ELSEVIER

USE OF INTRALESIONAL VERAPAMIL TO DISSOLVE PEYRONIE'S DISEASE PLAQUE: A LONG-TERM SINGLE-BLIND STUDY

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ABSTRACT

Objectives. Multiple conservative therapies for the treatment of Peyronie's disease have been offered with variable and poor response rates. Calcium channel blockers have been shown in vitro and in vivo to inhibit secretion and synthesis of extracellular matrix, including collagen, glycosaminoglycans, and fibronectin, as well as causing increased collagenase and anti transforming growth factor-beta activity. Calcium antagonists, including verapamil, are effective in stimulating the remodeling and degradation of extracellular matrix in tissue by altering the metabolic pathways of fibroblasts. Recently, a pilot study (1994) showed preliminary promising results in treating plaque caused by Peyronie's disease. This randomized single-blind placebo-based study (1994 to 1996) was undertaken to confirm the hypothesis.

Methods. In this randomized single-blind study, 14 patients completed the study and were divided into two groups: the verapamil treatment group (n = 7) or the control saline group (n = 7). Verapamil or saline was injected directly into the Peyronie's plaque once a week for 6 months. Patients were evaluated before and after treatment with duplex ultrasound to confirm the extent of the lesion and to measure volume of the plaque, and by interview and mailed questionnaire 3 months after treatment. Patients being treated with oral calcium antagonists were excluded from the study.

Results. A decreased plaque volume was measured in 57% of the verapamil-treated men versus 28% in the control group ($P < 0.04$). Penile curvature demonstrated an improvement trend of 37.71 ± 9.3° to 29.57 ± 7.3° in the verapamil-treated patients, but the difference was not significant ($P < 0.07$). Plaque softening was noted in all patients treated with verapamil. There was significant objective improvement in plaque-associated penile narrowing in all patients in the verapamil group. Subjective plaque-associated erectile dysfunction (quality of erection) showed improvement in 42.87% of the verapamil group versus none in the control group ($P < 0.02$). There was no local or systemic toxicity except for an occasional ecchymosis/bruise at the injection site. After a positive clinical response, plaque size, penile angulation, and symptoms continued to improve. Decrease in plaque size was noted in each of the responders in the first 3 months.

Conclusions. This randomized single-blind study suggests that intralesional injection of calcium channel blocker may be a reasonable approach in some selected patients for the treatment of Peyronie's disease with noncalcified plaque and penile angulation of less than 30°. Patients whose plaque failed to respond to intralesional verapamil therapy within 3 months or whose angulation was greater than 30° at presentation were more likely to benefit from surgery.

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Francois Gigot de la Peyronie[1,2] is credited with first describing a disease that is characterized by a fibrous plaque formation involving the tunica albuginea. The plaque typically forms on the dorsal or dorsolateral surface of the penis under the neurovascular bundle, but may involve any area of the corpus cavernosum. Induration of the tunica albuginea results in focal loss of elasticity with impaired shaft elongation during penile erection. In the early stage of the disease, bending around the plaque during penile erection may result in pain. In severe cases, the bend may interfere with vaginal penetration or may cause dyspareunia. In severe Peyronie's disease, the penis distal to plaque (hourglass deformity) may be flaccid during erection.

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Although the exact etiology remains unknown,[3,4] the following theories have been proposed: frequent chronic irritation,[1] vasculitis,[5] genetic causes,[6–10] delaminate injury,[11] inherited predisposition and repeated trauma,[12] autoimmune insult,[13] and free oxygen radical injury.[14]

Despite numerous options for treatment, none have been clearly successful and the disease remains a therapeutic dilemma for urologists.[15] Various oral drugs including vitamin E,[16,17] para-aminobenzoate (POTABA),[18] procarbazine,[19–22] colchicine,[23] tamoxifen,[24] intralesional injection of steroids,[24,25] alone or in combination with hyaluronidase, collagenase,[26,27] orgotein,[28–32] parathyroid hormone,[33] dimethyl-sulfoxide (DMSO),[29] interferon,[34] a combination of para-aminobenzoate and vitamin E,[35] ultrasound therapy along with hydrocortisone therapy,[36] and vitamin E combined with hydrocortisone[14] have been attempted. With POTABA and colchicine there is a significant incidence of gastrointestinal toxicity. In addition, there is the danger of bone marrow depression with colchicine. A controlled trial of POTABA in comparison to vitamin E failed to show any therapeutic benefit.[20] Parathyroid injections have had no long-term success.[33] DMSO has been shown to cause cataract formation. Interferon-2β treated cultures of fibroblast from Peyronie's disease exhibit inhibited fibroblast proliferation and collagen production but there are no in vivo study reports.

