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INTRALESIONAL VERAPAMIL INJECTION IN TREATMENT OF PEYRONIE'S DISEASE. PRELIMINARY RESULTS.

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Objective To evaluate the efficacy of intralesional verapamil injection in the treatment of Peyronie's disease.

Patients and Methods Twenty-six patients with Peyronie's disease were divided into two groups: the verapamil treatment group (study group) including 13 patients and the saline group (control group) including another 13 patients. The patients' age ranged from 35 to 58 years with a mean age of 43.75 years. The patients in the study group were subjected to a weekly injection of 10 mg verapamil hydrochloride (5 mg / 2 ml) into the plaque for the duration of six weeks. At the same time, the patients in the control group received a weekly injection of normal saline into the plaque, also for the duration of six weeks. The patients' response to the injections was evaluated subjectively with respect to pain and sexual dysfunction and objectively with respect to the plaque volume and the degree of curvature.

Results Following therapy, pain was improved in 8 of 9 patients (88.9) of the patients in the verapamil group, while in the control group it was stationary in 6 of 8 patients (75%) and had progressed in 2 of 8 patients (25%). Curvature was improved in 5 of 10 patients (50%) and remained unchanged in 5 of 10 patients (50%) of the study group, while no improvement could be recorded in any of the patients of the control group. Three of five patients (60%) of the study group reported an improvement in sexual function, while no improvement was reported in the control group.

Conclusion Verapamil may be considered a safe, effective non-surgical remedy for the treatment of Peyronie's disease with an acceptable outcome in selected patients.

Key Words Peyronie's disease, plaque, verapamil

INTRODUCTION

In 1743, François de la Peyronie described a connective tissue disorder characterized by a fibrous inelastic plaque involving the tunica albuginea of the corpora cavernosa[1]. The typical symptoms of this so-called Peyronie's disease include pain, curvature during erection and difficulty during coitus. On examination there is a palpable plaque or induration of the tunica albuginea of the corpora cavernosa. The plaque is typically formed on the dorsal or dorsolateral surface of the tunica albuginea which results in focal loss of elasticity and a diminished rigidity during erection. The exact aetiology of the disease has not been established. Various predisposing factors, such as repeated trauma to the penis[2], a genetic predisposition because of its association with Dupuytren's contracture and the HLA-B7 antigen[3], frequent chronic irritation[1], an inherited predisposition as an autosomal dominant mode of transmission in some families[4], an auto-immune aetiology[5], vasculitis[6], a delaminated injury[7] and a free-oxygen radical injury[8] have been suggested.

Numerous methods have been described for the treatment of Peyronie's disease ranging from simple oral agents[9], intralesional steroids[10], different modalities of energy transfer[11-13] to surgical modalities[14]. None of them has proved to be clearly successful and the disease remains a challenge to urologists.

Verapamil is the only injectable calcium channel blocker that has been tried in recent years as an intralesional therapy for Peyronie's

Table 1: Response to Intralesional Verapamil Injection

	Before Treatment	After Treatment	P Value
Pain	69.2% (9/13)	7.7% (1/13)	P<0.001
Plaque volume (mean ± SD)	1.71 ± 0.22 cm^3	0.51 ± 0.48 cm^3	P<0.001
Curvature	76.9% (10/13)	38.5% (5/13)	P<0.05
Angle of curvature (mean ± SD)	19.92 ± 11.55°	17.46 ± 10.41°	P<0.05
Erectile dysfunction	38.5% (5/13)	15.4% (2/13)	P>0.05

Table 2: Response to Intralesional Saline Injection

	Before Treatment	After Treatment	P Value
Pain	61.5% (8/13)	61.5% (8/13)	P>0.05
Plaque volume (mean ± SD)	1.61 ± 0.22 cm^3	1.86 ± 0.25 cm^3	P<0.001
Curvature	84.6% (11/13)	84.6% (11/13)	P>0.05
Angle of curvature (mean ± SD)	20.53 ± 9.42°	20.53 ± 9.42°	P>0.05
Erectile dysfunction	46.2% (6/13)	46.2% (6/13)	P>0.05

disease[15]. The rationale of this treatment has been based on the ability of verapamil to inhibit synthesis and secretion of extracellular matrix molecules including collagen, fibronection and glycosaminoglycans[16,17]. . Furthermore, it has been proved that verapamil will increase collagenase and transforming growth factor-beta (TGF-b) activity[18,19] and that it is effective in stimulating the remolding and degradative metabolic activity of fibroblasts[20-22]. In addition, verapamil was found to affect cytokine expression associated with inflammation including the platelet-derived growth factor, interleukin-6 and interleukin-8[23].

The purpose of this study was to evaluate the efficacy of intralesional verapamil in patients with Peyronie's disease.

PATIENTS AND METHODS

This study was done at the urology department of Assiut University Hospital, Assiut, Egypt, between December 1998 and October 2001. Twenty-six patients presenting with Peyronie's disease were included in the study. Their age ranged from 35 to 58 years with a mean age of 43.75 years. The duration of the disease ranged from 16 to 34 months.

