



Efficacy and Safety of Verapamil Intralesional Injection in Peyronie's Disease Using the Kalsi Technique

Saleh B*, Dallash M, Koura M, Ibrahim M and Kalsi J

Department of Urology, Frimley Health NHS Foundation Trust / Wexham Park Hospital, UK

Abstract

Objectives: To assess the efficacy and safety of Intralesional Verapamil Injections (ILV) as a minimally invasive treatment option for patients with Peyronie's Disease (PD), and to describe the procedure technique.

Materials and Methods: Patients with chronic phase PD and an inability to have penetrative intercourse were started on the ILV treatment protocol after thorough counselling about the treatment plan and alternative treatment options. A direct questionnaire was used to assess the study outcomes in terms of improvement in penetrative intercourse and any post-procedure side effects. The degree of penile angulation was also visually measured to the nearest 10° during an artificial erection at the beginning of treatment then regularly prior to each treatment session.

Results: 26 patients have either completed the six-injection protocol or had enough improvement with a lower number of injections. The penile curvature ranged from 30° to 90°, with a median of 50.3°. Twenty patients had a curvature of a 45° or more.

Nineteen patients (73%) reported satisfactory post procedure improvement in their ability to achieve penetration.

Conclusion: Our study strongly supports the use of ILV as a non-invasive treatment option that can "in carefully selected patients" provide a significant subjective and objective improvement in pain, penile deformity, degree of curvature and sexual function with no significant side effects. We believe that ILV should be offered as a first line option to patients with Peyronies disease with a significant curvature. It is especially helpful in patients who already have a degree of erectile dysfunction.

Introduction

Peyronie's Disease (PD) is an acquired penile abnormality characterized by fibrosis of the tunica albuginea which may be accompanied by pain, deformity, Erectile Dysfunction (ED), and/or distress [1].

PD can have a major psycho-sexual impact on patients and their partners. Many men with PD experience emotional distress, depressive symptoms and relationship difficulties. As many as 81% of men with PD indicate "emotional distress" [2].

Erectile dysfunction is known to occur in at least 20% of men with PD and is recognized to negatively affect their quality of life. Up to 77% of men with Peyronies report significant psychological effects (Gelbard et al., 1990).

Epidemiology

Depending on the type of the studied population, PD prevalence may range from 0.4% to 20.1%, with more recent studies reporting higher figures, especially in older population, and patients with diabetes mellitus and erectile dysfunction [3,4].

Dupuytren's Disease (DD) is another, strongly – linked risk factor for PD. Shindel et al. reported that up to 26% of DD patients have PD-like symptoms [5]. Nugteren, on the other hand found that 22% of PD patient may have DD [6].

The familial aggregation of PD among specific Histocompatibility Antigens (HLA), including HLA-B7 and the association with certain conditions of excessive fibrosis strongly suggests genetic predisposition for abnormal wound healing response [7].

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*Correspondence:

Bassam Saleh, Department of Urology,
Frimley Health NHS Foundation Trust
/ Wexham Park Hospital, Wexham St.
Slough, SL2 4HL, UK

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Pathogenesis

Microtrauma is the most widely accepted inciting event in the pathogenesis of PD. A dysregulated inflammatory response and aberrant wound healing is characterized by an imbalance in fibrosis and fibrinolysis, which can result in fibrotic plaque formation and an excessive fibrosis associated with PD [8]. TGF- β is a key factor in fibrosis, other pathways have been identified as well (Figure 1) [9].

Patients with PD may present during the acute phase, characterized by pain, slight penile curvature, and nodule formation, or in the chronic phase, with a stable plaque size, penile curvature without pain and in some instances, severe ED [10,11].

Treatment

Treatment options for PD can be classified as conservative (which includes oral medications, intralesional injections, shock wave treatment and penile traction devices) and surgical procedures [12]. With the exception of NSAIDs for the pain management during the acute attack, and the PDE5Is for the associated ED, no oral medical treatment is recommended for the treatment of PD [1,12]. Among all other conservative treatment modalities, high-quality evidence was provided only for the Collagenase Clostridium Histolyticum intralesional injection therapy [13].

Although surgery can be very effective, it is associated with significant potential side effects, including penile shortening and erectile dysfunction [14,15]. Therefore, surgery is usually preserved for the severe cases, or in case of ED not responding to medical therapy [16].

Materials and Methods

Patients referred to the Andrology clinic with PD had a standard assessment for the severity of the problem, impact on the quality of life, phase of the disease, and associated Erectile Dysfunction (ED). The patients were counselled about the available treatment options including surgery for patients with a penile angulation causing an inability to have sexual intercourse. SHIM questionnaires were completed at the start and the end of the treatment course. All patients with a penile Doppler ultrasound finding of poor erectile response or of a venous leak were counselled for treatment options other than penile straightening.

Patients who were eligible and chose to have the ILV treatment option were provided with clear information about the treatment protocol, and the potential side effects. Our protocol was up to six treatment sessions, six to eight weeks apart, to be performed under general anesthesia with a penile block. Two vials of Verapamil 5 mg/2 ml each were diluted in 16 ml of water.

The Kalsi Technique

After preparing the patient under GA, a penile block is performed with 10 ml of plain Bupivacaine 0.5%. The patient is then examined for the plaque, which is then marked. A tourniquet is then applied at the base of the penis using a soft Jacques catheter, followed by artificial erection with injection of Saline into the glans penis through a green butterfly. The degree and direction of the angulation is assessed "visually by two members of the operating team in our study", and documented along with any other associated deformity. The maximum angulation point is marked with a skin marker pen, then the tourniquet is released. The diluted Verapamil preparation - described above - is then injected into the plaque with a 25G needle

using a multiple-entry technique that aims at mechanically breaking the scar tissue and maximize delivery and even distribution of the medication across the plaque. Remodeling of the curvature in the opposite direction of the curvature is then performed for 5 min followed by a light dressing with a blue gauze.

