e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2024; 14(1); 226-230

Original Research Article

A Hospital Based Prospective Comparative Assessment of the Efficacy of Oral Verapamil versus Intralesional Verapamil Injection in Patients of Peyronie's Disease

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Received: 12-10-2023 / Revised: 24-11-2023 / Accepted: 18-12-2023

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Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to compare the efficacy of oral verapamil versus intralesional verapamil injection in patients of Peyronie's disease.

Methods: The present study was conducted at department of Urology, Rajendra Institute of medical sciences (RIMS), Ranchi, Jharkhand, India for one year and 40 patients were randomly divided into two groups (20 in each group). None of the 40 patients lost to follow up. Patients in group I received oral verapamil and group II patients received intralesional verapamil injection.

Results: A total of 40 patients were enrolled in this prospective study. The median of the duration of PD was 3 months in both groups (range 1–6). Of the 40 patients randomised, 20 and 20 subjects in the group I and in the group II, respectively, completed the study protocol. No statistically significant differences emerged between groups at baseline. At baseline, moreover, no significant difference emerged in terms of plaque size and penile curvature when comparing patients with and without comorbidities. At 3-month follow-up, plaque size decreased by -1.60 mm (IQR=1.60–2.10 mm) in Group I and -1.20 mm in Group II, showing no statistically significant differences between the 2 treatment schedules (p=0.10). As regards penile curvature, it decreased by -9.40° (IQR=4.50°–13.00°) in group I and -4.55° (IQR=2.50°–7.50°) in Group II (p<0.01). The median difference between pre- and post-treatment IIEF-15 was 1.0 (95% confidence interval [CI]=1.12–1.94) in Group I and 0.0 (95% CI=-0.04–0.14) in Group II (p<0.05), while the zmedian difference for VAS score was -4.0 (95% CI=-4.11–-3.65) in Group I and -1.0 (95% CI=-0.50–2.01) in Group II (p<0.05).

Conclusion: Verapamil injections seem to provide an effective minimally invasive option in the acute phase of PD and might have the potential to lower penile pain and ameliorate IIEF, as compared with other intralesional agents.

Keywords: Verapamil, Plaque, Peyronie's Disease, Intralesional Injection.

Introduction

Peyronie's disease (PD) is defined as a chronic benign condition characterised by the formation of localized fibrous inelastic scars at the level of the tunica albuginea of the penis. This condition can lead to penile curvature, painful erections and erectile dysfunction (ED). PD is believed to affect 3% to 9% of the male population, with a higher prevalence among patients suffering from ED, diabetes and cardiovascular disease. [1-4] PD presents 2 different phases: active or acute and stable or chronic. It is paramount to distinguish between acute and chronic phase of the condition, since management is different in the 2 phases. Plaque formation and calcification generally take place during the acute phase [5,6], which can last for up to 18 months. [7] In the chronic phase, penile pain will be reduced, and penile deformity stabilized. Transition to the chronic phase is defined when curvature remains stable for at least 3 months. [8] Treatment of PD includes both medical and surgical approaches and the management is tailored to the phase of the disease, the degree of deformity, the quality of the erections and patient's choice. [9,10]

Many therapeutic approaches have been mentioned in the medical literature since de La Peyronie's description of in duration penis plastic a. Surgical as well as nonsurgical options are available.

Nonsurgical therapy involves extracorporeal shockwave therapy, radiotherapy, iontophoresis, oral agents such as vitamin E, colchicine, tamoxifen, Potaba and intraplaque injection of compounds including collagenase, steroids, Orgotein, interferon alpha 2B and verapamil. Currently, intralesional injections of corticosteroids and verapamil represent the most common treatments offered for the management of acute phase of PD. [10,11]

Injection of pharmacologically active agents directly into penile plaques represents another treatment option as it allows a localised delivery of a particular agent that provides higher concentrations of the drug inside the plaque. The rationale for intralesional use of verapamil (a calcium channel blocker) in patients with Peyronie's disease is based on in vitro data that demonstrated transport of extracellular matrix molecules, which included collagen, fibronectin and glycosaminoglycans as a calcium- dependent process, along with a concomitant increase in collagenase activity, a modification of the inflammatory response in the early phase of the disorder and the inhibition of fibroblast proliferation in the plaques. [12]

The aim of the present study was to compare the efficacy of oral verapamil versus intralesional verapamil injection in patients of Peyronie's disease.

