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The Use of Tadalafilin Patients with Chronic Prostatitis/Chronic Pelvic Pain Syndrome

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Abstract

Background The treatment of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) can be a frustrating challenge to physicians and many drugs had been used with variable results.

Objective To evaluate the safety and the efficacy of adding 5 mg tadalafil for patients with CP/CPPS with the conventional treatment.

Methods Thirty five patients received tamsulosin 0.4 mg capsule once daily, levofloxacin 500mg tablet once daily and indomethacin rectal suppository 100 mg once daily served as control group. Another 35 patients received the alpha blocker, levofloxacin and NSAID as above with tadalafil 5 mg once daily for 1 month period comprised tadalafil group. The NIH Chronic Prostatitis Symptom Index (NIH-CPSI) assessment was completed by each patient at baseline and 4 weeks after the drug therapy to assess the response to treatment. We consider in our study the chronic prostatitis/CPPS or category IIIa or b according to NIH classification system.

Results No significant difference in mean age and baseline score in between groups was found. After one month of starting treatment, it had been found that NIH-CPSI/pain, urinary and quality of life domains were significantly changed from (12.8±1.44, 5.9±1.77 and 8.8±1.82) at baseline to (9.6±1.04, 3.55±0.99 and 3.88±1.31) respectively in group A. In group B also there was a significant reduction in the NIH-CPSI among patients in this group; the baseline NIH-CPSI/pain, urinary and quality of life domains were (13.4±1.66, 5.8±1.85 and 9.3±1.92) and changed to (6.28±0.90, 2.65±0.86 and 2.69±1.43) respectively after treatment. The total NIH-CPSI was 27.5±4.78 and changed to 17.03±3.91 after treatmentin group A and 28.5±4.49 changed to11.62±3.59 in group B.

Conclusion The use of tadalafil in patients of CP/CPPS with conventional treatment for 1 month was safe and has high efficacy in reducing the symptoms for the patients and improving the quality of life.

Keywords Tadalafil, chronic prostatitis, chronic pelvic pain syndrome

Introduction

Prostatitis is the most common diagnosis in urology clinic below 50 year of age and 2-10% of community had prostatitis-like syndrome. The first who described the inflammation of prostate was Legneau in 1815, but it was Verdes, in 1838, who presented the first accurate description of the pathology of the prostatitis. In 20th century, more detailed description of prostatitis done and further bacterialand cytological localization studies of lower urinary tract was carried out [1].

The initial and mainstay treatment of prostatitis in most of the last century was the repetitive prostatic massage. The introduction of antibiotics especially the sulphanilamide in 1930 became the main treatment.The next era of prostatitis management began in the 1960s with Meares and Stamey's description of the four-glass lower urinary tract segmented localization

study.Afterthat new era of treatment started with the introduction of alpha blocker and nonsteroidal anti-inflammatory drugs which then became the standard treatment for the patient of CP/CPPS. The syndrome becomes chronic after 3 months of symptoms. The symptoms wax and wane overtime and the patients become free of pain between attacks. The most common form of prostatitis is the lymphocytic infiltration of prostatic stroma immediately adjacent to prostatic acini, the peripheral zone is mostly affected. Prostatitis had 2 classification systems (traditional and the NIH national institute of health) [1,2].

Phosphodiesterase 5 (PDE5) Inhibitor mediated relaxation of prostatic duct smooth muscle increases washout of prostatic reflux products reducing prostatic inflammation and consequent prostatitis symptoms. The presence of both Nitric Oxide Synthase and PDE5 in human prostatic tissue and the effect of nitric oxide donors and PDE5 inhibitors in vitro indicate PDE5 inhibitors relax prostatic smooth muscle. Significant retrograde urinary flux into prostatic ducts has been described and suggested as the mechanism of chronic prostatitis and it is postulated that PDE5 inhibitors alter prostatic reflux hence prostatitis symptoms [3].

Tadalafil is a selective PDE5 similar to sildenafil and vardenafil. It is administered orally for the treatment of erectile dysfunction (ED). Tadalafil has the longest duration of action (~36 hours) among the current PDE5 inhibitors [4].In patient group we added tadalafil tablet 5mg once daily as the drug of 5PDI with long duration of action that permit us for once daily administration[5].

