

# Effect of intralesional verapamil for treatment of Peyronie's disease: a randomized single-blind, placebo-controlled study

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## Abstract

**Purpose** We aimed to assess the effect of intralesional verapamil on the treatment of Peyronie's disease.

**Materials and methods** This randomized study involved 80 patients. First, they were divided into two groups. The first group (case: 40 patients) received intralesional verapamil and the second group (control: 40 patients) local saline injection. They were followed about 24 weeks and evaluated for the size of plaques, plaque softening, reduction of pain and amelioration of penile deformity and erectile dysfunction (estimated by the International Index of Erectile Function) before and after treatment.

**Results** Reduction of plaque size was seen in 17.5% of the case group and 12.8% of the control group ( $P: 0.755$ ). Pain was reduced in 30% of the case group and 28.2% of the control group ( $P: 0.99$ ). Curvature was decreased in 17.5% of the case group and 23.1% the control group ( $P: 0.586$ ). Plaque softening was seen in 30% of the case group compared with 25.6% improvement in the control group ( $P: 0.803$ ). Also we found 5% and 2.6% improvement in sexual dysfunction in the case and control groups, respectively. ( $P: 0.985$ ).

**Conclusion** Although in some studies verapamil has been found to be effective in the treatment of Peyronie's disease, we did not find any improvement in comparison with the control group. Furthermore, larger scale studies are warranted to assess the effect of this drug on the treatment of Peyronie's disease.

**Keywords** Peyronie's disease · Intralesional injection · Verapamil

## Introduction

Peyronie's disease (PD) is a localized connective tissue disorder that affects the tunica albugina of the penis. The result is bending and deformity of the erected penis, difficulty in vaginal penetration and change in erectile capacity [1, 2].

This disease was first described in 1743 by the French surgeon, Francois de la Peyroni. According to multivariate logistic regression analysis, the risk factors for PD are: a history of genital and/or perineal injuries, transurethral prostatectomy, cystoscopy, diabetes mellitus, hypertension, lipoma, drugs such as propranolol, Dupuytren's contracture, smoking and alcohol consumption [3].

While PD was once considered to be relatively uncommon, recent studies suggest that its prevalence is similar to that of diabetes or urolithiasis. A recent epidemiological study reported an overall prevalence of 3.2% [4, 5].

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While severe penile deformity and erectile dysfunction are best treated with surgery, numerous oral and intralesional drugs have been used to resolve pain, minimize penile deformity and arrest progression of disease [6–8].

The use of verapamil, a calcium antagonist, is based on its ability to alter fibroblast production of extracellular matrix, macromolecules and collagenase [9–11]. In some studies, verapamil has been shown to be safe and effective in the treatment of Peyronie's disease [12–14]. Previously, in a pilot study, no improvement was found after verapamil therapy; thus, this study was conducted to ascertain the role of this drug in the treatment of Peyronie's disease.

## Materials and methods

Between March 2002 and October 2005, 80 patients were enrolled in this prospective, single-blind study. The sample size was measured by a statistician considering previous studies. Inclusion criteria were: (1) patients who had Peyronie's disease as defined by the presence of a palpable plaque upon examination by the same urologist (M.S.); (2) patients who underwent a full course of therapy.

Exclusion criteria were: (1) any history of exposure to oral agents for the treatment of Peyronie's disease (such as potassium para-aminobenzoate, colchicines and tamoxifen), transdermal verapamil, shock wave therapy or prior intralesional agents within 3 months; (2) patients with calcified plaques; (3) patients who had ventral curvatures; (4) patients who had congenital penile curvature or chordee with hypospadias.

Patients were informed about the nature of disease and the available treatment modalities. Full written consent was obtained before enrollment. We randomized the patients according to a computer-generated random table in two groups: case and control. Patients were blinded to the group to which they belonged. The sonographer was also blinded to the treatment group to which the patients belonged.

