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REVIEW

Peyronie's disease: A contemporary review of non-surgical treatment

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Peyronie's disease;
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ABBREVIATIONS

PD, Peyronie's disease;
ED, erectile dysfunction;
ICSM, International Consultation on Sexual Medicine;
SWT, shockwave therapy

Abstract In this review I discuss the current non-surgical treatment options for Peyronie's disease (PD), which remains a therapeutic dilemma for the treating physician. This is despite a large array of treatments that have been used since the time of de la Peyronie in the mid-18th century. Part of the problem with finding an effective treatment is the incomplete understanding of the aetiopathophysiology of this scarring disorder. Published articles in peer-reviewed journals were assessed, recognising that most of the reported trials are compromised by being single-centre studies with no placebo control. Various treatment options have emerged, most with limited and unreliable benefit, but a few treatments have shown a consistent, albeit incomplete, response rate. Currently the only scientifically sensible oral agents appear to be pentoxifylline, L-arginine, and possibly the phosphodiesterase type-5 inhibitors. The current intralesional injection treatment options include verapamil and interferon, with a reported benefit in reducing deformity and improving sexual function. Intralesional clostridial collagenase is in the midst of phase-3 trial analysis by the USA Food and Drug Administration. External mechanical traction therapy has recently emerged as a technique to reduce the curvature, recover lost length, and possibly obviate surgery. Currently there is no clear, reliable and effective non-surgical treatment for PD, but it appears that several of the available treatments can reduce the

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deformity and improve sexual function, and might at least stabilise the disease process.

Introduction

In 1743 François Gigot de la Peyronie offered the first treatment for 'indurio penis plastica' [1]. This acquired connective-tissue, wound-healing disorder of the tunica albuginea of the corpus cavernosum was subsequently named after him. Recent demographic studies indicate a prevalence of up to 8.9% in adult men [2], and although PD typically affects men aged 45–60 years, PD has been reported in males as young as 15 years [3]. Studies showed that an overabundance of myofibroblasts in the damaged tunica can lead to plaque formation, and that altered scar remodelling appears to be responsible for the persistent scar, which can result in several deformities of the penis, including curvature, narrowing, indentation, hinging and penile shortening [4,5]. In addition to the morphological changes, PD can also be associated with pain, significant psychological distress, and often results in sexual dysfunction [6,7].

In the following sections I outline a series of caveats to provide a fundamental understanding of PD, as there are many misconceptions about this medical condition. One such misconception is that PD is a rare disorder, which contemporary demographic studies have disproved by showing that 3–9% of men have PD [2,8]. Another false conception is that the penile deformity associated with PD tends to resolve spontaneously, which is still erroneously believed to occur by many physicians [9].

Although the literature indicates that 3–13% of men presenting with PD might have some spontaneous improvement, in 30–48% of patients the PD might get worse in the first 12–18 months after presentation if left untreated [10]. PD is frequently associated with erectile dysfunction (ED), and studies [11–14] indicate that 40–50% of men with PD complain of ED at the time of diagnosis. In the author's experience, up to 80% of patients with PD will note some reduction in rigidity, many of whom had ED before developing PD.

Surgery remains the standard treatment, and provides the most rapid and reliable treatment option once the disease process is stable. Currently there is no non-surgical cure for this disorder, but treatment provides the potential to stabilise scar progression, reduces deformity, and improves function [15]. In light of this, non-surgical treatment should remain a therapeutic option, and should be offered, if possible, as early as possible in the active phase. However, it should be recognised that if non-surgical therapy is used, treatment-related change occurs at 'glacial speed'. Therefore, any reports indicating a significant improvement of curvature after, e.g., 6 weeks of treatment, should be considered dubious.

Clearly the diagnosis is easy but treatment remains a therapeutic challenge for the practising urologist. Informed consent for any treatment for PD is critical, as these patients are both physically and psychologically devastated by the effects of PD and need to have appropriate expectations set to understand the limitations of treatment. The physician's goal is to make the penis functionally straight, not compromise rigidity, and to avoid treatment-related morbidity.

