Research Paper

Treatment of Chronic Prostatitis with Phosphodiesterase Type 5 Inhibitors

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Our major aim was to systematically study the effectiveness of phosphodiesterase type 5 inhibitors in treating chronic prostatitis stage III and performed meta-analysis to evaluate the changes occurred in post-treatment scores of National Institutes of Health chronic prostatitis symptom index, international index of erectile function and international prostate symptom score. This meta-analysis was conducted according to the preferred reporting items for systematic reviews and meta-analyses guidelines. Comprehensive research was performed by using online resources like PubMed and the Wiley online library database to gather the relevant literature produced from the y 2010 to 2022. Two authors were assigned to independently collect the relevant information including author name, region of study, study design, treatment, publication year, sample size, voiding parameters, study inclusion and exclusion criteria, urological conditions, drug type, international prostate symptom score, international index of erectile function score, etc. In final screening 17 relevant studies were found. Out of these 17, 5 contained surgical procedure while 4 were narrative analysis. One study was incomplete regarding information. Finally, 7 studies were included for analysis. Total of 584 patients were involved in the selected studies. Three out of seven are from Italy region while two are from Japan and one was from Korea and Egypt respectively. Most of these studies used tadalafil monotherapy while one placebo-controlled trial. A significant difference in pain score, international prostate symptom score domain and National Institutes of Health chronic prostatitis symptom index were observed after consuming 5 mg tadalafil monotherapy. Everyday consumption of oral phosphodiesterase type 5 gave positive outcomes in terms of voiding. A significant difference was observed after using tadalafil monotherapy in the majority of the studies. Hence, tadalafil alone can be used to treat the type III chronic prostatitis.

Key words: Phosphodiesterase type 5 inhibitors, chronic prostatitis, tadalafil, ciprofloxacin

The prostate is the male sexual gland that has ability to secrete prostatic fluid, which forms the main part of the ejaculated sperm volume. The prostate grows under the testosterone control where the hormone made by the testicles and adrenal glands[1,2]. Chronic prostatitis as a usual disease, is categorized as Category III prostatitis by the United States National health institution. It has a lifetime prevalence rate about 1.8 %-8.2 %[3]. Chronic prostatitis is categorized as category III prostatitis by the United States National health institution. This condition is characterized by severe abdominal, pelvic and perineal pain associated with irritating low urinary tract symptoms. This condition is also marked by the absence of Urinary Tract Infection (UTI) and is associated with sexual dysfunction or painful voiding. Patients of chronic prostatitis also reported Lower Urinary Tract Symptoms (LUTS) including urgency, frequency, hesitancy and poor interrupted flow[4-6]. A patient with chronic prostatitis presents with pelvic pain or discomfort for more than 3 mo and this forms the basis of clinical diagnosis. Previous literature has reported chronic prostatitis prevalence ranging between

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2.2 %-13.8 %. There has been a number of studies which reports association between bacterial infection or pelvic floor dysfunction and chronic prostatitis, however the etiology still remains unknown[7,8]. Although it is more commonly seen in younger age groups, but it can affect individuals of any age groups[9]. The quality of life of an individual is also compromised as it causes severe pain and sexual disorder. The sexual disorder can present with a myriad of symptoms, most common being erectile dysfunction, which is reported in 30 %-50 % of cases. Evidences suggest that Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) is an independent risk factor for erectile dysfunction with an odds ratio of 3.62. Severe pain and sexual problem affect the patient's quality of life. The nature of sexual diseases is highly heterogeneous however 30 % to 50 % of cases of chronic prostatitis reported erectile dysfunction. This indicates that CP/CPPS is the independent factor causing erectile dysfunction with 3.62 odd ratios[10-12]. After observing symptoms like chronic pain, mental stress and sexual dysfunction, patients generally feel depression and worry, which makes patients incorrect cognition of the illness and therapy[3].

The common pathophysiological pathways of prostatitis pain and sexual dysfunction are not completely understood however previous literatures claim that elevated Rho-kinase activation and impaired nitric oxidase synthase in pelvic muscles may cause high intraprostatic pressure and thus interferes with smooth muscle relaxation of penile tissues this in turn results in prostatitis or erectile dysfunction[12-14]. Atherosclerosis and metabolic syndrome also plays a major role in prostate-associated sexual dysfunction[13]. Growing evidence suggests that Phosphodiesterase Type 5 (PDE5) inhibitors may have a major role in the treatment of CP/CPPS[15,16].

