Review Article

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

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Background: Peyronie's disease (PD) remains a therapeutic dilemma for the treating physician. This is in spite of a large array of treatments which have been used since the time of de la Peyronie in the mid 18th century. Part of this problem is due to an incomplete understanding of the etiopathophysiology of this scarring disorder. Having a better understanding of the how and why the scarring occurs may help prevent progression, but ultimately reversing the existing scar remains the real challenge.

Methods: This review discusses the current non-surgical treatment options for Peyronie's disease. Published articles in peer-reviewed journals are used, recognizing that the majority of the published trials are compromised by being single-center studies without a placebo control.

Results: A variety of treatments options have emerged, most with limited and unreliable benefit, but a few treatments have shown a consistent albeit incomplete response rate. Could this suggest that all PD is not the same and that the heterogeneous nature of this scarring disorder may account for why some patients respond and others do not? Further investigation of this diverse response rate may yield insights into the pathophysiology of PD. In the meantime, there have been many oral treatments offered for PD. Currently the only scientifically sensible treatments appear to be pentoxifylline, L-arginine, and possibly the phosphodiesterase type-5 inhibitors. Intralesional injection has been used for many years. The current treatment options include verapamil and interferon, with reported benefit with respect to reduced deformity and improved sexual function. Intralesional clostridial collagenase is in the midst of phase 3 trial analysis by the FDA in the USA and may become the newest and only FDA approved treatment for Peyronie's disease. External mechanical traction therapy has also recently emerged as a technique to reduce curvature, recover lost length, enhance girth, and possibly obviate surgery.

Conclusions: It appears at this time that there is no clear, reliable and effective non-surgical treatment for Peyronie's disease, but it does appear from the published literature that several of the available treatments can result in reduction of deformity, improved sexual function, and may at a minimum stabilize the disease process so that deformity does not get worse particularly during the acute phase of this scarring disorder. Combination therapy in an effort to create a synergy between the chemical effects of oral and injectable drugs with the mechanical effects of external traction therapy may provide the best opportunity today for reduction of deformity in the man with Peyronie's disease.

Keywords: Peyronie's disease; verapamil; traction

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Peyronie's disease (PD) is an acquired connective tissue disorder affecting the tunica albuginea of the corpus cavernosum. Since the description of PD in 1743 by the French physician François Gigot de la Peyronie,

demographic studies have indicated a prevalence of up to 8.9% (1). It typically affects males between the ages of 45 and 60 years, however men as young as 15 years have been reported (2). Studies have demonstrated that an overabundance of myofibroblasts in the damaged tunica may lead to plaque formation and that altered scar remodeling appears to be responsible for the persistent scar (3,4). Development of the fibrous scar can result in multiple deformities of the penis including curvature, narrowing, indentation, hinging, and loss of penile length. In addition to the morphological changes, PD plaques can also cause significant pain, psychological distress, and often results in sexual dysfunction (5,6).

The following is a series of caveats which provide a fundamental understanding of PD, as there are many misconceptions about this medical condition. These include that PD is not a rare disorder, as contemporary demographic studies have shown that 3% to 9% of men have PD (1,7). The penile deformity associated with PD does not tend to resolve spontaneously as previously thought and is still considered to occur by many physicians (8). In fact, the literature indicates that somewhere between 3% and 13% of men presenting with PD may have some spontaneous improvement, but up to 30% to 48% of patients may get worse in the first 12 to 18 months after presentation if left untreated (9). Peyronie's disease is frequently associated with erectile dysfunction (ED). Studies indicate that 40% to 50% of men complain of ED at the time of diagnosis (10-13). In the author's experience, up to 80% will note some reduction in rigidity, many of whom had ED before developing Peyronie's. At this time, there is no non-surgical cure for this disorder, but treatment does appear to be able to stabilize scar progression and possibly reduce deformity and improve function (14). As a result, non-surgical treatment should be considered, particularly in the active phase. It should also be recognized that if non-surgical therapy is used, that treatment-related change occurs at "glacial speed", and therefore any reports indicating significant improvement of curvature after, for example, 6 weeks of treatment should be considered dubious. Surgery remains as the gold standard treatment and the most rapid and reliable treatment option once the disease process is stable. Diagnosis is easy, but treatment remains a therapeutic challenge for the practicing urologist. Finally, informed consent for any PD treatment 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.

The pathogenesis of Peyronie's disease is not clearly understood, but 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. Of note, only 25-30% of men presenting with PD recall a traumatic event, suggesting that the high pressures that occur within the penis during coitus may create forces which the tunic cannot withstand, resulting in a silent microfracture. Discussion of the putative etiologic and pathological factors causing PD is beyond the scope of this article, except to note that it appears that the PD plaque does not resolve due to absent or malfunctioning metalloproteinases and/or elevated levels of tissue inhibitors of metalloproteinases (TIMPs) resulting in a scar which does not undergo normal remodeling (4).