Although the pathogenesis of PD has yet to be clearly understood, the current paradigm suggests that it is a wound-healing disorder occurring in a genetically susceptible individual whose tunica albuginea responds inappropriately to an inciting event, most commonly trauma, with a proliferative fibrotic reaction, resulting in an exuberant, inelastic scar that does not resolve. Notably, in the author's experience, only 25–30% of men presenting with PD recall a traumatic event. This suggests that the high pressures occurring within the penis during coitus might create forces that the tunic cannot withstand, resulting in a silent micro-fracture. It is beyond the scope of this review to discuss the putative aetiological and pathological factors causing PD, except to note that research has suggested that PD plaques do not resolve due to absent or malfunctioning metalloproteinases and/or elevated levels of tissue inhibitors of metalloproteinases, resulting in a scar that does not undergo normal remodelling [5].

Many reports have evaluated possible risk factors and comorbidities that are associated with PD. Patients were significantly more likely to have PD if they had diabetes, dyslipidaemia or a psychological disorder ($P < 0.05$ for each) [16]. Another study, by El-Sakka and Tayeb [17], showed that of 1133 men with diabetes, 8.1% were found to have PD, and the PD was significantly associated with ED ($P < 0.001$) and the duration of ED ($P < 0.05$), but not the severity of ED. Other associations include ageing, smoking, obesity, hypertension, and ischaemic heart disease [17,8,18].

Men considered candidates for non-surgical treatment include those with PD in the active (acute) phase (defined as <12 months from the onset of symptoms), those who have an unstable or progressive deformity and/or painful erections (particularly to palpation), and any patient who is not psychologically ready or interested in surgery, regardless of the duration or severity of their disease [15].

Discussion of treatment options

The aim of this review is to assess the contemporary non-surgical treatment options for PD. Unfortunately, there are many methodological concerns with most of the published trials, which has resulted in a paucity of studies that satisfy the upper levels of evidence-based medicine. However, this does not mean that we should not use or ignore these treatments altogether, especially when there is some consistency in the study results.

Only a few well-designed and controlled trials investigating the clinical benefits of oral therapy for PD have been conducted over the past two decades, and of the published placebo-controlled trials, there is no evidence of benefit with the use of oral vitamin E, Potaba, colchicine, tamoxifen, carnitine, or omega-3 fatty acids [15,19]. However, animal-model studies showed a reduction of scar progression, and scar regression, when the animal ingested pentoxifylline, L-arginine, or any of the three phosphodiesterase-5 inhibitors (sildenafil, vardenafil, tadalafil) via their drinking water [20]. As a result, these drugs have recently emerged as popular oral agents for the treatment of PD. Clearly, placebo-controlled human trials are necessary before these agents are considered as the standard of care. In 2010, the International Consultation on Sexual Medicine (ICSM) concluded in their report [15] that 'there is evidence that there is no benefit with respect to deformity reduction with any oral therapy'. Table 1 provides a list of contemporary oral treatment options, outlining the purported mechanisms of action, efficacy as assessed in published studies, and the recommendations made by the ICSM [15].

Another treatment option that has been used for many years is injection therapy, starting with intralesional steroid injection. The rationale here is reasonable, as steroids have anti-inflammatory and possibly anti-fibrotic properties, but for the objective measures, no real benefit has ever been published, and side-effects from repeated exposure to steroids have been reported [19].

Most of the nine published human trials on intralesional verapamil were not controlled, but showed consistently that 30–60% of patients had a measurable reduction of curvature when the patient was used as his own control, with a mean reduction of curvature in the responder group being 15–30° [19]. A single more recent single-blind prospective trial comparing intralesional verapamil with saline showed no treatment advantage [21]. Intralesional verapamil makes scientific sense, as studies have shown decreased PD-derived fibroblast proliferation and decreased extracellular matrix production *in vitro* [22–24]. A recent animal model study showed a reduction in cellular proliferation, decreased myofibroblast activity, and increased metalloproteinase activity when verapamil was exposed to PD plaque-derived fibroblasts in tissue culture [25]. The lack of multicentre placebo-controlled trials is the primary limitation for many physicians to use intralesional verapamil injection. Unfortunately these studies will probably never be done, as verapamil is an inexpensive, generic medication [26].

Table 1 Oral therapies for PD.

