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Original Research Article

Intralesional Injection of Verapamil for Peyronie's Disease: Experience in Indian Patients

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Abstract: Verapamil, a calcium channel blocker, is useful for the treatment of Peyronie's disease. We report our experience of intralesional injection of verapamil among Indian patients with Peyronie's disease. A total of 42 consecutive patients with Peyronie's disease were treated with intralesional injection of verapamil between September 2015 and January 2017. Patients with Peyronie's disease if suitable were offered treatment with intralesional injection of verapamil 10 mg (biweekly for 6 months). Change in plaque size, penile curvature, pain and impartment in sexual performance were assessed. Overall, the mean age was 41 years. Majority (85.7%) of patients had single plaque, 54.8% of patients had mild penile curvature. Overall, plaque size was reduced in 23 patients from 2.42 cm to 1.01 cm in length, from 1.12 cm to 0.53 cm in width and from 1.41 ml to 0.60 ml in volume. Twenty-eight patients had decrease in penile curvature and 95.23% of patients were relieved of pain during erection. Thirty-one patients reported improved quality of erection. Overall, the verapamil was well tolerated with no new safety signals. Intralesional verapamil injection reduced pain, plaque size and penile curvature in Indian patients with Peyronie's disease. Intralesional verapamil can be considered as a first-line treatment in the great majority of patients.
Keywords: Intraplaque, penile deformity, non-surgical treatment, calcium channel blocker.

INTRODUCTION

Peyronie's disease is an acquired connective tissue disease of the tunica albuginea of the corpus cavernosum, characterized by plaque or induration of the penile shaft, penile curvature, pain, and erectile dysfunction [1]. Peyronie's disease may significantly impact sexual performance and satisfaction, which may adversely affect their relationship with partner [2]. The overall prevalence of Peyronie's disease ranges from 0.39% to 13.1% in adult men [3] However, it is possible that the true prevalence may be underreported owing to hesitation or embarrassment to seek medical advice. Peyronie's disease most commonly affects males during their mid fifth to sixth decade of life; however, around 10% of patients are younger than 40 years [4]. The etiology of Personae's disease is poorly understood. Theories have suggested that penile trauma, both acute and repeated microtrauma (which occurs during intercourse), may lead to Personae's disease; however, most patients may not recall any such event. The diagnosis of Personae's disease is based on history and physical examination, followed by penile ultrasound.

The goal of Peyronie's disease treatment is to reduce plaque formation and pain, and to reduce the penile curvature. Early detection and treatment may improve functional and psychological outcomes. For mild to moderate cases, several non-surgical treatments may be considered which include pharmacological therapy, intralesional injections, radiation and devices for penile traction; however, surgery is typically reserved for patients with stable disease.

Verapamil, a calcium channel blocker, inhibits the transport of extracellular matrix proteins as collagen, fibronectin, and glycosaminoglycans. Verapamil may be useful for the treatment of acute phase of disease to stabilize the progression, reduce the size of plaque, and possibly reduce penile curvature. Several studies have evaluated the effect of verapamil in the management of Peyronie's disease [5-15]. These studies have mixed outcomes demonstrating challenges to interpret and implement them in the clinical practice. Few studies support the efficacy of intralesional verapamil in stabilizing or reducing curvature [5-9]; however, few studies did not show significant benefits [13-14]. Hence, in this paper we report our experience of intralesional injection of verapamil among Indian patients with Peyronie's disease.

METHODS

42 consecutive patients with Peyronie's disease were treated with intralesional injection of verapamil between September 2015 and January 2017 at the Department of Urology, Nil Ratan Sircar Medical College and Hospital, Kolkata. Patients with Peyronie's disease visiting at Nil Ratan Sircar Medical College and Hospital were offered, if clinically suitable, intralesional injection of verapamil. The diagnosis of Peyronie's disease was confirmed based on symptom history, physical examination, local examination, penile ultrasound (with Duplex study) to assess plaque number, size, site, presence of calcification. Additionally, sexual history was noted. Penile curvature was classified as mild (<30°), moderate (30° to 60°), and severe (>60°) according to the Kelami classification [16].

Treatment with verapamil

Each patient received biweekly injections of verapamil 10 mg into the Peyronie's plaques for 6 months (total 12 injections). Four patients received two series of injections owing to incomplete resolution of symptoms and two patients for new plaque site. The verapamil 10 mg/1 ml of plaque was injected using insulin syringe by holding the plaque between index finger and thumb. Precaution was taken not to insert the needle into the corpus cavernous, dorsal nerves and arteries. After the injection, patients were asked to compress the puncture sites for 2-5 minutes to reduce ecchymosis and/or hematoma. Blood pressure was monitored for 30 minutes after injection. Patients were asked to abstain from intercourse for 24 hours.