Materials and Methods

The present study was conducted at department of Urology, Rajendra Institute of medical sciences (RIMS), Ranchi, Jharkhand, India for one year and 40 patients were randomly divided into two groups (20 in each group). None of the 40 patients lost to follow up. Patients in group I received oral verapamil and group II patients received intraplaque verapamil injection. Results from both the groups were compared in terms of change in plaque size, pain, penile curvature and sexual life.

The patients were evaluated by detailed history (including enquiry about sexual and erectile dysfunction) and physical examination. Plaque length was measured by calipers and color Doppler was done to confirm the size and volume of plaque. All the patients were followed for a period of 3 years.

Inclusion Criteria

1. Age range 25 to 75 years.
2. Clinical evidence of Peyronie's disease (plaque/pain/curvature)
3. Duration of symptoms for at least 1 year.

Exclusion Criteria

1. Any history of previous treatment for Peyronie's disease.
2. Patient on calcium channel blocker therapy for some other reasons.

Technique- Group I patients were advised to take oral verapamil 40 mg daily for 6 months.

Group II penile blockage was given with 2% lidocaine. The verapamil was injected into the plaque with an insulin syringe. Punctures were done in plaque at appropriate places to distribute the drug uniformly throughout the plaque. Instillation was done by fanning technique. The verapamil was injected as 20 mg in 2 mL (1 mg/0.1 cc) weekly for 6 weeks- cycle was repeated after 6 months. The injection site was compressed for 10 minutes to prevent haematoma formation. Blood pressure and heart rate were continuously monitored throughout the procedure. No systemic or local toxicity was noted except for mild ecchymosis in 2 patients. The needle was inserted into the dorsolateral or lateral side depending up on the location of plaque to prevent nerve injury.

Results

Table 1: Baseline characteristics of subjects

	Group I	**Group II**
Age, yr, mean (±SD)	51.4 ±10.5	53.0 ±11.9
Comorbidities N%		
Smoking habit	8 (40)	9 (45)
Hypertension	9 (45)	10 (50)
Dyslipidaemia	4 (20)	3 (15)
Diabetes	4 (20)	4 (20)
Plaque volume, cm3, mean (±SD)	1.72 ± 0.48	1.75 ±0.45
Plaque position, n,%	15	15
Dorsal	6 (40)	5 (33.34)
Lateral	7 (46.66)	9 (60)
Ventral	2 (13.34)	1 (6.66)
Penile curvature (°)	35.0 (25.0–45.0)	35.0 (27.0–48.0)
Plaque size (mm)	10.40 (7.50–13.4)	11.20 (8.50–14.30)
IIEF-15 score	20.0 (18.0–22.0)	19.0 (16.0–23.0)
VAS score	4.0 (4.0–5.0)	4.0 (4.0–5.0)

A total of 40 patients were enrolled in this prospective study. The median of the duration of PD was 3 months in both groups (range 1–6). Of the 40 patients randomised, 20 and 20 subjects in the group I and in the group II, respectively, completed the study protocol. No statistically significant differences emerged between groups at baseline. At baseline, moreover, no significant difference emerged in terms of plaque size and penile curvature when comparing patients with and without comorbidities.

Table 2: Mean changes of primary outcomes between groups from baseline to final follow-up

	Group I	Group II	P-value
Plaque size (mm)	-1.60 (1.60–2.10)	-1.20 (0.80–1.30)	0.12
Penile curvature (°)	-9.40 (4.50–13.00)	-4.55 (2.50–7.50)	<0.01
IIEF-15 score	1.0 (1.12–1.94)	0.0 (-0.04–0.14)	<0.05
VAS score	- 4.0 (-4.11–-3.65)	-1.0 (-0.50–2.01)	<0.05

At 3-month follow-up, plaque size decreased by -1.60 mm (IQR=1.60–2.10 mm) in Group I and -1.20 mm in Group II, showing no statistically significant differences between the 2 treatment schedules (p=0.10). As regards penile curvature, it decreased by -9.40° (IQR=4.50°–13.00°) in group I and -4.55° (IQR=2.50°–7.50°) in Group II (p<0.01). The median difference between pre- and post-treatment IIEF-15 was 1.0 (95% confidence interval [CI]=1.12–1.94) in Group I and 0.0 (95% CI=-0.04–0.14) in Group II (p<0.05), while the zmedian difference for VAS score was -4.0 (95% CI=-4.11–-3.65) in Group I and -1.0 (95% CI=-0.50–2.01) in Group II (p<0.05).

