J Urol. 2003 May;169(5):1775-8.
Tunica albuginea tissue analysis after electromotive drug administration.
Levine LA, Estrada CR, Shou W, Cole A.

Source

Department of Urology, Rush Medical College, Chicago, IL, USA.

Abstract

PURPOSE:

To minimize patient discomfort electromotive drug administration has been used as noninvasive transdermal therapy for Peyronie's disease. We directly measured the tissue concentration of verapamil after electromotive drug administration to investigate whether this treatment modality is an effective drug delivery system.

MATERIALS AND METHODS:

A total of 19 tunica albuginea samples from 16 men undergoing surgical treatment for Peyronie's disease were used for analysis. Of these 16 men 14 underwent electromotive drug administration, including 12 with 10 mg. verapamil and 2 with 10 mg. verapamil plus 0.05 mg. epinephrine. In 2 men partial plaque excision was performed and the tunica albuginea samples were directly injected with verapamil. Another 3 men who served as controls had no exposure to verapamil. Electromotive drug administration was performed at an output of 2 mA. for 20 minutes. Tissue analysis was done using liquid chromatography-tandem mass spectrometry.

RESULTS:

Control tunica albuginea samples showed a verapamil level that was undetectable up to 109 ng./gm. The 14 verapamil electromotive drug administration treated specimens demonstrated undetectable to 37,510 ng./gm. verapamil. Overall 10 of the 14 electromotive drug administration treated tunica albuginea specimens (71.5%) contained measurable levels of verapamil. Adding epinephrine to the drug solution did not appear to enhance drug delivery. The concentration of verapamil in the 2 direct verapamil injection tunica albuginea samples was 166,898 and 118,411 ng./gm., respectively. There were no surgery or electromotive drug administration related complications.

CONCLUSIONS:

Electromotive drug administration is a safe and noninvasive treatment modality. Verapamil was detected in 71.5% of tunica albuginea specimens after electromotive drug administration with a wide range of verapamil levels. To our knowledge whether these levels affect change in Peyronie's disease plaque, resulting in improvement in penile deformity, is unknown and requires further placebo controlled trials

Expert Opin Pharmacother. 2011 Apr;12(6):931-44.

Current status and new developments in Peyronie's disease: medical, minimally invasive and surgical treatment options.

Gur S, Limin M, Hellstrom WJ.

Pag2

Source

Department of Urology, Health Sciences Center, Tulane University, New Orleans, Louisiana 70112, USA.

Abstract

INTRODUCTION: Peyronie's disease (PD) is a wound-healing disorder of the tunica albuginea of the penis which affects 3-9% of adult males. Clinically, any combination of plaque formation, penile pain, angulation and erectile dysfunction may appear. This condition may progress, stabilize or, uncommonly, regress during the initial acute phase (6-18 months). AREAS COVERED: Information regarding this review was searched in PubMed until August 2010. Vitamin E, paraaminobenzoate and colchicine are sparingly employed oral medical therapies. Intralesional injections as a minimally invasive therapy for PD includes injection with verapamil, interferon-α-2b, and collagenase. Men suffering with PD who have significant penile deformity precluding successful coitus can be appraised for surgical correction. Surgery is considered the gold standard and includes plication, incision and grafting- or penile-prosthesis-related procedures. EXPERT OPINION: This paper provides a broad overview of the subject of PD, available nonsurgical options and surgical approaches that will aid in the routine clinical diagnosis and management of PD. Increased public and medical awareness of PD prevalence, presentation, diagnosis and treatment options will serve well the large population of men who suffer in silence with this common condition

J Pak Med Assoc. 2010 Apr;60(4):291-3.

Evaluation of intralesional injection of verapamil in treatment of Peyronie's disease.

Heidari M, Nejadi JR, Ghate A, Delfan B, Iran-Pour E.

Source

Shohadaye Ashayer Hospital, Lorestan University of Medical Sciences, Lorestan, Islamic Republic of Iran.

Abstract

OBJECTIVE:

To evaluate the effect of intralesional injection of verapamil in Peyronie's plaque with confirmed lesion.

METHODS:

This randomized clinical trial was carried out between March 2005 and March 2006 on 16 patients with Peyronie's disease who were referred to the Urology Clinic of Shohadaye Ashayer Hospital in Khorram Abad, Iran. Performing a comprehensive physical exam, the genitalia of the patients were checked to confirm the diagnosis and reject other sexual disorders. Besides, parameters such as penis curving, lesion size were measured. Then, based on the 10-point visual analogue scale, sexual satisfaction of patients and their wives were recorded in a questionnaire. Patients got intralesional verapamil every 14 days and were treated for 6 months. After that, the parameters were assessed and data collected was analyzed using paired t-test. P-value < 0.05 was considered statistically significant.

RESULTS:

On average, lesion size and penis curving decreased 30%. Almost 20% of patients and their wives were satisfied with the outcome of the treatment. No significant side effect was seen during the treatment.

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CONCLUSION:

Injection of calcium channel blockers are effective for treatment of the Peyronie's disease; however, more studies with more patients are needed

Medical Management of Peyronie's Disease

WAYNE J. G. HELLSTROM

From the Department of Urology, Tulane University School of Medicine, New Orleans, Louisiana.

Abstract

Peyronie's disease (PD) is a wound-healing disorder in which a fibrotic plaque forms in the tunica albuginea layer of the penis. It clinically presents as any combination of penile pain, angulation, and erectile dysfunction. Recent studies indicate that PD has a prevalence of 3%–9% in adult men. Although the exact etiology has not been established, PD likely results from a predisposing genetic susceptibility combined with an inciting event such as microtrauma during intercourse. During the initial acute phase (6–18 months), the condition may progress, stabilize, or regress. For this reason authorities recommend a more conservative treatment approach, with a trial of oral and/or intralesional pharmacotherapy, before surgical reconstruction is considered. Oral therapies most commonly employed include tocopherol (vitamin E) and paraaminobenzoate (Potaba), with colchicine, tamoxifen, propoleum, and acetyl-L-carnitine being used less often. There are a limited number of long-term placebo-controlled studies with these oral agents, and for the most part, studies have failed to show a consistent beneficial effect. Intralesional injection therapy for PD is more commonly used as a first-line therapy. The current standard of care includes injection with interferon-α-2b, verapamil, or collagenase. Interferon-α-2b, in particular, has been documented in a large, multicenter, placebo-controlled study to show significant benefit over placebo in decreasing penile curvature, plaque size, penile pain, and plaque density. However, intralesional interferon is associated with posttreatment flu-like symptoms unless patients are premedicated with a nonsteroid anti-inflammatory agent. Other available therapies that have not consistently shown efficacy in placebo-controlled studies include corticosteroids, orgotein, radiation, and extracorporeal shockwave therapy. Surgery is considered when men with PD do not respond to conservative or medical therapy for approximately 1 year and cannot perform satisfactory sexual intercourse. Ongoing basic research in PD will likely identify future targets for medical exploitation.

Key words: Penis, erectile dysfunction, penile curvature

Peyronie's disease (PD) is a localized connective tissue disorder characterized by changes in the collagen composition that cause abnormal scar formation in the tunica albuginea of the penis. Although the condition was recognized earlier in the medical literature, the eponymous term arose after Francois Gigot de la Peyronie, the personal physician to King Louis XV of France, reported on a series of 3 patients with nodules and curvature of the penis in 1743.

PD has historically been thought to be a rare, insignificant condition. The first description of the natural history of PD (Williams and Thomas, 1970) reported that the disease was one of "gradual resolution." They further stated that none of the 21 patients described in their study experienced a worsening of their condition. This led them to advocate observation and reassurance as primary therapy. Their study was hindered by a small number of study subjects, inadequate follow-up, and lack of a standardized approach and evaluation of patients with PD. Nevertheless, the results of this study led clinicians to adopt a conservative approach of watchful waiting as standard treatment for PD.

In 1990, a questionnaire-based study (Gelbard et al, 1990) revealed that among 97 patients with PD, only 13% experienced a resolution of their symptoms. They further noted that 40% of respondents perceived that their disease had progressed, and 48% considered that their condition had remained unchanged at follow-up. In addition to disease progression, these authors reported that 77% of patients experienced detrimental psychological consequences as a result of their disease process. Another study (Kadioglu et al, 2001) provided additional support to the idea that PD was a progressive condition in a retrospective review of 307 men with this condition. They reported that spontaneous resolution was a rare occurrence and that 30.2% of those not receiving any treatment experienced substantial deterioration. Additionally, 62.5% of patients found their disorder to be "disabling," and poorer outcomes and symptoms were associated with the presence of coexisting diabetes mellitus, hypertension, or lipid abnormalities. Results from these studies suggested that despite a general perception that the condition was benign, PD is progressive and can result in significant emotional and psychological consequences in the afflicted.

