Central European Journal of Urology

ORIGINAL PAPER

FUNCTIONAL UROLOGY

The effectiveness of the combination of rectal electrostimulation and an antidepressant in the treatment of chronic abacterial prostatitis

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Citation: Shulyak A, Gorpynchenko I, Drannik G, et al. The effectiveness of the combination of rectal electrostimulation and an antidepressant in the treatment of chronic abacterial prostatitis. Cent European J Urol. 2018 [Epub ahead of print].

Article history
Submitted: May 9, 2018
Accepted: Dec. 4, 2018
Published online: Jan. 10, 2019

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Introduction Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a complex medical problem. Comorbid depression and chronic pain are highly prevalent in individuals suffering with chronic abacterial prostatitis (CAP) perhaps due to the direct or indirect effects of cytokines. Cytokines interact with the neuronal environment, and thus modulation of the duration of inflammation may alleviate depressive and pain symptoms. The aim of our study was to evaluate the effectiveness of combination of rectal electrostimulation and a selective serotonin reuptake inhibitor, sertraline, in the treatment of patients with chronic abacterial prostatitis and to determine the dynamics and links of pro-inflammatory and anti-inflammatory cytokine levels in the ejaculate.

Material and methods The interrelation of CP/CPPS symptoms, depression and cytokines in patients with CAP was studied. For the assessment of severity of CP/CPPS the National Institutes of Health (NIH)-Chronic Prostatitis Symptom Index (CPSI) was used. For the assessment of depression, the Patient Health Questionnaire-9 (PHQ-9) was used. The levels of cytokines [Interleukin (IL)-1beta (IL-1β), IL-8, IL-10, tumor necrosis factor-alpha (TNF-α) and transforming growth factor-β1 (TGF-β1)] in semen were assessed by ELISA (Diaclon, DRG, Ukrmedservice). All enrolled patients (n = 81) with CAP aged 19 to 38 years received basic treatment with rectal electrostimulation every other day for 10 sessions lasting 15 minutes each. Patients in Group 1 (n = 42) who additionally received oral sertraline with an initial dose of 50 mg gradually being increased to 200 mg were treated for 1 month. Patients in Group 2 (n = 39) received basic treatment only. Distribution of patients was random. All the statistical analyses were performed using SPSS.

Results The data from patients in Group 1 and Group 2 demonstrated that after treatment, a statistically significant ($p < 0.05$) decrease in the concentration of pro-inflammatory cytokines (TNF-α, IL-1β, IL-8) in ejaculate was observed. At the same time, there was a significant increase ($p < 0.05$) in the content of anti-inflammatory cytokines (IL-10 and TGF-β1) in Group 1 only. Clinical efficacy of combined treatment of patients with CP/CPPS was 83% in Group 1 and 62% in Group 2 compared to the symptoms of prostatitis, and 76% in Group 1 and 41% in Group 2 compared to the symptoms of depressive disorders.

Conclusions The results demonstrate the effectiveness (83%) of the combination of rectal electrostimulation and an antidepressant (sertraline) in the treatment of CAP, and also show the role of neuro-immune regulation and its disorders (including depressive disorders) in the pathogenesis of CAP.

Key Words: chronic abacterial prostatitis ‹› chronic pelvic pain syndrome ‹› cytokines ‹› depression ‹› rectal electrostimulation ‹› sertraline

doi: 10.5173/ceju.2018.1719

INTRODUCTION

Chronic abacterial prostatitis (CAP) is the most common variant of chronic inflammation of the prostate gland, which is also presented as a special case of chronic pain syndrome. An important feature of this disease is a very weak link between the patient's subjective feelings and objective findings both in maximum and average chronic inflammation (n = 8224, correlation coefficient 0.036 and 0.057 respectively, p <0.001) [1]. It was found that leukocytes do not correlate with severity of symptoms of chronic prostatitis [2]. It is known that the symptoms of CAP and the resulting neuro-psychological disorder(s) are mutually reinforced and significantly influence the patient's quality of life [3]. The explanation of this phenomenon lies within the concept of altered neuro-immune-endocrine regulation of the prostate gland, which arguably leads to manifestations of its inflammation and the development of pathological pain. Therefore, in addition to a well-accepted significant role of immune factors and their connection to fertility, we also must accept the important link between the brain and immune system and their potential role in CAP.