Table 1.The classification system of prostatitis syndrome[1]

Traditional	National institutes of health	Description
Acute bacterial prostatitis	category I	Acute infection of prostate gland
Chronic bacterial prostatitis	category II	Chronic infection of prostate gland
	Category III chronic pelvic pain syndrome (CPPS)	Chronic genitourinary pain in the absence of uropathogenic bacteria localized to the prostate gland employing standard methodology
Nonbacterial prostatitis	Category IIIA (Inflammatory CPPS)	Significant No. of WBCs in expressed prostatic secretions, post-prostatic massage urine sediment (VB3), or semen
Prostatodynia	Category IIIB (non-Inflammatory CPPS)	Insignificant No. of WBCs in expressed prostatic secretions, post-prostatic massages urine sediment (VB3), or semen.
	Asymptomatic inflammatory prostatitis	WBSs (&/or bacteria) in expressed prostatic secretions, post-prostatic massage urine sediment (VB3), semen or histologic specimens of prostate gland.

In this study we include category IIIa and b as they had the same clinical features and course of the disease [6,7].

Method

The study was carried out from the January 2012 to September 2012 by participation of 70 patients from the Baghdad Medical city/Urology OutpatientClinic and divided into 2 groups; group A as control and group B as tadalafil group, and the duration of treatment was for 1 month to both groups provided that a written questionnaire was given to both groups pre and post study for assessment of treatment responsecalled NIH chronic prostatitis symptoms index(NIH-CPSI).The NIH Chronic Prostatitis Symptom Index (NIH-CPSI)assessment was completed by each patient at baseline and 4 weeks after the drug therapy.

Group A (35) patients received treatment of alpha blocker (tamsulosin 0.4 mg capsule once daily), levofloxacin 500mg tablet once daily and NSAID (indomethacin rectal suppository 100 mg once daily) and Group B received the alpha blocker, levofloxacin andNSAID as above with tadalafil 5 mg once daily for 1 month period after documentation of chronic prostatitis and performing 4 glasses test as following:

Patient voided the first 10 ml in 1st glass (VB1) then voided the next 30 ml in the 2nd glass (VB2) which represent the midstream urine afterthat prostatic massage was performed and the prostatic secretion was collected in another glass which represented (EPS) and finally let the patient void after prostatic massage and collect it in a separate glass (VB3) the result of microscopic examination of these 4 glasses represent the localization study of inflammatory process. The three urine specimens were centrifuged for 5 minutes and the sediment examined under high power for leukocytes (including aggregates of leukocytes), macrophages, oval fat bodies, erythrocytes, bacteria, and fungal hyphae. A wet mount of a drop of EPS can be examined under a coverslip in a similar manner and the 4 samples sent for histopathological examination [8].

We considered in our study the chronic prostatitis/CPPS or category IIIa or b according to NIH classification system.The inclusion criteria were patients from age 20 to 49 year old with prostatitis like symptoms that documented by history, clinical examination and 4glass test and persistence of symptoms more than 3 months that classified as category IIIa or b.

The exclusion criteria were patients who had acute and chronic bacterial prostatitis, age more than 50 years old to exclude the cases of benign prostatic hyperplasia, sexually transmitted disease documented infection, any patient who had urethral catheter, prostate surgery, urethral stricture or peptic ulcer, and patients with ischaemic heart disease on nitrate.

By using SPSS (statistical package for social sciences) software for windows version 20, all data of both groups were entered and analyzed using appropriate statistical tests and procedures.

Descriptive statistics for baseline characteristics were presented as mean ± standard deviation (SD).

Multiple tables then had been conducted and comparative statistics were performed using students' paired (t) test to assess the significance of reduction in NIH-CPSI before and one month after treatment within each group.Independent two sample students' (t) test was used to assess the difference in between group regarding the NIH-CPSI. The level of significance of ≤ 0.05 was assumed. Finally all data and results were presented in tables and or graphs.

Results

The overall mean age of studied population was (34.7 ± 5.2) years with a range of (20-49) years. For group A, the mean age was (34.1 ± 4.8) years while for group B was (33.6 ± 3.9) years. No significant difference in mean age of both groups had been found, $P > 0.05$ (Table 2).