Current epidemiological estimates of the prevalence of PD range from 3.2%, as described in a 1999 questionnaire study involving 4432 respondents from Cologne, Germany (Schwarzer et al, 2001), to 8.9%, as reported in a 2004 study of 534 men who presented to American urologists for routine prostate screening (Mulhall et al, 2004). Disease onset is commonly associated with preceding trauma and most often occurs in older men (mean age, 53 years; range, 19–83 years), although reports (Mulhall et al, 2006) have documented that the majority of men with PD in their series had no specific recollection of trauma and 10% of patients experienced symptom onset before 40 years of age.

Pathophysiology

Despite PD being recognized by the medical community for >250 years, there has been meager advancement by researchers toward understanding the underlying etiology of PD and providing effective modalities for preventing and curing the condition. PD is commonly perceived to be a disorder of inappropriate wound healing, with its development probably resulting from an underlying genetic predisposition in addition to the presence of an inciting event (Bjekic et al, 2006). As mentioned, microtrauma has been hypothesized to contribute to the initiation of PD.

Evidence for an underlying genetic predisposition towards PD can be found in its association with other collagen diseases such as Dupuytren's disease. One study comparing the gene expression profiles of patients with PD and Dupuytren's found similar alternations in genes responsible for collagen degradation, ossification, and myofibroblast differentiation (Qian et al, 2004).

Clinical Evaluation

No standard clinical assessment of PD has been established to date. Patients presenting with PD typically exhibit any single presentation or a combination of penile plaque, curvature, penile pain, and erectile dysfunction (ED). Plaques are typically located on the dorsal or lateral aspect of the penis, causing an upward or lateral deflection during erection. As many patients are embarrassed by or unaware of the presence of PD, they are unlikely to mention the topic unless specifically questioned about it by a treating physician.

All assessments of PD should begin with a thorough history, gathering information about disease onset and duration, the presence of precipitating trauma, the degree of penile deformity, curvature and erectile rigidity/dysfunction, and the subjective level of sexual ability. It is also important to understand the degree of emotional and psychological impact that this disease has on the patient's interpersonal relationships, as this may encourage a more thorough and possibly aggressive treatment approach. A more detailed medical and sexual history can often be rapidly obtained through the use of standardized questionnaires, such as the International Index of Erectile Function (IIEF) and the Peyronie's Disease Index (Levine et al, 2003). These may also serve as means for the objective follow-up to measure treatment efficacy over time. Information obtained about a patient's medical history should focus on risk factors associated with ED, such as hypertension, hyperlipidemia, diabetes, or the presence of coronary artery disease.

Physical examination begins with a standard genitourinary evaluation and includes observation for the presence of Dupuytren's contracture or Lederhose scarring (plantar fibromatosis), both of which are associated with an increased incidence of PD. Objective measurements include documentation of the stretched penile length, plaque characteristics, location and size, and the presence or absence of tenderness to palpation.

Laboratory studies do not serve an essential role in the diagnosis or management of PD, but may include serum testosterone, glucose, prostate-specific antigen, and lipid panel according to the clinical presentation (eg, ED). Objective imaging may be obtained via penile duplex Doppler ultrasonography (PDDU) to record penile vascular flow, venous leakage, and erectile response, as well as plaque size and location and presence of calcifications. Penile curvature can be measured by using a standard instrument, such as a protractor, or by using photographs taken from multiple angles. Although vasoactive injections can cause bruising, pain, and prolonged erections, obtaining accurate baseline measurements is valuable. These measurements provide a standard against which progression or regression of the disease can be measured at future visits.

Taking into account the natural history of PD and the results of appropriate clinical evaluation, considerations for appropriate therapy can be made on the basis of the patient's erectile status, the presence of bothersome symptoms such as pain, the patient's motivation for treatment, and the patient's overall psychological status (Levine and Greenfield, 2003). In most patients, the standard of care involves an initial trial of either oral or intralesional therapies during the first 6–12 months of treatment (Kendirci and Hellstrom, 2004). Commonly prescribed oral therapies include tocopherol (vitamin E) and para-aminobenzoate (Potaba), with colchicine, tamoxifen, propoleum, and acetyl-L-carnitine used less frequently. Intralesional therapy involves repeated injections of verapamil, interferon-α-2a or -2b, or collagenase directly into the penile plaque over 2-week intervals (biweekly) for approximately 6 months. Other available intralesional therapies include corticosteroids and orgotein, which have not shown any efficacy to date.

Oral Pharmacotherapy

Oral pharmacotherapies and their proposed mechanisms and effects are summarized in Table 1.

Tocopherol (Vitamin E)— Tocopherol is a fat-soluble compound that functions as a natural antioxidant to reduce the number of oxygen free radicals produced in energy metabolism. It has also been shown to play a role in DNA repair and in immune modulation (Traber et al, 1999). The widely accepted use of tocopherol in the treatment of PD has been hypothesized to inhibit fibrosis by acting as a scavenger of oxygen free radicals. In vitro studies examining the effect of free radicals on human cavernosal cells have exhibited a direct association with increased collagen production (Ahuja et al, 1999). It is logical to conclude that inhibition of free radicals (ie, with use of tocopherol) should decrease the rate and degree of fibrosis. However, in vivo data have failed to show any benefit in patients with PD to date.

The first reported use of tocopherol was in a 1948 study of 23 patients that found a 91% reduction in plaque size with complete resolution of pain and a 78% decrease in penile curvature (Scardino and Scott, 1949). However, a double-blinded, placebo-controlled, crossover study (Pryor and Farrell, 1983) failed to show similar beneficial effects for tocopherol relative to placebo. In this study, of 40 patients with PD, an improvement in pain was noted among 35% of those receiving tocopherol, but no significant changes were observed in plaque size or penile curvature.

Despite the lack of definitive evidence for tocopherol in the treatment of PD, urologists commonly prescribe this agent at once-daily doses of 400 IU because of its wide availability, low cost, and minimal to absent adverse effects. Additionally, because many patients with PD experience psychological effects, tocopherol

may also serve to provide a psychological placebo benefit to patients wishing to do something (as opposed to nothing) to alter the course of their disease.

Para-Aminobenzoate (Potaba)— Para-aminobenzoate (Potaba) is a compound that was introduced in 1959 as a possible therapy for PD after it was shown to decrease collagen production in vitro when added to fibroblast cell cultures (Zarafonetis and Horrax, 1959). Its mechanism of action is hypothesized to involve the enhancement of 3 endogenous antifibrotic properties of tissues: oxygen uptake, glycosaminoglycan (GAG) secretion, and monoamine oxidase activity. Monoamine oxidase is known to break down circulating monoamines that include adrenaline, noradrenaline (epinephrine, norepinephrine), dopamine, and serotonin. Therefore, increased monoamine oxidase activity decreases serotonin, which may play a role in preventing fibrogenesis.

Despite its long history of use, human study data on the efficacy of para-aminobenzoate for PD are limited.

Currently, para-aminobenzoate is considered to be a first-line therapy for PD. Its adverse effect profile is minimal, with nausea and anorexia occurring most frequently. A recent German questionnaire study of 636 urologists treating PD revealed that the majority of their patients (76%) were treated with either para-aminobenzoate (46%) or tocopherol (29%) (Hauck et al, 2005). A recent double-blinded, placebo-controlled PD trial has shown that para-aminobenzoate showed a response rate of 74.3% over placebo 50.0% (P = . 016) (Weidner et al, 2005). These authors suggested that this oral agent may stabilize the disorder and prevent progression of penile curvature.

Colchicine— Colchicine is a medication that is commonly employed in the treatment of acute attacks of gout. Its exact mechanism of action in PD is unknown but is hypothesized to involve a reduction in lactic acid production by leukocytes (thus leading to decreased uric acid deposition) and decreased phagocytosis (with resultant anti-inflammatory effects). It is postulated that the anti-inflammatory properties of colchicine may decrease collagen synthesis and up-regulate collagenase activity.

One study (Kadioglu et al, 2000) examined the efficacy of colchicine administered to 60 men with PD presenting in the acute phase of the disease process. Patients had mean disease duration of 5.7 ± 4.3 months at the time of treatment, and results at follow-up (10.7 ± 4.7 months later) showed improvement in penile deformity in 30% of men, no improvement in 48.3%, deterioration in 21.7%, and resolution of pain in 95%. The authors concluded that the best results were observed in patients exhibiting no vascular risk factors or ED, those presenting within 6 months of disease onset, and those with <30° of curvature. Because this study lacked appropriate controls, few conclusions can be drawn from it about the efficacy of colchicine in patients with PD.

To date, there is no general consensus regarding the use of colchicine in the treatment of PD. The efficacy of treatment increases when the drug is given to patients with fewer vascular risk factors, no comorbid ED, and less significant curvature (<30°), and those presenting early in their disease process. Colchicine, when administered in a regimen of 0.5 mg 3 times daily, is most commonly associated with adverse gastrointestinal effects (nausea, vomiting, diarrhea), but it is generally considered to be a safe medication for the long term.

