

A Comparative study of Effectiveness of combination of Intralesional Triamcinolone, Hyaluronidase with Oral Vitamin E over intralesional triamcinolone alone in Peyronie's Disease.

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Abstract

Background: Peyronies disease (PD) is a localised penile fibrotic disease which impairs men's health physiologically and also psychologically. It is manifested by a palpable penile scar, painful erection, and deformity. Different modalities of nonsurgical treatment options exist, among which the injection of pharmacologically active agents directly into the penile plaque results in localized delivery and higher drug concentrations inside the plaque. With this rationale the study is planned to compare the effectiveness of combination of intralesional injection of triamcinolone, hyaluronidase, with daily oral vitamin E and without vit. E in the treatment of PD. **Methods:** Total 16 Patients with PD presenting at our OPD RIMS RANCHI from December 2020 to December 2022 were included in the study after obtaining the informed consent. They were divided into 2 groups (group A and group B). A freshly prepared solution of a mixture of Triamcinolone and Hyaluronidase was injected at the periphery as well as in the plaque once in 3 weeks. The patients were given concurrently daily oral vitamin E in group A (11/16) and in group B (5/16) without vitamin E followed up for every three weeks for six months for the improvement of symptoms. **Results:** The study involved 16 patients (mean age = 50 ± 10 years; range 25–70 years). After 6 months of treatment, 8/11 group A patients showed 72.72% reduction in plaque size as compared to 40% in group B (2/5) and 81.81% reduction in curvature (9/11) in group A while 3/5 patients showed improvement in group B (60%). **Conclusions:** This pilot study showed that the combination of intralesional steroid injection therapy with daily oral vitamin E is more effective in reducing the plaque size, penile curvature, and erectile dysfunction, as compared to intralesional injection alone.

Keywords: Peyronies Disease, Intralesional triamcinolone, Vitamin E, IIEF-15 score.

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I. Introduction

Peyronie's disease (PD) is a localized penile fibromatous connective tissue disorder and is characterized by a fibrous indurated inelastic plaque. This may be manifested by painful erection, varying degrees of curvature deformity with dorsal or dorsolateral bending, firm to hard cord like indurated plaque, erectile dysfunction. These may lead to adverse effects on men's physical and psychological health. This may also lead to difficulty with coitus, or sometimes it becomes impossible. Recent studies indicated a prevalence of 3.2–13.0% in adult men.

The exact aetiology of this fibrotic disease is not entirely known, although in recent years pathophysiological knowledge has evolved and new studies propose the penile trauma (micro- or macro-trauma) as cause of the disease. Forceful penetration and penile trauma have long been thought to be causative factors as PD a disorder of wound healing and as such maybe considered to the formation of hypertrophic scar. In majority of cases, it is found to be isolated, while in some cases it may be associated with some other fibrotic disease like keloids. The most commonly associated comorbidities are diabetes, hypertension, lipid abnormalities, tissue ischaemia, erectile dysfunction, smoking and excessive consumption of alcohol, and also Dupuytren's contracture.

Pathogenesis of the disease starts with the fibrous infiltration of connective tissue of corpora cavernosa which then spread to involve tunica albuginea, along with overexpression of transforming growth factor b (TGF-B1), plasminogen activator inhibitor 1 (PAI-1), inducible Nitric Oxide synthase (iNOS), and profibrotic factors, and leads to formation of fibroelastic tissue with dense collagen.

Current several non-surgical therapies with varying success include intralesional steroids, clostridial

collagenase, verapamil gel or injections, procarbazine, vitamin E, para-aminobenzoate, colchicine, tamoxifen, propolis, cortisone, pentoxifylline, superoxide dismutase, iontophoresis, and extracorporeal shock wave therapy. At present there is no gold standard available for the non-surgical therapy of PD, however, certainly the most appropriate approach should be multimodal therapy. Surgical treatment options available are Nisbet's operation and 16-dot plication technique and it is indicated only when the patients have failed conservative therapy and the disease was stabilized for at least 3 months (although a 6–12-month period has also been suggested) and when there is impossible to perform a sexual intercourse because of painful erectile dysfunction and severe degree of curvature.