The baseline NIH-CPSI/ pain domain was (12.8 ± 1.44) in group A and (13.4 ± 1.66) among group B, The baseline NIH-CPSI/urinary domain was (5.9 ± 1.77) in group A and (5.8 ± 1.85) among group B. The baseline NIH-CPSI/ quality of life domain was (8.8 ± 1.82) in group A and (9.3 ± 1.92) among group B. No significant difference in baseline score in between groups, $P > 0.05$. The baseline total NIH-CPSI was (27.5 ± 4.78) in group A and (28.5 ± 4.49) among group B.

After one month of starting treatment, it had been found that NIH-CPSI/ pain, urinary and quality of life domains were significantly changed from (12.8 ± 1.44, 5.9 ± 1.77 and 8.8 ± 1.82) at baseline to (9.6 ± 1.04, 3.55 ± 0.99 and 3.88 ± 1.31) respectively in group A, $P < 0.05$.In group B also there was a significant reduction in the NIH-CPSI among patients in this group; the baseline NIH-CPSI/pain, urinary and quality of life domains were (13.4 ± 1.66, 5.8 ± 1.85 and 9.3 ± 1.92) and changed to (6.28 ± 0.90, 2.65 ± 0.86 and 2.69 ± 1.43) respectively after treatment, $P < 0.05$. The total NIH-CPSI was (27.5 ± 4.78) and changed to (17.03 ± 3.91) after

treatment, in group A and (28.5 ± 4.49) changed to (11.62 ± 3.59) in group B, $P < 0.05$ (Table 3).
On comparing the mean reduction in between studied group it had been significantly found that despite both groups get areduction in the NIH-CPSI but the reduction among groupB was much higher than that in group A, $P < 0.05$ (Figure 1).

Table 2. Baseline patients' characteristics

Variable	Group A	Group B
Age (years)	34.1 ± 4.8	33.6 ± 3.9*
Baseline NIH-CPSI/ pain domain	12.8 ± 1.44	13.4 ± 1.66*
Baseline NIH-CPSI/ urinary symptoms domain	5.9 ± 1.77	5.8 ± 1.85*
Baseline NIH-CPSI/ Quality of life	8.8 ± 1.82	9.3 ± 1.92*
Baseline NIH-CPSI/ Total	27.5 ± 4.78	28.5 ± 4.49*

*P value > 0.05

Table 3. Comparison of NIH-CPSI before and onemonth after treatment in both groups

Patient Group	NIH/CPSI pain domain		
	Before treatment	1 month after treatment	Mean reduction
Group A Group B	12.8 ± 1.44 13.4 ± 1.66	9.6 ± 1.04* 6.28± 0.9*	3.2 ± 1.28 7.12 ± 1.14
NIH-CPSI/ urinary symptoms domain			
Group A Group B	5.9 ± 1.77 5.8 ± 1.85	3.55 ± 0.99* 2.65 ± 0.86*	2.35 ± 1.36 3.15 ± 1.47
NIH-CPSI/ Quality of life			
Group A Group B	8.8 ± 1.82 9.3 ± 1.92	3.88 ± 1.31* 2.69 ± 1.43*	5.49 ± 1.52 6.61 ± 149
NIH-CPSI/ Total			
Group A Group B	27.5 ± 4.78 28.5 ± 4.49	17.03 ± 3.91* 11.62 ± 3.59*	10.47 ± 4.07 16.9 ± 4.32

*P value <0.05 compared with before treatment

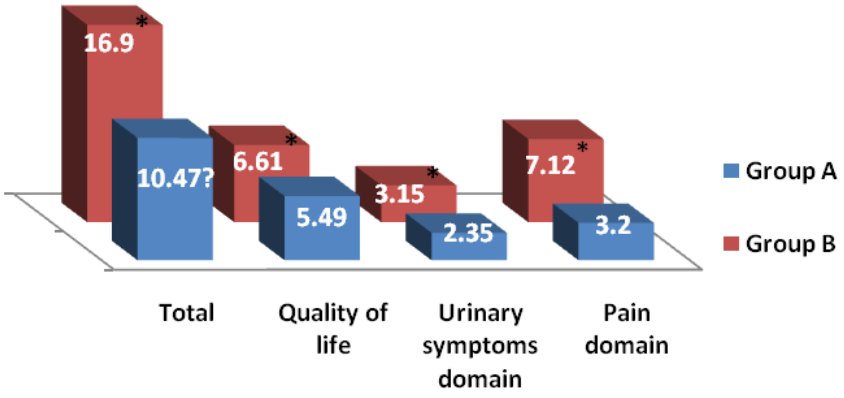

Figure 1. Comparison of mean reduction in NIH-CPSI one month after treatment in both groups (P < 0.05)