Tamoxifen— Tamoxifen is a nonsteroidal estrogen receptor antagonist that is most commonly employed in patients with estrogen receptor–positive breast carcinoma. One proposed mechanism of action in patients PD is modulation of transforming growth factor β secretion from fibroblasts.

Tamoxifen was first used as a potential treatment for PD in a 1992 study that treated 32 patients with PD with tamoxifen 20 mg twice daily over a 3-month period (Ralph et al, 1992). Tamoxifen improved penile pain in 80%, reduced erectile deformity in 35.5%, and was associated with plaque shrinkage ≥1 cm in 34.3% of patients. Greater improvement was observed in patients who were in the earlier stages of PD (<4 months) than in those receiving treatment later in the disease process.

However, the efficacy of tamoxifen in PD was called into question by the results of a 25-patient, placebocontrolled study of tamoxifen 20 mg twice daily for 3 months (Teloken et al, 1999). Investigators used penile radiography, ultrasound, and pharmacologically induced erections (using alprostadil [prostaglandin E_1]) to objectively compare baseline status prior to treatment with follow-up 4 months later. No statistically significant differences between tamoxifen and placebo with respect to decreased penile pain (66.6% vs 75%, respectively), reduction in penile deformity (46.1% vs 41.7%, respectively), or decrease in plaque size (30.7% vs 25%, respectively) were observed. Critics of the study point out that patients with PD would probably have experienced better results had they received tamoxifen treatment earlier in the course of the disease. However, in the absence of more conclusive data demonstrating a beneficial effect of tamoxifen on PD, this drug cannot be recommended for routine treatment in patients with PD.

Propoleum— Information regarding the composition, mechanism of action, and efficacy of propoleum is limited, because the substance is patented in Cuba and its use restricted to that country. Propoleum came into use after a Cuban patient with PD began taking the substance for giardiasis and noted that his PD had improved.

Because there is little information regarding the properties of propoleum, and the substance cannot be obtained outside of Cuba, clinical knowledge of the drug is limited. Appropriately designed, placebo-controlled, double-blinded efficacy studies performed by additional research groups are necessary to support or dispute currently published findings (Lemourt et al, 1998, 2003).

Acetyl-L-Carnitine— To date, only 1 study has been conducted to evaluate the efficacy of acetyl-L-carnitine. It is hypothesized to inhibit acetyl coenzyme A. In this randomized study involving 48 patients with PD, subjects were given either tamoxifen 20 mg twice daily or acetyl-L-carnitine 1 g twice daily for 3 months (Biagiotti and Cavallini, 2001). Penile curvature, plaque size, and pain were assessed using PDDU. Results comparing acetyl-L-carnitine with tamoxifen showed that acetyl-L-carnitine was significantly more effective than tamoxifen at reducing pain (92% vs 50%, respectively) and inhibiting disease progression (92% vs 46%, respectively), whereas both drugs were statistically shown to significantly reduce mean plaque size. Only acetyl-L-carnitine was statistically shown to significantly reduce penile curvature (from 15.9° to 8.9°). Although no control was provided in the study, because tamoxifen has been previously shown to be similar to placebo, it can be inferred that acetyl-L-carnitine is possibly effective at reducing pain and at decreasing overall disease progression in patients with PD.

Pentoxifylline— There have been anecdotal reports (not placebo-controlled) about various agents (eg, pentoxifylline) (Brant et al, 2006; Bella et al, 2007; Taylor and Levine, 2008). Although such reports are interesting, they underscore the need to perform large-scale placebo-controlled studies to further explore novel mechanisms of action in clinical cases of PD.

Intralesional Pharmacotherapy

In addition to oral treatments for PD, another option for conservative therapy is injection of pharmacologically active agents directly into penile plaques (Table 2). One advantage of intralesional treatment compared with oral treatment is localized delivery of a particular agent, which provides higher concentrations of the drug than might be tolerated if given systemically. Several drugs have been used to treat penile plaques with varying degrees of efficacy, including corticosteroids, orgotein, collagenases, verapamil, and interferon-α-2a or -2b.

Corticosteroids— Corticosteroids are candidates for treatment of PD because of their anti-inflammatory effects via inhibition of phospholipase A2 and suppression of the immune response (Tranchant et al, 1989). The first documented use of intralesional corticosteroids for PD (Bodner et al, 1953) reported a decrease in plaque size and penile pain following dexamethasone injection. A second study (Winter and Khanna, 1975) of 21 patients with PD conducted in 1975 failed to confirm these earlier findings, even though a high percentage of the patients who had previously failed other therapies noted decreased pain and plaque size. Investigators concluded that the results of intralesional corticosteroid injections did not differ significantly from what would be expected from the natural history of the disease.

Because of the lack of conclusive evidence showing benefit and because of the adverse effects experienced with long-term use of corticosteroids (eg, local tissue atrophy, thinning of skin, immune suppression), corticosteroid injections are not currently advocated as an intralesional therapy for PD.

Orgotein— Orgotein is a pharmaceutical version of copper/zinc superoxide dismutase that possesses anti-inflammatory properties. Superoxide dismutase occurs physiologically in cells, such as polymorphonuclear leukocytes, and generates large amounts of superoxide radicals for various biological purposes, including the destruction of foreign materials (tissue, bacteria). Through its actions, superoxide radicals are converted to the more benign H_2O_2 and O_2 molecules. Because superoxide radicals have the potential to further exacerbate inflammation and generate fibrosis, it was hypothesized that orgotein might potentially reduce the fibrosis associated with PD.

Although orgotein had been used in the treatment of inflammatory urinary tract conditions as early as 1974, its first use as an intralesional injection in patients with PD was not until 7 years later. Two independent studies involving a total of 45 patients found that patients treated with orgotein exhibited decreases in penile pain, curvature, and plaque size, and 19 of 22 patients who previously were unable to engage in sexual activity displayed marked improvement, with some experiencing a complete restoration of normal erectile function (Bartsch et al, 1981; Gustafson et al, 1981). However, these preliminary studies were limited by lack of appropriate controls and flawed experimental design.

Although additional uncontrolled studies have since reported the beneficial effects of intralesional orgotein, no randomized, placebo-controlled, double-blinded studies have been published to date that clearly identify a statistically significant effect of this therapy (Revelli et al, 1990; Primus, 1993). Adverse effects reported for orgotein include pain, swelling, stiffness, dysesthesias, and skin rashes (Uthman et al, 2003). Because information on orgotein is limited, in part by its restricted use in the United States because of reported toxicity with off-label use, it is unlikely to be prescribed for the intralesional therapy of PD.

Collagenase— Collagenase is a physiological enzyme (also classified as specific matrix metalloproteinase 1, 8, and 13) that is capable of degrading interstitial collagens, such as type II collagen. The first examination (Gelbard et al, 1980) of the effect of collagenase on PD plaques took place in 1985. These investigators utilized highly purified clostridial collagenases (PCCs) to test their effect on various human tissues in vitro, including human pericardium, human corpus cavernosum, tunica albuginea, and PD plaques. Results from these experiments demonstrated a considerable reduction in the size of the PD plaque, along with microscopic fraying and dispersal of collagen bundles, when compared with plaques injected with normal saline. Predictably, elastic fibers, vascular smooth muscle, and axonal myelin sheaths were not affected by collagenase application.

Following up on these in vitro results, this research team performed an in vivo pilot study that involved injecting intralesional PCC (mean dose 2328 units) in 31 men with PD (Gelbard et al, 1985). After 4 weeks of treatment, 65% of patients exhibited objective improvement, 93% reported elimination of pain, and the ability to have intercourse was restored in 75% of patients. Additionally, the researchers noted that penile plaques were either altered significantly or absent in 4 patients and reduced by 20%–100% in 16 others.

Interestingly, a study evaluating the presence of IgG antibodies to collagenase in healthy men vs those with PD found that antibodies were present in 34% of healthy men vs 58% of men with PD (Hamilton et al, 1986). These data suggest the possibility that collagenase activity is up-regulated in patients with PD or that effective collagenase activity is decreased because of an autoimmune response against the protein.

Because of its documented efficacy, intralesional collagenase therapy has been used to treat patients with PD; nevertheless, further studies are necessary to confirm a beneficial response to PCC. A multicenter, controlled study is currently being initiated in the United States.

Verapamil— Verapamil is a calcium channel antagonist that is thought to selectively inhibit calcium ion flux in both cardiac muscle and cells responsible for intracardiac conduction, as well as in coronary and systemic arteries. The rationale for its use in the intralesional treatment of patients with PD is based on in vitro data that demonstrate transport of extracellular matrix molecules that include collagen, fibronectin, and GAGs as a calcium-dependent process (Roth et al, 1996). In addition to resulting in decreased intracellular calcium, verapamil has been shown to increase collagenase activity, affect cytokine expression associated with early inflammation and wound formation, and inhibit in vitro fibroblast proliferation in PD plaques (Roth et al, 1996; Mulhall et al, 2002).

