Review Article

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Nonsurgical Interventions for Peyronie's Disease: Update as of 2016

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Peyronie's disease (PD) is a debilitating condition of the penis that leads to significant pain, erectile dysfunction, and emotional distress in men. PD is likely underreported due to lack of knowledge of the disease and the absence of well-established available treatments. Surgical treatment can lead to sustained improvements, but is often associated with penile shortening and places the patient at risk for perioperative morbidity. Nonsurgical management has been studied for several years as an alternative to surgery for men with PD. Currently, much of the data on nonsurgical management is conflicting, with only one treatment that has been recently approved by the US Food and Drug Administration. Significant effort has been devoted to advancing non-surgical treatments for PD that can be implemented outside of the operating room. This review aims to describe the research behind current nonsurgical therapies for PD and to highlight the recent advances that have been made within the last three years.

Key Words: Erectile dysfunction; Injections, intralesional; Penile induration

INTRODUCTION

Peyronie's disease (PD) is defined as an acquired fibrosis of the tunica albuginea, resulting in pain, deformity, erectile dysfunction (ED), and/or distress [1]. The overall incidence of PD is estimated to be between 3% and 9% of older men; however, this is most likely a significant underestimate due to unclear diagnoses and patient underreporting [1]. PD is thought to arise from microvascular trauma during sexual intercourse leading to inflammation, an aberrant deposition of fibrin, and ultimately plaque formation [2]. PD is categorized into two stages: active and stable disease. The active stage is characterized by penile pain with erections, with or without an induration or deformity. During the stable phase, the pain has typically resolved and patients exhibit a non-progressive deformity that may result in ED or inability to adequately engage in sexual intercourse [1]. In addition to the physical symptoms, patients can have significant psychiatric disturbances that should not be understated. The majority of men with PD endorse some degree of emotional difficulty, while one-half endorse clinically significant depression or relationship problems [3]. The chronicity of symptoms and the occurrence of significant emotional distress highlight the importance of diagnosing and treating PD in affected men.

The diagnosis of PD involves a focused history and physical examination, along with an intracavernosal in-

jection with or without Doppler ultrasound to evaluate the erect penis [1]. Recently, a validated questionnaire was developed to help in the diagnosis and assessment of the severity of PD, known as the Peyronie's Disease Questionnaire (PDQ). The PDQ is a 15-question tool to assess the presence, progression, and severity of symptoms in men with PD [4]. The PDQ consists of three categories: (1) psychological and physical symptoms, (2) penile pain, and (3) symptom bother. The PDQ was externally validated in 2013 and was found to exhibit good consistency and utility in assessing men's symptoms and distress due to PD [5]. Recent studies have further described the utility of the PDQ. Coyne et al [6] analyzed over 500 men from the IMPRESS I and II trials and showed that after 1 year of treatment for PD, patients showed moderate to large decreases in their PDQ scores, particularly in the penile pain category. They concluded that, in addition to being a good assessment of initial symptoms and distress, the PDQ can effectively track patients' responses to treatment. A similar study found that scores on the PDQ scales of symptom bother and the psychological and physical domains were significantly correlated with objective improvements in penile curvature. Moreover, all PDQ domains were significantly correlated with improvements in the International Index of Erectile Function (IIEF) and erectile function scores [7]. The PDQ is an easy-to-use, externally validated questionnaire that can be used to assess the severity of PD symptoms as well as to track improvements in both clinical and research settings.

Once the diagnosis is made, the patient should be counseled on both surgical and nonsurgical interventions. In 2015, the American Urological Association (AUA) developed its first-ever clinical guidelines on the diagnosis and management of PD [1]. Within these guidelines, the committee reviewed data from the past 50 years to give the most up-to-date recommendations for the management of PD. In this article, we aimed to review their recommendations that are relevant for nonsurgical management, highlighting recent advances in the nonsurgical management of PD with a focus on new data from the last 3 years.

