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Original Research Article.

Intralesional Verapamil for the Treatment of Peyronie's Disease: A Prospective Study

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ABSTRACT

Background: Peyronie's disease is an inflammatory, fibrotic penile disorder affecting men in age range of 19-83 years. It occurs as an acute or chronic phase and rarely cases resolve on their own. Several treatment options are available including oral, intralesional and surgery. Although several clinical trials have been performed, they lack significant and corroborated results hence there is a need to attempt prospective research to elucidate the most effective therapies. The aim of this study is to determine the efficacy of intralesional injection of verapamil over normal saline.

Methods: This was a randomized parallel group study conducted between March 2013 and February 2017 which randomized patients with Peyronie's disease into two groups to receive verapamil or normal saline intralesional injections, with inclusion criteria of penile curvature with or without plaque. After 6 biweekly injections, all above parameters and satisfaction score was reexamined. Patients were evaluated by history, physical examination, questionnaire, ultrasonography and color Doppler study of the penis.

Results: A total of 53 patients were enrolled (verapamil, n=28; control, n=25). Overall, among verapamil group attenuated curvature, erectile dysfunction and reduced plaque size were found in 82%, 64.2%, 67.8% of and 60.7of patients respectively. Pain decreased in both groups considerable to 97% and 91%. Overall satisfaction level was higher in verapamil group that is82% to control group of 40%.

Conclusion: Intralesional verapamil is a good treatment choice with absence of invasive procedures and overall good success rate and patient acceptability.

Keywords: Intralesional, Plaque, Penile Curvature.

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INTRODUCTION

Peyronie's disease (PD) is penile inflammatory disorder associated with plaque formation, erectile dysfunction and anatomical deformity that affects the quality of life of men and their partners as well. The pathophysiology of this disorder is least understood. Multiple treatment options like oral therapies include potassium aminobenzoate, vitamin E, colchicine, carnitine, pentoxyfylline, omega 3 fatty acids and intralesional treatments comprise of steroids, calcium channel blockers, interferons, collagenase clostridium histolyticum and stem cells are available.[1] The therapy for PD depends on the disease severity, patient preference and physician's expertise. European Medical Association has classified potassium aminobenzoate as 'possibly effective' oral agent for treatment of PD. According to USFDA, potassium aminobenzoate was the most commonly prescribed oral therapy, although the review presented by Sullivan et al (2015), only 10% chose it as first line and 9% patients utilized intralesional agents as first-line therapy with verapamil being the most common first choice (67%).[2] These treatments have not shown much improvement in the pain, plaque size and penile curvature. Surgery is another option in advanced disease accompanied by functional impairment but patients are reluctant to have invasive treatment methods which may lead to loss of penis length.[3,4]

Some novel methods of treatment like extra-corporeal shockwave therapy, radiotherapy, iontophoresis have been introduced.[5] Although, various surgical and non-surgical methods of treatments, each with their own pros and cons are existing the urologists are struggling with its treatment modalities. Numerous trials have been done till date to determine the significant benefits and obtain data in the treatment of PD. The most recommended option is FDA-approved intralesional injections of collagenase clostridium histolyticum (CCh). This is an expensive medication,

moderately efficacious for men with chronic phase rather than acute phase.[6,7] Usually CCH causes adverse events, including penile ecchymosis, swelling, pain, and corporal rupture.[8] Amighi et al (2019) reported a modified injection procedure, named the 'fan' technique, for the treatment of PD. The study enrolled 152 patients who received 1323 injections and the results showed that fan reduced procedural morbidity but bruising or swelling were reported. Further clinical studies are essential to validate these results.[9]

Verapamil is a calcium channel blocker that was first presented in 1994 for PD. It was introduced in the therapy for PD due to the fact that enhances growth of urothelial cells and decrease collagen III production by both urothelial and smooth muscle cells and anti-inflammatory action. Intralesional injection causes plaque to dissolve thus reducing its size and improving penile curvature.[10] In addition, it affects cytokine expression associated with the early phases of wound healing and inflammation, including platelet-derived growth factor-BB, interleukin-6, and interleukin-8.[11] A total of nine studies involving verapamil drug were performed, of which 7 were randomized and only two were prospective non-randomized. Only one study by Rehman et al (1998) demonstrated that verapamil compared with normal saline was reasonable in some selected patients for the treatment of PD with non-calcified plaque and penile angulation of less than 30°.[12,13]