Inclusion criteria were as follows: patients with evident disease for more than one year, a plaque volume of less than 2.0 cm^3, no history of previous oral, intralesional or surgical treatment for at least 6 months before inclusion into the study. Patients with a history of medication with calcium channel blockers or cavernosal injection for erectile dysfunction and patients with a history of penile fracture were excluded from the study.

The patients were divided into two groups: Group I included 13 patients treated with verapamil (study group), while Group II included another 13 patients who received an injection of normal saline (control group). All patients were evaluated by a thorough clinical examination followed by penile duplex ultrasonographic examination during maximum erection induced by intracavernosal injection of 60 mg papaverine to confirm the plaque volume (length x width x depth) and to measure the degree of angulation with a Goniometer[24,25].

Table 3: Comparison of Post-Treatment Results in the Study Groups

	Verapamil Group	Saline Group	P Value
Pain	7.7% (1/13)	61.5% (8/13)	P<0.001
Plaque volume (mean ± SD)	0.51 ± 0.48 cm^3	1.86 ± 0.25 cm^3	P<0.001
Curvature	38.5% (5/13)	84.6% (11/13)	P<0.05
Angle of curvature (mean ± SD)	17.46 ± 10.41°	20.53 ± 9.42°	P>0.05
Erectile dysfunction	15.4% (2/13)	46.2% (6/13)	P>0.05

Vascular risk factors including smoking, diabetes mellitus and hyperlipidaemia were found in six patients of the verapamil group and in five of the control group.

Painful erections were elicited in 9 patients and 8 patients in the verapamil and control group, respectively. A curvature ranging from 22° to 29° was described in 10 patients of Group I, while 11 patients of Group II showed a curvature of between 19° and 28°. The plaque volume ranged from 1.4 to 2.0 cm^3 in the study group and from 1.3 to 2.0 cm^3 in the control group. Erectile dysfunction was complete in two and partial in three patients in the verapamil group, while in the control group three patients had partial and three others had complete erectile dysfunction.

Technique: A dose of 10 mg verapamil (5 mg / 2ml) was injected into the plaque using a ½-inch, 25-gauge needle on a 5 ml syringe. Distribution of the drug inside the whole plaque was achieved by a gentle sustained pressure on the syringe's pistol against the resistance of the plaque. More than one puncture through the plaque was done, followed by compression of the site of injection for 5 minutes. The intralesional verapamil injection was preceded and followed by a measurement of the pulse rate/minute and the blood pressure. The injection was repeated weekly for 6 weeks. The saline injection in the control group was done by intralesional injection of 4 ml of normal saline by the same technique weekly for 6 weeks.

Follow up was done by a patient's questionnaire, local examination and penile duplex ultrasonography after one month from the last injection and then every three months until the end of the study.

The statistical analysis was done by chi square test and t-test. The p value was considered significant when it was less than 0.05.

RESULTS

The response to verapamil and saline injection was evaluated both subjectively and objectively as shown in Tables 1,2 and 3.

Subjective improvement of the pain in response to verapamil was reported in 88.9% (8/9 patients), a regression of pain was noticed after the second injection in all but one patient (11.1%) who still had unaltered pain (P<0.001). In the control group the pain remained unchanged in 6 patients (75%) and increased in 2 patients (25%).

In the study group the plaque volume decreased from 1.17 ± 0.22 cm^3 before treatment to 0.51 ± 0.48 cm^3 after treatment (P<0.001), while in the control group it increased from 1.61 ± 0.22 cm^3 before treatment to 1.86 ± 0.25 cm^3 after treatment (P<0.001). In the verapamil group plaque softening was noticed in all patients after the third injection. Complete disappearance of the plaque was demonstrated in 10 patients (76.9%) during the first follow-up visit one month after the sixth injection; all of them had suffered from the disease for a period between 16 and 24 months and the plaque volume ranged from 0.8 to 1.5 cm^3.

Curvature was improved in 50% (5/10) of the patients treated with verapamil and remained unchanged in the remaining 50% (5/10) of the patients (P<0.05), while no improvement was noticed in the control group. The angle of curvature decreased from 19.92° ± 11.55° before treatment to 17.46° ± 10.41°

post-treatment in the verapamil group ($P<0.05$), while no change in the degree of curvature was noticed in the control group.

The quality of erection was evaluated subjectively in both groups. In the verapamil group three patients (60%) with partial erectile dysfunction showed an improvement, while the two patients (40%) with complete erectile dysfunction remained unchanged. All six patients (46.2%) with erectile dysfunction in the control group remained unchanged.

Apart from mild transient pain at the site of injection no local or systemic side effects were recorded. The mean follow-up time was 23.5 months (range 12-34 months).

DISCUSSION

The last two decades have witnessed an expansion in the management of Peyronie's disease. Most urologists accept that acute or even minor repeated mechanical trauma to the erect penis may result in a septal fiber disruption and microvascular injury with fibrin exudation. Fibrin stimulates fibroblast activation and proliferation which leads to deposition of extracellular collagen matrix in the tunica albuginea as a plaque[26].

