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Terazosin or baclofen in young men with chronic orchialgia: A cohort study of 499 patients

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Abstract

Purpose: We aimed to investigate the comparative efficacy of terazosin and baclofen in young men with chronic orchialgia using National Institutes of Health Chronic Prostatitis Symptom Index measurement.

Patients and methods: Of 499 young men with chronic orchialgia, 255 received a daily 2 mg terazosin at bedtime and 244 received 10 mg baclofen during a period of 3 months. A daily 10-min hot-tub hip-bath rest was administered for all patients. Moreover, all patients with grade 3 and 18 patients with grade 2 varicocele underwent varicocelectomy. The National Institutes of Health Chronic Prostatitis Symptom Index score was assessed at baseline and 3 months later.

Results: Both terazosin and baclofen groups experienced a significant reduction in mean National Institutes of Health Chronic Prostatitis Symptom Index score (24.78 and 24.81 at baseline to 19.68 and 19.60 after the treatment for terazosin and baclofen groups, respectively). However, there was no significant difference between the groups with regard to post-treatment National Institutes of Health Chronic Prostatitis Symptom Index score after adjustment for the pre-treatment score ($p = 0.987$). A total of 85 patients (33.4%) in terazosin group and 74 patients (30.3%) in baclofen group underwent varicocelectomy. Addition of the varicocelectomy to the treatment as a multimodal approach had no further improvement in the National Institutes of Health Chronic Prostatitis Symptom Index score.

Conclusion: Although a significant reduction was observed in mean National Institutes of Health Chronic Prostatitis Symptom Index score for both terazosin and baclofen groups, there was no significant difference between the treatments. Moreover, addition of varicocelectomy to terazosin or baclofen could not significantly decrease National Institutes of Health Chronic Prostatitis Symptom Index score; thus, varicocelectomy may not be appropriate for men who have some success with medical management. Further randomized studies are warranted.

Keywords

Chronic orchialgia, varicocele, terazosin, baclofen, chronic pelvic pain syndrome

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Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a subgroup of (nonbacterial) prostatitis that can present in 2%–10% of men.[1,2] Chronic orchialgia of pelvic pain is defined as intermittent or constant scrotal pain lasting 3 months or longer in the setting of chronic pelvic pain syndrome.[3,4] Chronic orchialgia could be as a result of torsion, tumor, epididymitis, trauma, hernia, hydrocele, urinary

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tract disease, lower back disorder, referral pain, and psychological pain.[5] Despite multiple factors, some cases are considered idiopathic.[6] Most men with chronic orchialgia are in their young age up to 30s.[5] Disorders associated with chronic orchialgia include infertility (9.7%), varicocele (8.8%), mid and distal ureteral stones (7.1%), chronic prostatitis (5.3%), lumbar pain (4.4%), stress (4.4%), epididymal cysts (4.4%), irritable bowel (4.4%), infection (3.5%), previous operation (2.7%), driving (2.7%), hernia (2.7%), and hydrocele (1.8%).[7]

During the last 30 years, many treatments have been investigated in pilot studies for CP/CPPS and chronic orchialgia using α-blockers, antibiotics, nonsteroidal anti-inflammatory agents, pentosan polysulfate, allopurinol, quercetin, finasteride, and hyperthermia.[8–10] In addition, surgical options include spermatic cord blocks, varicocelectomy, epididymectomy, vasovasostomy, microsurgical denervation of the spermatic cord (MDSC), and orchiectomy.[5] Since varicocele is an important factor in patients with chronic orchialgia,[11] varicocelectomy has been suggested for the pain management.[12]

Although there are no formal guidelines for the diagnosis, evaluation, and management of chronic orchialgia in the literature,[5] European Association of Urology (EAU) guideline has recommended starting with general treatment options for chronic pelvic pain.[13]

In this prospective cohort study, we compared the efficacy of terazosin and baclofen with or without varicocelectomy on the chronic orchialgia pain in young men based on National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) measurement.