Treatment (dose)	Mechanism of action	Efficacy	ICSM guideline [15]
Vitamin E (400 IU daily to twice daily)	Antioxidant reduces oxidative stress of reactive oxygen species shown to be increased in PD	NB for pain, curvature, or plaque size	NB for deformity
Colchicine (2.5 mg daily)	Inhibits fibrosis and collagen deposition by inhibiting neutrophil microtubules	NB for pain, curvature, or plaque size	NB for deformity
Potassium aminobenzoate (3 g every 6 h)	Stabilises tissue serotonin monoamine oxidase activity; antifibrotic effect due to a direct inhibitory effect on fibroblast glycosaminoglycan secretion	Mean decrease in plaque size in 74.3%, no improvement in curvature	NB for deformity
Tamoxifen (40 mg daily)	Affects the release of TGF from fibroblasts and blocks TGF receptors	No demonstrable improvement in pain, curvature, or plaque size	NB for deformity
Carnitine (1 g twice daily)	Reduces both collagen fibre deposition and elastogenesis	No significant improvement in pain, curvature or plaque size	NB for deformity
Pentoxifylline (400 mg twice daily)	Nonspecific phosphodiesterase inhibitor, antifibrotic presumably	36.9% with mean decrease in curvature of 23°	Further studies required to confirm findings

NB, no benefit; TGF, transforming growth factor.

A biological modifier considered to have similar properties to verapamil is interferon-2β. Previous studies showed no significant benefit, but a double-blind, placebo-controlled multicentre trial showed an advantage to interferon over saline [27]. The greatest value of this trial was that saline was used as the placebo control, and therefore the question addressed was whether a placebo injection such as saline could result in an improvement in the deformity. The results appear to be clinically not meaningful, as only 9% of patients had a measurable improvement with saline, with a mean curvature correction of 9°. Therefore, use of a saline injection has little value for the patient with PD.

Finally, intralesional collagenase has also been used. Reported on since the early 1980s, it was recently submitted for approval by the USA Food and Drug Administration under the name Xiaflex™ (Auxilium Pharmaceuticals, Malvern, PA, USA). Overall it appears that with Xiaflex there is a 30–37% reduction in curvature, compared to an 11–21% reduction with saline.

The initial phase-2b trial determined that intralesional Xiaflex in combination with manual modelling provided a better outcome, and therefore in phase 3, all patients underwent modelling during the protocol [28]. During the four treatment cycles of the study, participants received an injection with a fixed dose and volume of drug into the plaque, followed by 1–3 days of no treatment, at which point another injection was made. At 1–3 days later, the penile plaque was manually modelled by the investigator in the office, followed by a 6-week interval before beginning the next cycle. The other primary endpoint examined during the course of the phase-3 trial was the 'bother' domain score from the questionnaire, which is undergoing final validation during this trial. The active drug arm showed a statistically significant reduction of bother ($P = 0.045$) over placebo. Importantly, the only serious adverse events reported were three penile fractures in over 550 men receiving active drug. The remainder of the adverse events were primarily related to local ecchymosis and haematoma.

For topical therapy, the ICSM concluded that 'as there are no independent controlled trials and no evidence of adequate levels within the tunica albuginea, no recommendation is possible for topical verapamil.' [15]. I recommend against it, as it is expensive and has not been shown to be beneficial.

Shockwave therapy (SWT) has also been used and reported on in several studies. There are now two published, placebo-controlled trials, neither of which has shown any meaningful improvement in the deformity. The study by Palmieri et al. [29] enrolled 100 men who had PD for $\geqslant$12 months and had undergone no previous treatment to receive 2000 shocks weekly for 4 weeks, vs. exposure to a non-functional transducer. At 24 weeks there was some worsening of plaque size and curvature in the placebo group, but there was no significant improvement in the active-treatment group. Although the difference between those receiving the SWT and the placebo was considered statistically significant, the actual difference between the two groups was slightly more than 3°, which would not be considered clinically meaningful. The more recent, smaller study (30 men) by Chitale et al. [30], using SWT vs. a sham treatment, showed no significant change between the groups in any of the outcome variables evaluated. Therefore, the conclusion by the ICSM was that 'there is evidence that extracorporeal shockwave therapy does not improve Peyronie's disease-related deformity.' [15]

Vacuum therapy has been suggested as a potential treatment for PD. The first and only report published on this device, by Raheem et al. [31], examined 31 men with PD with a mean duration of disease of 10 months. After completing a 12-week, twice-per-day 10-min application in this uncontrolled study, 67% had some reduction of curvature of 5–25°, and 35% had a mean increase in stretched penile length of 0.5 cm. There was no improvement in penile girth, and 51% were satisfied with the results and required no further treatment. The conclusion by the authors was that vacuum therapy can improve or stabilise the curvature in PD and might reduce the need for surgery.