### Injection technique

At first, dorsal nerve penile block using 1% lidocaine was done. After grasping the plaque between the index finger and thumb, verapamil (10 mg diluted in

**Table 1** Demographic characteristics in patients

	Case	Control	<i>P</i> value
Mean age (years)	57.20 ± 14.40	55.10 ± 11.22	0.98
Time to onset (months)	20.60 ± 4.2	22.00 ± 4.8	0.99
Mean plaque size (cm <sup>2</sup> )	3.20 ± 0.4	3.40 ± 0.9	0.95

10 ml of distilled water) was injected into the plaque with a 10-ml syringe and a 25-gauge needle twice weekly for 12 weeks. Patients had postinjection blood pressure measurements. Precaution was taken not to insert the needle into the corpus cavernosum, dorsal nerves and arteries. The patients were asked to compress the injection site for 5 min to decrease echymosis. The same procedure was performed for patients in the control group with saline (10 ml).

The evaluation was based on the medical history, physical examination, ultrasonography and IIEF questionnaire.

Erectile dysfunction severity is classified into five categories based on the IIEF-5: severe (5–7), moderate (8–11), mild to moderate (12–16), mild (17–21) and no ED (22–25). All of the first four categories were considered as the ED group.

The plaque size was measured by ultrasonography. The pain was subjectively self-evaluated by patients.

Penile deformity was assessed with a protractor at maximum rigidity, and improvement of curvature was defined as an objectively measured curvature of at least 10°. Plaque softening as a subjective datum was recorded by querying the patient about its improvement. The patients were evaluated before and 24 weeks after treatment.

Statistical analysis was done using chi-square and paired test. *P* values <0.05 were considered significant.

## Results

There were no statistically significant differences between the groups in age, onset of the disease, initial plaque size, signs and symptoms (Tables 1 and 2).

The mean curvature at baseline was  $49.71^\circ \pm 9.3^\circ$  and  $45.57^\circ \pm 9.7^\circ$  in the case and control groups, respectively. The mean plaque area (maximum length × maximum width) was  $3.20 \pm 0.4$  and

**Table 2** Signs and symptoms in case and control groups

	State	N case (%)		N control (%)		P value
Pain	Yes	21 <sup>a</sup>	52.5	23 <sup>b</sup>	57.5	0.822
	No	19	47.5	17	42.5	
Curvature	Yes	23	57.3	24	61.5	0.820
	No	17	42.5	15	38.5	
Erectile dysfunction	Yes	18 <sup>c</sup>	45	20 <sup>d</sup>	51.3	0.739
	No	22 <sup>e</sup>	5%	19 <sup>f</sup>	48.7	

<sup>a</sup> The mean score was 3.95

<sup>b</sup> The mean score was 4.05

<sup>c</sup> The mean IIEF score was 15.25

<sup>d</sup> The mean IIEF score was 15.05

<sup>e</sup> The mean IIEF score was 23.65

<sup>f</sup> The mean IIEF score was 23.64

$3.4 \pm 0.9 \text{ cm}^2$  in the case and control groups, respectively.

One man dropped out of the case group after the first visit without completing other data, such as curvature and erectile dysfunction assessment. Other patients underwent the full course of treatment.

At the follow-up visit, 24 weeks after treatment, the mean curvature at baseline was  $47.57^\circ \pm 7.3^\circ$  and  $43.43^\circ \pm 8.9^\circ$  in the case and control groups, respectively. The mean plaque area (maximum length  $\times$  maximum width) was  $2.89 \pm 0.39$  and  $3.02 \pm 5.7 \text{ cm}^2$  in the case and control groups, respectively. We compared these data before and after treatment in the case and control groups using the paired test. No significant changes were seen ( $P$  value = 0.91 and 0.87 for mean curvature and plaque size, respectively).

An at least  $5^\circ$  decrement in curvature, any decrement in plaque size or ED severity based on IIEF-5 was considered as improvement.

Any subjective improvements of pain or plaque softening were considered as positive response (Table 3).

## Discussion

Peyronie's disease frequently develops in response to acute or repeated trauma to an erected penis with microvascular injury and fibrin deposits, leading to recruitment and activation of inflammatory cells, followed by matrix formation and development of fibrotic plaque [15].