Calcium channel blockers have been shown in both in vitro and in vivo studies to inhibit synthesis/secretion of extracellular matrix molecules, including collagen, glycosaminoglycans, fibronectin, as well as increasing collagenase and transforming growth factor-beta (TGF-β) activity. Calcium channel blockers such as verapamil are effective in stimulating the remodeling and degradation of extracellular matrix in tissue. Because the concentration of verapamil required to induce the degradative metabolic response in fibroblasts in the laboratory exceeds the maximum safe serum level by 100-fold, only intralesional therapy is possible. At present, verapamil is the only calcium channel blocker available in injectable form. A pilot study[37] showed promising results with an intralesional injection of verapamil into plaques caused by Peyronie's disease. The purpose of the present study was to test the effect of intralesional verapamil in a single-blind, placebo-based study.

MATERIAL AND METHODS

Patient Sample

A total of 18 men ranging in age from 37 to 67 years (mean 52) entered into this randomized single-blind study. Four men dropped out in the first month of the study, 1 preferring surgical intervention and 3 because of scheduling conflicts. The mean duration of the disease in these men prior to therapy was 16 months (range 11 to 24). The patients were evaluated by detailed history, physical examination, biothesiometry, and penile plethysmography. Plaque length was measured by calipers (Vmoeleov OP-270, Germany) and duplex ultrasound to confirm the extent of the lesion and to measure volume of the plaque. The volume of the plaques averaged 1.4 cc (range 1.5 to 2.7) before therapy. Seven patients had been treated unsuccessfully with oral vitamin E, and 1 patient had new plaque formation after previous Nesbit plication. Twelve patients completed the treatment in 6 months and 2 patients completed treatment in 4 months (total n = 14). Of the 2 patients who completed the study in 4 months, 1 left the state because of family emergency and the other dropped out because of personal reasons. Both of these patients were available for final interview and examination. Patients being treated with oral calcium antagonists were excluded from the study. The patients were divided into treatment group (n = 7) and control group (n = 7). The patients in the treatment group received intralesional injections of verapamil in an isotonic saline vehicle, whereas the control group received injections of saline alone. This study was approved by the institution review board of the Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY. Inclusion criteria were as follows: (1) age range 35 to 70 years with clinical evidence of Peyronie's disease, that is, pain and plaque along with deformity of the penis of at least 1-year duration; (2) discontinuation of any previous oral or other medication for Peyronie's disease for at least 3 months. Exclusion criteria were any history of calcium channel blocker therapy or therapy interfering with calcium channel blockers.

Technique

After local penile blockage with 2% lidocaine, the verapamil or saline was injected into the plaque with a 10-mL syringe and a 25-gauge needle once a week (Figure 1). Approximately 4 to 8 plaque punctures were performed at each sitting in an effort to distribute the drug uniformly through the plaque. The verapamil was injected 1 mg/0.1 cc (10 mg/1 cc). The dosage ranged from 10 to 27 mg. This dosage was chosen after consultation with a pharmacist, taking into consideration the response rate in the pilot study by Levine *et al.*[37] The patient was asked to compress the injection site for 5 minutes to decrease ecchymosis. Blood pressure and heart rate were continuously monitored throughout the procedure and after injection for the first 3 months, and because no patient exhibited any drop in blood pressure or any related cardiac effects, monitoring was discontinued for the remaining 3 months. No systemic, local, acute, or chronic toxicity was noted except for an occasional transient ecchymosis/bruise at the injection site. To prevent the incidental injury to the dorsal nerve fibers or dorsal arteries, the needle was inserted into the dorsolateral or lateral side depending upon the location of plaque. Precaution was taken not to instill the drug into the corpus cavernosum. Slight gentle pressure into the syringe was required for injection into the tunica albuginea, whereas instillation into corpus cavernosum did not require pressure.