The choice of the 10 mg dose was regarded the highest safe intravenous dose by the pharmaceutical industry [17], and was adapted by earlier studies [18]. Diluted Verapamil (10 mg/20 mL) was found to be more effective than less diluted formulae in terms of the plaque area reduction, penile curvature, erectile function, end-diastolic velocity of the left and right cavernosal arteries, and pain [19].

Results

Twenty-six patients have either completed the six-injection protocol or had enough improvement with a lower number of injections. The penile curvature ranged from 30° to 90°, with a median of 50.3°. Twenty patients (77%) had a curvature of 45° or more. Nineteen patients (73%) reported satisfactory post-procedure improvement in their ability to achieve penetration.

Pre- and post-treatment SHIM score records were available for nineteen patients. Pre-treatment Erectile Dysfunction (ED) was present in all patients (100%). Almost half of cases (9 patients, 47%) had severe or moderate ED score, and a similar number had mild to moderate score. One patient (5%) had only mild degree of ED (appendix 1).

The post-treatment ED improvement "either a score increases of 5 or more, or improvement in the SHIM severity class" was reported in 12 (65%) of cases, with higher improvement rate in the severe and moderate ED groups (78%) compared to the mild-moderate ED group (56%).

Table 1: SHIM score distribution before and after the treatment.

Patient Number	SHIM Score	
	Before	After
1	5	5
2	15	16
3	8	12
4	12	12
5	16	21
6	10	16
7	9	9
8	10	24
9	16	16
10	15	15
11	5	16
12	10	15
13	5	10
14	14	20
15	11	16
16	19	19
17	14	18
18	16	19
19	16	17

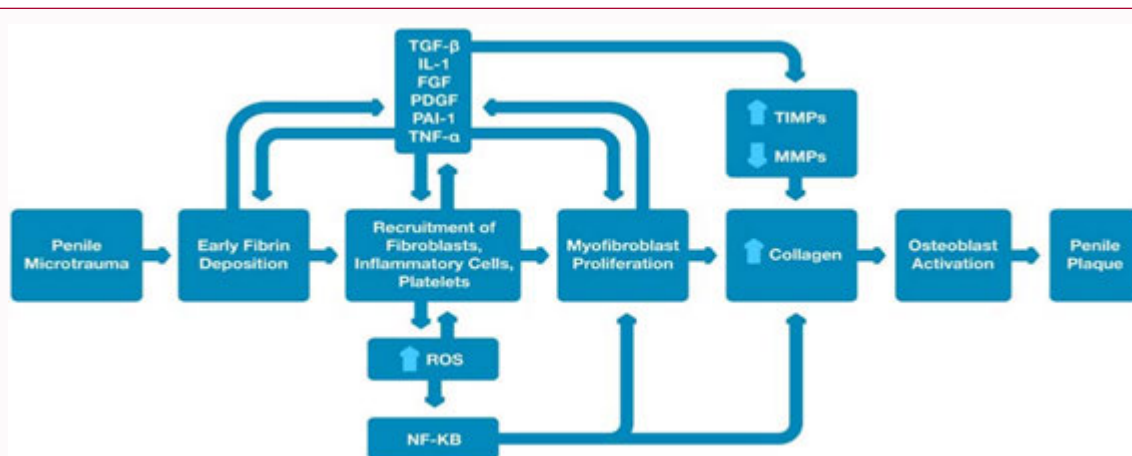


Figure 1: Inflammatory and fibrotic response after cell damage in Peyronie's disease [9].

The average SHIM score improvement across all subgroups was 5.4 points. (7.1 in the severe & moderate ED groups, and 4 in the mild-moderate group) eight patients (67%) reported concomitant use of a PDE5 inhibitors, and two used a penile vacuum pump.

Discussion

PD can result in a significant sexual health problem that can adversely affect both patients and their partners in the long run. Since François Gigot of *La Peyronie's* description of the “*induration penis plastica*”, multiple treatment modalities have been tried, with many non-invasive options failing to provide significant improvement. Although surgical treatment options have shown to be effective, they can be associated with major side effects associated with them. Between 1984 and 1990, new insights were gained about the role of calcium channels in fibroblasts activity and the pathogenesis of scar tissue [20-23].

Such research findings paved the way for considering calcium channel blockers in the treatment of PD. Since Levine et al. published his work on Verapamil intralesional injection for the treatment of PD in 1994, the approach received a growing interest as a minimally invasive treatment approach for PD [8], and several studies were published, with heterogenous clinical outcomes. In 2002, Levine et al. reported their experience in treating 156 patients with intralesional Verapamil injections, with the longest followed up being 81 months (average 31 months). They reported clinical effectiveness in pain and penile curvature reduction and subjective improvement in sexual function and erectile capacity. They also reported good clinical safety profile of the treatment [24].

Many of the published studies about ILV for PD were criticized because of lack of a placebo-controlled randomized study design, lack of standardized objective parameters to assess clinical outcomes, and/or study size. In our study, it was deemed appropriate to utilize practical parameters which directly reflects patient subjective improvement and overall satisfaction. We have also carefully assessed for any treatment-related side effects/complications.

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