Patients and methods

Study protocol and outcome

Between September 2015 and October 2016, men aged 18–35 years with clinical diagnosis of chronic orchialgia (at least 3 months of scrotal pain) were included in a prospective cohort study at a referral hospital in Tehran, Iran. Exclusion criteria were positive urine cultures, serum creatinine >2 mg/dL, malignancy, and inflammatory bowel disease. Physical examination, digital rectal examination (DRE), two-glass pre-massage and post-massage test, and essential laboratory tests, such as blood cell counts, serum creatinine, urine analysis, and urine culture, were performed at baseline for the patients. The study protocol was approved by a local institutional review board. A written consent was obtained from the patients. The NIH-CPSI score was assessed at baseline and 3 months later. The NIH-CPSI is a 13-item questionnaire (total score range from 0 to 43), including score 0–1 (six items), 0–3 (two items), 0–5 (three items), 0–6 (one item), and 0–10 (one item) about pain or discomfort (score range 0–21), urinary symptoms (score range 0–10), and quality of life (score range 0–12). The NIH-CPSI has been shown to be reliable, valid, and responsive to change.[14,15] This questionnaire is straightforward, but a higher weight for the items with wider score ranges could adversely affect the performance characteristics of the questionnaire.[16] The NIH-CPSI was previously applied in Iranian population by Falahatkar et al.[17]

In this study, we aimed to investigate the compared efficacy of terazosin and baclofen in the treatment of chronic orchialgia, assessed by the NIH-CPSI score at baseline and after a period of 3-month treatment. A total of 499 patients completed the 3-month follow-up. Of these, 255 former patients received a daily terazosin 2 mg at bedtime and the remaining 244 patients received baclofen 10 mg during a period of 3 months. All patients were asked to sitz bath in hot water tube every day for approximately 10 min during the course of treatment. All patients with grade 3 (141 patients) and 18 patients with grade 2 varicocele underwent inguinal microscopic varicocelectomy. Ciprofloxacin was prescribed for 4 weeks to patients who had more than five WBC in pre- or post-DRE. Cases with bacterial prostatitis were excluded from the study by urine analysis.

Statistical analysis

To compare the NIH-CPSI score pre- and post-treatment, a paired *t* test was used. The baseline-adjusted post-treatment NIH-CPSI score was compared between the two groups by analysis of covariance (ANCOVA) test. The statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). A value of $p < 0.05$ (two-sided test) was considered significant.

Results

No complication was reported in either group. At baseline evaluation, the treatment groups were relatively homogeneous with regard to demographic data (Table 1). The baseline characteristics including age, sexual history, DRE tenderness, and semen WBC were also identical in patients treated with and without varicocelectomy.

Of 750 patients assessed for eligibility, 215 were excluded; thus, 535 received the treatments. Of these, 499 (93.3%) completed the follow-up assessment. Both terazosin and baclofen groups experienced a significant reduction in mean NIH-CPSI score (24.78 and 24.81 at baseline to 19.68 and 19.60 after the treatment for terazosin and baclofen groups, respectively). However, there was no significant difference between the groups with regard to post-treatment NIH-CPSI score after adjustment for the pre-treatment score ($p = 0.987$). A total of 85 patients (33.4%) in terazosin group and 74 (30.3%) in baclofen group underwent varicocelectomy. A plot of the NIH-CPSI score for all subgroups with/without varicocelectomy is indicated in Figure 1. As shown in the figure, addition of the varicocelectomy to the treatment as a multimodal approach had no further improvement in the NIH-CPSI score. As

Table 1. Patient characteristics.