Candidates for non-surgical treatment include those in the active (acute) phase, which is defined as less than 12 months from onset of symptoms, those who have unstable progressive deformity and plaque, painful erections (particularly to palpation or with development of erection), and any patient who is not psychologically ready or interested in surgery regardless of the duration or severity of their disease (14).

The goal of this article is to review the contemporary non-surgical treatment options for PD. There are methodical concerns with most of the published trials, resulting in a paucity of studies which satisfy the upper levels of evidence-based medicine. This does not mean that we should not use them or ignore these treatments altogether, especially when there is some consistency in the study results. Regardless, careful consideration of treatment is in order. Over the past two decades there have been only a few well-designed and controlled trials investigating the clinical benefits of oral therapy for PD, but when one reviews 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 (14,15). Pentoxifylline and L-arginine have emerged as popular new oral agents for treatment of Peyronie's. This is based upon animal model studies which demonstrated reduction of progression of scar and some regression of scar when the animal was allowed to drink pentoxifylline,

L-arginine, or any of the three PDE5 inhibitors (sildenafil, vardenafil, tadalafil) in their drinking water (16). The International Consultation on Sexual Medicine published their report in 2010 in the Journal of Sexual Medicine and concluded "there is evidence that there is no benefit with respect to deformity reduction with any oral therapy" (14).

Injection therapy has also been used for many years, starting with intralesional steroid injection. The rationale here is reasonable, as steroids have anti-inflammatory and possibly anti-fibrotic properties, but no real benefit with respect to objective measures has ever been published, and side effects from repeated exposure to steroids have been reported (15).

Intralesional verapamil makes scientific sense, as studies have shown decreased Peyronie's disease-derived fibroblast proliferation and decreased extracellular matrix production *in vitro* (17-19). A recent animal model study demonstrated reduction of cellular proliferation, decreased myofibroblast activity, and increased metalloproteinase activity when verapamil was exposed to PD plaque derived fibroblasts in tissue culture (20). In the 9 published trials of intralesional verapamil, the majority were non-controlled, but showed consistently that 30% to 60% of patients had measured reduction of curvature when the subject was used as his own control, with a mean reduction of curvature in the responder group being between 15 to 30 degrees (15). A single more recently published single-blind prospective trial comparing intralesional verapamil to saline did not show a treatment advantage (21). The primary limitation for many physicians to use intralesional verapamil injection is the lack of multicenter placebo-controlled trials, which will likely never be done, as verapamil is an inexpensive generic medication (22).

Interferon 2β is considered a biological modifier that may have similar properties to verapamil. Previous studies did not show significant benefit, but a double-blind, placebo-controlled multi-center trial did show an advantage to interferon over saline (23). 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 improvement of deformity. In fact, only 9% of patients did have measured improvement with saline, with a mean curvature correction of 9 degrees. This appears clinically not meaningful, and therefore use of saline has little value to the Peyronie's patient.

Finally, intralesional collagenase has been used and reported on since the early 1980s. It was recently submitted for FDA approval in the United States under the name Xiaflex (Auxilium Pharmaceuticals, Malvern, PA). Overall it does appear that with Xiaflex there is between a 30% to 37% reduction of curvature as compared to an 11% to 21% reduction with saline. The initial phase 2b trial determined that modeling in combination with intralesional Xiaflex provided an outcome advantage, and therefore in phase 3, all patients underwent modeling during the protocol (24). There were four treatment cycles which included an injection of a fixed dose and volume of drug into the plaque followed by 1-3 days of no treatment, at which point another injection is performed, and 1 to 3 days later penile plaque modeling is performed by the investigator in the office. There was a six week interval before beginning the next cycle. The other primary endpoint which was 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. Active drug did demonstrate a statistically significant reduction of bother (P=0.0451) over placebo. Importantly, the serious adverse events reported in the publicly released "top-line" data shows that there were only 3 penile fractures in over 550 men receiving active drug. The remainder of the adverse events was primarily related to local ecchymosis and hematoma.

With respect to topical therapy, the International Consultation 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" (14). In my opinion, don't use it, as it is expensive and has not been shown to be beneficial.

