TADALAFIL THERAPY IN PATIENTS WITH CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME: RANDOMIZED, CONTROLLED TRIAL

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ABSTRACT

Background: *The management of chronic prostatitis still considers problematic cases 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:*** *A total of 107 male patients with chronic prostatitis/CPPS were randomly allocated to two treatment groups; the first of which 51 patients received tamsulosin 0.4 mg capsule once daily, levofloxacin 500mg tablet once daily and declofenac 100 mg once daily for one month comprised control group. While the second one 56 patient, in additions to standard medications they received Tadalafil 5 mg once daily for 1 month considered as study group. The NIH Chronic Prostatitis Symptom Index assessment was completed by each patient at baseline and after treatment discontinuation to assess the response to treatment.* ***Results:*** *No significant difference in baseline between groups. After one month of treatment, NIH-CPSI/pain, urinary and quality of life were significantly improved from (12.8±1.44, 5.9±1.77 and 8.8±1.82) at baseline to(7.1 ± 1.04, 2.5 ± 0.99 and 2.8 ± 1.31) (P value < 0.05) respectively in study group. In control group there was a significant reduction in the NIH-CPSI among patients; 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(9.7± 0.9, 3.6 ± 0.86 and 4.1 ± 1.43) (P value< 0.05) respectively after treatment.* ***Conclusion:*** *Use of tadalafil in patients of CP/CPPS with standard treatment was safe and effective in reducing symptoms and improving the quality of life.*

Keywords: Chronic Prostatitis. Tadalafil Therapy

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 syndrome becomes chronic after 3 months of symptoms. Chronic prostatitis, which has been proven to be bacterial and which is commonly termed chronic pelvic pain syndrome (CPPS), is a highly prevalent, very difficult-to-treat disease (1).

Prostatitis describes a combination of infectious diseases (acute and chronic bacterial prostatitis), CPPS or asymptomatic prostatitis. Chronic prostatitis/chronic pelvic pain syndrome classified as category III according to NIH classification of prostatitis syndromes (2).

Most men with “chronic prostatitis” have chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), characterized by pelvic pain (i.e., perineal, suprapubic, testicular, penile) variable urinary symptoms and sexual dysfunction (primarily pain associated with ejaculation).The National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) is a reliable means of capturing the symptoms and impact of CP/CPPS(7). The etiology of this syndrome is not fully known, the evaluation has been controversial and treatment is, unfortunately, frequently unsuccessful. Focused multimodal therapy appears to be more successful than empiric monotherapy (3).

PDE5 inhibition leads to increased cGMP, which is a second messenger in certain cellular signaling pathways. PDE5 inhibition partially reversed prostatic tissue strip contraction, supporting a role for cGMP in prostatic smooth muscle tension. Increasing cGMP also had an antiproliferative effect on cultured human prostatic smooth muscle cells. Several reports described LUTS improvement in patients undergoing ED treatment with PDE5 inhibitors (4,5). Tadalafil is a PDE5 inhibitor that effectively treats ED. The half-life of tadalafil is 17.5 hours with steady-state plasma concentrations achieved after 5 days of once daily dosing (5).

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP) - specific phosphodiesterase type 5 (PDE5). The PDE5 isoenzyme has been identified in the smooth muscle cells of corpus cavernosum, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum, as well as in the prostate, urethra, and bladder (6)

In our study, we added tadalafil tablet 5mg once daily in patient group as the drug of PDE5 with long duration of action that permit us for once daily administration in patients with category IIIa and b as they had the same clinical features and course of the disease.

PATIENTS AND METHODS

1. Study design, patient selection

This randomized controlled study was conducted between January 2013 and February 2014. . Patients were consecutively enrolled from patients referred to the urology clinics for treatment of prostatitis like symptom. The size of the research Sample was determined by using the GraphPad Prism sample size calculator (GraphPad Software, La Jolla, CA, USA). On the basis of previous study [4] and after addition of 10% dropout rate a total sample size of 84 (42 in each group) was sufficient to provide a power of 80%. All patients underwent thorough history-taking including a written questionnaire for assessment of treatment response called NIH chronic prostatitis symptoms index (NIH-CPSI) which was completed by patient at baseline and 4 weeks after the drug therapy, physical examination, urinalysis, midstream urine culture, and measurement of serum creatinine.

