ORIGINAL ARTICLE

Tadalafil Monotherapy versus Tadalafil Combined Pumpkin seed oil in Treatment of Men with Chronic Pelvic Pain Syndrome

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Abstract

Background: ***Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a clinical condition defined by pelvic and perineal discomfort along with symptoms affecting the lower urinary tract, also accompanied by sexual dysfunction.***

Aim and objectives: ***To investigate the efficacy of Tadalafil monotherapy versus Tadalafil combined with Pumpkin seed oil (PSO) in the treatment of men with CP/CPPS who complain of erectile dysfunction(ED).***

Patients and methods: ***This randomized prospective study was performed at the Urology Department of Al Azhar University Hospitals in Cairo, Egypt, from November 2023 to October 2024. The study included 50 patients diagnosed with (CP/CPPS), all patients were assigned randomly into Group(A) which consisted of 25 patients who were given 5 mg of Tadalafil at bedtime for (12)weeks and Group(B), which also consisted of 25 patients who received 5 mg of Tadalafil along with a 1010 mg (PSO) capsule at bedtime for (12)weeks and patients followed monthely for (3)months.***

Results: ***In Group(A),12 patients(48%) showed clinically significant improvement, while 11 patients(44%) in Group(B) experienced similar improvements.***

Conclusion: ***Both Tadalafil and the combination of Tadalafil with (PSO) significantly improved symptoms in CP/CPPS patients with mild to moderate ED. However, the addition of (PSO) did not show greater effectiveness compared to Tadalafil alone, except for the pain domain.***

Keywords: (CP/CPPS); erectile dysfunction ; tadalafil; Pumpkin seed oil

1. Introduction

The exact cause is unknown, and treatment options debated, which include various monotherapies, such as alpha-blockers and phytotherapeutics, have been suggested. Early recognition of (CP/CPPS) with appropriate treatment improves outcome and minimizes morbidity.[1]

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a clinical urological syndrome affecting an estimated 2.2–13.8% of men across various populations. The exact cause of CP/CPPS has several potential factors identified, including undetected bacterial infections, psychogenic influences, retrograde urine flow into the prostatic ducts, and pelvic floor dysfunction.[2] Sexual dysfunctions in CP/CPPS vary widely, with multiple studies indicating that 30–50% of patients experience erectile dysfunction (ED). (CP/CPPS) is recognized as a distinct risk factor for (ED), with an odds ratio of 3.62.[3] Studies on the use of pumpkin seed oil (PSO) for patients with prostatic issues have shown that it can inhibit testosterone-induced prostatic hyperplasia. This intervention led to a remarkable reduction in prostatic weight.[4] Grimsley and his team noted in their clinical study that in CP/CPPS patients, the use of Phosphodiesterase-5(PDE5) inhibitors was also associated with improvements in prostatitis symptoms.[5]

This study aimed to investigate the efficacy of Tadalafil monotherapy versus Tadalafil combined with Pumpkin seed oil (PSO) in the treatment of men with CP/CPPS who complain of erectile dysfunction(ED).

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2. Patients and methods

The study was a prospective randomized trial executed at the Urology Department of Al Azhar University Hospitals in Cairo, Egypt, from November 2023 to October 2024. The study received approval from the local review board, and all participants provided written informed consent.

The study included male patients aged 45 years or younger with a history of CP/CPPS lasting at least one year. These patients had persistent or recurrent symptoms despite undergoing previous treatment with 4–6 weeks of antibiotics and/or alpha-blockers, and also reported erectile dysfunction. After a thorough medical history was taken, each patient completed Arabic-translated, validated versions of the Chronic Prostatitis Symptom Index (CPSI) and the International Index of Erectile Function (IIEF-5). All participants also underwent abdominal and digital rectal exams, laboratory tests (urine analysis and culture, serum creatinine, the Meares–Stamey four-glass test), uroflowmetry, and abdominal ultrasound.