Injection of drugs at plaque is an alternate and considered as most effective non-surgical treatment as pharmacologically active agents are delivered directly into the penile plaque resulting in higher drug concentrations inside the plaque. One of those long to be known is Intralesional steroid which reduces the inflammatory milieu responsible for peyronies plaque progression via inhibition of phospholipase A2 and suppression of immune response and by decreasing collagen synthesis, so it useful to terminate the initial symptoms of PD. Hyaluronidase is the major enzyme responsible for lysis of the peyronie's plaque and is also useful in various dermatological procedures.

Vitamin E was the first oral therapy proposed for the treatment of PD as a potent antioxidant and is also thought to have antifibrotic effects and can also reduce collagen deposits within the tunica albuginea. Vitamin E in addition interacts with hydroxyl radical (hydroxide, the more damaging ROS) donating a hydrogen atom to restore the molecule to normal inert state (Sikka & Hellstrom, 2002).

The aim of this study was to compare the possible effectiveness of combination therapy of intralesional triamcinolone, hyaluronidase with oral vitamin E and without vitamin E in PD treatment. **Methods-**

This is a comparative study designed to investigate the benefits of combination of oral vitamin E with intralesional triamcinolone injections. Study period was between december 2020 - december 2022, during which 27 patients were selected but only 16 patients were enrolled for the study, because 11 patients lost follow-up sittings due to Covid era. They were counselled about the nature of the disease, treatment options and the procedure and the procedural sessions and a written informed consent was obtained. A detailed history was recorded including onset and duration of symptoms, detailed past medical history focusing on risk factors for ED such as dyslipidaemia, atherosclerotic disease, history of tobacco use, and diabetes, and sexual history, treatment history, personal (chronic tobacco use or alcohol consumption) or family history of wound healing disorders including keloids, dupuytren's contracture.

Exclusion criteria were as follows: -any medical treatment for sexual dysfunction, before or during the study; supplementation with traditional herbs or vitamins in the previous 6 months; penile curvature that does not allow sexual intercourse, patients opted for surgical treatment for gross deformity.

Patients were divided into 2 groups as "Group A" (11/16) who were treated with Intralesional injection of triamcinolone 2ml (40mg/ml for initial 2 sittings with subsequent sittings of doses 10mg/ml) along with injection hyaluronidase 1ml (1500IU) in same syringe once in 3 weeks and once daily oral Vitamin E 400mg. "Group B" (5/16) were treated with same without daily doses of vitamin E. All are treated and observed for up to 6 months with once in 3 weeks follow-ups. In addition to medical history and physical examinations, USG was done to detect the size of fibrotic plaque before the 1st sitting and also after 6 months. Results were observed in terms of plaque size and penile curvature. The patients were categorised according to the plaque size and degree of curvature. 5/16 patients had plaque size of less than 2cm, and 11/16 pts had plaque size of 2-4cm. None of them had size of > 4cm. 7/16 patients had <30^o of curvature, 9/16 had 30-60^o.

The questionnaire-based score according to International Index of Erectile Function (IIEF-15) (Rosen et al., 1997) of all patients were recorded. The answers that we evaluated, addressed specifically the aspects of Erectile Function (IIEF-EF normal score: 26–30). Patients who had a total score of less than 26 were identified as having erectile dysfunction. The baseline mean score was 25 with a range of 23-27.

