

ORIGINAL RESEARCH—PEYRONIE'S DISEASE

Topical Verapamil HCl, Topical Trifluoperazine, and Topical Magnesium Sulfate for the Treatment of Peyronie's Disease—A Placebo-Controlled Pilot Study

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ABSTRACT

Introduction. Transdermal and intralesional verapamil has been reported to be useful in the treatment of Peyronie's Disease. This study evaluates a topically applied calcium channel blocker (verapamil hydrochloride 15% gel), a topically applied calmodulin blocker (trifluoperazine), and a topically applied weak calcium channel blocker (magnesium sulfate), each incorporated in a transdermal vehicle.

Aim. This pilot study was conducted to assess the efficacy of a 15% verapamil gel applied topically to the penile shaft twice daily for the treatment of Peyronie's Disease.

Main Outcome Measure. To assess improvement in curvature, plaque size, resolution of painful erections, and improvement in erection quality.

Methods. Two simultaneous, three armed, double blinded, placebo-controlled studies were conducted. After randomization into one of four groups, patients were treated for 3 months. At the end of 3 months' treatment using blinded drug, each patient was treated with open label topical verapamil for 6 months. The studies were completed after each patient had been treated and evaluated for 9 months after randomization.

Results. Fifty-seven patients were randomized. In total, 94.4% of patients treated for 9 months with topical verapamil experienced improvement in curvature with an average percent curvature change of 61.1% compared with 43.6% curvature improvement at 3 months. At 9 months the average percent plaque change was 84.7% compared with 55% at 3 months. Pain resolution at 9 months was 100% compared with 87.5% at 3 months. Patient perception of erection quality also increased at 9 months to 81.8% compared with 72.7% at 3 months.

Conclusions. Topical verapamil gel proved effective in eliminating pain on erection, decreasing the size of plaque, decreasing curvature, and improving erection quality in patients with Peyronie's Disease. Treatment results improved significantly after 9 months' treatment as compared with 3 months' treatment. **Fitch WP III, Easterling WJ, Talbert RL, Bordovsky MJ, and Mosier M. Topical verapamil HCl, topical trifluoperazine, and topical magnesium sulfate for the treatment of Peyronie's Disease—A placebo-controlled pilot study. J Sex Med 2007;4:477–484.**

Key Words. Peyronie's Disease; Calcium Channel Blocker; Topical Verapamil; Placebo

Introduction

Fibrosis of the penile tunica albuginea was first described by Francois de la Peyronie in 1743

[1]. The fibrotic process is characterized by palpable fibrotic plaque, penile curvature, pain with erections, and decreased quality of erection. The incidence of Peyronie's Disease in the general

male population has been reported to be as high as 3.67% [2–4].

Aggeler et al. demonstrated that antimicrotubular agents, calcium antagonists, and calmodulin blockers resulted in a change in fibroblast cell shape [5]. Kelly demonstrated with in vitro experiments the importance of calcium in fibroblast exocytosis [6].

Levine et al. reported that intralesional verapamil injection of Peyronie's plaque resulted in an 84% resolution of pain, improvement in curvature in 62% of patients, and improved sexual performance in 71% of patients [7].

The purpose of this study was to evaluate a topically applied calcium channel blocker (verapamil hydrochloride), a topically applied calmodulin blocker (trifluoperazine), and a topically applied weak calcium channel blocker (magnesium sulfate), each incorporated in a transdermal vehicle for the treatment of Peyronie's Disease.

Methods

Two simultaneous three armed, double blinded placebo-controlled studies were conducted in this pilot study. The first study was a comparison of topical verapamil 15% vs. topical trifluoperazine 10%, and topical placebo. The second study compared topical verapamil 15% vs. topical magnesium sulfate 10% and placebo. After signing an informed consent, patients were assigned a protocol number by drawing. Each group had similar demographics, symptoms, and duration of symptoms. After randomization into one of four groups, patients were treated for 3 months. The drug preparations were applied to the entire penile shaft (excluding the glans) twice daily. The 0.5 mL dose was measured with a paper dosimeter. Patients were seen and evaluated at 1-month intervals. Plaque was measured with calipers and the surface area calculated. The person measuring plaque size was blinded as to active treatment vs. placebo. Pain was measured by a "Yes" or "No" answer as the treatment objective was the total elimination of pain. Degree of curvature and erection quality were described.

At the end of 3 months' treatment using blinded drug, each patient was treated with open label verapamil gel for an additional 6 months. Patients continued to be seen and evaluated at 1-month intervals. The study was completed after each patient had been treated and evaluated for 9 months.