Characteristics	All patients ($n=499$)	Terazosin group ($n=255$)	Baclofen group ($n=244$)
Age (years)			
Mean (SD)	21.61 (3.48)	21.49 (3.20)	21.75 (3.68)
Varicocele, *n* (%)			
Grade 0	55 (11.0)	25 (9.8)	30 (12.3)
Grade 1	234 (46.9)	116 (45.5)	118 (48.4)
Grade 2	69 (13.8)	33 (12.9)	36 (14.8)
Grade 3	141 (28.3)	81 (31.8)	60 (24.6)
Varicocelectomy, *n* (%)			
Yes	159 (31.9)	85 (33.4)	74 (30.3)
No	340 (68.1)	170 (66.6)	170 (69.7)
Sexual history, *n* (%)			
Yes	155 (31.1)	79 (31)	76 (31.1)
No	344 (68.9)	176 (69)	168 (68.9)
DRE tenderness, *n* (%)			
Yes	377 (75.6)	193 (75.7)	184 (75.4)
No	122 (24.4)	62 (24.3)	60 (24.6)
Semen WBC			
Median (range)	3 (1–5)	3 (1–5)	3 (1–5)

SD: standard deviation; DRE: digital rectal examination; WBC: white blood cell.

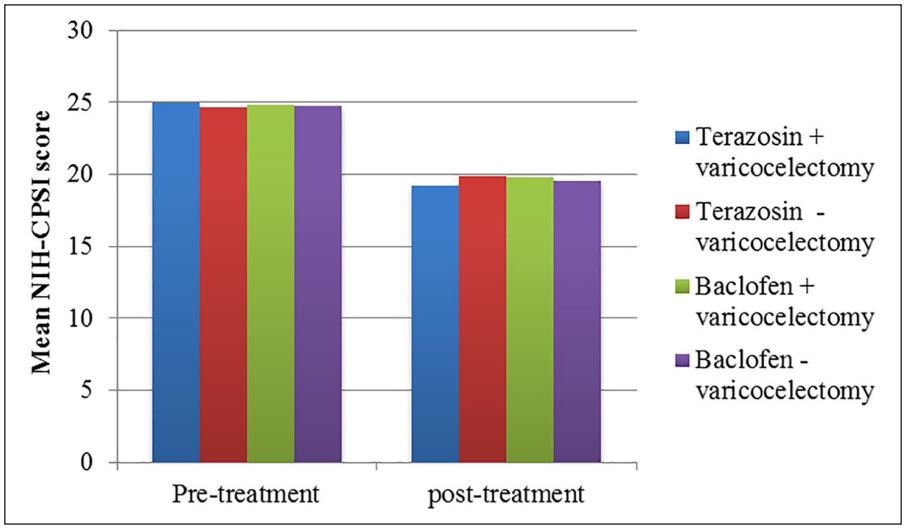

Figure 1. Pre- and post-treatment NIH-CPSI score for the four subgroups.

indicated in Table 2, statistically significant differences in NIH-CPSI score were found between all subgroups pre- and post-treatment. Although significant within-group differences were found for all subgroups ($p<0.001$), there were no significant between-group differences after the treatment ($p>0.05$). Moreover, no associations and interactions were found between the age, sexual history, and varicocele grade with the baseline NIH-CPSI score.

Discussion

Among men with chronic scrotal pain, even after visiting an average of 4.5 urologists and undergoing an average of 4.7–7.2 procedures, 18.6% never receive a satisfactory explanation for their pain.[18] Up to now, the particular etiology and pathophysiology of chronic scrotal pain are not fully understood.[19–22] Since 25%–50% of cases are noted to be idiopathic, it is hard for physicians to determine the best treatment option.[23]

Commonly, men with chronic pelvic pain have chronic orchialgia.[4] Lian et al.[24] proposed that the methods of approaching men with CP/CPPS may help men suffering from chronic orchialgia. Moreover, the EAU guideline has recommended starting with general treatment options for chronic pelvic pain.[13] Conservative therapies for patients with idiopathic chronic orchialgia (ICO) include heat, ice,

Table 2. Comparison between pre- and post-treatment NIH-CPSI score in all subgroups.