Tadalafil is a successful oral medication to inhibit PDE5 and doctors use it as a treatment option for men who have erectile dysfunction[17]. Studies prove that tadalafil can decrease Rho-kinase activity. Studies conducted on male rats reported that tadalafil treatment significantly suppresses pelvic pain and prostatic inflammation. This treatment also regulates the Nitric Oxide (NO)/cyclic Guanosine Monophosphate (cGMP) which helps in reducing prostatic smooth muscle contractions. Additionally, tadalafil also decreases the inflammatory markers and minimize atherosclerosis and inflammation[18-20]. A study by Grimsley *et al.*[21] reported that PDE5 inhibitors treatment can significantly decrease the prostatitis symptoms in CP/CPPS patients associated with erectile dysfunction.

However, only a few studies are conducted to measure the effectiveness of PDE5 inhibitors for treating chronic prostatitis patients[22-25]. In view of this, our study aims to systematically review all the relevant literature conducted in the years between 2010 and 2022 and perform meta-analysis to conclude the results.

MATERIALS AND METHODS

This meta-analysis study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Comprehensive literature search was done using online database like PubMed and the Wiley online library to gather the relevant literature between the y 2010 to 2022. Following keywords were used with various combinations to search the relevant database: Chronic prostatitis, type III prostatitis, CPPS, chronic prostatitis treatment, oral phosphodiesterase inhibitors, tadalafil, Viagra, tamsulosin, ciprofloxacin. Manual cross-referencing of the reference list of the selected articles was done to ensure that no relevant article is missed in the study.

Study selection:

The selection of the articles was done based on the following inclusion and exclusion criteria.

Inclusion criteria: Patients sexually active, age between ≥18 to ≤45 y old with persistent prostatitis like symptoms for more than 3 mo that are documented by history, clinical examination and Meares-Stamey 4-glass test and classified as category IIIA or IIIB; patients with type III CP/CPPS associated with erectile dysfunction for at least 6 mo; National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) pain sub-score≥4; total International Prostate Symptom Score (IPSS)≥8.

Exclusion criteria: The studies were not conducted on participants having active UTI, symptoms for less than 3 mo; those studies in which patients were diagnosed with UTI, acute and chronic bacterial prostatitis, benign prostatic hyperplasia, having sexually transmitted disease or documented infection, invasive prostate-related procedures (transurethral resection of the prostate, transurethral incision of the prostate or transurethral needle ablation), LUTS without significant pain, significant signs and symptoms of obstructive voiding, or prostate volume of >50 cm were excluded;

studies that performed urethral catheterization on urethral stricture or reported peptic ulcer, neurogenic bladder dysfunction or bladder calculi.

Information sources:

Comprehensive research was performed using online resources like PubMed and Wiley online library database to gather the relevant literature from 2010 to 2022.

Search strategy:

Following keywords with various combinations were used to access the data: chronic prostatitis, Type III prostatitis, CPPS, chronic prostatitis treatment, oral phosphodiesterase, tadalafil, Viagra, tamsulosin, ciprofloxacin. To identify the additional studies, we also performed manual research on the reference list of selected articles.

Study selection process:

Two independent authors, Sheetal Kalra and Puneeta, having 15 y of experience in handling meta-analysis, were assigned to review the patient's age, diagnostic method, duration of erectile dysfunction, NIH-CPSI pain sub-score and IPSS scores. Baseline parameters were critically reviewed and those studies with less or zero baseline and post-treatment outcomes were omitted. These two authors also rejected all the case studies and duplicate articles. Those studies that met the following inclusion criteria were finalized for the study and meta-analysis.

Data extraction:

Two authors were assigned to independently collect the relevant information, including author sir name, region of study, study design, treatment name, publication year, sample size, voiding parameters, study inclusion and exclusion criteria, urological conditions, drug type, IPSS, International Index of Erectile Function (IIEF), etc. In the case of disagreement, a third reviewer was asked to resolve the matter with consensus. After the data collection process, two independent authors processed the quality assessment of included articles.

Outcomes or endpoints of research:

The primary outcomes were phosphodiesterase inhibitor drug characteristics, case and control group mean age, drug type, duration, and pre and post-treatment scores, including mean NIH-CPSI score, mean IPSS score, and mean IIEF scores. Adverse events and discontinuation of the drugs were considered as study endpoints. However, the secondary outcomes involve quality of life, urinary domain, voiding parameters and LUTS.

Quality assessment:

Cochrane risk of bias was used for quality assessment with scores ranges from 0-7 scales. The main items of this scoring include title, abstract, sample size calculations, allocation of patients and allocation concealment.