Data Analysis and Statistics

Objective and subjective data were gathered at completion of the study. Objective assessment was done by direct interview, physical examination, and measurement of plaque length and width by two independent investigators with calipers, confirmed by penile ultrasound. Subjective data were gathered by questionnaire 3 months after completion of the study. The data are expressed as mean and standard error of the mean (SEM). The groups were compared using the unpaired Student's t test at a significance of $P < 0.05$ by statistical software (STATVIEW 4.5, Abacus Concepts, Berkeley, Calif).

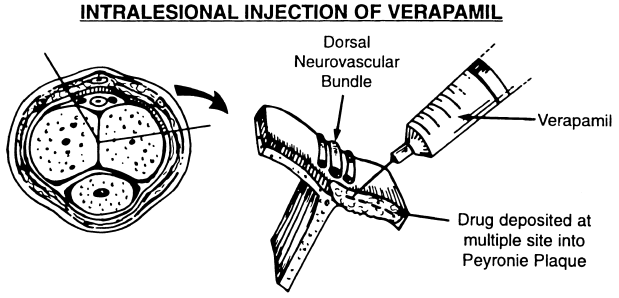

FIGURE 1. *Cross section of shaft of penis and dorsal neurovascular bundle. Part of the figure has been enlarged to show the relationship of the neurovascular bundle to the plaque and the injection technique. First local block is obtained with 0.2% lidocaine. Then the verapamil (1 mg/0.1 cc [or 10 mg/1 cc] of plaque volume as determined by ultrasound or calculated as previously mentioned) is injected into the plaque with a 10-mL syringe and 25-gauge needle. Injections are given weekly. Approximately 4 to 6 plaque punctures are needed per injection to distribute the drug uniformly through the plaque. The injection site should be compressed for 5 minutes to decrease ecchymosis. To prevent the incidental injury to the dorsal nerve fibers or dorsal arteries, the needle is inserted into the dorsolateral or lateral side depending upon the location of plaque. Precaution is taken not to instill the drug deep into corpus cavernosum. Slight gentle pressure into syringe is always needed to inject into the tunica albuginea as compared to easy instillation into the corpus cavernosum.*

RESULTS

The results are described in Tables I and II. All patients who responded to verapamil did so in the first 3 months.

(1) Plaque size and volume: plaque length decreased from 3.1 ± 0.5 cm pretreatment to 1.8 ± 0.4 cm post-treatment in the verapamil group versus 2.9 ± 0.5 cm pretreatment to 3.0 ± 0.2 cm post-treatment in the control group ($P < 0.03$). Plaque width decreased from 1.7 ± 0.95 cm pretreatment to 0.8 ± 0.1 cm post-treatment in the verapamil group versus 1.59 ± 0.31 cm pretreatment to 1.81 ± 0.57 cm post-treatment in the control group ($P < 0.05$). Plaque volume decreased from 1.421 ± 0.23 cm^3 pretreatment to 0.63 ± 0.19 cm^3 post-treatment in the verapamil group versus 1.37 ± 0.27 cm^3 pretreatment to 1.39 ± 0.29 cm^3 post-treatment ($P < 0.04$).

(2) Penile curvature: penile curvature showed an improvement trend of 37.71 ± 9.3° to 29.57 ± 7.3° in 28.57% of the verapamil-treated patients versus no improvement in the control group, but the difference was not statistically significant ($P < 0.07$).

(3) Quality of erections (subjective): the quality of erections improved from 5.69 ± 6.5 pretreatment to 7.4 ± 0.37 post-treatment in 42.86% of the verapamil group versus 6.28 ± 0.52 pretreatment to 6.3 ± 0.44 post-treatment in the control group ($P < 0.02$).