Shockwave therapy (ESWT) has also been used and reported on in multiple studies. There are now 2 published, placebo-controlled trials, which have shown virtually no improvement with respect to deformity. The study by Palmieri *et al*. (25) enrolled 100 men with PD for at least 12 months and no prior treatment. They received 2,000 shocks weekly for 4 treatments versus 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. It should be noted that although the difference between those receiving the shockwave therapy versus the placebo were considered statistically significant, the actual difference between the two groups was a bit more than 3 degrees, which would not be considered clinically meaningful. The more recent, smaller study (N=30) by Chitale *et al*. (26) using shockwave versus sham showed no significant change between the two groups in any of the

outcome parameters evaluated. Therefore, the conclusion by the International Consultation is that "there is evidence that extracorporeal shockwave therapy does not improve Peyronie's disease-related deformity" (14).

Vacuum therapy has been touted as a potential treatment for Peyronie's disease. The first and only paper published on this by Raheem *et al*. examined 31 men with PD with a mean duration of disease of 10 months (27). They completed a 12-week, twice-per-day 10 minute application trial. In this non-controlled study, 67% had some reduction of curvature between 5 and 25 degrees, and 35% had a mean increase in stretched penile length of 0.5 cm. There was no girth improvement, and 51% were satisfied with the results and required no further treatment. The conclusion by the authors was that vacuum therapy can improve or stabilize Peyronie's disease curvature and may reduce the need for surgery.

There is a larger published experience with trials using external penile traction therapy for PD. Traction has been recognized in other tissue models (i.e., bone, muscle, skin) to induce cellular proliferation by three different identified mechanisms (28-31). It has also been noted that traction when applied to Dupuytren's contracture tissue can change the orientation of the collagen fibers parallel to the traction forces, and has been shown to induce increased production of metalloproteinases (32). There are two published pilot studies using external traction as solo therapy for Peyronie's disease, the first of which by Levine *et al*. (33) demonstrated an objectively measured improvement of curvature in all patients (N=10) ranging from 10 to 45 degrees, as well as an increase in length in all patients from 0.5 to 2 cm. There was also noted subjective enhancement of girth, and a measured improvement in IIEF-EF of 4 points at the end of this 6 month trial. Most importantly in this initial pilot study, there was no change in sensation, skin lesions, or new erectile dysfunction reported. The study by Gontero *et al*. (34) only showed minimal improvement of curvature (N=15), but there was measured improvement in length, with a mean increase of stretched penile length of 1.3 cm. The goals of penile traction therapy for PD is to stop 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 is that for the man who has a severe curvature (i.e., >70°), but might not be a good candidate for grafting, could undergo a 3-6 months course of traction and possibly reduce the deformity so that he would then either avoid surgery altogether or possibly benefit from a less invasive and complicated operation such as a plication procedure.

Until a more reliable, effective, non-surgical treatment emerges, it appears at this time that combination therapy has the greatest potential for success. Here the goal is to create a synergy between the chemical effects of the selected oral and injectable drugs combined with the mechanical effects of external traction or vacuum therapy. Only one recently published study examines combination therapy with three elements (daily pentoxifylline 400 mg TID and L-arginine 1,000 mg BID, every two weeks intralesional verapamil injections, and daily external traction for 6 months). In this study, 54% were considered responders with at least 10 degrees of measured improvement and a mean curve reduction in the responder group of 27 degrees (range, 10-65 degrees) (35). Length gain of 0.5 to 2 cm was also noted in patients using traction. Interestingly, only 12% of patients dropped out of 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 measured improvement of length and curvature was a mean duration of traction for 3 hours per day during this 6 month study. There was also evidence of a dose response curve, in that men who used the device for a longer period of time had progressively better results with respect to deformity and length. The results of traction following surgery have also been recently published in a sizable study by Rybak *et al*. (36). In this trial, men who used traction after either a plication operation or grafting procedure did not personally report any loss of length compared to those who elected not to use traction postoperatively. When examining measured length change in the plication population, only 9% gained length without traction (mean 0.6 cm, range, –1.75 to +0.5 cm), but 75% gained length compared to their preoperative stretched length with traction (mean +0.9 cm, range, 0.25-1.75 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 does appear that traction postoperatively enhances penile healing in a "straight direction" and can prevent length loss, but more importantly, may also result in some recovery of lost length.

My hope is that this review of contemporary non-surgical management of Peyronie's disease will be useful for your practice. Peyronie's disease is a problem which is seen worldwide and is likely one that is far more prevalent than previously thought. There are emerging non-surgical treatments which may offer hope of effective, more reliable

results, but the current approaches may still prevent progression or result in reduced deformity and improved sexual function. Surgery remains as the gold standard therapy, but should only be offered when the patient is in the stable phase and understands the risks of incomplete straightening, further loss of length, diminished sensation, and erectile dysfunction.

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