Statistical analysis:

The relevant information was conceived on the excel sheet. Statistical Package for the Social Sciences (SPSS) version 23.0 was used for data analysis. The quantitative parameters are summarized as mean and Standard Deviation (SD). Pooled prevalence was estimated by using the DerSimonian-Laird technique with a fixed-effects model. It was used to generate proportions with 95 % Confidence Intervals (CI) and model-fitted weights. Cochrane Q test and I square (I^2) statistics were used to determine the heterogeneity across the studies. $I^2>50$ % and $p<0.10$ was considered significant. Publication bias was estimated by using the Egger's regression analysis and its significance was set at p value<0.05.

RESULTS AND DISCUSSION

In final screening 17 studies were found relevant. Out of these 17, 5 contained surgical involvement while 4 were narrative analysis. One study was incomplete regarding information. Finally, 7 studies were included for analysis. Total of 584 patients were involved in selected studies. 3 out of 7 were of Italy region while 2 were of Japan and 1 was of Korea and Egypt respectively. Most of these studies used tadalafil monotherapy while one placebo-controlled trial (fig. 1).

The sample size ranges from 14 to 80 patients. All of these studies were case-control except one in which no control group was involved. The inclusion criteria of these studies apply to sexually active patients of age group 18 or above having chronic prostatitis type III. The survey of Cantoro *et al.*[22] includes patients consuming phosphodiesterase inhibitors for the first time. They induce the drug when prostatitis volume reaches 15 to 25 ml. However, the analysis of Matsukawa *et al.*[23] has patients with 20 ml prostatitis volume. Except for these two mentioned studies, clarification of prostatitis volume was missing in others. UTI was the common exclusion criterion of the selected studies. Detailed

characteristics are mentioned in Table 1[22-30].

Pre-treatment outcomes were explained here. Patients with a mean age of 32.04 y were observed in a study by Cantoro *et al.*[22] with mean pre-treatment IPSS, IIEF and NIH-CPSI scores of 13.52±1.49, 12.41±0.66 and 17.51±1.92, respectively. They examined the overall pre-treatment scores before classifying patients into case-control groups. However, the study of Kong *et al.*[26] used both monotherapy and combined therapy using levofloxacin. The mean NIH-CPSI, IPSS and IIEF scores in the monotherapy group were 22.1±1.5, 12.0±1.2 and 18.8±6.2. The combined therapy group reported 14.1±1.0 baseline score of IPSS, 18.2±6.0 for IIEF and a comparatively lower NIH-CPSI score of 19.5±1.6. A study by Benelli *et al.*[27] only reported case groups. NIH-CPSI score was not mentioned in the study of Sebastianelli *et al.*[30] while the study of Yamanishi *et al.*[28], Benelli *et al.*[27] and Matsukawa *et al.*[23] missed the IIEF scores. Two studies also missed the IPSS score information. Detailed data presentation of baseline outcomes is shown in Table 2.

Post-treatment outcomes were shown here. Post-treatment IPSS, IIEF and NIH-CPSI scores are detailed in Table 3 and Table 4, while subdomain analysis of NIH-CPSI scores constitutes in Table 5. One study missed the NIH-CPSI score, whereas IIEF post-treatment outcomes were missing in three studies. IPSS scores were also not observed in two studies. Subdomain analysis of NIH-CPSI score was conducted in all studies except two. The subdomains include pain, urinary symptoms and quality of life. However, the overall score was mentioned in all studies. Analysis of voiding parameters also noted many missing outcomes, including Qmax range, volume and Post-Void Residual (PVR) volume. Detailed analysis is shown in Table 5. IPSS subdomain analysis is shown in Table 6. In fig. 2 and fig. 3, significant changes were observed in pre and post-treatment NIH-CPSI and IPSS scores.