Use of intralesional injections of verapamil in patients with PD was popularized in a nonrandomized, uncontrolled study (Levine et al, 1994) of biweekly injections of verapamil 10 mg given over a 6-month period that led to subjective decreases in penile narrowing (reported by 100% of patients) and curvature (among 42% of patients) and objective decreases in plaque volume of ≥50% demonstrated in 30% of patients. Patients also reported benefits with respect to plaque softening and erectile function.

There has only been 1 randomized, placebo-controlled, single-blinded study of verapamil (Rehman et al, 1998). This study included 14 patients with PD and consisted of weekly injections of verapamil or placebo for 6 months with pretreatment and posttreatment PDDU used to objectively measure results. Comparing verapamil with placebo, the data obtained showed statistically significant improvements in mean plaque-associated penile narrowing, statistically significant subjective improvements in mean erectile function (42.87% vs 0%, respectively) and subjective softening of plaques in verapamil-treated patients. The mean change in penile curvature with verapamil was not statistically significant (reduction from 37° at baseline to 29°; $P < .07$).

In patients with PD, adverse effects of the therapy that have been reported thus far include nausea, lightheadedness, penile pain, and ecchymosis. No cardiovascular events have been documented, and the adverse effects of verapamil are generally considered to be mild. Because only 1 study evaluating the efficacy of verapamil has included a placebo arm, additional studies are required to more fully document the benefit of verapamil in terms of altering the natural history of PD.

Interferon-α-2a or -2b— Interferons are a class of endogenously produced, low-molecular-weight cytokines that function to regulate the normal immune response to foreign antigens. Currently, 3 types of natural interferons have been identified: α, β, and γ. The first suggested use of interferons for the treatment of PD was initiated in a study (Duncan et al, 1991) that treated cultured fibroblasts derived from PD plaques with a human recombinant interferon. Results showed that although the α, β, and γ forms of interferon led to inhibition of fibroblast and collagen production, interferon-γ also caused an increase in GAG and fibronectin production. From these data, the authors hypothesized that interferon-α and -β were reasonable agents for use as intralesional therapies for PD.

The first placebo-controlled study involving interferon-α-2b (Judge and Wisniewski, 1997) examined the effects of interferon 1.5 x 10^6 units administered intralesionally 3 times weekly over a 3-week period in 13 patients with PD of ≥12 months' duration. These investigators found that 6 of 10 patients achieved complete resolution of erectile discomfort and significant improvements in penile deformity (mean improvement 20°), with those presenting with smaller initial plaque lengths (<4 cm) showing the greatest improvements. One interesting study that employed magnetic resonance imaging (MRI) to quantitatively assess plaque size in patients with PD prior to and following treatment with interferon-α-2a supported the finding that interferon therapy was more likely to benefit patients presenting with smaller plaques (Polat et al, 1997). Among subjects classified as having plaques 0.5–1 cm in length, complete resolution (at least below the resolution capacity of MRI) was seen, whereas those with plaque lengths of 1.5 and 2 cm achieved mean plaque reductions of 90% and 83.3%, respectively.

The most scientifically definitive study to date on the efficacy of intralesional interferon-α-2b in PD is a single-blinded, multicenter, placebo-controlled, parallel study involving 117 patients published in 2006 (Hellstrom et al, 2006). Fifty-five patients were given interferon-α-2b 5 x 10^6 units at 2-week intervals over a period of 12 weeks, and each patient was evaluated for penile curvature, plaque characteristics (size, density), penile pain, erectile function, and penile hemodynamics using PDDU and IIEF questionnaires. Significant improvement was seen in actively treated patients compared with placebo (intralesional injection of the same volume of saline) for mean penile curvature (reduction from 49.9° to 36.4° in the interferon group vs 50.9° to 46.4° in the placebo group), mean penile plaque size (reduction from 4.8 to 2.2 cm^2 in the interferon group vs 4.5 to 3.6 cm^2 in the placebo group), mean plaque density (reduction from 2.29 to 1.52 in the interferon group vs 2.07 to 1.84 in the placebo group [range 0–3 for both groups]), pain resolution (67.7% of patients in the interferon group vs 28.1% of patients in the placebo group), and penile blood flows, whereas mean IIEF scores were not significantly different before and after treatment (interferon 18.3 to 20.8 vs placebo 17.9 to 19.0). These results provide the best efficacy evidence to date supporting the use of intralesional interferon in patients with PD.

Transdermal Pharmacotherapy

In addition to oral and injection routes of drug delivery, topical and transdermal approaches to the treatment of PD have been investigated. Topical preparations of β-aminopropionitrile, hydrocortisone, and verapamil have been reported in uncontrolled trials to have effects ranging from none to significant reductions in pain, penile deviation, and size of PD plaques (Gelbard et al, 1983; Miller and Ardizzone, 1983). However, the true efficacy of topical preparations was called into question following a study (Martin et al, 2002) in which verapamil levels were measured in excised samples of tunica albuginea following 2 applications of topical verapamil. This study showed that verapamil was not present in any of the tunical samples obtained and was recovered in small amounts in the urine. Despite minimal systemic absorption, the lack of demonstrable verapamil in sampled tunica albuginea suggests that there is no scientific basis for its use. As such, topical therapies are not currently recommended by any credible erectile authorities in the treatment of PD. However, a recent publication by Fitch et al (2007) suggests that long-term (9-month) therapy does provide benefit. Obviously a multicenter placebo-controlled study is needed.

To overcome limitations of topical therapies, emphasis has more recently been placed on testing modalities such as iontophoresis, which enhances the local uptake of drugs. Iontophoresis involves the application of an external electric force to induce further (electromotive) penetration of topical medication and has been evaluated to date with topical verapamil, dexamethasone, and orgotein (Schieroni et al, 1985). This is in contrast to a later study (Martin et al, 2002) that demonstrated no uptake of verapamil in tunica albuginea following topical application. A study (Levine et al, 2003) reported that 71.5% of excised tunica albuginea samples from 14 men who received iontophoresis and topical verapamil therapy prior to undergoing surgical treatment for PD were found to contain measurable levels of verapamil. A subsequent prospective, controlled study evaluated the efficacy of electromotive verapamil and dexamethasone vs electromotive lidocaine (lignocaine) in 96 men with PD (Di Stasi et al, 2004). Men were randomized to receive either verapamil 5 mg ± dexamethasone 8 mg or 2% lidocaine with a 2.4-mA electric current for 20 minutes, 4 times weekly for 6 weeks. Compared with baseline, significant decreases in median plaque volume (reduction from 824 to 348 mm^3) and penile curvature (reduction from 43° to 21°) were seen in the actively treated groups, whereas no changes in plaque volume or curvature were seen in the control group. Significant pain relief was

experienced transiently in the control group and permanently in the treatment arm. These results support those of a previous uncontrolled study that reported plaque reduction in 82%, curvature decrease in 84%, and pain elimination in 88% of 49 men who received verapamil and dexamethasone treatment with iontophoresis (Di Stasi et al, 2003).

Conclusions

PD is a common disorder that often presents with any combination of penile pain, curvature, penile plaque, or ED. The disorder may have an underlying genetic predisposition and become manifest with an inciting event such as trauma. Following the initial evaluation of a patient presenting with PD, the recommended standard of care involves an initial trial of oral and/or intralesional pharmacotherapy in the acute phase (first year) of this condition.

Among available oral treatments, tocopherol para-aminobenzoates are the most commonly prescribed agents because they are inexpensive, have a mild adverse effect profile, and provide a psychological placebo benefit. Colchicine, tamoxifen, propoleum, and acetyl-L-carnitine are additional oral therapies that are also occasionally prescribed in other countries and are still considered investigational in nature. Oral treatments are more likely to be successful if initiated early in the course of a patient's disease and, for the most part, prevent progression rather than curing the condition.

Intralesional injection therapies have become more popular over the last 2 decades and provide an additional minimally invasive modality for patients with PD. The intralesional approach allows for direct delivery of a particular agent at concentrations that might otherwise be toxic systemically. Use of corticosteroids or orgotein is not currently recommended, and there have been no randomized, placebo-controlled studies clearly documenting their efficacy. Use of collagenase is supported by the results of studies that have revealed significant benefits for this therapy when employed early in the course of PD. Verapamil has been shown in 1 placebo-controlled and numerous uncontrolled studies to have beneficial effects in PD. Interferon-α-2a or -2b has been reported in peer-reviewed multicenter placebo controlled studies to have efficacy in improving penile curvature, plaque size and density, and to reduce penile pain.

As the definitive pathophysiology of PD has yet to be elucidated, further research is required in this area. Currently, oral pharmacotherapy has shown negligible success in improving penile pain, curvature, and plaque size in patients with PD. Intralesional therapy using various agents (eg, collagenase, verapamil, and interferon) is growing in clinical acceptance and popularity as a minimally invasive approach for the initial treatment of PD. As our scientific understanding of the underlying mechanisms of this perplexing condition increase we can anticipate the development of novel medical therapies for PD.