Patients were excluded from the study if they had chronic prostatitis symptom index (CPSI) score ≤ 14 (mild symptoms), an international index of erectile dysfunction-5 (IIEF-5) score of 22 or higher, abnormal findings on digital rectal examination(DRE) findings or prostatic specific antigen (PSA) levels, a history of uncontrolled diabetes, cardiovascular disease or were using nitroglycerin medications. Additional exclusion criteria included the presence of bladder or ureteral stones, urethral stricture, neurogenic disorders affecting the lower urinary tract, and renal or hepatic dysfunction. Also, Patients with current urinary tract infection or bacterial prostatitis were excluded from participation in the study.

Fifty patients who satisfied the inclusion criteria were randomly assigned to two groups, with 25 patients in each group. Group (A) received 5 mg of Tadalafil once per day at bedtime for twelve weeks, while Group (B) received 5 mg of Tadalafil along with a 1010 mg (PSO) capsule, also at bedtime for 12 weeks.

The primary objective of our study was to assess the total CPSI score and its domain sub-scores at the 12-week follow-up, as well as the IIEF-5 scores. We compared these scores between Group (A) and Group (B), as well as with their baseline values. Furthermore, clinically significant responders were defined as patients who showed an improvement of at least 25% in their total CPSI score.

All data are presented as mean ± standard deviation(SD). The CPSI score change for each patient was determined by subtracting the baseline score from the score at the 12th week (ΔCPSI = 12th week score - baseline score), with negative values signifying symptom improvement. Statistical analysis was performed using two-tailed paired and unpaired tests to compare domain scores both within each group and between the two groups. The Chi-square test was used to compare categorical variables between the groups. A p-value of less than 0.05 was regarded as statistically significant for all the analyses conducted.

The Mean was (-19 ± 13.4) with a range of (-41.7 – 0).

3. Results

By the end of the study, both Group (A) and Group (B) comprised 25 patients each.

Table 1. Comparison of studied groups (A and B) as regard CPSI(Baseline score – 12thweek score – Δ).

CPSI TOTAL SCORE		GROUP(A) (N=25)	GROUP(B) (N=25)	T	P VALUE
BASELINE SCORE	Mean± SD Min – Max	23.2 ± 3.5 18 – 30	24.3 ± 3 19 – 30	1.13	0.27
12TH WEEK SCORE	Mean± SD Min – Max	19.1 ± 3.6 15 – 27	18.6 ± 3.5 12 – 27	0.51	0.61
Δ CPSI	Mean± SD Min – Max	-17.4 ± 8 -26.9 – 0	-23±13.9 -43.5 – 0	1.7	0.11

no significant difference observed between Group (A) and Group (B) concerning the change in CPSI(ΔCPSI) (P = 0.11). The mean change in Group (A) was -17.4 ± 8, while in Group (B), was -23 ± 13.9.

Table 2. Comparison of CPSI (Baseline score – 12thweek score) in patients of groups (A) and (B).

CPSI TOTAL SCORE		BASELINE SCORE	12TH WEEK SCORE	*T*	*P VALUE*
GROUP(A) (N=25)	Mean ± SD Min – Max	23.2 ± 3.5 18 – 30	19.1 ±3.6 15 – 27	9.6	<0.001
GROUP(B) (N=25)	Mean ± SD Min – Max	24.3 ± 3 19 – 30	18.6 ± 3.5 12 – 27	7.6	<0.001

High statistically significant (P<0.001) decreased CPSI (12thweek score) {mean= (19.1 ± 3.6)} when compared with Baseline score {mean= (23.2 ± 3.5)}in patients of group (A).

High statistically significant (P<0.001) decreased CPSI (12thweek score) {mean= (18.6 ±3.5)} when compared with Baseline score {mean= (24.3 ± 3)}in patients of group (B)

Table 3. Comparison of studied groups (A and B) as regard IIEF5 (Baseline score –12thweek score – Δ).