ORAL THERAPIES

1. Vitamin E

Vitamin E has long been used in the treatment of PD due to its easy accessibility and good tolerance. The presumed mechanism of Vitamin E is decreasing inflammation through eliminating oxygen free radicals. Randomized controlled trials (RCTs) of vitamin E alone or in combination with other therapies (intralesional interferon [IFN] $\alpha 2\beta$ or propionyl-L-carnitine) failed to show any improvement in penile curvature, plaque size, IIEF scores, or intercourse satisfaction [8,9]. More recently, Paulis et al [10] suggested in a randomized study that vitamin E in combination with intralesional verapamil (ILV) and additional antioxidants led to a significant improvement in penile curvature, plaque size, and IIEF scores. Despite these contradictory findings, vitamin E remains one of the most common initial treatments for PD [11,12].

2. Tamoxifen

Tamoxifen and its use for PD was first described in 1992. Tamoxifen increases transforming growth factor beta secretion from fibroblasts and thereby decreases the inflammatory response in the tunica albuginea [13]. Despite this theoretical benefit, one RCT revealed no significant improvement in pain, curvature, or plaque size compared to placebo [14]. Tamoxifen as a treatment for PD is not recommended by the AUA and is rarely used in other countries [1,11].

3. Potassium para-aminobenzoate

Potassium para-aminobenzoate (Potaba; Glenwood, LLC, Englewood, NJ, USA) displays anti-inflammatory and anti-fibroblast activity, making it theoretically useful in treating PD. One small RCT suggested that para-aminobenzoate led to a decrease in plaque size and prevented PD progression, but had no effect in terms of reducing penile curvature. That study further reported that the drug was well-tolerated overall with minimal adverse events [15]. These findings have led urologists to occasionally prescribe para-aminobenzoate as a therapy for PD [11,12]. However, more recent findings have highlighted several concerns with this agent. In a retrospective study, Park et al [16] compared PD patients receiving para-aminoben-

zoate or combination therapy with tamoxifen, acetyl-L-carnitine, and a phosphodiesterase type 5 inhibitor (PDE5i). An overall improvement in penile curvature was found in both groups, but significantly improved rates of sexual intercourse were only found in the combination group. However, more importantly, they reported a dropout rate of approximately 66% in the para-aminobenzoate group, most commonly due to gastrointestinal side effects. These findings contradict the reported overall good tolerability of this drug in the prior RCT. Overall, para-aminobenzoate use in PD should be approached with caution given its questionable efficacy and its potentially severe side effects.

4. Phosphodiesterase type 5 inhibitors

The long-term routine use of PDE5i has been shown to counteract the development of plaques in a rat model of PD [17]. These important preclinical findings have led to its use in the treatment and prevention of progression in PD. Palmieri et al [18] showed that tadalafil, in combination with extracorporeal shock wave treatment, resulted in significantly improved IIEF scores and mean quality of life scores. In a recent study, tadalafil in combination with ILV was shown to lead to a significant decrease in plaque size and an improvement in IIEF scores compared to either group alone [19]. While these studies did not clearly show a benefit in improvement of PD-specific symptoms from PDE5 inhibitors alone, their findings suggest that a PDE5i in combination with other forms of therapy are particularly useful in men with concomitant PD and ED.

INTRALESIONAL THERAPIES

1. Intralesional collagenase

Intralesional collagenase clostridium histolyticum (CCh) has emerged as one of the most commonly studied nonsurgical therapies for PD in recent years. Intralesional CCh (Xiaflex®; Auxilium, Chesterbrook, PA, USA) is a purified mix of 2 collagenases that leads to a breakdown of the collagen when injected into the PD plaque, which, along with manual modeling, can lead to a reduction in penile curvature [20-22].