COMMENT

Most urologists interested in sexual dysfunction in men agree that acute or repeated mechanical trauma (sexual or nonsexual) to the tunica albuginea is delivered via the septal fibers, which are responsible for maintaining the axial rigidity during erection. Trauma with an erect penis results in tissue disruption and microvascular injury (focal vasculitis) that leads to exudation of fibrin.[5] Fibrin triggers fibroblast activation and proliferation that results in excessive deposition of extracellular collagen matrix in the tunica albuginea.[11,38,39] The formation of excessive fibrous tissue may also be triggered in genetically predisposed individuals, either from abnormal fibroblastic activity or decreased fibrinolysis. Calcium channel blockers have been shown to inhibit synthesis/secretion of extracellular matrix molecules, including collagen, glycosaminoglycans, and fibronectin, as well as increasing collagenase and TGF-β activity. During the last two decades, tremendous achievements have been made in calcium channel blockers and their role in collagen synthesis by fibroblast, both at the structural and biochemical levels. Better understanding ultimately led to their clinical studies in humans for fibromatosis. Calcium channel blockers such as verapamil are effective in stimulating the remodeling and degradation of extracellular matrix in tissue. Because the concentration of verapamil required to induce the degradative response in fibroblasts in the laboratory exceeds the safe serum level by 100-fold or more, only intralesional therapy is possible at present.

Fibroblast, Collagen Metabolism, and Calcium Channel Blockers

Diegelmann and Peterkofsky[40] provided evidence that calcium channel blockers alter cell shape and tissue remodeling via epigenetic control of the extracellular matrix. Ehrlich *et al.*[41] described experiments with antitubulin agents that resulted in inhibition of collagen synthesis and secretion of osteoblasts and fibroblasts. Dietrich and Duffield[42] demonstrated that calcium antagonist verapamil can alter synthesis of collagen and noncollagen proteins. Aggeler *et al.*[43] demonstrated that calcium antagonists as well as a calmodulin blocker change fibroblast shape. They induced detachment of rabbit synovia fibroblasts from their substrate, resulting in altered morphology of the fibroblast, decreased collagen synthesis, and a marked increase (20-fold) in the secretion of collagenase. The altered cells were noted to alter the secretion of extracellular matrix proteins on a con-

TABLE I. *Response to intralesional verapamil injection*

Parameter	Method of Measurement	Verapamil Group Pretreatment (n = 7) (Mean ± SEM)	Verapamil Group Post-treatment (n = 7) (Mean ± SEM)	Control Group Pretreatment (n = 7) (Mean ± SEM)	Control Group Post-treatment (n = 7) (Mean ± SEM)
Plaque length (cm)	Objective	3.1 ± 0.51	1.89 ± 0.39*	2.9 ± 0.55	3.02 ± 0.23
Plaque width (cm)	Objective	1.67 ± 0.95	0.8 ± 0.14†	1.59 ± 0.31	1.81 ± 0.57
Plaque volume (cm^3)	Objective	1.42 ± 0.23	0.63 ± 0.19‡	1.37 ± 0.27	1.39 ± 0.29
Penile curvature (degrees)	Objective	37.71 ± 9.3	29.57 ± 7.3§	33.57 ± 9.7	31.43 ± 8.9
Quality of erections (scale 1 to 10)#	Subjective	5.69 ± 0.65	7.4 ± 0.37**	6.28 ± 0.52	6.3 ± 0.44

KEY: SEM = standard error of the mean.
* P <*0.03 (plaque length post-treatment verapamil versus control group).*
† P <*0.05 (plaque width post-treatment verapamil versus control group).*
‡ P <*0.04 (plaque volume post-treatment verapamil versus control group).*
§ P <*0.07 (penile curvature post-treatment verapamil versus control group).*
# *Quality of erections scaled 1 to 10 (1 = no erection; 10 = very rigid erection).*
** P <*0.02 (quality of erections post-treatment verapamil versus control group).*

centration-related basis, which correlates positively with the degree of cell shape change. Once triggered, the increased rate of collagenase synthesis persists for up to 1 week, even after the agents are removed and the cells reanchored onto the substrate. Kelly[44] demonstrated that the secretion of extracellular matrix is calcium dependent (regulated exocytosis).