Assessment and analysis

Each patient was provided with Peyronie's disease self-administered questionnaire. Penile ultrasound (with Duplex study) was repeated after 6 months (after 12 injections) to assess any changes in plaque size (width, length or volume) or penile curvature. Colour Doppler USG (in selected cases) was also repeated. Resolution of plaque related symptoms and overall sexual satisfaction were noted. The pain was subjectively evaluated by patients. The data are presented using summary statistics and appropriate figures.

RESULTS

Overall, the mean age was 41 years. Three patients had Dupuytren's contracture and one patient had a positive family history of Peyronie's disease. Nine patients reported onset of disease symptoms following penile trauma during sexual intercourse. The mean (range) time between the onset of disease symptom (symptoms or curvature) and the diagnosis of Peyronie's disease was 7 months. Overall, 85.7% (n=36) of patients had single plaque, 71.4% (n=30) of patients had plaque located in the middle of the penis. A total of 54.8% (n=23) of patients had mild penile curvature followed by moderate (40.5; n=17). The mean plaque volume was 1.4 ml, 83.3% had pain during erection and 26.2% had erectile dysfunction (Table 1).

Table−1. Demographics and baseline characteristics

Parameter	Frequency N=42
Age (years), mean (range)	41 (31 – 54)
Number of plaque 1 2 3	 36 (85.7) 5 (11.9) 1 (2.4)
Plaque sites* Proximal Middle Distal	 7 (16.7) 30 (71.4) 7 (16.7)
Plaque volume (mL), mean (range)	1.4 (0.3 – 3.5)
Penile curvature Mild Moderate Severe	 23 (54.8) 17 (40.5) 2 (4.8)
Pain during erection	35 (83.3)
Erectile dysfunction	11 (26.2)
Time between the onset of disease symptom and the diagnosis of Peyronie's disease (months), mean (range)	7 (1 – 11)
Data presented as n (%), unless otherwise specified. *Not exclusive.	

Table 2 summarizes the response after 12 intralesional verapamil injections. Figure 1a shows change in plaque volume and Figure 1b shows change in penile curvature. Overall, plaque size was reduced in 23 patients from 2.42 cm to 1.01 cm in length, from 1.12 cm to 0.53 cm in width and from 1.41 ml to 0.60

ml in volume. Twenty-eight patients had mean decrease in curvature from 38.76° to 27.69° and 95.23% of patients were relieved of pain during erection. Thirty-one patients reported improved quality of erection. Overall satisfaction score was good in 29 (69.04%) patients and moderate in 9 (21.42%) patients.

Overall, the verapamil was well tolerated with no new safety issues. Pain at injection site was reported by 18 patients, nausea by nine patients and headache by 4 patients. Most of these were reported during initial injections. All these adverse events were mild and were resolved within few hours of injection.

Table−2. Summary of response after 12 intralesional verapamil injections

Parameter N=42	**Pre-treatment**	**Post-treatment**
Objective response, mean (SD)		
Plaque length (cm)	2.42 (0.20)	1.01 (0.15)
Plaque width (cm)	1.12 (0.11)	0.53 (0.10)
Plaque volume (ml)	1.41 (0.16)	0.60 (0.23)
Plaque curvature (degrees)	38.76 (4.52)	27.69 (5.18)
Subjective response, n (%)		
Decreased plaque size	-	33 (78.57)
Decreased penile curvature	-	28 (66.66)
Improved quality of erection	-	26 (61.90)
Reduction in pain during erection	-	40 (95.23)
Overall response Excellent Moderate Poor	 - - -	 29 (69.04) 9 (21.42) 4 (9.52)
Data presented as mean (SD), unless otherwise specified.		

Table−3. Comparison with other studies

	N	**Drugs**	**Dosage**	**No of injections**	**Improved curvature (%)**	**Plaque size reduction (%)**	**Pain reduction (%)**	**Improvement of sexual function (%)**
Bennet (2007) [5]	94	Verapamil	10 mg every 2 weeks	6	38	NA	84	26
Moskovic (2011) [6]	131	Verapamil	10 mg every 2 weeks	6	26	-	-	-
Heidari (2010) [9]*	16	Verapamil	10 mg every 2 weeks	6	27	27	-	20
Shirazi (2009) [14]	80	Verapamil	10 mg every 2 weeks	6	17.5	17.5	30	5
Zucchi (2010) [19]	56	Verapamil + Betamethasone	10 mg/4 mg every 2 weeks	12	51	43	100	72
Arena (1995) [20]	39	Verapamil	10 mg every 2 weeks	12	PD>1yr: 10.2 PD<1yr: 50	48.7 (softening)	90.9	-
*Improvement in % compared with pretreatment.								