Although side-effects, such as headache, dyspepsia, myalgia and Back pain occurred more in patients who were given tadalafil (P< 0.05), no significant side-effects was detected so as to require exclusion of a patient from the study, and medical intervention was not performed in any of the patients because of side-effects (Table4).

Table 4. Side-effects between the two groups

The adverse effect	Group AN (%)	Group BN (%)
Headache	5 (14.2)	6 (17.1)
Flushing	0	2 (5.7)
Dyspepsia	3 (8.6)	5 (14.2)
Abnormal ejaculation	10 (28.6)	10 (28.6)
Myalgia	0	5 (14.2)
Back pain	0	3 (10)
Dizziness	6 (17.1)	7 (20)
Limb pain	0	2 (5.7)
Nasal congestion	2 (5.7)	3 (8.6)
Nausea	2 (5.7)	3 (8.6)
Diarrhea	1 (2.8)	2 (5.7)
Serious adverse events	0	0

Discussion

Over decades CP/CPPS was adifficult disease to treat that start with repetitive prostatic massage that permits frequent prostatic evacuation and decrease the pain for the patients [(1)], after that with introduction of antibiotics and subsequent addition of NSAID became the main treatment for this group of patients [(9)], which then overcome by the revolution of alpha blocker especially the highly selective group [(10-12)]. The latest fashion for treating patients with CP/CPPS is the combination therapy of agents termed the "three As" antibiotics, nonsteroidal anti-inflammatory drugs and α_1-blockers [(13)].

In our study, tadalafil in asmall dosewas introduced in addition to the conventional combination therapy "three As" to assess its safety and efficacy in improving the patients symptoms.

The efficacy of tadalafil in relieving the patients' symptoms may be due to PDE5 inhibitor mediated relaxation of prostatic duct smooth muscle which increases washout of prostatic reflux products reducing prostatic inflammation and consequent prostatitis symptoms [(3)].

This drug relieves lower urinary tract symptoms in patients with CP/CPPS because the PDE5 inhibition leads to smooth muscle relaxation in the bladder neck and prostate. This in turn permits increased urine flow and decreased urinary retention. How this agent relieves the pain associated with CP/CPPS is less clear, however it may be due to increased frequency of the sexual activity that will relieve the congestion of prostate and decrease the pain which is the main complain of our patients.

Mehik *et al* stated that alfuzocin improves the chronic prostatitis pain symptoms alone [(14)], while Nickel *et al* [(15)] use levofloxacin as the antibiotic of choice for chronic prostatitis symptoms improvement. Yoshimura *et al* [(16)] stated that levofloxacin had arole in CP/CPPS as it had immunomodulatory action on cytokine production by human peripheral blood mononuclear cells. Jeong *et al* [(17)] use both levofloxacin and doxazocin alone and in combination, the symptoms improvement was greater in combination group.

In our patient group we noticed that the addition of tadalafil to the combination therapy of NSAID, antibiotic, alpha blocker achieveda marked improvement in patient symptoms especially the pain over the control group who use the NSAID, antibiotic and alpha blocker only. Caldwell *et al* [(18)] also stated that acombination therapy better than monotherapy for treatment

of CP/CPPS although the PDE5 inhibitor was not included in their study. Similar results to our study were reported by Park *et al* who showed the use of tadalafil in addition to levoflxacin achieved significant symptomatic improvement in young and middle aged patients with CP/CPPS [19].

The addition of tadalafil to the conventional combination therapy of CP/CPPS was highly effective in improving the patients symptoms as reflected by significant improvement in the NIH-CPSI and was safe because no significant side-effects was detected so as to require exclusion of a patient from the study, and medical intervention was not performed in any of the patients because of side-effects.

Conclusion

The use of tadalafil in patients of CP/CPPS with conventional treatment for 1 month is safe and has high efficacy in reducing the patientsymptoms.

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