		GROUP(A) (N=25)	GROUP(B) (N=25)	T	P VALUE
IIEF5					
BASELINE SCORE	Mean ± SD Min – Max	17.5 ± 1.9 15 – 21	17.3 ± 1.8 14 – 20	0.37	0.72
12TH WEEK SCORE	Mean ± SD Min – Max	20.2 ± 2.7 15 – 25	20.7 ± 2.9 14 – 25	-0.552	0.58
Δ IIEF5	Mean ± SD Min – Max	16.3 ± 17.7 -11.1 – 46.7	20.6 ± 20.7 -17.7 – 57.1	-0.75	0.46

Table 4. Comparison of studied groups (A and B) as regard Pain, Voiding Symptoms , quality of life (Qol) and IIEF5 (Baseline score –12thweek score – Δ).

		GROUP(A) (N=25)	GROUP(B) (N=25)	T	P VALUE
PAIN SUBSCORE					
BASELINE SCORE	Mean ± SD Min – Max	11.7 ± 2.8 7 – 16	11.9 ± 2.9 6 – 17	-0.15	0.884
12TH WEEK SCORE	Mean ± SD Min – Max	10.5 ± 3 5 – 15	9.4 ± 2.1 6 – 15	1.37	0.18
ΔPAIN	Mean ± SD Min – Max	-11.8 ± 8.3 -28.6 – 0	-19 ±13.4 -41.7 – 0	2.2	0.036
VOIDING SYMPTOMS SUBSCORE					
BASELINE SCORE	Mean ± SD Min – Max	5.3 ± 1.4 4 – 8	5.7 ± 1.3 3 – 8	-1.07	0.29
12TH WEEK SCORE	Mean ± SD Min – Max	4.3 ± 1.8 2 – 8	4 ± 1.8 1 – 7	0.396	0.69
ΔVOIDING SYMPTOMS	Mean ± SD Min – Max	-20.9± 20.4 -60 – 0	-29.3±28.1 -75 – 0	1.14	0.26
QUALITY OF LIFE (QOL) SUBSCORE					
BASELINE SCORE	Mean ± SD Min – Max	6.2 ± 1.4 4 – 8	6.4 ± 1.1 4 – 9	-0.61	0.56
12TH WEEK SCORE	Mean ± SD Min – Max	4.4 ± 1.7 2 – 7	4.4 ± 1.5 2 – 7	-0.037	0.97
Δ QOL	Mean ± SD Min – Max	-30.4± 17.8 -60 – 0	-32.1± 18.2 -60 – 0	0.32	0.75

A statistically significant (P= 0.036) difference between studied groups (A and B) as regard Pain (before treatment). In group (A), the mean was (-11.8 ± 8.3) with range of (-28.6 – 0). While in group(B) the mean was (-19 ± 13.4) with range of (-41.7 – 0).

4. Discussion

Despite symptomatic inflammatory conditions of the prostate being common and accounting for 2million outpatient visits annually in the United States, there is no universally accepted therapy for CP/CPPS. The use of alpha-blockers is currently debated. In addition to antibiotics and anti-inflammatory drugs, numerous other treatment options, like phytotherapeutics, have been explored. Due to the lack of proven effectiveness with traditional treatments, there is an increasing need for alternative therapies. Furthermore, as CP/CPPS often requires long-term management, Phytotherapeutic options are attractive due to their low risk of side effects.[1]

The therapeutic effect of Pumpkin Seed Oil (PSO) is believed to stem from its ability to inhibit α-reductase, the enzyme that converts testosterone into dihydrotestosterone. Research has indicated that (PSO) can help prevent testosterone-induced prostatic hyperplasia in patients with prostate issues, as noted by Marks et al.[4]

The (PSO) has proven to be highly effective in managing BPH-related lower urinary tract symptoms with minimal side effects, and considering that (CP/CPPS) is a long-term condition requiring extended treatment, patients may prefer herbal options like PSO over synthetic medications, which have a higher potential for side effects. Based on the existing evidence, PSO would be effective in managing CP/CPPS, particularly in alleviating lower urinary tract symptoms (LUTS), while offering an excellent safety profile.[6,7,8]