Pain and depression are the most frequently combined symptoms of chronic inflammation, which suggests common mechanisms of their pathogenesis [4, 5, 6]. One common substrate between depression and pain are cytokines, which provide a protective inflammatory response following the recognition of pathogen-associated molecular patterns (PAMP) and damaged molecules of a macroorganism (DAMP) by Toll-like and NOD-like receptors. In this respect, cytokines [interleukin-1β (IL-1β), tumor necrosis factor alpha (TNF-α), IL-6 and interferon – alpha] are mostly recognized, as their increased levels are associated with depression, activation of pain receptors and pain sensitivity. In contrast, anti-inflammatory cytokines are able to reduce inflammation, depressive symptoms and pain sensitivity [7, 8]. Thus, immune factors can affect the state of the nervous system that can clinically be presented as increased anxiety and depression.

We believe that by having a curative effect on immuno-neuro-endocrine disorders, we can count on the additional benefit in the treatment of patients with CAP. The aim of this study was two-fold: to evaluate the effectiveness of combination of rectal electrostimulation and a selective serotonin reuptake inhibitor, sertraline, in the treatment of patients with chronic abacterial prostatitis and to determine the dynamics and links of pro-inflammatory and anti-inflammatory cytokine levels in the ejaculate.

MATERIAL AND METHODS

The study protocol was approved by the Ethics Committee (protocol 6, April 17, 2015) and all the participants were treated in agreement with the Guidelines of the Declaration of Helsinki. The study involved 81 patients with chronic abacterial prostatitis according to National Institute of Health (NIH) criteria [9]).

The disease duration ranged from three to seven years. These patients underwent regular treatments (Table 1) without stable effect (for more than 3 months). Before entering the study, patients were treatment-free for at least 3 months. Patients were between 19 and 38 years old. The questionnaire NIH-Chronic Prostatitis Symptom Index (NIH-CPSI) was used to assess chronic prostatitis symptoms [10]. Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9) [11]. Both questionnaires were completed during the patients' interview. The inclusion criteria were the score of 10 or above when using a NIH-CPSI tool, indicating medium to severe symptoms of CAP, and 10 or above when using the PHQ-9 questionnaire, indicating medium to severe depression symptoms.

Study participants were divided into two groups: Group1 (n = 42) and Group 2 (n = 39). All patients received basic treatment consisting of rectal electrostimulation (Galva 5, Zimmer, Germany), for 10 sessions lasting 15 minutes each. Patients of Group 1 additionally received oral treatment with sertraline. The initial dose of 50 mg was gradually increased by 50 mg over the period of 1 week up to 200 mg or an achieved effect. Sertraline treatment duration was 1 month. In our previous experience, we observed the effectiveness of sertraline in majority of cases in the first 3–4 weeks of treatment, though the rest of the patients with CAP had no improvement with treatment any later. This explains the

Table 1. *Methods of previous courses treatment for patients with chronical abacterial prostatitis*

Method of treatment	Group 1 n = 42, abs. (%)	Group 2 n = 39, abs. (%)
	Age-19 to 38	
Antibiotic	42 (100)	39 (100)
Nonsteroidal antiinflammatory	42 (100)	39 (100)
Physiotherapy	29 (69)	28 (72)
α-blockers	27 (64)	29 (74)
Phytotherapy	26 (62)	25 (64)
Reflexology	7 (17)	5 (13)
Psychotherapy	5 (12)	4 (10)

duration of the treatment. Distribution of patients by groups was conducted randomly.
Clinically effective reduction was considered when significant indicator in NIH-CPSI was reduced by 6 points. Effective decrease in depressive manifestations was considered when the rate in PHQ-9 was reduced by 6 points. Determination of cytokines [TNF-α, IL-1β, IL-8, IL-10, transforming growth factor-β1 (TGF-β1)] in the ejaculate was performed using ELISA multichannel photometer 'Sunrisi' using kits (Diaclon, DRG, Ukrmedservice).
For the statistical analysis, we used the Student's t-test, Wilcoxon (z score) and Pearson's rank correlation tests. The average values (M) and standard deviation (SD) or the median (Me) and interquartile ranges (Q25; Q75) were calculated according to a normal distribution. The treatment effect was assessed by risk ratio (RR). All the statistical analyses were performed using SPSS.