Footnotes

This paper is based on a presentation at a Special Symposium on April 12, 2008, "Therapeutic Strategies for Male Sexual and Hormonal Health", associated with the American Society of Andrology Annual Meeting, for which the presenting author received an honorarium.

Dr Hellstrom has nothing to disclose.

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Int Urol Nephrol. 2009;41(1):113-8. Epub 2008 Jul 1.

The effectiveness of transdermal electromotive administration with verapamil and dexamethasone in the treatment of Peyronie's disease.

Tuygun C, Ozok UH, Gucuk A, Bozkurt IH, Imamoglu MA.

Source

Department of Urology, S.B. Diskapi Yildirim Beyazit Training and Research Hospital, Hosdere Caddesi, 115/72 Yukari-Ayranci, Ankara, 06550, Turkey, tuyguncan@yahoo.com.

Abstract

AIM:

To determine the effectiveness of transdermal electromotive administration (TEA) of verapamil and dexamethasone in the treatment of Peyronie's disease (PD).

METHOD:

Totally, 51 patients with PD were prospectively included in the study. All patients were evaluated by history, subjective score scales, physical examination, photographs, and penile USG, before and after therapy. All patients were treated with TEA of the combination of verapamil and dexamethasone. The treatment plan included a total of 20 sessions (at 3-day intervals for a period of 2 months), each with a duration of 20 min. At the end of the study, improvements in penile plaques, penile deviation, pain on erection, and erectile dysfunction were determined.

RESULTS:

The findings in 41 of the 51 patients were eligible to present. Median patient age was 52 years. Median duration of disease at presentation was 8 months. Remarkable reduction in palpable plaques and in penile angulation was observed in 10 patients (24%) and 11 (26%) patients, respectively. There were significant decreases in median plaque volume from 72 mm(2) to 45 mm(2) ($P < 0.001$), and in median penile angulation from 25 degrees to 15 degrees ($P < 0.001$). Impaired sexual activity and pain on erection had completely resolved in 11 (55%) patients and in 16 (80%), respectively.

CONCLUSION:

The results of our study have shown that TEA of the combination of verapamil and dexamethasone is a more effective therapy for improving subjective symptoms rather than objective symptoms. Therefore, we think that this treatment can be individualized according to the clinical features of PD patients

J Sex Med. 2008 Apr;5(4):954-64. Epub 2007 Nov 27.

Urologist practice patterns in the management of Peyronie's disease: a nationwide survey.

Shindel AW, Bullock TL, Brandes S.

Source

Washington University in Saint Louis-Department of Surgery, Division of Urology, St. Louis, MO, USA. shindela@urology.ucsf.edu

Abstract

INTRODUCTION:

Peyronie's disease (PD) is a poorly understood clinical entity. Aim. We endeavored to determine how contemporary urologists in the United States manage PD.

METHODS:

A randomly generated mailing list of 996 practicing urologists was generated from the American Urologic Association member directory. A specifically designed survey was mailed with a cover letter and a postage-paid return envelope.

MAIN OUTCOME MEASURE:

Our survey assessed several practice-related factors and asked questions of how the subject would manage various presentations of PD in their practice. Four cases were presented: case 1, a healthy 55-year-old man with painless 30 degrees dorsal curvature of 16 months duration; case 2, a 60-year-old man with 35 degrees dorsal curvature, 4/10 pain on visual analog scale, of 6 months duration; case 3, a 62-year-old man with painless 60 degrees dorsal curvature and erectile dysfunction responsive to alprostadil suppository of 2 years duration; and case 4, a 50-year-old man with mid-shaft waist deformity, foreshortening, no pain/curvature/erectile dysfunction.

RESULTS:

Responses were received from 236 (24%) practicing urologists. Vitamin E was the preferred initial management for 70% of respondents, with observation, Potaba (Glenwood, Englewood, New Jersey, USA), colchicine, verapamil injections, and verapamil gel favored by 32, 20, 12, 7, and 10% of respondents, respectively. Fifty-seven percent of respondents performed surgery for PD, with penile prostheses, Nesbit procedure, grafting, and plication used by 76, 66, 55, and 51% of respondents, respectively. Medical therapy and/or observation was the preferred management for all of the cases except case 3, for which penile prosthesis placement and referral were the favored options by 39 and 30% of urologists, respectively.

CONCLUSIONS:

Medical therapy is the initial treatment for PD among American urologists. Penile prosthesis is the treatment of choice in impotent patients. Most American urologists conform to recommended practice patterns in the management of PD.

J Sex Med. 2007 Mar;4(2):477-84.

Topical verapamil HCl, topical trifluoperazine, and topical magnesium sulfate for the treatment of Peyronie's disease--a placebo-controlled pilot study.

Fitch WP 3rd, Easterling WJ, Talbert RL, Bordovsky MJ, Mosier M.

Source

Urology Consultants, P.A., San Antonio, TX, USA. janice@urologyconsults.com

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

Rev Urol. 2003 Summer; 5(3): 142–148. PMCID: PMC1473022

Peyronie's Disease: A Review
Mark Jalkut, MD, Nestor Gonzalez-Cadavid, PhD, and Jacob Rajfer, MD
Department of Urology, University of California Los Angeles, Los Angeles, CA

Abstract
Peyronie's disease is an acquired benign condition without known systemic sequelae with presenting symptoms that include the presence of a plaque or induration of the penile shaft, penile curvature or deformity during erection, penile pain, and erectile dysfunction. This article reviews the natural history of the disease, discusses the disease's etiology (widely thought to involve minor penile trauma with subsequent aberrant wound healing), and outlines proper clinical evaluation of Peyronie's disease patients. Medical treatments can be systemic (colchicine, potassium aminobenzoate, vitamin E), intralesional (steroids, verapamil, collagenase, interferons), or topical. Surgical therapy for Peyronie's disease (plication, graft-based, and prosthetic techniques) should be reserved for the man who has failed conservative therapy and whose curvature, indentation, or erectile dysfunction precludes intercourse. Regardless of the surgical procedure, the patient should be made aware of the inherent risks of surgery.
Key words: Peyronie's disease, Erectile dysfunction, Plication techniques, Graft-based techniques, Prosthesis

Peyronie's disease, first described in 1743,[1] is an acquired benign condition without known systemic sequelae that usually presents with a palpable induration or plaque and curvature or indentation of the erect penis. Occasionally, erectile dysfunction (ED) may be associated with Peyronie's disease, and at times the erections may be painful. During the past decade, significant advances have been made in understanding the pathophysiology of the disease, testing novel medical treatments of Peyronie's disease, and improving the surgeon's ability to successfully reconstruct the "deformed" penis. The current era of phosphodiesterase therapy for the treatment of ED seems to have increased the number of patients presenting for treatment of Peyronie's disease and has simultaneously required that our treatments reliably preserve potency. The disease remains, however, an entity imperfectly understood, without a cure, and with a treatment limited only to those severely disabled men who are willing to accept significant complications.

Clinical Features and Natural History

The presenting symptoms of Peyronie's disease include the presence of a plaque or induration of the penile shaft, penile curvature or deformity during erection, penile pain, and ED. A 35-year retrospective study of men in Rochester County, Minnesota, demonstrated the average age of onset of Peyronie's disease to be 53 years, with a prevalence of 388.6 per 100,000 men (0.4%).[2] A recent questionnaire study of men aged 30 to 80 years in Germany revealed that 3.2% of respondents reported palpable penile plaques.[3] This may underestimate the true incidence of penile plaques, as demonstrated by an autopsy study that found lesions of the tunica albuginea in 22 of 100 men with no known symptomatic disease.[4] Although it has been claimed that Peyronie's disease is becoming more prevalent, this is most likely due to the recognition of a bent penis during tumescence in men with ED who are now being treated with phosphodiesterase therapy. ED, estimated to be present in 30% of cases, plays an integral role in Peyronie's disease.[5] Four factors that contribute to ED in Peyronie's disease are severe penile deformity preventing intercourse, a flail penis, impaired vascular function, and psychological distress or anxiety due to the appearance of the penis.[6] A flail penis may occur because of extensive circumferential plaque. Lopez and Jarow[7] reported that, in a study of 76 men with Peyronie's disease, 36% had arterial disease and 59% had veno-occlusive disease as causes of ED. Venous leakage is thought to occur when altered compliance prevents the passive transtunical occlusion of venous channels. ED is not only a possible symptom of Peyronie's disease but also remains a complication of any reconstructive surgery; therefore, its presence and degree is one of the most important factors to consider when weighing surgical options.

The natural history of Peyronie's disease was once thought to entail a slow, spontaneous resolution. However, a survey of 97 men with disease of 1- to 5-years duration reported that 14% had resolving symptoms, 40% had progressive disease, and 47% had stable symptoms.[8] Current understanding of the disease divides patients into an active phase and a mature or stable phase. The onset of disease at times is associated with painful erections and a changing configuration of the plaque and curvature of the erect penis. Up to one third of patients, however, may present with a painless curvature. The painful erections typically resolve over 6 months, and the penile deformity stabilizes by 12 months. The stable phase consists of a painless, stable deformity with a mature scar and, in many instances, development or progression of ED. Features associated with the disease that do not resolve spontaneously include signs and symptoms of longer than 2-years duration, Dupuytren's contractures, and calcified plaque.