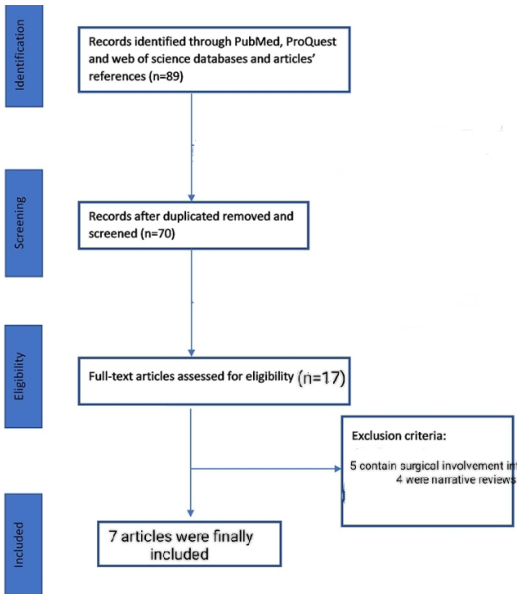

Fig. 1: Prisma inclusion criteria

TABLE 1: CHARACTERISTICS OF THE SELECTED STUDIES

Study (Year)	Location (country)	Sample size		Inclusion criteria	Exclusion criteria
		Group 1	Group 2		
Cantoro *et al.*[22] (2013)	Italy	20	24	Chronic prostatitis type III associated with erectile dysfunction since 6 mo Sexually active patients Not using any PDE-5 inhibitors before and prostate volume range 15 to 25 ml	Urinary system infections, neoplasia, congenital disorders, previous surgeries, urolithiasis and hyperactive bladder
Kong *et al.*[26] (2014)	Korea	48	40	Fulfilled the requirements for NIH category III CP/CPPS	Symptoms for less than 3 mo, UTI, invasive prostate-related procedures, LUTS without significant pain, significant signs and symptoms of obstructive voiding or prostate volume of >50 cm^3

Matsukawa *et al.*[23] (2020)	Japan	Case: 45	Control: 42	Age ≥45 y, pain sub score≥4, IPSS≥8 and prostate volume≥20 ml	Bacterial prostatitis had an active UTI, neurogenic bladder dysfunction or bladder calculi
Benelli *et al.*[27] (2018)	Italy	Case: 14	Not reported	Presence of CP/CPPS symptoms for at least 3 mo and negative Meares-Stamey test	Urinary infections or other urological disease and treated with antimicrobial drugs during the previous 3 mo
Yamanishi *et al.*[28] (2020)	Japan	80	81	Male patients with LUTS, Overactive Bladder (OAB) symptoms despite at least 8 w of treatment	Anticholinergics, cholinergics, beta (β)-agonists or antagonists, α-blockers, UTI etc.
Tawfik *et al.*[29] (2022)	Egypt	59	56	Recurrent/persistent symptoms after previous treatment	Mild symptoms (total CPSI score≤14), IIEF-5≥22, abnormal Digital Rectal Examination (DRE) or Prostate-Specific Antigen (PSA) values, bladder stones, lower UTI
Sebastianelli *et al.*[30] (2019)	Italy	25	50	Age>40 to 80 y, mild to severe erectile dysfunction, IPSS>7	Prostatic cancer, bladder lithiasis, UTI, bladder neck obstruction

TABLE 2: PRE-TREATMENT FINDINGS OF PATIENTS MENTIONED IN SELECTED STUDIES

Study (Year)	Age Mean/Median/ SD	Chronic prostatitis type*	Mean IPSS	Mean IIEF	Mean NIH-CPSI
Cantoro *et al.*[22] (2013)	32.04±3.15 y (All cases)	Type III	13.52±1.49	12.41±0.66	17.51±1.92
Kong *et al.*[26] (2014)	44.2±6.9 45.3±7.0 y	Type III	Group L: 12.0±1.2 Group ML: 14.1±1.0	Group L: 18.8±6.2 Group ML: 18.2±6.0	Group L: 22.1±1.5 Group ML: 19.5±1.6
Matsukawa *et al.*[23] (2020)	Case group: 67.9±6.9 Control group: 65.9±9.9	Type III	Case: 16.8±4.5 Control: 16.5±6.2	Not reported	19.7±4.6
Benelli *et al.*[27] (2018)	40.14±8.63	Type III	4±2.85	Not reported	27.57±4.18
Yamanishi *et al.*[28] (2020)	Group 1: 72.3±8.0 Group 2: 72.4±7.4	Type III	Group 1: 13.637±6.751 Group 2: 13.506±5.872	Not reported	Group 1: 12.363±5.733 Group 2: 12.333±5.438
Tawfik *et al.*[29] (2022)	Case: 39.9±3.9, Control: 39.7±4.7	Type III	Not reported	17.6±2.2	24.21±5.05
Sebastianelli *et al.*[30] (2019)	Case: 65.5±6.3 Control: 65.7±9.1	Type III	Case: 17±6.1 Control: 18.8±5.9	Case: 13.8±5.2 Control: 12±3.5	-

Note: *NIH classification; Group L: Only levofloxacin and Group ML: Monotherapy and combined therapy using levofloxacin

TABLE 3: POST TREATMENT OUTCOME OF PDE5 INHIBITORS

Study (Year)	Mean IPSS		Mean IIEF		Mean NIH-CPSI		Follow up duration	Outcome
	Study group	Control group or combined therapy group	Group 1	Group 2	Group 1	Group 2		
Cantoro *et al.*[22] (2013)	8.23±0.72	8.07±0.91	17.83±1.46	18.75±1.24	10.54±1.35	9.74±1.98	More than 60 d	Tamsulosin therapy has the same effectiveness of the most expensive combination therapy (tamsulosin and sildenafil)