Statistical Methods

The sample sizes for this trial were small. Because of the small sample size, the comparison of proportions between treatments (such as the proportion of patients showing improvement on clinical endpoints) was conducted using Fisher's Exact Test, rather than the more common chi-squared test. Expected counts for some cells in each contingency table are certainly less than 5, making the chi-squared test invalid.

Comparisons between treatments of the average percent change in clinical endpoints were performed using the Wilcoxon Rank Sum Test. This nonparametric procedure provides valid inference regardless of the distribution of the variables which cannot be adequately assessed with limited sample sizes.

For the treatment comparisons of verapamil at 3 months with verapamil at 9 months, methods appropriate for paired data were used. For proportions of patients achieving improvement, McNemar's test was used. For average change from baseline endpoints, the Wilcoxon Signed Rank test was used.

Results

Fifty-seven patients with Peyronie's Disease were evaluated and randomized into one of six subgroups:

Group One

- Topical verapamil 15% (10 patients).
- Topical trifluoperazine 10% (seven patients).
- Topical placebo (10 patients).

Note: because of serious side effects (anxiety, agitation, blurred vision, insomnia, and depression) with trifluoperazine 10%, enrollment was terminated after enrolling seven patients.

Group Two

- Topical verapamil 15% (10 patients).
- Topical magnesium sulfate 10% (10 patients).
- Topical placebo (10 patients).

Demographics

The patients' ages ranged from 30 years to 83 years with the mean age being 56.3 years (Tables 1–4).

Fifty-three patients completed the study.

Topical Verapamil

Of the 20 patients randomized to topical verapamil, two patients (11.1%) experienced contact

Table 1 Age distribution (57 patients)

<30 years	0
30–39 years	1
40–49 years	14
50–59 years	22
60–69 years	14
70–79 years	5
>79 years	1
Minimum age	30 years
Maximum age	83 years
Mean age	56.3 years

Table 2 Duration of disease prior to treatment

<0.5 year	9 patients
0.5–1.0 year	13 patients
1.1–2.0 years	8 patients
2.1–5.0 years	19 patients
>5.0 years	8 patients
Mean value = 3.35 years	54 patients
The duration of symptoms prior to randomization ranged from 2 months to 15 years with a mean of 3.35 years.	

Table 3 Symptoms (57 patients)

Palpable plaque	57 patients (98.2%)
Mean plaque size (cm ²)	3.04
Penile curvature	56 patients (98.2%)
Mean degree of curvature	45 degrees
Painful erections	20 patients (37.0%)
Decreased quality of erections	39 patients (72.2%)
Of these 57 patients, 56 had palpable Peyronie's plaque, 56 patients complained of penile curvature, 20 patients complained of painful erections, and 39 patients reported decreased quality of erections.	

dermatitis, and subsequently one of these patients withdrew from the study. One patient was lost to follow up. At 3 months, 87.5% of the eight patients with pain experienced complete pain resolution. Of the 18 patients with curvature, 14 (77.8%) had reduction in curvature. The average improvement in degrees of curvature after 3 months of treatment with topical verapamil was 43.6%. Of the 18 patients with palpable plaque, 18 (100%) had reduction in plaque size after 3 months' treatment with topical verapamil. The average reduction in plaque size in this group of

patients was 55% after 3 months' treatment with topical verapamil. Of the 11 patients with diminished quality erections and treated with topical verapamil, eight patients (72.7%) experienced improved quality of erections.

In comparing patients with Peyronie's Disease with less than 6 months' duration with patients with greater than 12 months' duration, we saw no statistical significant difference in results related to duration of disease.

Topical Trifluoperazine

Of the seven patients started on topical trifluoperazine, five (71.4%) had serious side effects including anxiety, agitation, blurred vision, insomnia, and depression. Three patients (42.9%) with curvature experienced improvement of curvature. The average improvement in degrees of curvature was 9.5%. Five patients (71.4%) had plaque reduction. The average plaque reduction was 15.8%. Of the three patients with pain, two (66.7%) had total pain relief. Three (50%) of the six patients with decreased quality of erection had improvement with topical trifluoperazine. In comparing trifluoperazine with placebo, there was no statistically significant difference in results. Because of the severity of side effects, treatment with topical trifluoperazine was discontinued prior to completion of randomization.