In a phase IIB study, Gelbard et al [23] analyzed 147 patients randomized to receive CCh or placebo with or with-

out modeling. They observed a significant improvement in penile curvature in the CCh group compared to placebo, although this improvement was only present in the modeling group. In this study, they also found a 96% rate of the incidence of adverse events, although they were mostly mild and related to infection-site bruising and edema. The majority of patients were able to complete all three injections. In order to further study the effects of CCh on PD, the parallel multi-institutional phase-III, double-blind, randomized, placebo-controlled IMPRESS I and II trials were conducted [24]. These two trials enrolled 417 and 415 patients with PD and randomized them to either CCh with modeling or placebo with modeling. In both trials, men in the CCh group were shown to exhibit a 34% improvement in penile curvature, compared to 18% in the placebo group, as well as a significantly decreased PD bother score. Both studies similarly showed good overall tolerance of CCh, with generally mild adverse events, although 3 instances of corporal rupture requiring operative intervention took place. The results of these trials led to US Food and Drug Administration (FDA) approval for Xiaflex® in men with PD and penile curvature between 30° and 90° [25]. Importantly, due to the exclusion criteria of these studies, CCh is only FDA-approved for dorsal and lateral plaques greater than 30°. A more recent phase-III open-label study substantiated these results by analyzing 347 men with PD treated with intralesional CCh and reported significant decreases in penile curvature and improvements in the PD symptom bother score, accompanied by low overall rates of serious adverse events [26,27]. Overall, these well-designed trials have led to intralesional CCh becoming the only FDA-approved drug for PD.

Since the publication of these important trials, several additional encouraging studies have supported the efficacy and safety of intralesional CCh. A recent ad-hoc analysis of the IMPRESS I and II studies examined various subgroups, including the degree of curvature, PD duration, degree of plaque calcification, and baseline erectile function, finding that a significant reduction in penile curvature and PD symptom bother scores were present in all groups [28]. These findings support the possibility that the utilization of CCh is generalizable to most men with PD. Some investigators have questioned whether modest reductions in curvature are likely to lead to functional sig-

nificance for patients [29]. Based on recent observational studies, it would appear that significant functional improvement may be expected in patients' subjective assessment of their improvement as well as their ability to engage in adequate sexual intercourse [30,31].

It is important to recognize the safety profile of CCh, as one of the main benefits of the conservative management of PD is avoiding the morbidity of definitive surgical corrections. Carson et al [32] pooled data from 6 clinical studies, resulting in a total of more than 1,000 patients, and showed that 0.9% of patients experienced serious adverse events: namely, 5 penile hematomas and 4 corporal ruptures. All serious adverse events were effectively managed either surgically or conservatively without long-term sequelae. Additionally, prior treatment with CCh does not appear to be a contraindication for definitive surgical repair, thus alleviating any concern that CCh treatment may preclude patients from definitive repair in the case of unsatisfactory response [33].

Intralesional CCh remains the best-studied intervention for PD and is currently the only pharmaceutical intervention that has been FDA-approved. Studies have shown an encouraging pattern of overall efficacy with minimal serious risks. Future studies are needed to assess the overall long-term effect of CCh and the likelihood of patients to require eventual surgical correction.

2. Intralesional interferon $\alpha 2\beta$

IFN $\alpha 2\beta$ is thought to improve curvature and reduce plaque size in PD by decreasing the rates of fibroblast proliferation and collagen synthesis [34]. In addition, recent studies have also suggested that IFN $\alpha 2\beta$ leads to an improvement in penile hemodynamics, supporting improved erectile function [35]. One RCT evaluated the efficacy of intralesional IFN $\alpha 2\beta$ compared to placebo [36]. In this trial, the IFN group exhibited significantly improved penile curvature, plaque size, and pain. However, no statistically significant difference in IIEF scores between the two groups was found. The mean curvature reduction was 13.5% in this study. Overall, the drug was very well tolerated, with the most common side effect being flu-like symptoms that lasted for less than 36 hours. Based on the exclusion criteria for that study, intralesional IFN $\alpha 2\beta$ can be utilized in men with curvature of at least 30° without calcified plaques [1].

A recent retrospective study similarly showed that IFN $\alpha 2\beta$ resulted in significantly improved penile curvature, with a mean improvement of 9° [37]. They further showed that this decrease in curvature was independent of both disease duration and the location (ventral *versus* dorsal/lateral) [37]. This finding is particularly important because this is one of the few studies to have examined ventral plaques, meaning that this observation has important implications for the generalizability of this treatment modality to patients with ventral PD.