Kong *et al.*[26] (2014)	−4.3±0.2	−1.1±0.2	7.8±1.8	0.2±2.4	−7.2±0.1	−3.2±0.2	6 w	No significant outcomes reported
Matsukawa *et al.*[23] (2020)	12.2±5.2	14.0±6.4	-	-	15.1±4.7	12.8±5.2	12 w	Significant outcomes of tadalafil observed
Benelli *et al.*[27] (2018)	0.214286±0.42		-		2.928571±2.43		12 w	Reduction in pain and significant improvement in quality of life
Yamanishi *et al.*[28] (2020)	11.934±7.204	9.961±6.478	Not reported	Not reported	11.303±6.769	8.584±5.334	12 w	Tadalafil/ mirabegron combination therapy is better than tadalafil monotherapy
Tawfik *et al.*[29] (2022)	-	-	21±1.8	17.46±3.56	19.1±5.26	23.79±5.2	6 w	Significant improvement of all CPSI domains (pain, micturition, Quality of Life (QOL) and total scores) compared to baseline
Sebastianelli *et al.*[30] (2019)	11.8±6.3	11.5±5.4	19.9±5.1	17.7±3.3	-	-	12 w	Tadalafil 5 mg daily monotherapy is able to improve erectile dysfunction and overall LUTS

TABLE 4: COMPARISON OF NIH-CPSI AFTER TREATMENT

Study (Year)	NIH-CPSI	Study group (Monotherapy)	Control group (Combined therapy or α-blockers)
Cantoro *et al.*[22] (2013)	NIH-CPSI/Total post treatment % Reduction	10.54±1.35	9.74±1.98
Kong *et al.*[26] (2014)	NIH-CPSI/Total post treatment % Reduction	15.1±4.7	12.8±5.2
Benelli *et al.*[27] (2018)	NIH-CPSI/Total post treatment % Reduction	2.928571±2.43	-
Yamanishi *et al.*[28] (2020)	NIH-CPSI/Total post treatment % Reduction	11.303±6.769	8.584±5.334
Tawfik *et al.*[29] (2022)	NIH-CPSI/Total post treatment % Reduction	19.1±5.26	23.79±5.2
Sebastianelli *et al.*[30] (2019)	NIH-CPSI/Total post treatment % Reduction	-	-

TABLE 5: VOIDING PARAMETERS OUTCOMES BETWEEN THE TWO GROUPS

Study (Year)	Voiding parameters	Study group (Monotherapy)	Control group (Combined therapy or α-blockers)	p-value
Cantoro *et al.*[22] (2013)	Qmax, ml/s	-	-	-
	Voided volume, ml	-	-	-
	PVR, ml	-	-	-
Kong *et al.*[26] (2014)	Qmax, ml/s	1.1±2.1	1.1±2.1	
	Voided volume, ml	−1.7±0.3	1.2±0.8	
	PVR, ml			
Matsukawa *et al.*[23] (2020)	Qmax, ml/s	11.2±3.9	10.8±3.8	
	Voided volume, ml	171±100	164±73	
	PVR, ml	20 (10-40)	30 (15-60)	
Benelli *et al.*[27] (2018)	Qmax, ml/s	20.14±3.50	-	<0.698
	Voided volume, ml	15.71±21.38	-	<0.822
	PVR, ml	-	-	-
Yamanishi *et al.*[28] (2020)	Qmax, ml/s	11.985±6.283	12.440±5.485	0.09
	Voided volume, ml	161.142±94.051	179.303±100.098	0.048
	PVR, ml	20.908±24.742	31.643±28.523	0.25
Tawfik *et al.*[29] (2022)	Qmax, ml/s	-	-	-
	Voided volume, ml	-	-	-
	PVR, ml	-	-	-
Sebastianelli *et al.*[30] (2019)	Qmax, ml/s	11.8±4	14.5±3.7	0.027
	Voided volume, ml	-	-	-
	PVR, ml	-	-	-

