Review Article

Contemporary Review of Treatment Options for Peyronie's Disease

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Peyronie's disease (PD) is a penile wound-healing disorder resulting in fibrotic plaque in the tunica albuginea, likely resulting from micro trauma. Due to variable disease presentations, a myriad of proposed treatment options, physician misconceptions about the disorder, and severe psychological distress in afflicted patients, PD can be a difficult to manage entity. This review seeks to provide a current and comprehensive overview of oral, topical, intralesional, mechanical, and surgical therapies for PD. UROLOGY 95: 16–24, 2016. © 2016 Elsevier Inc.

Peyronie's disease (PD) is a penile wound-healing disorder of the tunica albuginea resulting in fibrosis that can cause penile curvature, narrowing, shortening, hinging, pain, and inability to participate in penetrative sex. The reported incidence of PD is 3%-10%.[1,2] The prevalence may actually be higher as men are often reluctant to seek treatment due to embarrassment. Some men are not significantly bothered by their deformity and others lack knowledge of the condition and available treatment options. Urologists may continue to see more men presenting with PD as awareness of the disease and marketing for injectable agents continue to increase.

PD is often associated with significant psychosocial distress. It can be a difficult to manage entity with a confusing array of potential treatment options, many of which lack data in support of meaningful benefit. Primary care physicians and urologists have demonstrated incorrect assumptions about the prevalence and natural history of PD that can negatively affect diagnosis and treatment.[3] In this review, the authors seek to provide a comprehensive overview of the available medical and surgical treatment options for PD, focusing on the most effective treatment modalities and recent treatment advances.

NATURAL HISTORY AND ETIOLOGY

PD develops when fibrotic scar (Peyronie's plaque) develops in the tunica albuginea of the penis. The tunica albuginea is composed of an inner circular layer and outer longitudinal layer, both of which rely on a strong network of type 1 collagen and elastin.[4] Anchor sites of the tunica albuginea, especially along the dorsal septum, are susceptible to traumatic insults and vascular injury. Interestingly, the majority of men seeking treatment for PD do not recall a specific traumatic event. Instead, it is theorized that high intracavernosal pressures during sex may result in a sudden stretch on the tunica albuginea that exceeds its elastic capacity, resulting in a microfracture. In response to such trauma, inflammatory cells (macrophages, neutrophils, mast cells) release inflammatory mediators, including cytokines, transcription growth factor (TGF)-β, TGF-α, heparin-binding epidermal growth factor, fibroblast growth factor, and collagenases. In patients with normal wound healing, fibroblast migration and deposition of type I and type III collagen occur within days and, within weeks, a remodeling phase of collagen synthesis and degradation occurs. An appropriate balance of degradation by matrix metalloproteinases (collagenases) and inhibition of degradation by tissue inhibitors of metalloproteinases is essential to prevent long-standing fibrosis. One of the important characteristics of PD is an imbalance in this wound-healing process; Peyronie's plaques are highly enriched with tissue inhibitors of metalloproteinases. This imbalance may occur in response to oxidative stress and overexpression of TGF-β, platelet-derived growth factor, and/or fibroblast growth factor.[5-10]

The acute phase of PD is often associated with painful erections and changing deformity and/or curvature of the penis during the erect state. This phase can last from 6 to 18 months. Spontaneous regression is rare. The goal of treatment during the acute phase is to relieve symptoms of pain, mitigate scar formation, and prevent worsening penile curvature and/or deformity. The subsequent chronic phase of PD is typically more quiescent with resolution of pain and stabilization of the plaque and deformity. The goal of treatment in the chronic phase is to correct deformity and induce straightening to allow for penetrative sexual intercourse while also maintaining as much penile length as possible.[11,12]

MEDICAL THERAPIES

Nonsurgical therapies for PD may be appropriate as first-line options for symptomatic men in the acute phase of PD

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with unstable deformity and/or pain or in men with chronic phase PD who are poor surgical candidates or are not ready to consider surgical correction. A myriad of nonsurgical therapies have been proposed for use in PD. Unfortunately, medical therapies are backed by limited evidence of benefit.