**Table 3** Represents the results of this study. Outcome of management in case and control groups

	Improvement	N case (%)		N control (%)		P value
Pain	Yes	12	30	11	28.2	0.99
	No	28	70	28	71.8	
Decrease of curvature	Yes	7	17.5	9	23.1	0.586
	No	33	82.5	30	76.9	
Decrease of plaque size	Yes	7	17.5	5	12.8	0.755
	No	33	82.5	34	87.2	
Plaque softening	Yes	12	30	10	25.6	0.803
	No	28	70	29	74.4	
Erectile dysfunction	Yes	2	5	1	2.6	0.99
	No	38	95	38	97.4	

A number of oral agents have been investigated for the treatment of PD [16].

Vitamin E was the first oral therapy to be described for this condition [17]. The other agents that have been advised are colchicine (0.6 mg three times per day with meals), potassium aminobenzoate (12 g/day, four to six doses), tamoxifen citrate (20 mg twice a day) and carnitine (1 g twice daily) [18–21].

Direct injection of an agent into the Peyronie's lesion has an extensive history of investigation [12]. Steroids, collagenase, interferon and verapamil have been used [12].

A number of surgical procedures, such as the Nesbit-type operation plaque excision and dermal grafting, plaque incision and grafting and penile prosthesis have been tried [22–26].

One of the intralesional treatments that has been investigated several times is verapamil [14]. Anecdotal evidence shows some lessening of the scarring process after intralesional injections of a calcium channel blocker. The theory is based on the known action of verapamil in decreasing the production and secretion of extracellular matrix macromolecules by fibroblasts while increasing collagenase production in the same area. Calcium channel blockers significantly decreased both the constitutive and platelet-derived growth factor B-dependent collagen deposition in the ECM formed by human vascular smooth muscle cells and fibroblasts. The drugs inhibited the expression of fibrillar collagens type I and III and of basement membrane type IV collagen. Furthermore, Ca<sup>2+</sup> channel blockers specifically increased the proteolytic

activity of the 72-kDa type IV collagenase as shown by gelatin zymography and inhibited the transcription of tissue inhibitor of metalloproteinases-2 [11].

The use of verapamil as an intralesional injection was first reported by Levine et al. in 1994. In this non-controlled study, 14 men received biweekly injections of verapamil into the Peyronie's plaques for 6 months. Subjectively, there was significant improvement in plaque-associated penile narrowing in all patients and curvature in six (42%). Objectively, a decreased plaque volume of >50% was noted in four (30%) of the subjects. Plaque softening was noted in all patients, while 12 (83%) noticed that plaque-related changes in erectile function had improved [14].

In Di Stasi et al.'s prospective study, 96 patients were randomized to be treated with verapamil (5 mg) plus dexamethasone (8 mg) using transdermal electromotive administration. A 43% improvement in plaque size and curvature was noted [27].

Levin et al. published results of another non-placebo-controlled trial involving 156 men treated with intralesional verapamil therapy. Of 128 men who completed the study, 84% of those with pain had complete resolution [28]. But in the present study, the case and control patients did not differ significantly in response to treatment, although curvature change was relatively more compared with the other symptoms.

Sahin et al. evaluated the antifibrotic effect of verapamil and different intracavernosal agents on the corpus cavernosum. It was insufficient to prevent inflammation [29].

Bennett et al. also tried intralesional verapamil injection therapy in men with Peyronie's disease and found no statistically significant improvement in penile curvature, although the vast majority of patients reported that penile pain resolved after therapy [30].

It is not known why the response rate in our study is so different from that in others. We postulate many possibilities. First, most of the patients were referred to us after complete plaque formation. When we compare this latency with other studies (<18 months), it is significant. Medical and intralesional therapies are clinically and pathologically effective in early stages of the disease, before totally involving the tunica albuginea with plaque and scarring. Second, the size of plaques was larger in our study compared to that in other studies (<2 cm in other studies compared to 3 cm

in our study) [29], so it is more difficult to achieve complete drug distribution by injection to this large, hardened plaque tissue.

Many limitations warrant mention, such as the single blindness of this study, the small number of the patients and the short-term follow-up.

## Conclusion

Based on our study, intralesional verapamil is not effective in the treatment of Peyronie's disease. No statistically significant improvements were seen in pain, ED, penile curvature, plaque size and softening.

Thus, we recommend other larger, double-blind controlled trials to assess the effect of this drug in the setting of Peyronie's disease.

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