Topical Magnesium Sulfate

Of the 10 patients initially treated with topical magnesium sulfate, three (30%) had improvement in curvature while six (60%) experienced a decrease in plaque size. The average improvement in degrees of curvature was 14.1%. The average decrease in plaque size was 20.3%. Only one patient randomized to topical magnesium sulfate initially complained of pain, and this patient experienced complete resolution of pain after treatment with topical magnesium sulfate. Three patients (50%) of the six patients who complained of diminished erection quality experienced improvement. In comparing magnesium sulfate with

Table 4 Characteristics placebo vs. verapamil treated patients

Patient characteristics	Placebo	Verapamil
Time of disease onset	3 months to 10 years Average 3.1 years	2 months to 15 years Average 3 years
Plaque size (cm ²)	0.25–6.25 Average 2.99	0.25–12 Average 3.94
Pain on erection (%)	44.4	44.4
Curvature	5–80 degrees Average 45 degrees	20–120 degrees Average 49.2 degrees

Table 5 Topical verapamil vs. placebo at 3 months (percentage improved)

	Verapamil N = 18	Placebo N = 18	P value
Patients with curvature improvement	77.8%	29.4%	0.0067*
Average percent curvature change	43.6%	18.5%	0.015 [†]
Patients with plaque improvement	100%	33.3%	0.0001*
Average percent plaque change	55%	5.0%	0.0024 [†]
Patients with pain resolution	87.5%	37.5%	0.1189*
Patients with erection quality improvement	72.7%	25.0%	0.0220*

*Fisher's Exact Test.
[†]Wilcoxon Rank Sum Test.

placebo, there was no statistically significant difference in results.

Topical Placebo

The placebo effect may appear unrealistic. However, the small number of patients, along with the dramatic results achieved by five of the patients, indicates that additional studies need to be performed with much larger placebo populations. For example, one patient experienced an 83% curvature improvement and an 87% plaque improvement. Another patient experienced a 78% curvature improvement and a 64% curvature improvement. Another patient experienced a 33% curvature and a 100% plaque improvement. Another patient experienced a 100% curvature improvement along with an 84% plaque improvement, but only had a 5-degree curvature at the onset of the study.

Eighteen patients were treated with placebo. Two patients immediately discontinued the study. After 3 months of using topical placebo, five patients (29.4%) of 17 patients with curvature experienced decreased penile curvature. The average improvement in degrees curvature was 18.5%. Six patients (33.3%) had decreased plaque size while three patients had increased plaque size. The average reduction in plaque size was 5%. Of the 16 patients complaining of decreased quality erections who were treated with topical placebo,

four (25%) experienced improvement. Of the eight patients complaining of pain and treated with topical placebo, three patients (37.5%) experienced pain resolution.

Finally, it is possible that one or more of the chemical excipients that make up the placebo may have a positive treatment affect on the scar tissue. The fatty layer of the protective stratum corneum is reversibly modified to allow the carrier and active drug to traverse the stratum corneum and deposit in the diseased underlying tissue. Further research will be conducted to investigate this possible positive treatment effect of the placebo. Tissue remodeling is complex, and it is not inconceivable that one of the chemical excipients could affect one or more of the glycosaminoglycans, proteoglycans, growth factors, or cytokines involved in the healing and remodeling process (Table 5).

The data pertaining to the use of topical verapamil for 9 months was compared with the 3-month data (Table 6). After using topical verapamil for 9 months, 17 (94.4%) of patients experienced a decrease in curvature compared with 14 patients (77.8%) after 3 months of treatment. The average curvature reduction in degrees was 61.1% at 9 months compared with 43.6% at 3 months. One patient (5.6%) had total resolution of curvature at 3 months. Four patients (22.2%) had total resolution of curvature at 9 months. One hundred

Table 6 Topical verapamil at 3 months vs. 9 months

	Verapamil at 3 months N = 18	Verapamil at 9 months N = 18	P value
Patients with curvature improvement	77.8%	94.4%	0.8333*
Average percent curvature change	43.6%	61.1%	0.0117 [†]
Patients with plaque improvement	100%	100%	1.0000*
Average percent plaque change	55%	84.7%	0.0010 [†]
Patients with pain resolution	87.5%	100%	0.3174*
Patients with erection quality improvement	72.7%	81.8%	0.3174*

*McNemar's Test (for paired proportions).
[†]Wilcoxon Signed Rank Test (for paired data).

For completeness, statistical tests were performed for all endpoints comparing verapamil at 3 months to verapamil at 9 months, even though in some cases the use of a statistical test is clearly not needed. For example, when nearly all patients showed improvement at 3 months, there is no room left for further improvement at 9 months. Such a "ceiling effect" will cause the statistical comparison of the two time points to be nonsignificant, even though there is very clear evidence of an effect at 3 months, which is sustained through 9 months.

percent of patients using topical verapamil for 9 months had decreased plaque size. The average plaque size decrease at 9 months was 84.7% compared with 55% at 3 months. Seven patients (38.9%) experienced complete resolution of plaque at 9 months compared with five patients (27.8%) at 3 months. One hundred percent of the patients experiencing pain secondary to Peyronie's Disease had complete resolution of pain at 9 months compared with 87.5% at 3 months. Nine patients (81.8%) who experienced diminished quality of erections had improvement in erection quality after treatment with topical verapamil for 9 months compared with 72.7% at 3 months.