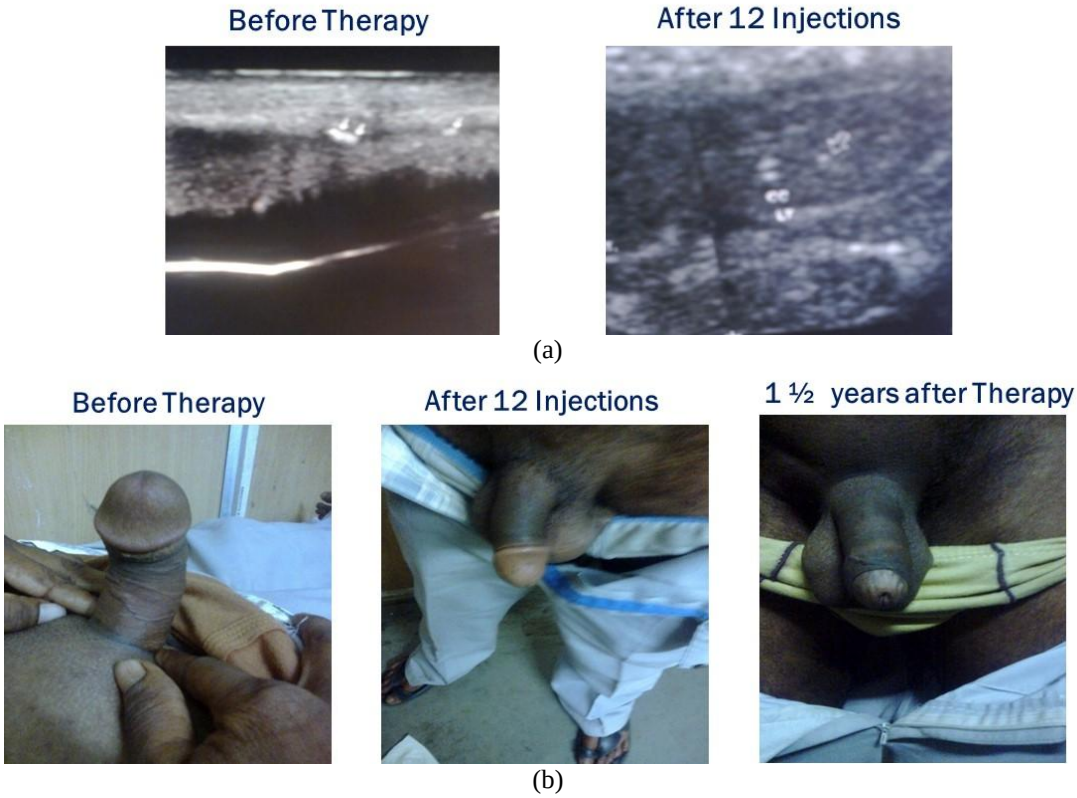

Fig-1: Change after therapy verapamil injection: (a) plaque volume and (b) penile curvature

DISCUSSION

This report of real world experience of Peyronie's disease treatment with verapamil in Indian patients demonstrated that verapamil intralesional injections significantly reduced plaque size and penile curvature. Additionally, verapamil improved the quality of erection. These results support the use of intralesional verapamil for the treatment of Peyronie's disease.

Though randomized placebo-controlled trials would be suitable for evaluating the treatment difference between verapamil and placebo or normal saline, this effort was made to examine treatment response in real world scenario in Indian patients. It may also be ethically difficult to offer a placebo or treatment that is known to have no effect in an invasive fashion in patients with Peyronie's disease. Hence, our clinical experience in real world scenario with verapamil in patients with Peyronie's disease may add significant information to the literature.

Several oral agents have been investigated for the treatment of Peyronie's disease including vitamin E, colchicine, potassium aminobenzoate, tamoxifen citrate and carnitine. However, direct intralesional injection has a long history of investigation including injections of steroids, collagenase, interferon and calcium channel blockers.

Typically, calcium channel blockers are used for the treatment off cardiac arrythmias and angina pectoris; however, the use of verapamil for the treatment of Peyronie's disease was reported in 1994.[8] Levine *et al* [8] reported a dose escalating observational study involving 14 patients with Peyronie's disease and treated with intralesional verapamil biweekly for 6 months [8]. Results showed that, more than 90% of patients had reduction in pain and More than 40% of patients had reduction in penile curvature. Later, Levine *et al.* [7, 17] conducted two more studies involving 46 patients and 156 patients and demonstrated benefits of intralesional verapamil. Since then, several studies have been conducted with mixed results of intralesional verapamil in patients with Peyronie's disease (Table 3). Our experience with verapamil supports the use of intralesional verapamil in patients with Peyronie's disease. We also observed that patients with early diagnosis or small plaque size tend to respond than patients with chronic disease and with large plaque size.

Recent American Urological Association (AUA) guideline [18], recommends that clinicians should not offer electromotive therapy with verapamil, and supports the intralesional verapamil for the treatment of patients with Peyronie's disease. Additionally, it recommends that patients should be counselled prior to beginning treatment with intralesional verapamil about potential adverse events, including penile bruising, dizziness, nausea, and pain at the injection site.