RESULTS AND DISCUSSION

Indices of cytokines and ejaculate survey results using NIH-CPSI and PHQ-9 in patients from Group 1 and Group 2 were collected and examined before and after the treatment. The data (Table 2) from patients of Group 1 and Group 2 demonstrate that after the treatment a statistically significant ($p < 0.05$) decrease in the concentration of pro-inflammatory cytokines (TNF-α, IL-1β, IL-8) in ejaculate was observed. At the same time, there was a significant increase ($p < 0.05$) in the amountof anti-inflammatory cytokines in ejaculate mainly related to IL-10 and TGF-β1 only in patients of Group 1, although the tendency to its increase was also observed in Group 2.
It is known that an increase of the levels of pro-inflammatory cytokines in the seminal plasma (IL-1β, TNFα, IL-6, IL8) is observed with CP / CPPS in the absence of a bacterial infection [12, 13]. The reasons for this are not well understood. In CP / CPPS, activation of cytokine production is possible through the interaction of PAMP and DAMP with the corresponding receptors in case of latent infection, DAMP – in case of infection absence, as well as dysregulation of the cascade of further reactions.
The increased levels of cytokines in CAP has central effects, which shows the role of inflammation in the development of pain and concomitant mental disorders [14]. We used the positive effect of antidepressants to improve the efficiency of rectal electrostimulation [15].
There was no significant correlation between the CAP-related symptoms, the depression-related symptoms and the concentration of cytokines in the ejaculate in both groups. The significant increase in number of patients may indicate a weak link in the research mentioned above [1] however we consider that link clinically insignificant.
At the same time we identified a moderate direct correlation between the CAP-related symptoms and the depression-related symptoms in study participants that is supported by the correlation between NIH-CPSI and PHQ-9 parameters in Group 1 ($r = 0.534$, $p < 0.001$) and Group 2 ($r = 0.347$, $p = 0.03$) before the treatment, and in Group 1 ($r = 0.452$, $p = 0.003$) after the treatment. However, this link is lost in Group 2 after the treatment that could be possibly explained by the absence of influence of the antidepressant in the course of the treatment. Mental disorders are also observed in a significant part of patients with chronic bacterial prostatitis. In our opinion, this presupposes common mechanisms for the development of mental disorders of patients with chronic bacterial and abacterial prostatitis [16].

Table 2. *Dynamics of cytokines ejaculate and the results of question in gof patients with chronical abacterial prostatitis before and after treatment*

Indicator	Group 1, n = 42		Group 2, n = 39	
	Before treatment M ±SD	After treatment M ±SD	Before treatment M ±SD	After treatment M ±SD or Me (Q25–Q75)
TNF-α (pg/ml)	16.6 ±2.4	10.9 ±1.7*	16.4 ±2.7	11.5 ±1.2*
IL-1β (pg/ml)	118.8 ±7.1	89.6 ±10.9*	121.8 ±7.1	98.8 ±10.3*
IL-8 (pg/ml)	12.7 ±2.1	6.4 ±1.3*	13.7±2.0	5.7 (5.1–8.0)*
IL-10 (pg/ml)	154.1 ±17.9	203.9 ±15.4*	178.3 ±13.2	184.3 ±22.9
TGF-β (pg/ml)	21.8 ±5.6	30.7 ±5.4*	21.4 ± 4.3	23.0 ±3.8
NIH-CPSI, points	19.9 ±4.7	9.5 ±4.0*	19.1 ±4.4	11.5 ±3.2*
PHQ-9, points	13.7 ±2.6	4.7 ±2.3*	13.1 ±2.8	8.9 ±3.2*

TNF-α – tumor necrosis factor-α; IL-1β – interleukin-1β; IL-8 – interleukin-8; IL-10 – interleukin-10; TGF-β1 – transforming growth factor-β1; NIH-CPSI – NIH-Chronic Prostatitis Symptom Index; PHQ-9 – Patient Health Questionnaire-9
*the difference before and after treatment which was statistically significant ($p < 0.05$)

Table 3. *The effectiveness of the combination of physiotherapy and antidepressant in the treatment of chronical abacterial prostatitis*

Indicator	Group 1, n = 42		Group 2, n = 39	
	Treatment is effective Abs. (%)	No effect Abs. (%)	Treatment is effective Abs. (%)	No effect Abs. (%)
NIH-CPSI, points	35 (83)	7 (17)	24 (62)	15 (38)
PHQ-9, points	32 (76)	10 (24)	16 (41)	23 (59)