Etiology
In 1957, Furey[9] initially suggested (and most investigators now concur) that minor sexual trauma is the major cause of Peyronie's disease. A survey of 732 patients demonstrated an association between penile trauma and both Peyronie's disease and ED.[10] Dorsal and ventral sheer stresses, common during sexual activity, could account for the typical dorsal location of plaques.[11,12]
Clinical research suggests that Peyronie's disease represents an aberration of localized wound healing. Fibrin deposition is one of the initial consequences of microvascular injury, and fibrin has been localized in the tunical tissue in most plaques, some years after development of the disease.[13] Perivascular round cell infiltration has been seen in tissue adjacent to diseased tunica in Peyronie's patients.[14] Plaques consist of dense, immature type 3 collagen with reduced and fragmented elastic fibers.
Experimental incision of the tunica in a rat model resulted in the formation of inflammatory changes seen in the acute phase of Peyronie's disease, including increased expression of transforming growth factor (TGF)-β1.[15–18] TGF-β1 has a pleiotropic effect on fibroblast activity, increasing collagen synthesis while inhibiting connective tissue breakdown via decreased collagenase expression. The ability of TGF-β1, a potent profibrotic cytokine, to induce its own production is considered key to the development of excessive scarring and fibrosis.[19]
Minor penile trauma is ubiquitous, however, and cannot fully explain the etiology of Peyronie's disease. Although Peyronie's disease has not been linked to any predisposed populations, there are several conditions associated with the disorder: Paget's disease of the bone, Dupuytren's contracture, and certain human leukocyte antigen subtypes. A family history can be elicited in 2% of cases.[20] Peyronie's disease presents in 16% to 20% of men with Dupuytren's contractures, a disease inherited in an autosomal dominant fashion.[21,22]
In addition to a genetic element, an autoimmune component may be present, as evidenced by the finding of abnormal serologic tests in 785 men with Peyronie's disease[23] and the finding of elevated anti-elastin antibodies in the sera of men with the disease.[24] It has been hypothesized that susceptible men respond to mechanical stress or microvascular trauma with a genetically aberrant wound healing process that involves the expression of growth factors and cytokines.
Our current thinking regarding the etiology of Peyronie's disease is that trauma to the tunica allows intravasation of fibrin from the blood into the tunica. It appears as if fibrin is responsible for initiating the release of the profibrotic compound TGF-β1 within the tunica, which induces the formation of reactive oxygen species (ROS), and it is ROS that leads to the pathologic hallmarks of Peyronie's disease (ie, increased collagen deposition, disorganization of the newly deposited collagen, decrease in the breakdown of the newly deposited collagen, and calcification of the plaque).

Clinical Evaluation
A review of the history and symptoms of a patient with Peyronie's disease should include the duration of the disease, the presence or absence (or resolution) of pain, an estimation of the degree of the penile deformity, and the orientation of the bend. The presence of penile shortening, an hourglass-type indentation, and the number and location of plaques will all affect treatment options. Questions regarding family history, presence of associated conditions, infections, and instrumentation are of interest but do not bear upon treatment of the disease. The most important information to obtain is how the disease impacts the lives of the patient and his partner and the patient's expectations of therapy.
Physical examination should include an assessment of the pubis-to-glans length (because most men recognize a shortening of the penis primarily in the erect state, but in many men it is also recognizable in the flaccid state), the number and position of plaques, and the degree of plaque calcification. Photographs of

the erect penis, as seen in Figure 1, or use of an intracorporeal injection to elicit an erection that demonstrates the degree and angle of the defect are helpful for following the course of the disease and for

surgical planning, if that is to be considered. Occasionally, sonography is useful in identifying the number and site of plaques as well as the presence of calcification, but we have found sonography to be of limited clinical use in our practice.

Treatment
Medical Treatment
Conservative therapy is the standard treatment of Peyronie's disease. Patients with evolving disease should be treated medically until the disease has become stable, typically a period of at least 6 months but more commonly 12 months. A number of treatments have been offered to men over the years, beginning with Peyronie's own use of mercury and mineral water. Unfortunately, there are few prospective, blinded, randomized, placebo-controlled studies with standardized outcomes of sufficient power to evaluate many of the proposed medical therapies. In evaluating medical therapies, as seen in Table 1, it must be remembered that the natural history of Peyronie's disease includes spontaneous resolution of pain, typically within 6 months, and in some men a small improvement in penile curvature. Medical treatments are administered systemically, locally, or intralesionally.

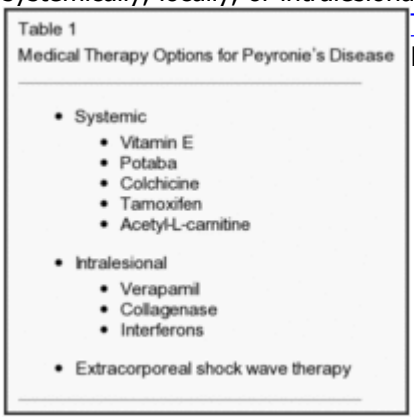

Table 1
Medical Therapy Options for Peyronie's Disease

Colchicine is an oral antimicrotubule agent that inhibits collagen secretion. It is administered at a recommended dose of 0.6 mg to 1.2 mg daily during the first week of treatment, then increasing up to 2.4 mg/d, in divided doses for a period of up to 3 months. The main adverse effect is gastrointestinal upset with diarrhea in up to one third of subjects. Other, more severe side effects include lowered blood counts and elevation of liver enzyme levels. In an uncontrolled study of 24 patients, colchicine was reported to decrease plaque size and improve penile curvature in 50% of patients.[25]

Potassium aminobenzoate (Potaba; Glenwood, Englewood, NJ) has been prescribed extensively for Peyronie's disease.[26] Its mechanism of action is not understood but may involve decreased fibrogenesis through altered serotonin levels. The drug is prescribed at 20 g/d for 3 months, although some practitioners give the drug for up to 12 months. This treatment is expensive and, in general, poorly tolerated. The most frequent reported side effect is gastrointestinal upset. In a review of 2653 patients, Potaba, in a non-controlled study, was reported successful in 57% of treated patients.[27]

Tamoxifen is thought to facilitate the release of TGF-β1 from fibroblasts and therefore to regulate the immune response.[28] In a placebo-controlled study of 25 patients with Peyronies's disease, there was no significant improvement in pain, curvature, or plaque size with tamoxifen, 20 mg twice daily, compared with placebo. Side effects of tamoxifen included gastrointestinal distress and alopecia.[29] Acetyl-L-carnitine, 1 g twice daily, was compared with tamoxifen in a randomized study of 48 patients. With a short follow-up, the patients who received acetyl-L-carnitine had greater decreases in penile pain and plaque size, with fewer adverse effects, compared with those who received tamoxifen.[30]

Vitamin E is commonly used to treat Peyronie's disease. In 1948, Scott and Scardino[31] reported a beneficial effect in 23 men treated with a dosage of 200 mg/d to 300 mg/d. In 1990, a controlled study of vitamin E

failed to demonstrate a significant difference in pain, bend, ability to have intercourse, and overall disease state compared with placebo.8 The proposed action of vitamin E is through its ability to scavenge free radicals like ROS. Many clinicians consider this inexpensive, virtually side effect-free drug a reasonable treatment to offer patients awaiting stabilization of disease, allowing the clinician to build a rapport with the patient.

Several intralesional therapies have been proposed and studied for the treatment of Peyronie's disease. Steroids have been injected into plaque in an effort to exploit their anti-inflammatory properties. Several short-term studies have been reported with good responses; however, intralesional steroids have many local adverse effects, including tissue atrophy and thinning of skin.32 The use of intralesional steroids may help persistent plaque pain, but they should not be used to treat curvature.

Intralesional injection of the calcium channel blocker verapamil has been reported for the treatment of Peyronie's disease.33 Calcium channel blockers affect cytokine expression associated with the early phases of wound healing and have been shown to increase the activity of collagenase.34 Verapamil, 10 mg in 10 mL of saline, is injected every other week for a total of 6 injections, with pain and bruising the most common reported adverse effects. In a recent prospective study of 156 men treated with intralesional verapamil, of those who completed the treatment, 60% had an objective decrease in curvature, 80% an increase in rigidity distal to the plaque, and 71% an increase in sexual function.35 This study is notable for objectively measuring penile curvature through dynamic penile duplex ultrasound and correlating these findings with subjective patient questionnaire results. Interestingly, those patients who responded to therapy included men with dynamic and stable disease and men with disease ranging from mild to severe.