Subgroup	*N*	Pre-treatment NIH-CPSI, mean (SD)	Post-treatment NIH-CPSI, mean (SD)	Within-group difference, mean (95% CI)	*p* value
Terazosin + varicocelectomy	85	25.00 (8.32)	19.22 (7.14)	5.78 (3.50–8.04)	<0.001
Terazosin − varicocelectomy	170	24.67 (8.23)	19.91 (7.18)	4.76 (3.16–6.37)	<0.001
Baclofen + varicocelectomy	74	24.86 (8.62)	19.78 (7.47)	5.08 (2.38–7.77)	<0.001
Baclofen − varicocelectomy	170	24.79 (8.15)	19.52 (6.93)	5.27 (3.71–6.83)	<0.001

NIH-CPSI: National Institutes of Health Chronic Prostatitis Symptom Index; SD: standard deviation; CI: confidence interval.

α-adrenergic antagonists, scrotal elevation, analgesics, anti-inflammatory agents, regional and local nerve blocks, antibiotics with objective evidence of infection, amitriptyline, antidepressants with doxepin, anticonvulsants, biofeedback, physical therapy, acupuncture, and psychotherapy for at least 3 months.[3,6,25–27] However, chronic pelvic pain in men has not been as sufficiently studied as chronic pelvic pain in women.[3,4] In a randomized controlled trial, Tantawy et al.[28] investigated how effective transcutaneous electrical nerve stimulation (TENS) is in pain reduction and how it consequently affects the quality of life in patients with ICO. The results demonstrated that TENS is effective in reducing pain and improving quality of life in cases of ICO. It appears that a combined treatment strategy addressing individual patient characteristics is more effective than a single therapy. It is known that α-receptors are present in the human bladder and may mediate relief of irritative urinary symptoms. In an animal study, it was suggested that terazosin may affect spinal cord and ganglia in the central nervous system, where α-receptors exist.[29,30] It was demonstrated that terazosin is an effective drug in treating patients with nonbacterial prostatitis.[31,32] In a randomized trial by Cheah and colleagues, terazosin therapy for patients with CP/CPPS was evaluated. In that study, patients who received terazosin had greater reductions in NIH-CPSI score than the placebo group; thus, terazosin proved superior to placebo for patients with CP/CPPS.[33] In addition, it was observed that CP/CPPS patients treated with terazosin had initial, long-term, and durable responses than those treated with placebo.[34] Also, Osborn and colleagues reported the effect of placebo, baclofen, and phenoxybenzamine, a nonselective α-blocker, on the CP/CPPS patients by a three-arm crossover study. This study was difficult to be interpreted because it used baclofen, a striated muscle relaxant, and also there was no washout period among the treatment arms.[35] However, in agreement with our study, previous data suggested that terazosin and other α-blockers may have a role in treating patients with chronic orchialgia, especially in patients who had not received α-blockers previously. Also, earlier research guidelines recommended that α-blockers merit priority for research in CP/CPPS.[8]

In a study of the relationship between varicocele embolization and orchialgia, it was shown that varicocele embolization and microsurgical surgery could relieve testicular pain in 74% of patients with moderate and severe grades of chronic orchialgia.[36] Muthuveloe et al.[36] demonstrated that varicocelectomy had beneficial effects on reducing the chronic orchialgia pain. In a meta-analysis, it was observed that subinguinal varicocelectomy and microsurgical varicocelectomy are effective techniques for resolving varicocele-related pain compared with other approaches.[37] In this study, 33.4% of patients in terazosin group and 30.3% in baclofen group underwent varicocelectomy; however, there was no significant difference between the groups with or without varicocelectomy. In other words, the results obtained in the study did not show the combination therapy is more effective than a single treatment. Thus, the physician should be diligent in ruling out specific etiologies for scrotal pain prior to managing orchialgia, and surgical intervention should be limited to cases when a clear indication is present. Figure 1 is depicted to indicate the lack of difference between the groups after the treatment, especially with and without the surgery; however, further research including a group of patients treated with varicocelectomy alone, and also a placebo group, is needed to answer the question of varicocelectomy and drug medication.