IFN $\alpha 2\beta$ is a reasonable alternative to CCh as an intralesional treatment, with modest efficacy and an overall excellent safety profile. Further studies are needed to better compare its efficacy to other treatments and to assess its functional significance for patients.

3. Intralesional verapamil

Calcium channel blockers (CCBs) are thought to ameliorate PD by decreasing the production of collagen by fibroblasts and increasing the production of collagenase [38]. Chung et al [39] demonstrated this mechanism in a rat model of PD, in a study utilizing immunohistochemical staining to assess the treatment effect of (ILV, showing that ILV led to a significant decrease in collagen and elastin fibers, as well as a twofold increase in collagenase activity.

ILV has been considered an optional treatment for PD for the last 20 years, although the data on its efficacy are conflicting. Rehman et al [40] studied 14 patients randomized to either ILV or saline and showed a significant improvement in plaque volume, but only a non-significant trend for improvement in penile curvature. They further showed that subjective erectile function demonstrated significant improvement in the verapamil group. However, a more recent RCT in 2009 studied 80 randomized patients and showed no significant difference in any objective or subjective measure of PD improvement [41].

Given these conflicting findings, several recent studies have continued to evaluate the efficacy of ILV for the treatment of PD. In particular, ILV has been studied in combination with other nonsurgical treatments and has been shown to be effective in improving IIEF scores and intercourse satisfaction when combined with oral antioxidants [42]. Another study showed that ILV improved penile cur-

vature and subjective PD symptoms, particularly in younger patients, without causing any major complications [43].

Given the inconsistencies in the data, significant controversy remains regarding the efficacy and utility of ILV in treating PD [44]. However, given its overall excellent safety profile, it remains a treatment option for patients with PD [1]. Further large-scale comparative studies are needed for ILV to become a standard of care or an FDA-approved therapy.

4. Novel intralesional therapies

In light of the overall success of intralesional therapies and recent endorsements by major urological organizations, additional novel drugs have been studied for the treatment of PD.

Hyaluronic acid (HA) is a glycosaminoglycan that has been shown to regulate the immune system by decreasing inflammatory cytokines, and thus has been used in multiple medical fields to reduce inflammation and scar formation [45]. More recently, some research groups have evaluated the potential role of HA as a treatment for PD. In a retrospective study of 83 carefully selected patients, Gennaro et al [46] found a significant reduction in penile plaque size and curvature, as well as improved penile rigidity A more recent prospective study of 65 patients likewise demonstrated improvement across all PD domains and reported no major complications [47]. HA is a promising novel therapy for PD that appears to have some efficacy in improving PD symptoms, but data comparing HA treatment to placebo or alternative therapies are lacking. Further prospective RCTs will need to be performed prior to the routine recommendation of HA.

Botulinum toxin is used in a number of medical fields to reduce fibrosis and scarring. With this in mind, one study evaluated botulinum toxin A as a treatment for PD [48]. This study was designed to assess safety, but also showed a significant improvement in all objective and PD symptom categories in 22 patients with no complications, thereby opening the door for future research on botulinum toxin as a treatment for PD. However, more safety and efficacy data from larger trials are needed prior to routine usage.

OTHER NONSURGICAL TREATMENTS

1. Mechanical traction

Penile traction therapy (PTT) has been studied as a treatment of PD, showing good tolerance and satisfaction but an overall minimal impact on objective PD outcomes when used in isolation [49]. Interestingly, one study evaluated the use of PTT in the acute phase of PD and showed an improvement in curvature, pain, and sexual function [50]. Treatments for the acute phase of PD have not been the subject of much research; thus, if this finding can be replicated in larger studies, PTT could represent an option for early intervention in PD and the prevention of progression. It is also well known that manual modeling is important for improvement when using intralesional therapies [23]. However, while modeling possibly improves curvature, it may have a negative effect on penile length when not performing simultaneous PTT [51]. Nonetheless, Yafi et al [52] studied patients undergoing intralesional IFN $\alpha 2\beta$ treatment and showed that those who received PTT daily had a very modest (3 mm), yet significant increase in stretched penile length. While PTT does not appear to be effective in isolation to treat PD, it may have a role in combination treatment, particularly with the goal of maintaining or improving penile length.