2-Inclusion and exclusion criteria

Patients 18 to 45 years old with persistence prostatitis like symptoms more than 3 months that documented by history, clinical examination and 4 glass tests and classified as category IIIa or b were eligible for enrollment. Patients who had acute and chronic bacterial prostatitis, age more than 45 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 ischemic heart disease on nitrate were excluded from study

3-Study procedure

Out of 168 patients have chronic prostatitis/CPPS, 61 patients' excluded from our study (38 patients not meeting inclusion criteria and 23 patients chose not to participate). The remaining 107 patients were randomized into two groups using computer random tables in a 1: 1 ratio. Group A (study group) 56 patients received treatment of alpha blocker (Tamsulosin 0.4 mg capsule once daily), Levofloxacin 500mg tablet once daily, NSAID (declofenac 100 mg once daily) with Tadalafil 5 mg once daily for 1 month and group B (control group) 51 patients received alpha blocker, levofloxacin and NSAID as above . All patients enrolled in our study provided writing well informed consent after approval of our hospital ethical committee.

4. Follow-up

Follow-up visits were scheduled on a weekly basis during the treatment period and after treatment discontinuation. At each follow-up visit, blood pressure, response to and compliance with treatment, and adverse effects were recorded.

5-Statistical analysis:

All data of both groups were entered and analyzed using SPSS (statistical package for social sciences) software for windows version 20. Descriptive statistics for baseline characteristics were presented as mean ± standard deviation (SD). Comparative statistics were performed using paired (t) test to assess the significance of reduction in NIH-CPSI before and one month after starting treatment within each group. Independent students' (t) test was used to assess the difference in between groups regarding the NIH-CPSI. Chi-square and Fisher Exact tests were used to compare between categorical variables. The level of significance of ≤ 0.05 was assumed.

RESULTS

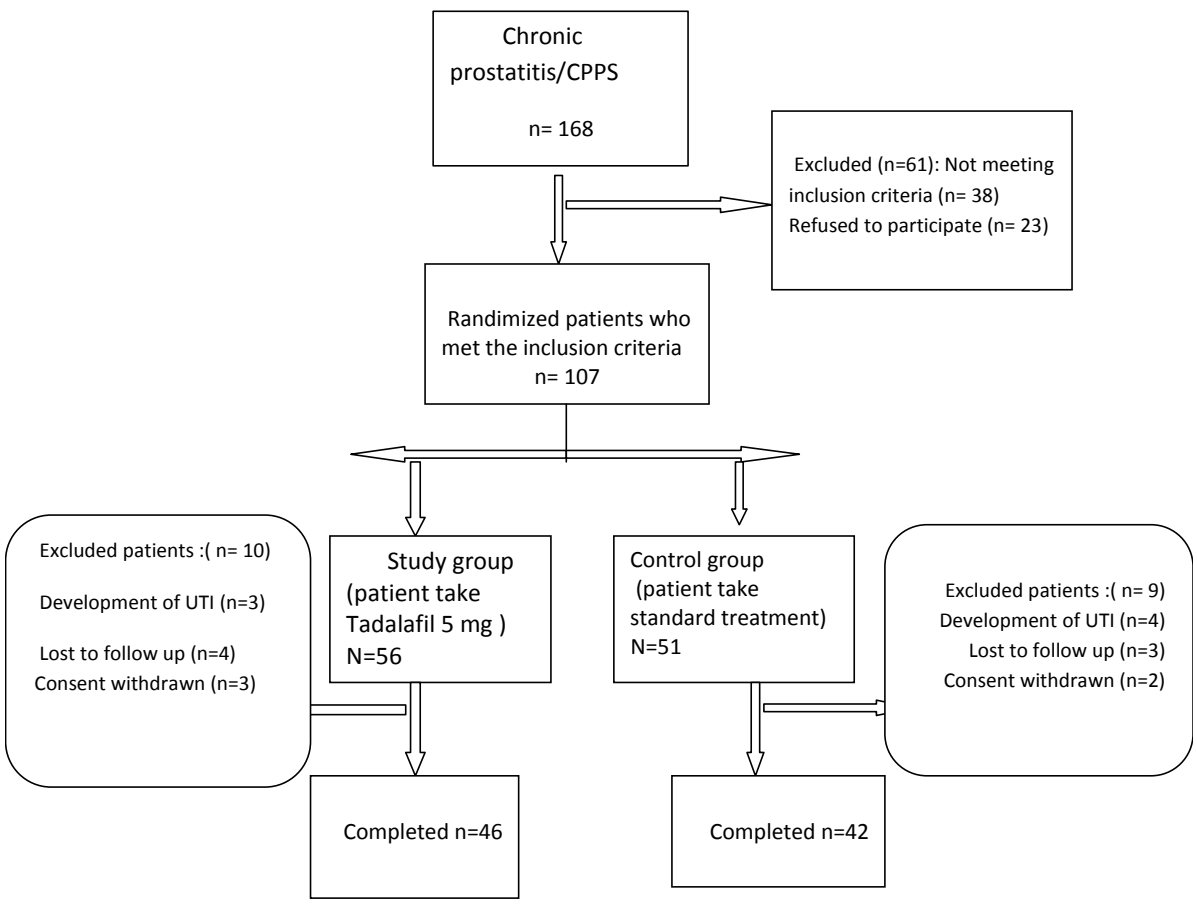

Fig1:

As shown in Fig. 1, a total of 107 patients were enrolled in this study and 88 patients completed the treatment. The 19 patients who did not complete the study included 10 patients from group A, 9 patients from group B, The overall study completion rate was 82.2%. The most common reason for discontinuation in the tadalafil group was lost to follow up (4 men or 7.1%) and in the control group it was development of UTI (4 or 7.8%).The overall mean age of studied population was (34.7 ± 5.2) years with a range of (18-45) years. For group A, the mean age was (29.8 ± 5.7) years while for group B was (30.6 ± 4.9) 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 (13.1 ± 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, $P > 0.05$.

After one month of 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 (7.1 ± 1.04, 2.5 ± 0.99 and 2.8 ± 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 (13.1 ± 1.66, 5.8 ± 1.85 and 9.3 ± 1.92) and changed to (9.7± 0.9, 3.6 ± 0.86 and 4.1 ± 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, $P < 0.05$. On comparing the mean reduction in between studied group it had been significantly found that despite both groups get a reduction in the NIH-CPSI but the reduction among group A was much higher than that in group B. (Table 2).

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 (Table3).

Table 1. Baseline patients' characteristics

Variable	Study group (n= 46)	Control group (n=42)	P- value
Age (years)	29.8 ± 5.7	30.6 ± 4.9	0.07
NIH-CPSI/ pain domain	12.8 ± 1.44	13.1 ± 1.66	0.06
NIH-CPSI/ urinary symptoms domain	5.9 ± 1.77	5.8 ± 1.85	0.06
Baseline NIH-CPSI/ Quality of life	8.8 ± 1.82	9.3 ± 1.92	0.05
Baseline NIH-CPSI/ Total	27.5± 4.78	28.2 ± 4.49	0.07

Table 2. Comparison of NIH-CPSI after treatment in both groups

	Study group	Control group	t-test	P-value
NIH-CPSI/ pain domain Post treatment % Reduction	7.1 ± 1.04 44.53	9.7± 0.90 25.95	12.485	< 0.001
NIH-CPSI/ urinary symptoms domain Post treatment % Reduction	2.5 ± 0.99 57.62	3.6 ± 0.86 38.98	5.540	< 0.001
NIH-CPSI/ Quality of life Post treatment % Reduction	2.8 ± 1.31 68.18	4.1 ± 1.43 55.91	5.883	< 0.001
NIH-CPSI/ Total Post treatment % Reduction	12.4 ± 3.91 54.90	17.3 ± 3.59 38.65	6.105	< 0.001

Values are presented as mean ± standard deviation or percentage. Post-treatment NIH-CPSI pain, urinary domains and Quality of life were compared between groups by using independent sample t-test (P): 0.04, 0.03

Table3. Side-effects between the two groups

The adverse effect	Study group (n= 46)	Control group (n=42)	Chi-square test	P-value
Headache	5 (10.8)	4 (9.5)	0.043	0.836
Flushing	2 (4.3)	1 (2.4)	0.258	0.611
Dyspepsia	4 (8.7)	4 (9.5)	0.018	0.893
Abnormal ejaculation	11 (23.9)	10 (23.8)	0.000	1.000
Myalgia	2 (4.3)	0	1.869	0.172
Back pain	2 (4.3)	0	1.869	0.172
Dizziness	4 (8.7)	5 (10.8)	0.246	0.620
Limb pain	1 (2.1)	0	0.924	0.336
Nasal congestion	3 (6.5)	2 (4.3)	0.127	0.722
Nausea	1 (2.1)	1 (2.4)	0.004	0.950
Diarrhea	2 (4.3)	1 (2.1)	0.258	0.611
Serious adverse events	0	0	0.000	1.000

Data as number (percentage)

DISCUSSION

Prostatitis is caused by an infection or by inflammation of the prostate gland, affect men of any age but it's most common in younger and middle aged men, typically between 30 and 50 (1,2). It's a complicated condition because there are several different types of prostatitis and some types are not well understood which make it difficult for doctors to know what causes it and how best to treat it. This can be frustrating for men who have it, but there are things you can do to help yourself. It can take some time to get a diagnosis, and you might need a number of tests (3, 7).

Chronic pelvic pain syndrome (CPPS) is the most common type of prostatitis which called chronic non-bacterial prostatitis or prostate pain syndrome. CPPS usually causes pain in the pelvic area includes the area between testicles and back passage (perineum). The pain can go on for a long time. Most men with prostatitis have CPPS – around 19 out of every 20 men (90 to 95 per cent) (8).