TABLE 6: POST-TREATMENT LUTS OUTCOMES BETWEEN THE TWO GROUPS

Study (Year)	Voiding parameters	Study group (Monotherapy)	Control group (Combined therapy or α-blockers)	p-value
Cantoro *et al.*[22] (2013)	IPSS total score	-	-	-
	IPSS-voiding	-	-	-
	IPSS-storage	-	-	-
	IPSS-QOL	2.02±0.56	1.82±0.25	0.574
Kong *et al.*[26] (2014)	IPSS total score	−4.3±0.2	−1.1±0.2	p<0.05
	IPSS-voiding	−3.0±0.2	−0.7±0.1	p<0.05
	IPSS-storage	−1.3±0.1	−0.4±0.1	p<0.05
	IPSS-QOL	−0.2±0.1	−0.1±0.1	p<0.05
Matsukawa *et al.*[23] (2020)	IPSS total score	12.2±5.2	14.0±6.4	-
	IPSS-voiding	7.2±3.8	8.0±4.1	-
	IPSS-storage	5.0±2.4	6.0±2.9	-
	IPSS-QOL	3.1±1.3	3.4±1.1	-

Benelli *et al.*[27] (2018)	IPSS total score	0.214286±0.42	-	-
	IPSS-voiding	-	-	-
	IPSS-storage	-	-	-
	IPSS-QOL	-	-	-
Yamanishi *et al.*[28] (2020)	IPSS total score	11.934±7.204	9.961±6.478	-
	IPSS-voiding	3.868±4.199	3.675±4.266	-
	IPSS-storage	6.882±3.216	5.403±2.725	-
	IPSS-QOL	3.974±1.286	3.455±1.401	-
Tawfik *et al.*[29] (2022)	IPSS total score	-	-	-
	IPSS-voiding	-	-	-
	IPSS-storage	-	-	-
	IPSS-QOL	-	-	-
Sebastianelli *et al.*[30] (2019)	IPSS total score	11.8±6.3	11.5±5.4	0.084
	IPSS-voiding	8±4.7	5.1±2.7	0.006
	IPSS-storage	3.8±3.4	5.3±2.7	0.08
	IPSS-QOL	2.1±1.7	2.1±1	0.321

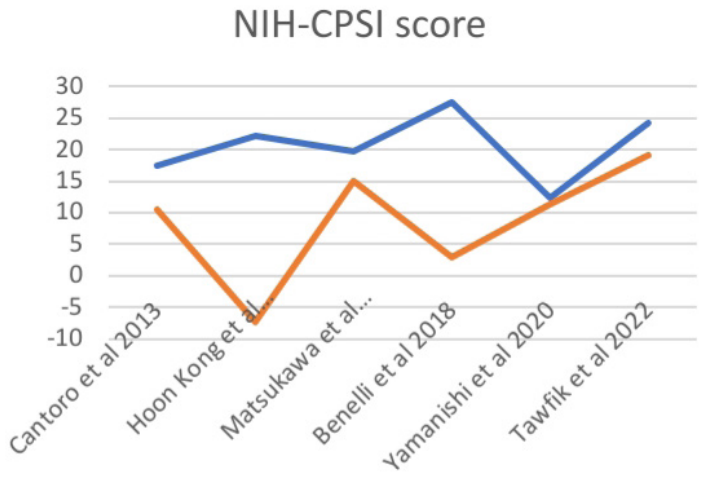

Fig. 2: Pre and post treatment NIH-CPSI outcomes of selected studies, ( ) Pre-treatment and ( ) Post treatment

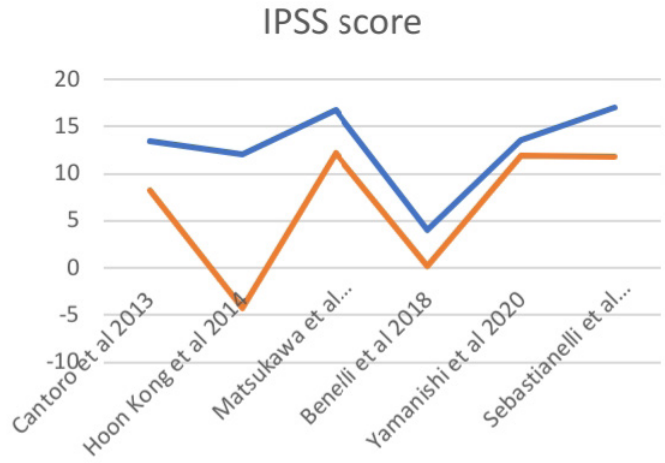

Fig. 3: Pre and post treatment IPSS outcomes of selected studies, ( ) Baseline score and ( ) Post treatment outcomes

The main items of Cochrane risk of bias were concerned with research title, abstract, sample size calculations, allocation of patients and allocation concealment. The quality assessment revealed that a single study had a sufficient amount of information while many of them neglect the element of blinding in their research. Sample size calculation was also not adequately addressed in the studies. So, overall two studies scored 5 points, two scored 4, one study scored 3 points while one scored at least 2 points. The highest score was observed as 7 in Tawfik's study and focused on set of all the points to minimize the risk of bias[29].