Gelbard and colleagues36 reported on the use of intralesional collagenase in a double-blind, placebo-controlled trial, with some benefit over placebo for mild disease but no significant improvement in more severe curvature. Several clinical trials of intralesional interferons have been reported. Interferons inhibit fibroblast proliferation in culture and increase the production of collagenase.37 Most patients receiving this treatment report transient flu-like symptoms. One study reported favorable results,38 but this has not been borne out in another published report.39

Several topical therapies have been reported, often employing iontophoresis for drug delivery. Treatment cocktails have included orgotein, steroid, and verapamil.40 Improvement as measured by history and ultrasound was reported in 62% to 90% of patients, depending on the treatment group, but none of these studies have been controlled.

Local extracorporeal shock wave therapy (ESWT) has been studied. Clearly, this therapy aims to fracture the calcified plaques, but the effect this has on the pathophysiology of the disease is unclear. Abdel-Salam and colleagues41 treated 24 patients with between 4 and 10 sessions of ESWT and reported a 59% improvement. A recent study of 42 patients treated with at least 3 sessions of ESWT (3000 shock waves 0.11–0.17 mJ/mm2) reported subjective improvement in 81% of patients, with 14% claiming excellent results and 50% endorsing significant improvements.42

Up to 30% of men with Peyronie's disease have concomitant ED. These patients should be treated no differently than patients with ED who do not have Peyronie's disease. Most such patients are started out on oral phosphodiesterase therapy and, if this fails, intracorporeal injections are then prescribed. The manufacturers of injectable alprostadil specifically state that their product is contraindicated in men with Peyronie's disease, but the reason for this is that up to 30% of men on long-term injectable therapy will develop palpable Peyronie's disease- like nodules of the tunica albuginea. It is theoretically possible that repeat needle puncture could exacerbate Peyronie's disease.

Surgical Therapy

The goal of surgical therapy is simply to make the 2 sides of the penis equal in size. Either lengthening the shorter side or shortening the longer side can accomplish this. When one attempts to lengthen the shorter side, a graft must be interposed and can be composed of autologous tissue, cadaveric tissue, or synthetic material. To shorten the longer side, a plication procedure is used. The ideal candidate for surgical therapy is a man who has failed conservative therapy and whose curvature, indentation, or ED precludes intercourse. When ED is present with Peyronie's disease, one option is a penile implant, which should straighten the penis and elicit an on-demand erection. Regardless of the surgical procedure that is agreed upon by the patient, he should be made aware of all inherent risks, including failure to completely straighten the penis, ED, shortening of the penis, sensory changes in the penis, and occasionally progression of disease.

Plication techniques. Tunical shortening procedures are performed on the convex aspect of the penis, opposite the location of greatest deformity. Nesbit43 first described the concept by excising an ellipse of

tunica albuginea in patients with congenital penile deformities. Pryor and Fitzpatrick44 first applied the technique to Peyronie's disease in 1979. Typically, the Nesbit ellipse is 1 mm wide for every 10 degrees of

deformation. In a study of 359 operations over a 15-year period, 82% of cases were successful, with men regaining their ability to have intercourse.45 Men who are good candidates for plication-based reconstruction are those patients with good erectile function and adequate penile length, without an hourglass-type narrowing. A study of patient failures identified 3 factors that were associated with poor outcome: impaired erectile function, penile shortening of greater than 2 cm, and penile deformity greater than 30 degrees.46 Several modifications of the Nesbit plication have been made, including the Yachia procedure, which relies on the horizontal closure of a longitudinal incision in a Heineke-Mikulicz fashion.47 This technique can be based on a long incision or several shorter cuts. Successful results of this procedure range from 80% to 95%, and the complications are similar to those of the Nesbit plication. Essed and Schroeder48 popularized simple plication without incising tunical tissue as a viable treatment of Peyronie's disease. A recent report by Gholami and Lue49 of 124 patients who underwent simple plication without excision, followed for a mean of 2.6 years, demonstrated a patient-measured outcome satisfaction of 96%. An advantage of the simple plication approach over the traditional Nesbit repair or the Yachia modification is the lack of dissection of the neurovascular bundle and the corpus spongiosum, thus limiting postoperative erectile impairment. It has been estimated that de novo impotence resulting from all variants of plication occurs in approximately 5% of cases.50

Graft-based techniques. Plication techniques are limited in their ability to straighten a severely bent penis secondary to the subsequent shortening they cause. Furthermore, certain clinical conditions, such as a circumferential plaque causing an hourglass deformity, cannot be treated by plication. Graft-based reconstruction procedures have therefore been developed to treat these more complicated problems. Devine and Horton51 first described successful repair of Peyronie's defects using dermal grafts. Long-term follow-up of graft excision techniques has shown low patient satisfaction; one study of 418 men demonstrated that 17% required further surgery for persistent curvature and that 20% of patients had significant erectile impairment.52 In 1991, Gelbard and Hayden53 proposed plaque incision and grafting as a method to decrease the complications associated with plaque excision, namely ED. ED following plaque excision is thought to be due to damage of the underlying erectile tissue, loss of compliance of the new graft, and new venous channels giving rise to veno-occlusive disease. A further complication of graft-based techniques is loss of sensation that occurs as a result of damage to the neurovascular bundle, owing to the increased dissection of Buck's fascia required to expose the tunica albuginea.

The search for an ideal grafting material continues. Autologous tissues employed for grafting have included temporalis fascia, tunica vaginalis, penile skin, and saphenous vein. Cadaveric tissues, such as dermis, fascia, pericardium, and porcine small intestine submucosa, have been employed, as have synthetic materials such as Gore-Tex and Dacron. A report on 113 men treated with saphenous vein grafting and followed for up to 18 months reported satisfactory straightening of the penis in 96%, de novo ED in 12%, and a change in penile sensation lasting longer than 6 months in 10%.54 Two new materials being used are porcine small intestine submucosa (Surgisis, Cook Urological, Spencer, IN) and human pericardium (Tutoplast, Mentor, Santa Barbara, CA), with satisfactory results being reported in small patient groups followed for 11 to 14 months,55,56 although our personal data are somewhat disappointing at 12 months with this latter product.

Prosthesis techniques. Penile prostheses in Peyronie's disease are currently reserved for men with ED not responsive to medical therapy. This technique provides excellent results and may be used with modern inflatable prostheses.57 In most patients with mild curvature, no further procedure is necessary. Wilson and colleagues58 have reported on the ability to further straighten the penis during prosthesis placement by performing intraoperative modeling without an increase in rate of revision. In cases of severe deformity, plaque incision with or without grafting may be necessary during prosthesis placement, with care taken to avoid damage not only to the implant59 but also to the neurovascular bundle.

Conclusion

Increasing knowledge of the pathophysiology of Peyronie's disease has fueled clinical and scientific interest in this fibrotic disorder. Current studies examining medical therapies for Peyronies's disease suffer from a

lack of prospective, controlled study design, and few reports include objective findings and outcomes. The last decade of surgical therapy can be best described as "less is more," trying to better match those procedures to men who will experience satisfactory outcomes while limiting unacceptable side effects. It is hoped that future therapies may be directed at curing the disease itself rather than limiting its mechanical sequelae.

Main Points

The presenting symptoms of Peyronie's disease include the presence of a plaque or induration of the penile shaft, penile curvature or deformity during erection, and penile pain; erectile dysfunction (ED) is estimated to be present in 30% of cases.

A review of the history and symptoms of a patient with Peyronie's disease should include the duration of the disease, the presence or absence (or resolution) of pain, an estimation of the degree of the penile deformity, and the orientation of the bend; the most important information to obtain is how the disease impacts the lives of the patient and his partner and the patient's expectations of therapy.

Conservative therapy is the standard treatment of Peyronie's disease, and patients with evolving disease should be treated medically until the disease has become stable, typically a period of at least 6 months but more commonly 12 months. Medical treatments are administered systemically, locally, or intralesionally.

The ideal candidate for surgical therapy is a man who has failed conservative therapy and whose curvature, indentation, or ED precludes intercourse. The goal of surgical therapy is simply to make the 2 sides of the penis equal in size, either by lengthening the shorter side (using a graft) or shortening the longer side (using a plication procedure).

Penile prostheses in Peyronie's disease are currently reserved for men with ED not responsive to medical therapy. This technique provides excellent results and may be used with modern inflatable prostheses.

Other Sections▼

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Pag.25

Urologiia. 2010 Nov-Dec;(6):40-4.

[Peyronie's disease: comparative results of conservative treatment].

[Article in Russian]
Kovalev VA, Karaguzhin SK, Abdulkhamidov AN, Danovich VM, Kyzlasov PS, Matskevich SV.

Abstract

Long-term clinical experience with conservative treatment of Peyronie's disease has demonstrated that clinical efficacy of this therapy comprises maily anesthesia while erectile problems are not solved. Introduction of the drugs into the fibrous plaque is not adequate and hard to perform. Some drugs affect only some components of pathogenesis. For stabilization of the process it is recommended to use transdermal electrophoresis or phonophoresis. The search for new effective drugs and methods continues

J Urol. 2007 Mar;177(3):972-5.