There is a larger published experience with trials using external penile traction therapy for PD. Traction has already been recognised in other tissue models (i.e. bone, muscle, skin) to induce cellular proliferation, which occurs by three different, separately identified mechanisms [32–35]. Traction has also been shown to induce an increased production of metalloproteinases, as well as a change in the orientation of the collagen fibres parallel to the traction forces when applied to Dupuytren's contracture tissue [36]. To date, there are two published pilot studies using external traction as the sole therapy for PD, the first of which, by Levine et al. [37], showed an objectively measured improvement of curvature in all 10 patients, of 10–45°, as well as an increase in penile length in all patients, from 0.5 to 2 cm. There was also a subjective enhancement in penile girth, and a measured improvement in the International Index of Erectile Function EF score of 4 points at the end of this 6-month trial.

Most importantly in this initial pilot study, there was no local change in sensation, skin lesions, or new erectile dysfunction reported. The study by Gontero et al. [38] only showed a minimal improvement of curvature (15 men), but there was a measured improvement in penile length, with a mean increase in the stretched penile length of 1.3 cm. The goals of penile traction therapy for PD are to stop the progression of scarring, recover penile length and girth, reduce curvature, enhance sexual function, and ultimately to avoid or simplify surgery. The value

of the last point can be demonstrated with the example of the man who has severe curvature (i.e. $>70°$) but who might not be a good candidate for grafting because of borderline ED. By undergoing a 3–6 month course of traction, a reduction in his deformity could possibly allow surgery to be avoided altogether, or he could benefit from a less invasive/complicated operation, such as a plication procedure.

Until a more reliable, effective, non-surgical treatment emerges, currently it appears that a combined therapy provides the greatest potential for success. The goal here is to create a synergy between the chemical effects of the oral and injectable drugs when combined with the mechanical effects of external traction or vacuum therapy. There is only one recently published study that examined combined therapy with three elements (once-daily pentoxifylline 400 mg and L-arginine 1000 mg twice daily, and every 2 weeks an intralesional verapamil injection, and daily external traction for 6 months). In this study 54% of men were considered responders, defined as $\geqslant 10°$ of measured improvement in curvature, with a mean (range) reduction of curvature in this group of 27 (10–65)° [39]. A length gain of 0.5–2 cm was also noted in the patients using traction.

Interestingly, only 12% of patients withdrew from the study, and only 11% ultimately went on to surgery. Possibly the most important information gained from this study pertaining to traction was that the minimum time to expect a measured improvement in length and curvature was a mean duration of traction for 3 h per day. There was also evidence of a dose response, in that men who used the device for a longer period had progressively better results for deformity and length. The results of postoperative traction have also been recently reported in a sizeable study by Rybak et al. [40]. In this trial, men who used traction after either a plication or grafting operation did not personally perceive any loss of length compared to those who elected not to use traction after surgery. When examining measured length change in the plication group, only 9% gained length without traction (mean − 0.6 cm, range − 1.75 + 0.5 cm), but 75% gained length compared to their preoperative stretched length with traction (mean + 0.9 cm, range +0.25 to +1.75 cm). In those who underwent a grafting procedure, 52% gained some length (mean + 0.2 cm, range −1 to +2.5 cm) without traction, but 89% gained more length (mean + 1.5 cm, range −1 to 6.5 cm) with traction. Therefore, it appears that postoperative traction enhances penile healing in a 'straight' direction and can prevent length loss, but more importantly, can also possibly result in some recovery of lost length.

Conclusions

PD is a worldwide problem, and probably far more prevalent than previously thought. Surgery remains the standard treatment, but should only be offered when the patient is in the stable phase of the disease, and understands the risks of incomplete straightening, further loss of length, diminished sensation, and ED. While there are emerging non-surgical treatments that may offer hope for more effective and reliable results, the current approaches might still prevent the progression of the disease, as well as reduce the deformity and improve sexual function.

Conflict of interest

No conflict of interest to declare.

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