Oral Medications

Given the inherent ease of administration and theoretic ability to provide balanced tissue penetration in the tunica albuginea, numerous oral agents have long been studied in patients with PD. Potoba, vitamin E, procarbaizine, colchicine, L-carnitine, pentoxifylline, tamoxifen, omega-3 fatty acids, coenzyme Q10, and phosphodiesterase type 5 inhibitors (PDE5-i) have all been trialed in PD patients.[13] Some experts recommend the use of pentoxifylline, L-arginine, and/or PDE5-i as oral therapy for PD based on elegant animal model studies showing antifibrotic qualities associated with enhanced local nitric oxide levels.[14] Unfortunately, human trials of oral agents are uniformly limited by small sample size and, to date, no single oral agent has shown a clinically meaningful or lasting benefit in a large randomized controlled trial. Furthermore, many of these agents have significant side effect profiles. A summary of mechanisms, available evidence, and side effects of oral agents trialed in PD patients is available in Table 1. Currently, in agreement with the most recent recommendations by the International Consultation on Sexual Medicine, the authors do not routinely recommend oral agents as monotherapy in the treatment of PD.[11]

Topical and Injection Therapies

Numerous topical agents have been trialed for use in PD, including beta-aminopropionitrile, liposomal recombinant human superoxide dismutase, and topical verapamil.[32-34] Similar to oral therapy studies, these trials have been limited by sample size and lack of appropriate objective measures. Although early studies of verapamil showed promising results, subsequent analysis of tunical biopsies after topical verapamil therapy revealed that the drug is unable to penetrate the tunica albuginea at a detectable level.[35] Topical compound therapies utilizing pharmacologic tissue penetration enhancers represent an intriguing area of ongoing research. Recently, a small placebo-controlled trial of topical nicardipine and superoxide dismutase compounded with emu oil in 22 men with untreated acute phase PD demonstrated significant improvement in multiple PD parameters (length gain, curvature reduction, pain scores) compared to placebo.[36] Larger controlled trials are needed to validate these findings.

To date, pharmacologic agents have been most effective when adequate concentrations are able to penetrate the tunica albuginea with electromotive assistance via iontophoresis or via intralesional injection (ILI). Iontophoresis utilizes application of an electrical field to facilitate penetration of a topical drug into the tunica albuginea. Detectable drug levels in the tunica albuginea after iontophoresis have been confirmed by biopsy.[37] In an unblinded study of 96 PD patients randomized to iontophoresis with verapamil (5 mg) + dexamethasone vs placebo (lidocaine), the verapamil group had improved curvature from 43° to 21°.[38] More recently, a double-blind placebo-controlled trial of verapamil (10 mg) iontophoresis vs placebo (saline) showed reduced curvature in both groups.[39] Future analysis will be required to determine if electrical current alone can induce plaque remodeling. Although some evidence for benefit exists, transdermal iontophoresis for the treatment of PD is not utilized widely.

ILI therapies have become the most promising nonsurgical treatment option for durable improvement in PD symptoms and curvature. Corticosteroids were the first ILI therapy used for PD but had unfavorable side effects and did not result in any significant measured improvement in curvature, plaque size, or sexual function.[40] More recently, in multiple small trials, ILI verapamil has resulted in decreased curvature, resolution of narrowing deformity, reduction of plaque volume, and improvement in sexual function. Most notably, over 90% of patients experience resolution of pain.[41,42] In the largest ILI verapamil trial (156 PD patients) to date, ILI verapamil resulted in decreased curvature (mean reduction 30°, range 5°-90°) in 60% of patients and improved sexual function in 71% of patients at mean follow-up of 30.4 months.[43] In contrast, a separate randomized trial of 80 PD patients treated with ILI verapamil vs saline found no significant difference in curvature, plaque size, or sexual function.[44] Variable results in these trials may be due to injection technique, patient selection (plaque size, plaque calcification, degree of curvature), or drug concentration. A randomized trial of 77 PD patients evaluating three different verapamil concentrations found the greatest improvements in plaque size, penile curvature, sexual function, and pain reduction in patients receiving 10 mg/20 mL ILI therapy.[45] Nicardipine, a dihydropyridine type calcium channel blocker, has also been used as an ILI agent for PD. Although not as thoroughly investigated as verapamil, a trial of 74 PD patients randomized to nicardipine (10 mg/10 mL) vs placebo showed improved sexual function and significant reductions in curvature, pain, and plaque size.[46]

Interferon (IFN) α-2b, administered as 12 biweekly injections, has also been used as an ILI agent in PD. It has been shown to provide curvature reduction (mean curvature reduction 9° to 14°), significantly reduced plaque size/density, and pain reduction in placebo-controlled and retrospective trials. Compared to calcium channel blockers, IFN α-2b does have a more robust side effect profile. In addition to ecchymosis, IFN α-2b can also cause significant swelling, inflammation, and possible flu-like symptoms. These minor side effects typically respond well to nonsteroidal anti-inflammatory agents.[47,48]

The most notable PD breakthrough in recent years is ILI therapy with collagenase clostridium histolyticum (CCH), which became the first pharmacologic agent to obtain Food and Drug Administration approval for the treatment of PD. It is approved for use in PD patients with minimally calcified palpable plaque and dorsal or dorsolateral curvature >30° and <90°.[49] CCH is produced by the bacteria