Discussion

Some feel that ultrasonic measurements of plaque should be performed while others prefer palpation and physical measurement. We unsuccessfully attempted ultrasound on 10 patients with palpable plaque. We found that calculating area using measurements with calipers was the most accurate and reproducible.

We felt that a simple "Yes" or "No" for the presence of pain was more objective than a visual analog pain scale which would have been appropriate had we been evaluating degrees of pain reduction as opposed to complete elimination of pain.

Curvature can be measured by patient estimation, with photography, and by using intracavernosal injection of vasoactive drugs. Photography can be misleading because of varying camera position. Vasoactive drug injection involves risks such as priapism, fibrosis of the tunica albuginea, and fibrosis of the cavernosal smooth muscle. Cavernosal injection may cause problems in enrolling and retaining patients in studies. We utilized patient estimation of curvature because error in patient estimation of curvature is diluted by the number of patients in the study. The most important aspect in quantifying curvature change is the patient perception of improvement or absence of improvement.

Measurement of erection quality may be the most controversial. While the baseline patient estimate may not be totally accurate, the patient and his partner certainly are able to discern the presence or absence of improvement. The treatment was designed to lessen curvature and eliminate pain as the primary outcomes. The important

clinical question related to erectile dysfunction is "does the treatment worsen the erectile dysfunction?" Our data clearly show that it does not. Perhaps the International Index of Erectile Function questionnaire should be utilized in future studies.

Important observations made during this study include:

- Based on the data shown in Table 5 comparing 3-month and 9-month treatment, patients should be treated with topical verapamil as long as there is continued measurable improvement in pain, plaque size, curvature, and erection quality.
- There may be a significant reduction in plaque prior to observed improvement in curvature.
- Successful treatment is directly related to patient compliance and physician follow-up. We suggest that physicians examine patients after 1 month of treatment with follow-up every 3 months thereafter.

The results reported using topical verapamil 15% are better than the reported results obtained by using intralesional verapamil injections for several reasons:

- Multiple injections into the plaque are traumatic and may cause an increase in inflammatory reaction.
- The plaque's density prevents adequate entry and medication deposition.
- Patients oftentimes do not return for follow-up treatment and observation because of the pain and trauma experienced with the first injections.

Specific data are presented in Table 7.

Topical verapamil is administered to the entire shaft of the penis. In addition to treating observed plaque, this also may reverse any undiagnosed fibrotic tissue that could be subject to injury. Additionally, a uniform concentration of verapamil is maintained throughout the entire plaque formation rather than randomly as administered by injection.

This product shows therapeutic promise because it has been formulated and designed to allow only negligible concentrations of active drug into the circulation and to allow for the majority of absorption and concentration of the active drug into the invading plaque. In 1990 Lee and Ping noted that the therapeutic serum levels of verapamil used for the treatment of hypertension and cardiac arrhythmias range from 0.01 to 0.2 μM .

Table 7 Topical verapamil vs. intraplaque verapamil injection

	Topical verapamil at 3 months (%)	Topical verapamil at 9 months (%)	Intraplaque verapamil injection (%)
Curvature improvement	77.8	94.4	62
Curvature worsening	0	0	8
No change in initial curvature	22.2	5.6	31
Plaque improvement	100	100	Reported as mean volume
Pain improvement	100	100	95
Pain resolution	87.5	100	84
Erection quality improvement	72.7	81.8	80

On the other hand, the concentration necessary to inhibit extracellular matrix collagen synthesis in their in vitro study was in the 100 μM range [8]. Because of this comparatively high dose, it appears necessary to administer verapamil locally to avoid systemic toxicity while exposing fibroblasts within the plaque to an adequate verapamil concentration. In order to maintain a 100 μM concentration, a sustained release of active drug must be maintained first to establish therapeutic drug equilibrium and thereafter to maintain therapeutic equilibrium. The Dow Pharmaceutical Science skin absorption study data of the product utilized in this study indicate that the product meets this criteria.

Martin et al. reported that the transdermal application of verapamil gel to the penile shaft fails to infiltrate the tunica albuginea [9]. The accuracy of this study is questionable for the following reasons: only eight patients were studied; none of the patients studied had Peyronie's Disease. Verapamil was applied twice before surgery and was removed prior to surgery. It is highly unlikely that two applications would result in equilibration between epidermal tissue and the tunica albuginea. Application occurred over only the sides of the penile shaft and not the entire penile shaft as described in this study.