Authors acknowledge following limitations of this study. There was an inherent selection bias, that may have affected the overall conclusion of the report. Additionally, we only analysed patients who received all 12 injections, however there were few patients who opted for intralesional verapamil and received 1-2 doses but did not return for further treatment. Hence, care must be taken when generalizing these results to overall population. No comparator was a common limitation for these kinds of studies.

CONCLUSION:

Results from this study showed that intralesional verapamil injection reduced pain, plaque size and penile curvature in patients with Peyronie's disease. Intralesional verapamil treatment should be considered as a first-line treatment in the great majority of patients with Peyronie's disease having pain, curvature less than 60 degrees and have a non-calcified plaque.

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REFERENCES

1. Jalkut M, Gonzalez-Cadavid N, Rajfer J. Peyronie's Disease: A Review. Rev Urol 2003;5:142–148.
2. Smith JF, Walsh TJ, Conti SL, Turek P, Lue T. Risk factors for emotional and relationship problems in Peyronie's disease. J Sex Med 2008;5:2179–2184.
3. Bilgutay AN, Pastuszak AW. Peyronie's disease: a review of etiology, diagnosis, and management. Curr Sex Health Rep 2015;7:117–131.
4. Hussein AA, Alwaal A, Leu TF. All about Peyronie's disease. Asian J Urol 2015;2:70–78.
5. Bennett NE, Guhring P, Mulhall JP. Intralesional verapamil prevents the progression of Peyronie's disease. Urology 2007;69:1181–1184.
6. Moskovic DJ, Alex B, Choi JM, Nelson CJ, Mulhall JP. Defining predictors of response to intralesional verapamil injection therapy for Peyronie's disease. BJU Int 2011;108:1485–1489.
7. Levine LA, Goldman KE, Greenfield JM. Experience with intraplaque injection of verapamil for Peyronie's disease. J Urol 2002;168:621–625. Discussion 625-626.
8. Levine LA, Merrick PF, Lee RC. Intralesional verapamil injection for the treatment of Peyronie's disease. J Urol 1994;151:1522–1524.
9. Heidari M, Nejadi JR, Ghate A, Delfan B, Iran-Pour E. Evaluation of intralesional injection of verapamil in treatment of Peyronie's disease. J Pak Med Assoc 2010; 60:291–293.
10. Di Stasi SM, Giannantoni A, Stephen RL, Capelli G, Giurioli A, Jannini EA, Vespasiani G. A prospective, randomized study using transdermal electromotive administration of verapamil and dexamethasone for Peyronie's disease. The Journal of urology. 2004 Apr 30;171(4):1605-8.
11. Greenfield JM, Shah SJ, Levine LA. Verapamil versus saline in electromotive drug administration for Peyronie's disease: a double blind, placebo controlled trial. J Urol 2007; 177:972–975.
12. Di Stasi SM, Giannantoni A, Capelli G, Jannini EA, Virgili G, Storti L, Vespasiani G. Transdermal electromotive administration of verapamil and dexamethasone for Peyronie's disease. BJU international. 2003 Jun 1; 91(9):825-9.
13. Rehman J, Benet A, Melman A. Use of intralesional verapamil to dissolve Peyronie's disease plaque: a long-term single-blind study. Urology 1998; 51:620–626.
14. Shirazi M, Haghpanah AR, Badiee M, Afrasiabi MA, Haghpanah S. Effect of intralesional verapamil for treatment of Peyronie's disease: a randomized single-blind, placebo-controlled study. Int Urol Nephrol 2009; 41:467–471.
15. Chung E, Garcia F, Young LD, Solomon M, Brock GB. A comparative study of the efficacy of intralesional verapamil versus normal saline injection in a novel Peyronie disease animal model: Assessment of immunohistopathological changes and erectile function outcome. J Urol 2013;189:380–384.
16. Kelâmi A. Classification of congenital and acquired penile deviation. Urol Int 1983;38:229–233.
17. Levine LA. Treatment of Peyronie's disease with intralesional verapamil injection. J Urol 1997; 158:1395–1399.
18. Nehra A, Alterowitz R, Culkin DJ, et al. Peyronie's Disease: AUA Guideline. J Urol 2015; 194:745–753.
19. Zucchi A, Perovic S and Costantini E. Intra-plaque injection of betamethasone and verapamil using a new plunger mechanism syringe with ergonomic leverage handling for the treatment of Peyronie's disease. J Androl Sci 2010; 17:23–29.
20. Arena F, Peracchia G, Di Stefano C, Passari A, Larosa M, Cortellini P. Clinical effects of verapamil in the treatment of Peyronie's disease. Acta Biomed Ateneo Parmense 1995; 66:269–272.