II. Results

The study involved 27 patients (mean age = 50 ± 10 years; range 25–70 years). Associated abnormalities Diabetes was seen in 9 patients (33.33%), tobacco and alcohol consumption in 9 patients (33.33%), deranged lipid parameters were seen in 2 patients (7.4%), low serum testosterone levels were seen in 3 patients (11.1%) and 3 patients had penile trauma (11.1%) leading to development of penile plaque. Thus, majority had one or other factors responsible for endothelial dysfunction. 11/27 patients were lost to follow-up due to covid period (6 belonging to group A, and 5 in group B). So, the total cases remained in the study were 16/27 among which 11 belongs to group A

while 5 to group B. The two different treated groups are homogeneous for a statistical analysis of results (patient age, diseases onset, presence and intensity of penile pain, plaque volume, calcification size, degree of curvature, presence or absence of erectile dysfunction and comorbidities). More than 90% reduction in pain was reported after 1st sitting in both groups and almost complete reduction was seen after 2nd sitting. Significant

improvement was seen in IIEF-15 score after 6 months of follow-up from the baseline score.

Penile plaque: The most common location of penile plaque was Dorsal, which was seen in 24 patients (88.88%). The other locations of the plaque were dorso-ventral in 2 patients (7.4%), right- lateral in 1 patient (3.7%). Among 16 patients, the size of the penile plaque was categorized in to 3 groups as, 5/16 patients (18.52%) had baseline penile plaque size of < 2cms, 11/16 patients (81.48%) had baseline plaque size of 2-4cms, none of them had baseline plaque size of more than 4 cm. After 6 months of treatment, 5/11 group A patients showed 85-90% reduction in plaque size while 3/11 patients showed mild improvement with total response rate of 72.72% as shown in table 1. Group B patients showed total response rate of 40% (2/5) table 2.

Reduction in size □	<1cm	1-2cm	>2cm	Patients in Group A
Baseline plaque size				
<2cm	2	1	0	3
2-4cm	3	3	2	8
>4cm	0	0	0	0
				11

Table 1: comparison of baseline penile plaque size and penile plaque size after 6 months of completion of treatment in Group A.

Reduction in size □	<1cm	1-2cm	>2cm	Group B
Baseline plaque size ↓				
<2cm	1	1	0	2
2-4cm	1	0	2	3
>4cm	0	0	0	0
				5

Table 2: comparison of baseline penile plaque size and penile plaque size after 6 months of completion of treatment in Group B.

Penile curvature: Among 16 patients, 7 patients had mild degree of curvature (<30°), while 9 patients had curvature of 30-60°. None of them had curvature of more than 60°. Patients with mild degree of curvature responded better in 'vitamin E group' with 100% response. Total response rate for Group A is 81.81% (table 3), while 60% response rate is seen among group B patients (table 4).

Reduction in Curvature □	0-15°	15-30°	>30°	Group A
Baseline Curvature of Penis ↓				
<30°	4 (100%)	0	0	4
30-60°	2 (28.57%)	3 (42.85%)	2	7
>60°	0	0	0	0
				11

Table 3: comparison of baseline penile curvature and penile curvature after 6 months completion of treatment in Group A patients.

Reduction in Curvature □	0-15°	15-30°	>30°	Patients in Group B
Baseline Curvature of Penis ↓				
<30°	2 (66.66%)	1	0	3
30-60°	1 (50%)	0	1	2
>60°	0	0	0	0
				11

Table 4: comparison of baseline penile curvature and penile curvature after 6 months completion of treatment in Group B patients.

Adverse effects: Local pain at injection site was the most common procedural adverse effect.

Local erythema was also reported in few cases during 1st injection which was relieved with oral analgesics and anti-inflammatory agents. Long term use of vitamin E haven't shown any adverse effects and is considered to be safe.

