conditions does not require the involvement of a notified body. In accordance with the “Regulation of medical devices outside the European Union,” low-risk products may only require a supplier’s declaration of conformity (SDOC), where the manufacturer is responsible for ensuring that the product complies with the relevant requirement and then produces a written self-declaration statement [21].



**Fig. 2.** Pain score Quality of life in 45 men with CP/CPSP according to the National Institute of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) before and after thermobalancing therapy and in the control group.



**Fig. 3.** Prostate volume in mL and uroflowmetry  $Q_{max}$  mL/s in 45 men with CP/CPPS before and after thermobalancing therapy and in the control group.