For meta-analysis, Wald test was performed to evaluate the effective size of mentioned studies. Cochrane diagnostic test was performed along with Roswin and Egger model to evaluate the risk of bias. The pooled prevalence of NIH-CPSI score was reported as 40 % with 98 % heterogeneity. The overall NIH-CPSI score ranges from -0.16 to 0.23 at 95 % CI. The study conducted by Yamanishi *et al.*[28], which weighted higher than the other studies, reported all the NIH-CPSI parameters including pain, voiding, urinary symptoms and quality of life. The Chi-square score of these studies was reported as 205.32 with a Degrees of Freedom (DF) value of 4. Egger regression test value was observed as 0.0951 which indicates a significant publication bias between studies (fig. 4). Meanwhile, the IPSS score had 98 % heterogeneity with an overall 30 % prevalence (95 % CI of -0.24 to 0.18). The Chi-square value was reported as 169.14 with a significant publication bias of 0.0446 (fig. 5). Only 10 % of the studies reported IIEF scores with 97 % significant heterogeneity results. Odds ratio of IIEF was reported as 1.07 (0.82 to 1.33). The study of Cantoro *et al.*[22] and Kong *et al.*[26] reported all the variables including total NIH-CPSI score, total IPSS score and total IIEF score with the weighted prevalence of 10.9 % *vs.* 0.3 %, 12.1 % *vs.* 0.7 % and 17.7 % *vs.* 14.0 % (fig. 6).

Traditionally antibiotics, anti-inflammatory and Alpha (α)-blockers were used to treat chronic prostatitis however these drugs failed to give successful outcomes[31]. Tadalafil at the dose of 5 mg daily shows improvement in LUTS and erectile dysfunction[32]. Experimental studies have shown positive outcomes of PDE5 inhibitors in the management of prostatitis[15,16,18]. Unfortunately, most of the literature was formed on Benign Prostatic Hyperplasia (BPH)-associated CP/CPPS or combination with other medications. Thus, we could only find two case-control studies[22,23]. In a study by Benelli *et al.*[27], a significant improvement was observed in all NIH-CPSI domains. The treatment duration was of 3 mo, while improvement in symptoms was noted within a month of treatment. Pain score was reduced from 13.7±3.7 to 5.4±2.2. Further reduction was observed by the 2nd and 3rd mo of the trial. A reduction of more than 25 % in CPSI score is assumed to show clinically significant improvement after treatment[33-35]. In the case-control study conducted by Tawfik *et al.*[29], 50.8 % of respondents have been observed to have signs of clinical improvement. Likewise, a study by Hiramatsu *et al.*[25] observed a reduction in pain score after a 3 mo treatment of tadalafil in chronic prostatitis patients associated with LUTS. They reported that the pre-treatment mean pain score as -10.0±7.8 which was improved to be −4.4±4.5 post-treatment.