Multiple studies have shown that a daily dose of 5 mg Tadalafil can significantly alleviate lower urinary tract symptoms (LUTS), irrespective of the severity or improvement in erectile dysfunction (ED). The literature strongly supports the use of PDE5 inhibitors such as Tadalafil for treating prostatitis, with solid experimental and pre-clinical evidence backing their effectiveness.[1]

In this study, there was no significant difference observed between Group (A) and Group (B) regarding the change in CPSI (ΔCPSI) (P = 0.11). Group A had a mean ΔCPSI of -17.4 ± 8, while Group B had a mean ΔCPSI of -23 ± 13.9. Likewise, no statistically significant difference was found between the groups in terms of the change in Voiding Symptoms (ΔVoiding Symptoms, P = 0.26) and Quality of Life (ΔQOL, P = 0.75). However, a statistically significant difference was observed between the groups regarding the change in Pain (Δ Pain, P = 0.036). In Group A,

the mean ΔPain was -11.8 ± 8.3, while in Group B, the mean ΔPain was -19 ± 13.4.

In contrast to other CPSI domain subscores, the pain subscore demonstrated a statistically significant improvement when PSO was added to Tadalafil. This observation is consistent with a 2022 placebo-controlled trial by Tawfik et al., which assessed Tadalafil monotherapy for managing CP/CPPS. Tawfik and his team found no significant improvement in the pain subscore when comparing Tadalafil to a placebo ($P > 0.05$). These findings further highlight the beneficial effect of PSO on pain.[2]

In comparison, Benelli et al. performed a non-controlled study with a 3-month follow-up, reporting that Tadalafil led to significant improvements across all CPSI domain scores. These improvements were evident as early as one month following treatment, with the most pronounced change seen in the pain subscore, which dropped from 13.7 ± 3.7 to 5.4 ± 2.2. Other subscores, including total CPSI, voiding, and quality of life, also showed reductions (from 27.6 ± 4.2, 5.2 ± 3.8, and 10.1 ± 1.9 to 8.8 ± 3.2, 1.4 ± 1.7, and 1.9 ± 0.8, respectively). These findings differ from our own, where pain improvement was less pronounced, with the pain subscore only decreasing from 11.7 ± 2.8 to 10.5 ± 3. The smaller sample size in Benelli's study (14 patients) may have limited its statistical power, and the study's inclusion criteria, which focused on patients with only a 3-month symptom duration, may have contributed to the larger improvements observed in their cohort.[1]

In 2020, Hiramatsu et al. discovered that three months of Tadalafil treatment led to a significant reduction in pelvic pain associated with LUTS. ($P < 0.05$). The pain subscore improved from 2.6 ± 3.6 to 1.2 ± 2.0, and there was also a notable reduction in voiding and QOL domains. However, these findings contrast with the results of our study, particularly in terms of pain improvement. One possible explanation for this discrepancy is that Hiramatsu's study focused on an elderly BPH population and did not include a control group, which may have contributed to the different outcomes observed.[9]

The lack of a statistically significant difference between the groups studied regarding the voiding symptoms subscore may suggest that PSO has no effect on voiding symptoms, with the improvement being attributed solely to the effect of Tadalafil. However, this could be considered a limitation of our study, as Tadalafil might have masked the potential impact of PSO on voiding symptoms. Therefore, further studies with a placebo-controlled design are needed to better assess the impact of PSO treatment specifically on voiding symptoms.