In Vitro Cellular Studies and Calcium Channel Blockers

In vitro experiments by Askey *et al.*[45] found that verapamil specifically inhibits fibroblast secretion. Lee and Ping[46] reported experiments with bovine fibroblasts exposed to increasing concentrations of verapamil and nifedipine, and found decreased incorporation of radiolabeled proline and sulfate into extracellular matrix collagen and glycosaminoglycans, respectively. They demonstrated that treatment of the fibroblast-populated collagen matrix with calcium channel blockers (verapamil hydrochloride [100 mol/L] and nifedipine [10 mol/L]) markedly reduced the incorporation of tritiated proline into the extracellular matrices of the fibroblast-populated collagen matrix. Therefore, it appears necessary to deliver verapamil directly to the fibrous tissue to avoid high blood level. Fitscha *et al.*[47] demonstrated, in a vascular lesion induced in an animal model, that treatment with calcium channel blocker (isradipine) treated fibroblasts results in decreased incorporation of proline and sulfate into collagen and glycosaminoglycans, respectively.

In Vivo Animal Studies and Calcium Channel Blockers

Steinleitner *et al.*[48] have shown that verapamil markedly reduced adnexal adhesions in rabbits. Kappas *et al.*[49] found that rats with a surgically created abdominal wound treated with verapamil (1 mg/kg administered intravenously) produced significantly fewer peritoneal adhesions than controls. Johnson *et al.*[50] reported that nifedipine resulted in improved wound healing (skin and facial wounds as well as enteric anastomoses) in animals treated with doxorubicin.

Clinical Human Studies, Including the Present Study and Other Calcium Channel Blocker Studies

Lee *et al.*[51] demonstrated that intralesional injection of verapamil hydrochloride directly into a burn scar markedly reduced its size. In a pilot, single arm study, Levine *et al.*[37] used verapamil to dissolve Peyronie's plaque and reported promising results. The findings of the present randomized single-blind study suggest that verapamil injection results in a significant decrease in plaque size. A decreased plaque length of 30% or more was noted in 57.14% of patients treated with verapamil versus only a 28.57% decreased plaque length in the control group ($P < 0.04$). There was no significant change in penile angulation after treatment, although a trend was noticed in one quarter (28.57%) of patients. The persistence of curvature may mean that although plaque size is reduced, the remaining collagen tissue is sufficient to cause chordee. The more dramatic improvement in penile narrowing (bottleneck deformity) than curvature associated with plaque injection may be due to the relatively thinner lateral extension of the plaque compared to the thicker midline plaque with septal extension, as previously described.[37] Penile pain improved in both groups though there is a significantly more rapid improvement in penile pain in the verapamil group (mean 4 weeks) than

TABLE II. ***Response of patients to self-administered questionnaire regarding intralesional therapy***

Parameter	Verapamil Group Post-treatment (n = 7)	Control Group Post-treatment (n = 7)
Plaque size		
Better >50%	3/7 (43%)	—
≥30%–50%	1/7 (14%)	—
≤30%	—	2/7 (29%)
Same	3/7 (43%)	3/7 (43%)
Worse	—	2/7 (29%)
Penile curvature (in degrees)		
Better >50%	—	—
≥30%–50%	—	—
≤30%	2/7 (29%)	—
Same	5/7 (71%)	6/7 (86%)
Worse	—	1/7 (14%)
Bottleneck		
Deformity/hourglass deformity		
Better	1/2 (50%)	—
Same	1/2 (50%)	1/1 (100%)
Worse	—	—
Quality of erection		
Better	3/7 (43%)	0/7 (0%)
Same	4/7 (57%)	5/7 (71%)
Worse	—	2/7 (29%)
Pain*		
Better	2/2 (100%)	3/3 (100%)
Same	—	—
Worse	—	—
Overall outcome		
Excellent†	1/7 (14%)	—
Moderate‡	5/7 (71%)	4/7 (57%)
Poor§	1/7 (14%)	3/7 (43%)

** Pain improved in both groups but more quickly in the verapamil group (4 weeks) than in the control group (10 weeks).*
† Excellent = normal sexual function, residual deformity less than 15%.
‡ Moderate = some improvement of erection or deformity 15°–30°, coitus possible.
§ Poor = absent erections or deformity greater than 30°, coitus impossible.

in the placebo group (mean 10 weeks). There was also no worsening of sexual dysfunction during the study, which is significant because of the potential injury to the dorsal neurovascular bundle of the penis. It seems calcium antagonists are best used for immature plaque (plaque of less than 2-year duration) with penile angulation of less than 30°. On the other hand, histologic evaluation of advanced disease has revealed islands of active fibroblasts randomly dispersed throughout plaques. Intralesional injection of verapamil at multiple sites into plaque appears to allow verapamil to inhibit the activity of these fibroblasts in older plaque, which may not be possible by other methods.