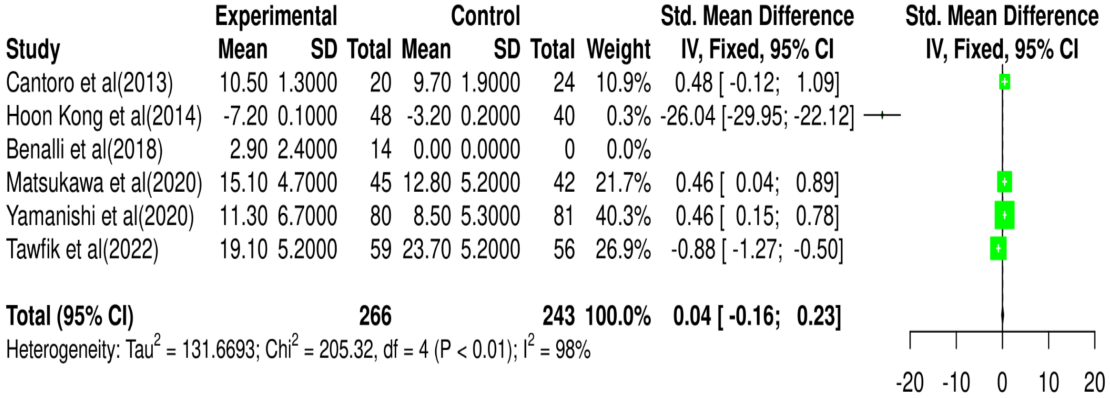

Fig. 4: Fixed effect model of NIH-CPSI

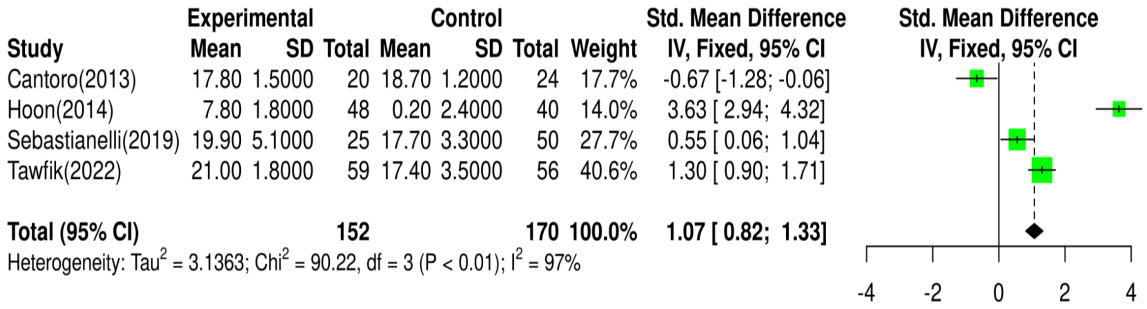

Fig. 5: Fixed effect model of IIEF score

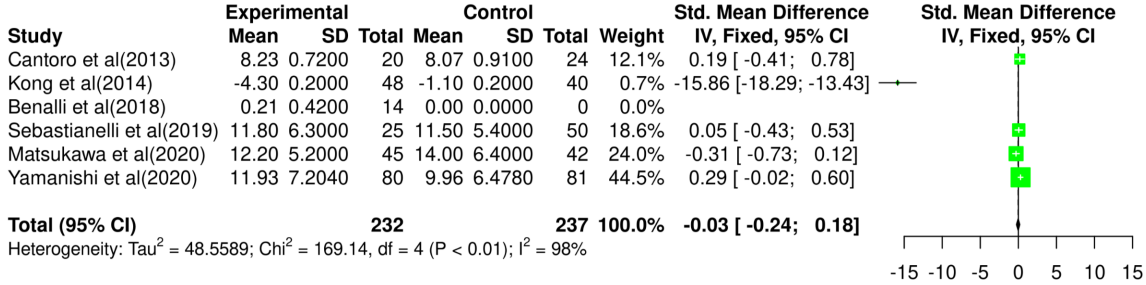

Fig. 6: Fixed effect model of IPSS score

Quality of life was also reportedly improved during the treatment. Tadalafil monotherapy was used in the study of Matsukawa *et al.*[23]. The study reports that only 4 of their patients showed ≥50 % improvement in CPSI score. Similarly, a study by Pineault *et al.*[24] conducted on 25 patients observed a significant reduction in CPSI total pain, urinary symptoms and quality of life scores after everyday consumption of 5 mg tadalafil for 1.5 y. In contrast, a placebo-controlled clinical trial observed no significant improvement in pain scores in both placebo and control groups. The short period of medication could be the reason for the results. However, PDE5 inhibitors show significant results in treating erectile dysfunction in mild and moderate cases. Improved IIEF-5 can be observed in the tadalafil group[29].

Erection dysfunction, headaches and dyspepsia were frequently reported after using tadalafil[23,26,28,30]. However, these effects were also observed in the study that tested the new PDE5 inhibitor sildenafil. Muscle aches and dizziness were the second most frequently reported subjects. In a survey by Sebastianelli *et al.*[30], the treatment emergence adverse effect was noted as 16 % in the tadalafil monotherapy group, while 22 % were reported in the tadalafil combined therapy group.

The negative impact of LUTS is highly observed in elderly patients, which affects the quality of life. Besides aging, many metabolic factors affect the LUTS and erectile dysfunction, including prostatitis enlargement and inflammation. PDE-5 inhibitors are proven to significantly suppress the inflammatory factor for treating both conditions. These drugs stabilize the glandular structural anatomy, reduce the tone of bladder muscles and affect the micturition reflex[36,37]. One of the meta-analyses also observed the positive role of PDE5 inhibitors in treating benign prostatic hyperplasia[38]. Meanwhile, only four out of seven studies reported the adverse effect of PDE5 inhibitors.

Our systematic study and meta-analysis was the first one that highlights the effectiveness of PDE5 inhibitors in treating type III chronic prostatitis through the relevant data is small. A monotherapy of 5 mg tadalafil has been found to significantly reduce pain score, IPSS domain and NIH-CPSI. A daily oral dose of PDE5 has been observed to have a positive impact in reducing voiding difficulties. A significant difference has been observed after using tadalafil monotherapy in the majority of the studies. Hence, tadalafil alone can be used to treat type III chronic prostatitis.

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