Furthermore, few details are provided concerning active ingredient, and no information is provided regarding whether verapamil or verapamil hydrochloride was used. Verapamil hydrochloride is preferred because of its stability. Drug vehicle and compounding technique are critical. The vehicle must be designed to traverse the stratum corneum to the extent that it reaches subdermal connective tissue but at the same time minimizes systemic absorption.

The compounding procedure must be reproducible and must provide a product of consistent characteristics such as viscosity, particle size, pH. Stability is essential. The drug must be protected from light to prevent degradation, and it must be

packaged in a material that is nonreactive chemically or physically to the active ingredient or any ingredient of the drug vehicle.

The authors state that it is unlikely that verapamil would be found in fibrotic scar tissue. However, treating fibrotic connective tissue is the essence of transdermal treatment and should lead to remodeling of fibrotic tissue.

Verapamil is extensively metabolized by cytochrome P4503A4, and only 3–4% is excreted unchanged in the urine. Based on the reported urinary concentration of 46 ng/mL, and using data provided by Saseen et al. [10] the back extrapolated plasma concentration would have to be 1400 ng/mL to achieve the reported urinary concentration, and the estimated dose to produce this plasma concentration is approximately equivalent to an oral dose of 960 mg daily. The observed urinary verapamil is most likely due to contamination. The conclusions noted in Martin's publication were addressed to and published by *The Journal of Urology*, Volume 173, p. 1830, May 2005.

The verapamil 15% formulation utilized in our study was evaluated by Dow Pharmaceutical Sciences. The bioavailability of this topically applied drug formulation of verapamil HCl was assessed utilizing an in vitro percutaneous absorption test. Radiolabeled (^3H) verapamil HCl absorption was measured utilizing Bronaugh flow-through diffusion cells and evaluated for potential effectiveness in the topical treatment of Peyronie's Disease.

Human abdominal skin was dosed with the subject formulation, and the absorption characteristics were evaluated every 6 hours for 24 hours. The kinetic profile of the drug's penetration was studied by plotting dose penetration vs. time. Epidermal, dermal, and receptor solution samples were assessed. In total, 87.58% of the applied dose was recovered. The receptor solution concentration correlates with the amount of drug systemically available following the application of a

clinically relevant dose to normal, non-occluded skin.

The PDLabs 15% topical verapamil HCl compound resulted in very low levels in the receptor solution (0.028%). This predicts very low levels of verapamil HCl systemic exposure following topical application, which is one desired characteristic of the product as the targeted area of treatment lies very close to the dermis of the skin. Untoward systemic effects are minimized. Dermal and epidermal levels of deposition suggest that the vehicle and the drug to a large degree partition in the epidermis, thereby creating a significant reservoir for sustained release of verapamil HCl from human skin without the use of mechanical depots of drug such as those manufactured in sustained release patches.

This combination of high dose loading and high epidermal deposition, following the application to skin, indicates that the PDLabs formulation of 15% verapamil HCl should result in effective, sustained delivery of the verapamil HCl to the Peyronie's plaque.

The mechanism of action involved with the use of topically applied calcium channel blockers and calmodulin blockers to treat fibrotic connective tissue disorders is not fully understood. However, the proposed mechanism of action involves blocking the cellular entry of divalent calcium or inhibiting the binding of calmodulin antagonists to calmodulin binding protein within the cell. The result appears to be a tissue remodeling effect that involves the production of a metalloproteinase (MMP) or serine protease that degrades matrix proteins such as collagen, laminin, and fibronectin. MMP, or collagenase, is highly dependent on divalent calcium and/or divalent zinc to become active. MMPs are commonly expressed by cells involved in tissue injury. MMPs are also signaled by inflammatory cytokines [11]. Further research is required to fully understand the interaction of ion channels and disease processes.

Conclusion

The data obtained from these studies confirm that a properly formulated topical verapamil 15% is an effective treatment for Peyronie's Disease.

Topical verapamil proves more effective than topical trifluoperazine, topical magnesium sulfate, and topical placebo for improving curvature, decreasing plaque, resolving pain, and improving erection quality in patients with Peyronie's Dis-

ease. This conclusion is reinforced by the 9-month data presented and supports the fact that an extended treatment period (more than a year) is necessary for some patients to experience optimal treatment results.

This was a pilot study, and the patient numbers were small, but the results were encouraging. Multicenter, randomized, double-blinded studies comparing verapamil with placebo should be performed in the future utilizing a larger patient population.

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