NIH-CPSI – NIH-Chronic Prostatitis Symptom Index; PHQ-9 – Patient Health Questionnaire-9

The reduction of subjective assessment of CAP symptoms became statistically significant in both groups. However, the clinical efficacy of treatment (Table 3) on the main symptoms of chronic prostatitis was significantly higher (RR = 1.35, 95% CI: 1.02–1.80) in Group 1 compared to Group 2. As to the dynamics of depressive manifestations, both groups experienced a significant reduction in depressive manifestations, but the clinical efficacy was significantly higher in Group 1 (RR = 1.86, 95% CI: 1.23–2.81).

Analysis of clinical efficacy of the treatment showed a superiority of the combined treatment of rectal electrostimulation and sertraline to improve the condition of patients with CAP. Clinical efficacy related to the actual symptoms of chronic prostatitis in Group 1 was 83% versus 64% in Group 2, and clinical efficacy related to symptoms of depression – 76% and 49%, respectively.

The mechanism of antidepressant drugs on chronic pain is direct action on neurons for pain and indirect improvement of depression and other emotional disorders, thereby improving the experience of pain and the ability to cope with pain. In a randomized, placebo-controlled study, 14 male patients with chronic pelvic pain received 13 weeks of treatment with sertraline 50 mg or placebo daily. The results showed some improvement in symptoms sertraline versus placebo but were not significantly different [17]. At the same time, relief of prostatitis symptoms was observed in the sertraline group compared with the state before the treatment, the symptoms of depression and anxiety remained unchanged.

Another randomized 6-month study indicated that there were no significant differences in NIH-CPSI scores between the sertraline combined with doxazosin group (n = 41) and the doxazosin group (n = 41) at 1, 3, and 6 months, and there was no significant difference in symptoms of depressions at 1 and 3 months, but there was significant difference at 6 months [18].

The study utilizing electrostimulation for chronic prostatitis tested a new high frequency urethral-anal prototype stimulation device in men with CP/CPPS twice weekly for 5 weeks. The results demonstrated a significant decrease in the NIH-CPSI ($p = 0.0002$) with no urethral, anal complaints or other side effects. Generally, the patients reported that a distinct perineal feeling and the pain syndrome were improved in 83% [19].

Close to rectal electrostimulation and a more accessible treatment for CAP – prostate massage was useful for 29% of patients, however it did not significantly improve the effect of antibiotics [20], although in another study it enhanced the effect of oral Chinese medicine [21]. Our choice was in favor of rectal electrostimulation due to its more standard effect, which is a problem with massage.

We tried to combine the benefits of an antidepressant (sertraline) and rectal electrostimulation in treatment of patients with CAP. The results of our research were unexpected to a certain extent. We supposed to achieve a significant decrease in NIH-CPSI and PHQ-9 parameters by the end of the 1 month of treatment in both Group 1 and Group 2 and also to find some advantages of combined treatment. However, the obtained results of the treatment turned out to be quicker and more which could be explained by the following:

1. Additional rational psychology and healthy lifestyle recommendations given by doctors during the treatment were not ignored by most patients.
2. A high rate of depressive disorders in the Ukraine increases the patients' sensitivity to antidepressant drugs to a certain extent [22].
3. Placebo effect was not taken into account.

Regarding the pathogenesis of the observed changes, the following should be added. During the study, we observed the dynamics of urological, psychological and immunological parameters. We consider it as a single protective process, coupled with certain interrelated pathological manifestations, such as pain, dysuria, depression. Our views are close to the concept outlined by Walker AK, 2014 [8], according to which the comorbidity of pain and depression is largely due to the interaction of the immune and nervous systems.

CONCLUSIONS

1. The results of the study demonstrate the effectiveness of the combination of rectal electrostimulation and an antidepressant (sertraline) in the treatment of CAP, and also show the role of neuro-immune regulation and its disorders (including depressive disorders) in the pathogenesis of CAP.
2. The obtained results suggest the link between CAP-related and depression-related symptoms in study participants that is supported by the correlation between NIH-CPSI and PHQ-9 parameters.
3. Further studies are needed to determine the role of this approach in the prevention of recurrence of CAP.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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