Transdermal verapamil (verapamil hydrochloride 15 % gel) has been reported by Fitch et al (2007) to be useful in the treatment of Peyronie's Disease. This study evaluated topically applied verapamil hydrochloride 15% gel which proved to be effective in eliminating pain, decreasing plaque size and curvature, and improving erection quality in patients.[14] Favilla et al (2014) evaluated the efficacy of intralesional verapamil injection with oral antioxidants compared with ILV monotherapy in patients with early onset of PD at 12-week follow-up. Significant improvement was observed in plaque size, penile curvature, visual analogue score, IIEF-15 and IIEF-15 subdomains change in both groups.[15] Comparatively verapamil is cheaper and has superior outcome for deformities with mild curvature.

Although PD was identified many years back, there are still large discrepancies in knowledge and management approaches. Prospective clinical studies are needed to elucidate standardized management guidelines and a more cohesive strategy to manage this common disease. Various studies have been done using intralesional verapamil till date but has created data that is very frail for substantiate verapamil use. The objective of this study was to evaluate the role of intralesional verapamil in patients of PD.

METHODS

This was a randomized parallel group study conducted between March 2013 and February 2017 which included patients with PD. Patients were randomized (1:1) into two groups to receive 12 injections of 10 mg intralesional verapamil (biweekly) or normal saline (NS).

The study protocol was approved by the institutional ethics committee. The study was conducted in accordance with the principles that have their origin in the Declaration of Helsinki. Written informed consent was obtained from each patient for participation in the study.

The patients satisfying inclusion criteria of penile curvature with or without plaque and discontinuation of any previous oral or other medication for Peyronie's disease for at least 3 months were enrolled for the study. The exclusion criteria involved patients with calcified plaque, penile curvature more than 60-degree, history suggestive of fracture penis and any history of calcium channel blocker therapy or therapy interfering with calcium channel blockers.

Patients were evaluated by history, physical examination, questionnaire, ultrasonography and color Doppler study of the penis. Photographs of the penis were taken to compare the curvature of the penis before and after the treatment. Color Doppler ultrasonography was also repeated after completion of the treatment schedule. Severity of erectile dysfunction was decided by scoring system based on questionnaire of IIEF-5.

Injection Technique

A dose of 10mg of verapamil diluted with normal saline was injected into the Peyronie's plaque using 25-gauge needle in test group and normal saline was injected in control group. A smaller gauge needle is not recommended because of risk of needle fracture. The plaque was grasped between index finger and thumb, and skin puncture performed. The needle was then passed in the plaque while leaving the drug within the needle tracts. In men with large plaques, the needle was removed and the process was repeated.

After the completion of injection, patient was asked to lightly compress the penis with both thumbs over the puncture sites to reduce the likelihood of ecchymosis and hematoma. Each patient's blood pressure was monitored for 30 minutes after drug injection. No significant complication like fall in blood pressure, significant hematoma was noted in any patient.

Data Analysis

The data were analyzed using SPSS statistical software (version 23). The data was obtained after the completion of study by direct interview, physical examination, and measurement of plaque length. The patients were evaluated for resolution of pain, decrease in curvature of penis, improvement in erectile dysfunction, increase in penile girth decrease in plaque size.

RESULTS

A total of 53 patients were enrolled in the study of which 28 (52.83%) patients were randomized to verapamil group and 25 (47.17%) to the control group. Period of follow-up ranged from 6 months to 24 months (mean follow-up period was 14 months). The overall median age of the patients was 52 years and the age ranged between 32 years and 65 years. Table 1 demonstrates plaque characteristics in verapamil and control group. The majority (>=75%) of patients in both groups had plaque on the dorsal side of the penis, and more than half of the patients in both the groups had plaque on the proximal penis. More than 85% of patients in both the groups had single plaque and >40% of patients had plaque size <2 cm. Overall, both the groups were comparable including curvature, erectile dysfunction and plaque (Table 2).