2. Topical therapies

Topical therapies would be an ideal modality for treating PD for many reasons, including ease of administration and the fact that they would eliminate the need for frequent injections and clinic visits. However, no topical therapy currently appears effective for PD. Particularly discouraging was a study that revealed that topical verapamil did not penetrate the tunica albuginea [53]. Electromotive treatments have been devised to improve tissue penetration, but they are not recommended for PD due to conflicting data [1].

In a recent study, Twidwell and Levine [26] assessed H-100, a combination of nicardipine, superoxide dismutase, and emu oil, as a treatment for PD. This combination was devised to combine the anti-inflammatory effects of a CCB and an antioxidant with the transdermal carrying effect of emu oil. In a trial designed to assess safety, 22 patients in the acute phase of PD were randomized to re-

ceive H-100 *versus* placebo. In the treatment group, significant reductions in penile curvature and pain level were obtained, as well as an increase in penile length. The drug was well tolerated overall, with skin rash as the only adverse event. Although this trial was designed to assess safety, its initial positive outcomes make it an encouraging novel treatment [54].

3. Extracorporeal shock wave treatment

Extracorporeal shock wave treatment (ESWT) has been utilized as a treatment for PD, particularly with the goal of reducing pain. RCTs have shown improvements in pain but no significant reductions in objective measures of PD severity [55]. A recent placebo-controlled RCT evaluating ESWT for PD showed a modest decrease in pain associated with PD, but actually showed a slight trend towards increased curvature and plaque size in the ESWT group. In addition, the authors pointed out that while ESWT may improve pain, this is the one symptom of PD that often resolves over time without intervention [56]. A recent meta-analysis agreed with these findings, suggesting that ESWT was most effective for pain reduction, but did not lead to appreciable improvements in penile curvature [57]. In this study, ESWT was well tolerated overall, despite the incidence of a few complications that did not require intervention, including penile bruising and urethral bleeding. ESWT can be considered in men with significant pain from PD, but they should be advised that it is unlikely to improve their curvature and that in many cases the pain will resolve over time without intervention.

4. Stem cells

Stem-cell therapy has garnered recent excitement as a potential treatment modality for PD, as it may be able to limit fibrosis if administered in the early acute phase. Castiglione et al [58] utilized a rat model of PD to study the efficacy of injecting adipose tissue-derived stem cells (ADSCs) in preventing plaque formation during the acute phase of PD. In this study, injecting ADSCs into the tunica albuginea was found to decrease the rate of fibrosis and elastosis. Most recently, Gokce et al [59] validated these results in a similar study assessing ADSCs along with IFN $\alpha 2\beta$ injections. They showed that ADSCs, both alone and in combination with IFN, resulted in improved erec-

tile response and decreased PD-like manifestations in a PD rat model. This rat model appeared successful, as improvements in erectile response were observed in the combined ADSC-IFN group compared to the only-ADSC group. Stem cells are still in the early preclinical phase as a treatment for PD, but as the field of regenerative medicine advances, stem-cell therapy may become a reality in the nonsurgical management of PD.

CONCLUSIONS

PD is associated with a significant emotional burden for affected patients, and is likely underdiagnosed and thus undertreated. Nonsurgical management allows patients to avoid the morbidities associated with surgery and still achieve improved functional and aesthetic outcomes. Oral therapies serve a very limited role in treatment for PD–and in fact may play no appropriate role–due to their limited efficacy and the fact that can cause unnecessary delays in definitive treatment. Intralesional CCh is the first FDA-approved medication for PD, and although not a gold standard at this point, it can be considered a reasonable alternative to surgery for patients desiring conservative treatment. Alternative intralesional therapies are promising, but additional large studies are needed to elucidate their true safety and efficacy profiles. Stem-cell therapy offers an intriguing new potential treatment, but is still in the preclinical phase. Overall, PD remains a challenging disease to treat, but the abundance of recent trials and experiments suggest a promising future for the nonsurgical treatment of PD.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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