CONCLUSIONS AND FUTURE STUDY

The injection of verapamil appears to be clinically safe for treating patients with Peyronie's disease if used judiciously. When compared with other methods of treatment, injection of verapamil appears to induce rapid, beneficial results in some patients for reduction of plaque size (Figure 2). The beneficial effects of intralesional verapamil are apparent within the first 3 months. For patients who respond to treatment, the injections should be continued for 6 months. The patient who fails to respond to intralesional verapamil or whose angulation is more than 30° at presentation should be considered a candidate for surgery. Also, use of calcium antagonists more potent than verapamil should be considered as they become commercially available in injection form. The injection of verapamil is clinically safe for patients with Peyronie's disease if precautions are taken to prevent injury to the dorsal neurovascular bundle. When compared with other methods of treatment, injection of verapamil appears to induce a rapid, beneficial effect in some patients (those with angulation of less than 30°) for reduction of plaque size. Patients with localized plaque are the best candidates

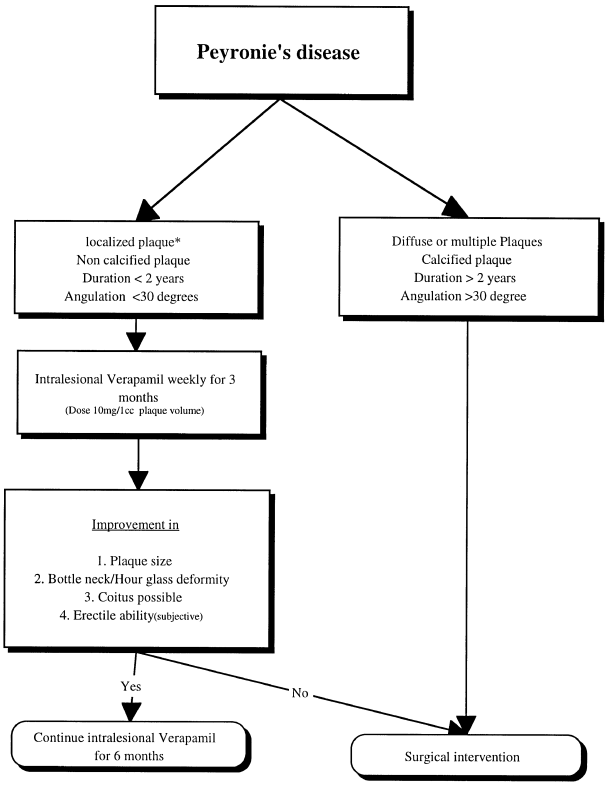

FIGURE 2. *Scheme for treatment of Peyronie's disease plaque with intralesional verapamil or surgical intervention. *Effect of size on responsive plaque to intralesional verapamil: plaque length less than 2.5 cm, 50 to 90% reduction in size; plaque length greater than 2.5 cm, less than 50% reduction in 6 months.*

for intralesional injection of verapamil. For patients who respond to intralesional therapy and whose plaque size is less than 2.5 cm, the plaque size may be reduced by 50% to 90% in 6 months, but if the plaque size is greater than 2.5 cm, then plaque will be reduced by less than 50% in 6 months. It seems that the best use of calcium antagonists is for noncalcified plaque having a duration of less than 2 years and with penile angulation less than 30°. Histologic evaluation of advanced disease has revealed islands of active fibroblasts that are randomly dispersed throughout plaques. It is conceivable that intralesional injection of verapamil at multiple sites into such plaque may allow verapamil to inhibit the activity of these fibroblasts in these older plaques as well. A randomized control study is advisable to further confirm these findings.

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