The calcium channel blocker verapamil has been shown to inhibit exocytosis of extracellular matrix macromolecule (collagen, fibronection and glycosaminoglycans) and to have a degenerative effect on fibroblasts[19,27].

In this study intralesional verapamil injection therapy resulted in an improvement of pain in 88.9% of the patients, an improvement in curvature in 50% of the patients, a reduction of the plaque volume from 1.71 ± 0.22 cm^3 to $0.51 + 0.48$ cm^3 and a reduction of the angle of curvature from $19.92 \pm 11.55°$ to $17.46 \pm 10.41°$. An improvement in sexual function could be achieved in 60% of the patients, while the curvature remained unchanged in 40% of the patients. Although the response to verapamil was noticed early between the second and third injection, the improvement seems to have increased and continued throughout the course of therapy.

On the other hand, intralesional saline injection in the control group showed no improvement in pain at all; on the contrary, it became worse in 25% of patients. There was also no improvement in the degree of curvature and erectile function. Regarding the plaque volume there was a significant increase in its volume from 1.61 ± 0.22 cm^3 to $1.86 \pm 0.25 cm^3$.

The first application of intralesional verapamil therapy in Peyronie's disease was reported by Levine and coworkers in 1994 with a dose escalating from 1 mg to 10 mg for 12 injections. Their results were a 91% improvement in pain, a 42% improvement in curvature and a 58% improvement in erectile function[28]. Teloken et al. reported that there were no advantages to verapamil over saline or steroids when injected around and not into the plaque[29]. In a later study on 45 patients treated with 10 mg verapamil every two weeks (12 injections), Levine reported a 97% improvement in pain, a 76% subjective decrease in curvature, a 9.5% increase in curvature and an unchanged condition in 14.5%. An improvement in sexual performance was reported in 72% of patients. Objective measurements demonstrated that curvature had decreased in 54%, increased in 11% and remained unchanged in 34%[30].

Similar to our study, Rehman et al. divided their patients into two groups, a verapamil group and a saline group. They subjected the patients of their study group to an intralesional injection of 10 mg of verapamil every week for 6 months, while the control group received saline injections for the same period of time. Their results were a decreased plaque volume in 57% of the verapamil group versus 28% in the control group ($P<0.04$). Curvature demonstrated an improvement from a pre-treatment value of $37.71 \pm 9.3°$ to $29.57 \pm 7.3°$ after treatment in the verapamil group, but the difference was not significant ($P<0.07$). The subjective plaque-associated erectile dysfunction showed an improvement in 42.87% of the patients of the verapamil group versus none in the control group ($P<0.02$)[31].

In conclusion, our results demonstrate that intralesional verapamil injection in Peyronie's disease is a safe, simple and effective remedy in selected patients. The ideal candidates are patients with early disease and a plaque volume of less than 1.5 cm^3.

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RESUME

Injection Intra-Lésionnelle de Vérapamil dans le Traitement de la Maladie de Lapeyronie Résultats Préliminaires

Objectifs: Evaluer l'efficacité de l'injection intra-lésionnelle de Vérapamil dans le traitement de la maladie de Lapeyronie. **Patients et Méthodes:** Vingt six patients présentant la maladie de Lapeyronie ont été divisés en deux groupes: le groupe d'étude composé de 13 patients traités par la Vérapamil et le groupe contrôle composé de 13 patients traités par une solution saline. L'âge des patients variait entre 35 et 58 ans avec une moyenne de 43.75 ans. Les patients du groupe d'étude avaient bénéficié d'une injection hebdomadaire de 10mg de Chlorhydrate de Vérapamil (5mg/2ml) dans la plaque durant six semaines. Pendant ce temps les patients du groupe contrôle bénéficiaient d'une injection hebdomadaire de solution saline dans la plaque pour la même durée. L'évaluation de la réponse a été réalisée de façon subjective concernant la douleur et la dysfonction sexuelle et de façon objective concernant le volume de la plaque et le degré d'incurvation de la verge. **Résultats** : Au bout du traitement, la douleur était améliorée dans 88.9% (8/9 patients) dans le groupe d'étude tandis que dans le groupe contrôle la douleur était restée stationnaire dans 75% (6/8 patients), et même s'est aggravée dans 25% (5/10 patients). L'incurvation de la verge s'est améliorée dans 50% (5/10 patients) et est restée inchangée dans 50% (5/10 patients) au sein du groupe d'étude, tandis qu'aucune amélioration n'a été notée dans le groupe contrôle. Six pour cent (3/5 patients) du groupe d'étude ont noté une amélioration des performances sexuelles alors qu'aucune amélioration n'était perceptible dans le groupe contrôle. **Conclusion:** La Vérapamil peut être considérée comme un traitement non chirurgical sûr et efficace de la maladie de Lapeyronie avec des résultats acceptables chez des patients bien sélectionnés.

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