As a limitation, our results were reported based on characteristics of patients in a single center, and it should be noted that our study population is not fully representative of the whole population. Furthermore, the short-term follow-up in the study was another limitation, and longer follow-up may yield different results. There should be another set of data for the patients (i.e. pre-medication, 3 months after medication, and after varicocele repair).

In conclusion, the results obtained in this study showed a significant reduction in mean NIH-CPSI score after treatment with terazosin or baclofen in patients with chronic orchialgia associated with nonbacterial CP/CPPS. However, there was no significant difference between the treatments. Moreover, addition of inguinal varicocelectomy to terazosin or baclofen could not significantly decrease NIH-CPSI score; thus, varicocelectomy may not

be appropriate for men who have some success with medical management. Further studies are needed to introduce a gold standard therapy for the patients.

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References

1. Nickel JC, Downey J, Hunter D, et al. Prevalence of prostatitis-like symptoms in a population based study using the National Institutes of Health chronic prostatitis symptom index. *J Urol* 2001; 165(3): 842–845.
2. Cheah PY, Liong ML, Yuen KH, et al. Chronic prostatitis: symptom survey with follow-up clinical evaluation. *Urology* 2003; 61(1): 60–64.
3. Kavoussi PK and Costabile RA. Orchialgia and the chronic pelvic pain syndrome. *World J Urol* 2013; 31(4): 773–778.
4. Hakenberg OW and Wirth MP. Chronic pelvic pain in men. *Urol Int* 2002; 68: 138–143.
5. Sigalos JT and Pastuszak AW. Chronic orchialgia: epidemiology, diagnosis and evaluation. *Transl Androl Urol* 2017; 6(Suppl. 1): S37–S43.
6. Davis BE, Noble MJ, Weigel JW, et al. Analysis and management of chronic testicular pain. *J Urol* 1990; 143(5): 936–939.
7. Ciftci H, Savas M, Yeni E, et al. Chronic orchialgia and associated diseases. *Curr Urol* 2010; 4: 67–70.
8. Nickel JC, Nyberg LM and Hennenfent M. Research guidelines for chronic prostatitis: consensus report from the first National Institutes of Health International Prostatitis Collaborative Network. *Urology* 1999; 54(2): 229–233.
9. Zaidi N, Thomas D and Chughtai B. Management of chronic prostatitis (CP). *Curr Urol Rep* 2018; 19: 88.
10. Doiron RC and Nickel JC. Management of chronic prostatitis/chronic pelvic pain syndrome. *Can Urol Associat J* 2018; 12: S161–S163.
11. Rottenstreich M, Glick Y and Gofrit ON. Chronic scrotal pain in young adults. *BMC Res Notes* 2017; 10(1): 241.
12. Schlegel PN and Goldstein M. Alternate indications for varicocele repair: non-obstructive azoospermia, pain, androgen deficiency and progressive testicular dysfunction. *Fertil Steril* 2011; 96(6): 1288–1293.
13. Engeler D, Baranowski AP, Borovicka J, et al. EAU guidelines on chronic pelvic pain, 2017, https://uroweb.org/wp-content/uploads/Chronic-pelvic-pain-2017-pocket.pdf (accessed Feb 2019).
14. Litwin MS, McNaughton-Collins M, Fowler FJ Jr, et al. The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic prostatitis collaborative research network. *J Urol* 1999; 162(2): 369–375.
15. Litwin MS. A review of the development and validation of the National Institutes of Health Chronic Prostatitis Symptom Index. *Urology* 2002; 60(Suppl. 6): 14–18; discussion 18–19.
16. Clemens JQ, Calhoun EA, Litwin MS, et al. Rescoring the NIH chronic prostatitis symptom index: nothing new. *Prostate Cancer Prostatic Dis* 2009; 12(3): 285–287.
17. Falahatkar S, Shahab E, Gholamjani Moghaddam K, et al. Transurethral intraprostatic injection of botulinum neurotoxin type A for the treatment of chronic prostatitis/chronic pelvic pain syndrome: results of a prospective pilot double-blind and randomized placebo-controlled study. *BJU Int* 2015; 116(4): 641–649.
18. Quallich SA and Arslanian-Engoren C. Chronic testicular pain in adult men: an integrative literature review. *Am J Mens Health* 2013; 7(5): 402–413.
19. Levine L. Chronic orchialgia: evaluation and discussion of treatment options. *Ther Adv Urol* 2010; 2(5-06): 209–214.
20. Kumar P, Mehta V and Nargund VH. Clinical management of chronic testicular pain. *Urol Int* 2010; 84(2): 125–131.
21. Tojuola B, Layman J, Kartal I, et al. Chronic orchialgia: review of treatments old and new. *Indian J Urol* 2016; 32(1): 21–26.
22. Yamamoto M, Hibi H, Katsuno S, et al. Management of chronic orchialgia of unknown etiology. *Int J Urol* 1995; 2(1): 47–49.
23. Lowe G. Extirpative surgery for chronic orchialgia: is there a role. *Transl Androl Urol* 2017; 6(Suppl. 1): S2–S5.
24. Lian F, Shah A, Mueller B, et al. Psychological perspectives in the patient with chronic orchialgia. *Transl Androl Urol* 2017; 6(Suppl. 1): S14–S19.
25. Strom KH and Levine LA. Microsurgical denervation of the spermatic cord for chronic orchialgia: long-term results from a single center. *J Urol* 2008; 180(3): 949–953.
26. Nickel JC, Siemens DR, Nickel KR, et al. The patient with chronic epididymitis: characterization of an enigmatic syndrome. *J Urol* 2002; 167: 1701–1704.
27. Tracy CR, Steers WD and Costabile R. Diagnosis and management of epididymitis. *Urol Clin Nor Am* 2008; 35: 101–108.
28. Tantawy SA, Kamel DM and Abdelbasset WK. Does transcutaneous electrical nerve stimulation reduce pain and improve quality of life in patients with idiopathic chronic orchialgia? A randomized controlled trial. *J Pain Res* 2018; 11: 77–82.
29. Malloy BJ, Price DT, Price RR, et al. Alpha1-adrenergic receptor subtypes in human detrusor. *J Urol* 1998; 160(3Pt. 1): 937–943.
30. Ishizuka O, Persson K, Mattiasson A, et al. Micturition in conscious rats with and without bladder outlet obstruction: role of spinal α1-adrenoceptors. *Brit J Pharmacol* 1996; 117: 962–966.