Table 3summarizes the overall response of patients to verapamil intralesional injection. There was a significant improvement in patient satisfaction, curvature of penis, erectile function and reduction in plaque size in patients who received verapamil. Pain decreased in both the groups considerable (97% and 91%, in verapamil and control groups, respectively). Overall satisfaction was higher in verapamil group (82%) than control group (40%).

Table 1: Baseline plaque characteristics

Parameters	Verapamil (N=28)	Control (N=25)
Site		
Dorsal	21 (75.0)	19 (76.0)
Lateral	7 (25.0)	6 (24.0)
Location		
Proximal penile	15 (53.6)	13 (52.0)
Mid penile	8 (28.6)	7 (28.0)
Distal penile	5 (17.8)	5 (20.0)
Number		
Single	25 (89.3)	22 (88.0)
Multiple	3 (10.7)	3 (12.0)
Size (cm)		
<2	12 (42.9)	11 (44.0)
2-4	10 (35.7)	9 (36.0)
>4	6 (21.4)	5 (20.0)

Table 2: Comparison of parameters

Parameters	Verapamil (N=28)	Control (N=25)
Curvature	19 (67.9)	18 (72.0)
Erectile dysfunction	9 (32.1)	8 (32.0)
Plaque	20 (71.4)	19 (76.0)

Table 3: Summary of response

Parameters	Verapamil (N=28)	Control (N=25)
Overall satisfaction	23 (82.1)	10 (40.0)
Improvement in curvature of penis	18 (64.2)	6 (24.0)
Improved erectile function	19(67.8)	8 (32.0)
Reduced plaque size	17 (60.7)	7(28.0)

DISCUSSION

Peyronie's disease is a very difficult to handle condition for both patient and the partner. Its occurrence is more prevalent in men of age group of 50-59 years.[16] In most cases the disease is misdiagnosed among many healthcare professionals causing a delay in the treatment. Experts say, these treatments are most effective when the condition is diagnosed early and treated by specialists. But more often men are hesitant to consult a physician about their condition. The use of the calcium antagonist for the verapamil treatment of PD was first considered in 1991 after research regarding its effects on scar formation.

Askey et. al (1988)[17] found that verapamil specifically inhibited fibroblast secretion of a membrane impermeable probe. Verapamil was found to affect cytokine expression associated with the early phases of wound healing and inflammation, including platelet-derived growth factor-BB, interleukin-6, and interleukin-8. Anderson et al (2000) found that verapamil had the most profound inhibitory effect on cell proliferation compared to other biologic agents, including prostaglandin-E1, interferon-alpha 2b, and colchicine.[18]

Teloken et al (1999) however, noted no advantage to verapamil over placebo or steroids because of faulty technique of verapamil injection around but not into the plaque so underscoring the importance of direct drug delivery to plaque fibroblasts.[19]

Shirazi M et al (2009) carried out a placebo-controlled trial in 40 patients and found that result was not significant for pain, curvature, plaque size and erectile dysfunction.[20] There are other oral and intralesional treatments in market but they are usually accompanied with high cost, side effects and no much improvement in the condition. Verapamil is cheaper in comparison to others and has shown superior results for abnormalities that are not purely curvature in nature.

Overall satisfaction observed was twice in verapamil group than control group. There was significant improvement in penile curvature and erectile dysfunction. Plaque size reduced drastically in verapamil group. Verapamil intralesional injection appears to be safe and acceptable in patients of PD. There were no significant adverse effects observed. Compared to the control group beneficial results were observed in patients treated with verapamil group.

The result of this study is encouraging and in concordance with majority of previous studies. The major limitation of this study is smaller sample size.

CONCLUSION

Intralesional verapamil may retard or possibly reverse plaque formation and progression of PD. The ideal candidates for intralesional verapamil treatment include those who present with pain and have a non-calcified plaque. Intralesional verapamil treatment may be tried as a first line agent for treatment of PD.

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