Nobody knows for certain what causes CPPS. Unlike other types of prostatitis it is not caused by a bacterial infection. There could be a number of causes, so that makes it difficult to diagnose and treat. Some men might just be more likely to get it than others, and there could be a number of things that trigger it (8, 9).

The possible causes of CP/CPPS include; urine getting into the prostate gland, previous infections in or around the prostate, an infection which doesn't show up in tests, inflammation of the nerves around the prostate gland, problems with nerves, so that they send pain signals to the brain even when there's nothing physically wrong, stress or anxiety, problems in the pelvic floor muscles and previous damage to the pelvic floor muscles (3, 8, 10).

There's some evidence that CPPS may be linked to other conditions such as chronic fatigue syndrome (CFS) and irritable bowel syndrome (IBS). Some patients with CPPS also have symptoms of these conditions. Irritable bowel

syndrome causes bowel problems such as pain or diarrhoea, and chronic fatigue syndrome causes long-term severe tiredness, but there's no evidence that CPSS is caused by a sexually transmitted infection (8, 11).

The management of patients with chronic pelvic pain attributed to chronic prostatitis has long been rather unsatisfactory. Even prolonged treatment with an antibiotics, non-steroidal anti-inflammatory drugs and α1-blockers seldom results in rapid resolution of the symptoms, and is commonly completely ineffective (4, 7, and 8).

Recently, many patients with CP/CPPS were disabled by unresponsive to standard treatment, or unable to tolerate non-steroidal anti-inflammatory analgesics. However many patients have immediate marked improvement of his symptoms when using phosphodiesterase type 5 (PDE5) inhibitor for sexual activity, but his symptoms returned once they cessation of the medication (5,6).

PDE5Is are therapeutic agents used for several urological and non-urological disorders, and experimental evidence suggest that their chronic use does not induce cellular and molecular prostatic alterations (5, 11, 12). The mechanisms involved in improvements observed in BPH/LUTS possibly include relaxation of the smooth muscles of the bladder and prostate by NO/cGMPc signaling or via improving RhoA/Rho-kinase (ROCK), and by reduction of the hyperactivity of the autonomic nervous system. PDE5Is can also direct and indirectly down-regulate prostatic inflammation/BPH/LUTS by inducing high levels of cGMP (7, 13, 14).

So that we studies effect of the treatment each time, with 5 mgs tadalafil daily, on persisting improvement of CP/CPPS symptoms. In our study, tadalafil in a small dose was introduced in addition to the conventional combination therapy to assess its safety and efficacy in improving the patient's symptoms.

The treatment of lower urinary tract symptoms with tadalafil at a dose of 5 mgs per day for a period of time have many beneficial effects may be resulted from an improvement of blood flow to pelvic organs as a consequence of its

anti-inflammatory and vasodilatory activity, as well as a relaxant effect on smooth muscle which has been previously suggested by many others (5, 6).

In our patient group we noticed that the addition of tadalafil to the combination therapy of NSAID, antibiotic, alpha blocker achieved a marked improvement in patient symptoms especially the pain over the control group who use the NSAID, antibiotic and alpha blocker only. Similar results to our study were reported the use of tadalafil in addition to levoflxacin achieved significant symptomatic improvement in young and middle aged patients with CP/CPPS (15).

In our study, 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.

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.

Because of the inflammation is a major factor in CP/CPPS progression, PDE5Is could also restore prostatic function, as they act as potent anti-inflammatory drugs. 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 (16, 17). Clearly the

hypothesis that daily treatment with a PDE5 inhibitor might be beneficial in men suffering from the prevalent condition of CP/CPPS needs to be formally tested in the context of a randomized controlled trial.

CONCLUSION

The use of tadalafil 5 mgs per day in patients of CP/CPPS with conventional treatment for 1 month is safe and has high efficacy in reducing the patient symptoms.

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ABBREVIATIONS AND ACRONYMS

Abbreviations	Acronyms
CPPS	Chronic Prostatitis/Chronic Pelvic Pain Syndrome
NIH-CPSI	National Institutes of Health-Chronic Prostatitis Symptom Index
BPH	Benign Prostatic Hyperplasia
cGMP	Cyclic Guanosine Monophosphate
ED	Erectile Dysfunction
EF	Erectile Function
IPSS	International Prostate Symptom Score
LUTS	Lower Urinary Tract Symptoms
PDE5	Phosphodiesterase 5
NSAID	Non Steroidal Anti Inflammatory Drug
PSA	Prostate Specific Antigen
CFS	Chronic Fatigue Syndrome
IBS	Irritable Bowel Syndrome
QOL	Quality Of Life