III. Discussion:

Peyronies disease (PD) is physically and psychologically devastating for men's health, and the study was done with the goal to improve symptoms and sexual function without adding treatment-related morbidity. Several studies have explored the utility of agents which are effective against scar like steroids, hyaluronidase, collagenase, mitomycin, verapamil, PDE-5 inhibitor. With this keeping in mind, the potential for surgical related morbidities, these are promising nonsurgical modalities for this poorly understood and yet devastating disease. The Intralesional steroid i.e., triamcinolone which reduces the inflammatory milieu responsible for peyronies plaque progression via inhibition of phospholipase A2 and suppression of immune response and by decreasing collagen synthesis, so it useful to terminate the initial symptoms of PD. Hyaluronidase is the major enzyme responsible for lysis of the peyronie's plaque and is also useful in various dermatological procedures. Vitamin E is a potent antioxidant and is also thought to have antifibrotic effects and can also reduce collagen deposits within the tunica albuginea, however, several studies have reported that vitamin E is ineffective to treat PD (Pryor & Farrell, 1983; Hashimoto et al., 2006; Hauck et al., 2006). Although vitamin E monotherapy is not useful as compared to placebo, other studies (Prieto Castro et al., 2003; Safarinejad et al., 2007) reported better results when vitamin E was administered in combination with another substance respectively propionyl-L-carnitine and colchicine, in the treatment of PD. As, till the date no study has been done with point of combination of intralesional steroid with oral vitamin E, this study would be a promising as a safer and effective approach for PD. A recently published study (Klein et al., 2011) has found that a dietary supplementation with vitamin E significantly increases the risk of prostate cancer among healthy men; the vitamin E analysed in the study corresponds to a synthetic ester of vitamin E (all-rac-alpha-tocopheryl acetate). However, it is important to mention that other studies instead found no overall association between vitamin E supplement use and prostate cancer, furthermore vitamin E supplementation in smokers was associated with reduced risks of this disease (Kirsh et al., 2006; Weinstein et al., 2007; Wright et al., 2007).

In this study, all patients were informed of the possible treatment modalities including nonsurgical conservative therapies and surgical procedure. However, all the patients have ruled out the possibility of a surgical operation, as they were counselled about indication of surgery which is to be done only in patients with stabilized disease (Kendirci & Hellstrom, 2004). In the initial development stage of PD, conservative medical treatment is recommended (Jalkut et al., 2003; Hauck et al., 2006; Taylor & Levine, 2008; Hellstrom, 2009). This recommendation should also take into consideration the results of this study. However, surgical treatment is indicated only when the patients have failed to respond to the conservative therapy and in case of the disease stabilized (Jalkut et al., 2003; Kendirci & Hellstrom, 2004; Hatzimouratidis et al., 2012) and when the patients are unable to perform a sexual intercourse due to painful erectile dysfunction and severe degrees of curvature (Hellstrom, 2009). In the present study, after a 6-month treatment no patient needed surgical therapy and were kept on follow-up monthly with multiple sittings of injections in those patients with only mild degree of improvements. This pilot study included 16 patients of symptomatic peyronies disease with mean age of 50 years and mean duration symptoms of 5.6 months. Penile plaque and curvature were seen in all patients, penile pain during erection was seen in 9 patients (56.25%) in contrast to William et al where penile pain during erection was seen in 27%, penile curvature in 95-100%, and a palpable plaque in 90% of the patients of PD. The Peyronies disease has been reported to be associated with Erectile dysfunction (ED), clinical depression, diabetes, hypertension, dyslipidaemia, low testosterone, obesity, smoking, and Dupuytren's contractures. In this study majority of them had diabetes and tobacco and alcohol consumption, three patients had low serum testosterone levels, two patients had dyslipidaemia, and another three-patient had penile trauma leading to development of penile plaque. The most common location of plaque was dorsal. The overall response rate seen after 8 intralesional injection therapy, in particular to plaque size was 72.72% in group A and 40% in Group B. 81.81% patients showed improvement in curvature in group A as compared to 60% in Group B. On subgroup analysis, patients with mild degree of curvature ($< 30^{\circ}$) showed complete improvement in curvature in Group A patients. The limitations of the study were as this pilot study was done with small number of patients and few (11) patients were lost to follow-up due to Covid period.

IV. Conclusion:

This comparative study showed that the combination of intralesional triamcinolone mixed with

hyaluronidase and oral Vitamin E is safe, well tolerated, and effective in reducing plaque size, penile curvature as compared to intralesional triamcinolone admixed with hyaluronidase without oral Vitamin E, over a short course and short-term follow-up. However, to draw stronger conclusions studies including a larger number of patients and longer follow-up is warranted.

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