Discussion

Peyronie's Disease (PD) is a disfiguring and psychologically devastating localised connective tissue disorder of the penis. It may cause formation of plaque, penile deformity, pain, erectile dysfunction, penile shortening, indentation, hourglass deformity of penis and emotional stress. Treating a patient of PD still poses a dilemma and frustrating situation for the practicing urologist till date. Since, it is a localised disease, a focal therapy appears to be most appropriate. Additionally, the patients are not easily convincible to undergo penile surgery. Although surgery remains the gold standard treatment option for patients with stable PD, it is not recommended for men in the active phase. On the other hand, collagenase clostridium histolyticum (CCH) represents the only licensed drug for the minimally invasive treatment of PD [13,14], however the acute phase of PD is not currently an indication for CCH therapy. [2,15]

A general explanation of PD pathogenesis, which has gained acceptance, is the abnormal response to endogenous factors such as tumour growth factor-beta (TGF-b), which are released in response to repeated microtrauma in genetically susceptible individuals. These mechanisms can lead to biological transformation of cells within the tunica albuginea, cell cycle dysregulation, genotypic changes and increased expression of cytokines and free radicals. Consequently, the inflammatory response determine an unregulated extracellular matrix deposition including fibronectin and collagen, and ultimately plaque formation, which does not appear to undergo proper scar remodelling, leaving an inelastic segment in the involved tunica albuginea. [16]

Pathology involved behind PD is still unclear, but studies show that it is a wound-healing disorder occurring in a genetically susceptible individual whose tunica albuginea responds inappropriately to an inciting event, most commonly trauma (silent microfracture) leading to a proliferative fibrotic reaction resulting in formation of plaque and persistent scar. [17,18] PD plaque does not resolve due to absent or malfunctioning metalloproteinase and/or elevated levels of tissue inhibitors of metalloproteinase (TIMPs). [18] Resultant fibrous scar causes multiple deformities of the penis including curvature, narrowing, indentation, hinging, loss of penile length, pain, psychological distress and sexual dysfunction. [19,20] Non-surgical treatment should be considered in the active phase (progressive deformity with painful erections) of the disease (less than 12 months from onset). Surgery is the gold standard treatment once the disease process is stable. Informed consent for any PD treatment must be taken as these patients are both physically and psychologically devastated. Urologist's aim is to make the penis functionally straight without compromising rigidity.

There is paucity of studies investigating the clinical benefits of oral therapy for PD, but the published placebo-controlled trials show that there is no evidence of benefit with the use of oral vitamin E, Potaba, colchicine, tamoxifen, carnitine or omega-3 fatty acids. [21,22] Injection therapy has also been used for many years starting with intralesional steroid injection. Intralesional verapamil shows decreased Peyronie's disease-derived fibroblast proliferation and decreased extracellular matrix production in vitro. [23-25] Nine non-controlled published trials of intralesional verapamil showed consistently that 30% to 60% of patients had measured reduction of curvature when the subject was used as his own control with a mean reduction

of curvature in the responder group being between 15 to 30 degrees. [22]

In 2007, Grasso et al [26] followed 110 patients for 6 years and reported 68% of younger patients (<50 years old) versus 31.5% of older patients (>50 years old) experienced progression of penile curvature with more patients in the older subgroup experiencing resolution of pain (69% vs. 20%). This was contradicted by Berookhim et al [27] who reported 176 men with uniplanar curvature on conservative management and were followed for >12 months. 67% experienced no change in penile curvature, 12% improved with a mean of 27° change and 21% worsened (mean change of angulation of 22°). These studies suggest that although pain from Peyronie's disease is often self-limiting, the clinical course of penile curvature is less predictable and needs treatment to prevent worsening loss of sexual function.

Conclusion

Verapamil injections seem to provide an effective minimally invasive option in the acute phase of PD and might have the potential to lower penile pain and ameliorate IIEF, as compared with other intralesional agents. Most of the patients are understandably hesitant to pursue surgery and are willing to undergo the repeated injections to achieve a less invasive approach to their deformities. Verapamil is appropriate for less stable disease and in softer plaques. The best results are seen when patients comply with manipulation of the plaque via a combination of stretching, gentle bending of the erect penis in the opposite direction of the curve and massage of the plaque. Further prospective studies with higher statistical power and larger cohorts will be required to confirm our preliminary findings.

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