31. Neal DE Jr and Moon TD. Use of terazosin in prostatodynia and validation of a symptom score questionnaire. *Urology* 1994; 43(4): 460–465.
32. Lacquaniti S, Destito A, Servello C, et al. Terazosine and tamsulosin in non bacterial prostatitis: a randomized placebo-controlled study. *Arch Ital Urol Androl* 1999; 71(5): 283–285.
33. Cheah PY, Liong ML, Yuen KH, et al. Terazosin therapy for chronic prostatitis/chronic pelvic pain syndrome: a randomized, placebo controlled trial. *J Urol* 2003; 169(2): 592–596.
34. Cheah PY, Liong ML, Yuen KH, et al. Initial, long-term, and durable responses to terazosin, placebo, or other therapies for chronic prostatitis/chronic pelvic pain syndrome. *Urology* 2004; 64: 881–886.
35. Osborn D, George N, Rao P, et al. Prostatodynia—physiological characteristics and rational management with muscle relaxants. *Br J Urol* 1981; 53(6): 621–623.
36. Muthuveloe DW, During V, Ashdown D, et al. The effectiveness of varicocele embolisation for the treatment of varicocele related orchalgia. *Springerplus* 2015; 4: 392.
37. Han D-Y, Yang Q-Y, Chen X, et al. Who will benefit from surgical repair for painful varicocele: a meta-analysis. *Int Urol Nephrol* 2016; 48(7): 1071–1078.