Verapamil versus saline in electromotive drug administration for Peyronie's disease: a double-blind, placebo controlled trial.

Greenfield JM, Shah SJ, Levine LA.

Source

Department of Urology, Rush University Medical Center, Chicago, Illinois 60612, USA.

Abstract

PURPOSE:

While surgery remains the gold standard of therapy to correct the acquired curvature of Peyronie's disease, the search for a less invasive therapy continues. Transdermal drug delivery was proposed to be superior to oral or injection therapy because it bypasses hepatic metabolism and minimizes the pain of injection. After electromotive drug administration with verapamil tunica albuginea specimens were demonstrated to contain detectable levels of the drug. Due to varying success with verapamil as injectable therapy for Peyronie's disease we performed a double-blind, placebo controlled trial to determine the effectiveness of verapamil delivered through electromotive drug administration.

MATERIALS AND METHODS:

A total of 42 men with Peyronie's disease volunteered to participate in this study, which was approved by our institutional review board. A genitourinary examination was performed on all patients, including plaque location, stretched penile length, objective measurement of curvature after papaverine injection and duplex ultrasound. Each subject was randomized to receive 10 mg verapamil in 4 cc saline or 4 cc saline via electromotive drug administration. A Mini-Physionizer (Physion, Mirandola, Italy) device was used at a power of 2.4 mA for 20 minutes. Treatments were performed 2 times weekly for 3 months. After 3 months each patient was reevaluated with physical examination and duplex ultrasound by a technician blinded to the treatment received. A modified erectile dysfunction index of treatment satisfaction questionnaire was also completed by each patient.

RESULTS:

A total of 23 patients were randomized to the verapamil treatment group (group 1) and 19 were randomized to the saline group (group 2). There were no significant differences between patient groups with respect to patient age, disease duration or pretreatment curvature. In group 1, 15 patients (65%) had measured improvement (mean 9.1 degrees, range 5 to 30), 5 (22%) had no change and in 3 (13%) the condition

worsened. In group 2, 11 patients (58%) had measured improvement (mean 7.6 degrees, range 5 to 30), 7 (37%) showed no change and in 1 (5%) the condition worsened. To better evaluate effectiveness the total number of patients experiencing significant improvement (20 degrees or greater) was calculated and compared. Seven patients (30%) in group 1 and 4 (21%) in group 2 achieved this criterion. Although a greater percent of patients treated with verapamil had improved curvature, the results were not statistically significant.

CONCLUSIONS:

Although a greater percent of patients treated with verapamil in our electromotive drug administration protocol had a measured decrease in curvature, the results were not statistically significant. Further research is necessary to determine whether electric current may have a role in the treatment of Peyronie's disease as well as if verapamil delivered via electromotive drug administration may have a role as effective treatment. Electromotive drug administration is a treatment option in the patient whose major complaint is pain or in the patient with mild curvature who does not wish to undergo intralesional therapy or surgical correction

Actas Urol Esp. 2005 Nov-Dec;29(10):955-60.

[Transdermal iontophoresis with dexamethasone and verapamil for Peyronie's disease].

[Article in Spanish]
Cabello Benavente R, Moncada Iribarren I, de Palacio España A, Hernández Villaverde A, Monzó JI, Hernández Fernández C.

Source

Hospital General Universitario Gregorio Marañón. Madrid. ramirocabello@telefonica.net

Abstract

OBJECTIVES:

To evaluate the effects of transdermal iontophoresis with verapamil and dexamethasone in patients with Peyronie's disease of less than one year of evolution.

MATERIAL AND METHODS:

We have treated ten patients twice a week during six consecutive weeks using iontophoresis with a Miniphysionizer dispositive. This device generates a 2mA electric current during 20 min which triggers the transdermal penetration of medication. In every session dexamethasone 8 mg and verapamil 5mg were administered inside a small self-adhesive receptacle on the penile skin overlying the fibrosis plaque. To evaluate the efficacy, penile curvature was measured by Kelami's test, while the plaque size was assessed by penile ultrasound. Other parameters like pain, erectile function and ability for vaginal intercourse were recorded using questionnaires. Safety parameters were also assessed during treatment.

RESULTS:

No improvement or progression in penile curvature was evidenced in any of the patients. The hardness of the plaque was reduced in 5 patients, becoming impalpable in 2 of them. Decrease in plaque volume was observed by penile ultrasound in 6. Pain improved in 8 patients, disappearing in 6 of them. One patient recovered his erectile function at the end of the treatment; whereas 3 referred that their ability for intercourse enhanced while 2 reported that treatment improved their sexual life in general. We didn't record

any significantly side effects, except for a transitory and slight dermal redness on the site of electrode placement.

CONCLUSIONS:

Transdermal iontophoresis is an effective treatment for pain control in early stages of Peyronie's disease. Efficacy in reducing **penile** curvature seems to be limited. Controlled clinical trials are needed, and perhaps

Urology. 2009 Sep;74(3):566-70. Epub 2009 Jul 14.

Effect of transdermal electromotive drug therapy on fibrogenic cytokine expression in Peyronie's disease.

Stancik I, Schäfer R, Andrukhova O, Oeser R, Plas E, Pflüger H.

Source

Department of Urology, Ludwig-Boltzmann Institute for Urology and Andrology, Hietzing Hospital, Vienna, Austria. igor.stancik@wienkav.at

Abstract

OBJECTIVES:

To assess the effect of transdermal electromotive drug therapy (EMDT) on transforming growth factor-beta (TGF-beta) and basic fibroblast growth factor (bFGF) expression and their receptors in plaques in patients with Peyronie's disease.

METHODS:

Tissue was obtained from 13 patients with stable Peyronie's disease who had undergone plaque excision because of penile curvature. Of the 13 patients, 7 underwent EMDT with dexamethasone, verapamil, and lidocaine as first-line therapy before plaque excision and 6 were therapy naive. TGF-beta and bFGF mRNA and protein expression and that of their receptors were measured using real-time polymerase chain reaction and Western blotting.

RESULTS:

The mean patient age was 52.83 years. The mean interval from the end of EMDT to plaque excision was 7.6 months, with stable disease for >or=5 months. The comparison of TGF-beta mRNA expression in the plaques showed no difference between the EMDT and therapy-naive patients (P = .17). Also, TGF-beta protein expression in the plaques was not significantly different between the EMDT and therapy-naive

patients (P = .443). TGF-beta receptor 1 mRNA expression in the plaques was significantly different between the EMDT and therapy-naive patients (P = .023), but no difference was found for TGF-beta receptor 2 mRNA (P = .292). The expression of bFGF mRNA (P = .0005) and bFGF protein expression (P = .034) in the plaques was significantly lower after EMDT. bFGF receptor mRNA expression (P = .619) showed no significant differences.

CONCLUSIONS:

Patients with Peyronie's had significantly lower bFGF mRNA and bFGF protein expression in the plaques after EMDT. Also, overexpression of TGF-beta protein and the TGF-beta receptor was identified in the EMDT plaques compared with the therapy-naive plaques

J Urol. 2004 Apr;171(4):1605-8.

A prospective, randomized study using transdermal electromotive administration of verapamil and dexamethasone for Peyronie's disease.

Di Stasi SM, Giannantoni A, Stephen RL, Capelli G, Giurioli A, Jannini EA, Vespasiani G.

Source

Department of Urology, Tor Vergata University, Rome, Italy. sdistas@tin.it

Abstract

PURPOSE:

Uncontrolled studies with intraplaque electromotive administration of verapamil and dexamethasone have demonstrated objective improvements in Peyronie's disease. We performed a prospective controlled study to assess the efficacy of intraplaque electromotive verapamil/dexamethasone vs electromotive lidocaine.

MATERIALS AND METHODS:

Patients with Peyronie's disease were randomized into a study group (47 patients) and a control group (49 patients). For each treatment session an electrode receptacle was sited over the plaque and filled with either 5 mg verapamil and 8 mg dexamethasone (study group) or 2% lidocaine (control group), and a 2.4 mA electric current was applied for 20 minutes. All patients were scheduled for 4 sessions per week for 6 weeks. Assessment before and after treatment included measurements of plaque volume and penile curvature, and pain on erection (from questionnaire).

RESULTS:

A total of 37 patients in the study group and 36 in the control group completed treatment courses. In the study group there were significant decreases in median plaque volume from 824 to 348 mm, and in penile curvature from 43 to 21 degrees. In the control group median volume and curvature were unchanged. The difference in results after treatment between the 2 groups was also significant. Significant pain relief

occurred in both groups, transient in the control group and permanent in the study group. All patients experienced temporary erythema at the electrode site. There were no other side effects.

CONCLUSIONS:

Intraplaque electromotive verapamil and dexamethasone induce substantial objective improvement in Peyronie's disease compared to electromotive lidocaine administration.