In 2018, Tantawy et al. conducted a study on the efficacy of (PSO) in managing CP/CPPS, and observed substantial improvements in all CPSI domain scores. However, this contrasts with our findings, particularly regarding the efficacy of PSO in CP/CPPS patients, especially with respect to voiding symptoms and QOL. A potential reason for this difference could lie in the method of administration. While Tantawy et al. used trans-perineal PSO phonophoresis along with low-intensity ultrasound (LIUS), which likely enhanced the absorption and effectiveness of the oil, our study relied on oral administration of PSO, potentially limiting its therapeutic effects.[10]

CP/CPPS can greatly impact a patient's QOL and is often associated with ED. On the other hand, erectile dysfunction is closely related to a decline in QOL. Due to this bidirectional relationship, any improvements in QOL resulting from tadalafil's effects on sexual function could potentially affect our CPSI outcomes. This could clarify the statistically significant positive correlation ($P < 0.001$) observed between the changes in CPSI (ΔCPSI) and QOL (ΔQOL) in both Group A and Group B.

In a placebo-controlled study by Wagenlehner et al., 12 weeks of pollen extract treatment (another phytotherapeutic agent) in men with CP/CPPS led to a notably greater improvement in symptoms when compared to the placebo group. The most notable benefit was a substantial reduction in pain. This resulted in a notable improvement in the overall CPSI score (The mean score dropped from 19.18 to 11.72 in the pollen extract group) and the quality of life (QoL) subscore. However, no significant changes were noted in the micturition subscore. These results align with the findings from our study.[11]

In our study, both Group A and Group B exhibited a statistically significant reduction in total CPSI scores ($P < 0.001$) after 3 months of treatment, when compared to their baseline scores. These improvements in CPSI scores are consistent with the results of earlier studies, such as those by Benelli et al. and Tantawy et al., which investigated the use of Tadalafil in treating CP/CPPS patients.[1,10]

To ensure consistency in outcomes across clinical trials for CP/CPPS treatment, many researchers propose that a reduction of 25% or more in the total CPSI score is generally considered to be clinically significant, as this level of improvement is typically recognized by patients as meaningful.[2]

In our study, A clinically significant improvement was seen in 12 patients (48%) in Group (A), while 11 patients (44%) in Group (B) showed similar improvements.

When comparing the studied groups (Group A and Group B) in terms of IIEF-5 (before treatment, after treatment, and ΔIIEF-5), we

found no statistically significant difference (P = 0.46) between the groups regarding ΔIIEF-5. In Group (A), the mean change was 16.3 ± 17.7, while in Group (B), the mean change was 20.6 ± 20.7. This suggests that adding (PSO) did not have a significant effect on erectile dysfunction.

A Limitation of the study was the selection criteria. Since CP/CPPS is a highly variable condition, achieving optimal therapy requires categorizing patients into clinically meaningful phenotypic groups, similar to the TNM system used in cancer staging. The UPOINTS system, which categorizes CP/CPPS patients into distinct subgroups, helps to optimize outcomes by tailoring treatment based on phenotype. This system allows for more customized treatment selection. Therefore, future studies should consider using the UPOINTS phenotype classification system to improve the precision and relevance of treatment approaches.

The use of CPSI and IIEF-5 questionnaires, while valuable, represents a limitation in our study as they are subjective tools to assess improvement in CP/CPPS patients. The absence of an objective method to evaluate improvements may introduce bias, as patients' perceptions of their symptoms may not always reflect actual clinical or physiological changes. Incorporating additional objective measures in future studies could offer a more thorough evaluation of treatment outcomes.

Since Tadalafil is not currently approved for treating CP/CPPS, it was prescribed exclusively to patients who had both CP/CPPS and concurrent erectile dysfunction (ED). The significant overlap between Tadalafil's effects on IIEF-5 scores and the QOL subscore could have influenced the outcomes of our study. As a result, Future controlled studies focusing on CP/CPPS patients without comorbid erectile dysfunction (ED) are essential to better isolate and assess the specific effects of Tadalafil on CP/CPPS symptoms.

4. Conclusion

This study demonstrated that both Tadalafil and Tadalafil combined with PSO significantly improved CP/CPPS in patients with ED. However, the addition of PSO did not show greater efficacy than Tadalafil monotherapy, except for the pain domain, where a more noticeable improvement was observed.

Disclosure

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