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The Advances in Non-Surgical Treatment of Peyronie's Disease

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Abstract

Peyronie's disease (PD), a condition of uncertain cause, is characterized by a plaque, or hard lump, that forms on the penis. The plaque develops on the upper or lower side of the penis in layers containing erectile tissue. Men with PD usually seek medical attention because of painful erections and difficulty with intercourse. Because the course of PD is different in each patient and some patients experience improvement without treatment, medical experts suggested waiting 1 to 2 years or longer before attempting to correct it surgically. During that wait, patients often are willing to undergo treatments whose effectiveness has not been proven. This review focuses on new developments for conservative treatment strategies for PD.

Keywords: Peyronie's disease; Nonsurgical therapy

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Introduction

A French surgeon, François de la Peyronie, first described PD in 1743 [1]. Early reports classified it as a form of impotence, now called erectile dysfunction (ED). PD can associate with ED [2]. However, experts now recognize ED as only one factor associated with the disease, which is not always present. PD manifests as a fibrous inelastic scar of the tunica albuginea, leading to deformity, curvature, shortening, narrowing of the penis, and painful erections that subsequently lead to painful or unsatisfying sexual intercourse [3]. Cases of PD range from mild to severe. In severe cases, the hardened plaque reduces penile flexibility, causing pain and forcing the penis to bend or arc during erection [4]. In many cases, the pain decreases over time, but the bend in the penis may remain a problem, making sexual intercourse difficult, which can disrupt a couple's physical and emotional relationship and lead to lowered self-esteem in man [5]. In a small percentage of patients with the milder form of the disease, inflammation may resolve without causing significant pain or permanent bending. One study found PD occurs in 1% of men [6]. Although the disease occurs mostly in middle-aged men, younger and older men can also acquire it [7]. The etiology of PD is not clear, which may be related to Dupuytren contracture, trauma, urethral device operation, infection and so on [8]. Dupuytren's disease is a palmar fibromatosis leading to progressive digital flexion contracture and appears to have the same physiopathology as PD [9]. Among the offspring of patients with Dupuytren contracture, 20% of men may develop PD. TGF-β1 is important in the pathogenesis of PD, which can not only increase the organization of collagen, proteoglycan, fibrin transcription and synthesis, but also increase the synthesis of tissue collagenase inhibitors, so as to prevent the breakdown of connective tissue [10]. Several studies related to Dupuytren' disease described alterations in the extracellular matrix, an increase of TGF-β1 which affected the expression of major extracellular matrix (ECM) proteins, fibronectin, and collagen [11]. A validated questionnaire has been developed to help diagnose and assess the severity of PD, called PDQ [12]; All PDQ domains were significantly correlated with improvements in the International Index of Erectile Function (IIEF) and erectile function scores [13].

The diagnosis of PD involves a focused history and physical examination. Once the diagnosis is made, the patient should be counseled on both surgical and nonsurgical interventions, both of which are the treatment methods of PD. Nonsurgical treatment, as an alternative treatment of PD, has been paid more and more attention in recent years. In this paper, we will review the nonsurgical medical treatment options that have been trialed.

Oral Therapy

Vitamin E

Vitamin E is a free radical scavenger with antioxidant properties. The first study of using vitamin E for PD treatment was published by Scott and Scardino in 1948 [14]. This non-controlled study with 23 participants showed that penile curvature was improved in 78% of the patients, with 91% reduction of induration and complete disappearance of pain [14]. Following studies never achieved as favorable results. Especially in a placebo controlled study of 40 patients, only 35% of the patients had pain improvement, and had a slight effect on the size of the induration and the curvature of the penis [15]. Nonetheless, vitamin E is still widely used because of its low price and no side effects [16].

Potassium para-aminobenzoate (POTABA)

POTABA can decrease the level of 5-serotonin by increasing the activity of monoamine oxidase, inhibit abnormal fibrous hyperplasia, and improve the application of tissue to oxygen [17]. In theory, it can reduce pain, improve penile curvature, and narrow penile induration, However, a small randomized controlled trial (RCT) did not show significant improvement [18]. The use of POTABA is limited due to maximum dose limitation, high costs, and severe gastrointestinal side effects, therefore it is not recommended.

Tamoxifen

Tamoxifen is believed to promote the release of transforming growth factor (TGF) by fibroblasts, and TGF plays an important role in regulating immune response, inflammation and tissue repair by inactivating macrophages and T lymphocytes [19]. One scholar reported that tamoxifen was beneficial for early inflammatory PD [20], but another RCT and placebo contrast showed no significant improvement in pain, curvature, and plate size [21]. Tamoxifen use in PD should be approached with caution given its questionable efficacy and its potentially severe side effects: Stomach discomfort and hair loss and so on.

Colchicine

In recent years, colchicine has also been used in the treatment of PD. Colchicine has anti-inflammatory effect, which can affect the activity of collagenase, reduce the synthesis of collagen, and inhibit the proliferation of fibroblasts [22]. It has been reported that the volume of penile induration can be reduced by 50% and the pain decreased by 78% after treated with this drug. Its efficacy remains to be determined [23]. The common side effects of the drug are gastrointestinal distress and diarrhea [24].

Injection Therpay

Intralesional verapamil

Verapamil was first used as an intralesional treatment for PD by Levine et al. in 1994 [25]. As a calcium channel antagonist, verapamil reduces the concentration of calcium ions in cells and increases the activity of collagen. It also inhibits fibroblast proliferation. The drug is thought to be able to change the structure of the induration gradually improve and the penis condition [26]. Many of the research data on verapamil's treatment of PD are contradictory. However, given its excellent overall safety profile, it remains a treatment option for patients with PD. The main side effect of the drug is ecchymosis.

Intralesional interferon (IFN) α2 β

Since the early 1990s, IFNs have also been tried to treat PD with intracranial injection [27]. It can reduce the synthesis of extracellular collagen, increase the synthesis of collagenase, soften the plaque and improve symptoms. An RCT evaluated the efficacy of IFNα2β by comparing it with placebo [28]. In this trial, the IFNα2β group showed a significant improvement in penile curvature, plaque size and pain However, there was no statistically significant difference in IIEF scores between the two groups. In general, the drug is well tolerated, but, due to its high cost and cold side effects, its use is limited.

Intralesional collagenase

Collagenase clostridium histolyticum (CCH) was the only drug approved by the US Food and Drug Administration (FDA) for the treatment of PD. Collagenase is an enzyme that promotes collagen breakdown. Its natural substrates are type I and type III collagen [29], which constitutes the most abundant types of plaque formed in PD. CCH was also found to directly increase fibroblast apoptosis to prevent tissue fibrosis [30]. The impact of collagenase as a potential intralesional agent for PD treatment was first examined by Gelbard et al. [31] in the 1980s. In 2012, Gelbard et al. [32] analyzed 147 patients randomized to receive CCH or placebo with or without modeling. The results showed that the curvature of the penis in the CCH group was significantly improved. In another study, Wayne et al. [33] examined the safety of collagenase clostridium histolyticum, which came to a conclusion that no clinically meaningful differences were observed with TRAE rates when CCH injections were administered at penile curvature deformity ≥30°vs. CCH injections at penile curvature deformity <30°. This finding highlighted the safety of continued CCh injections for patients who have achieved penile curvature deformity <30° after an initial treatment cycle of CCh. Goldstein et al. [34] further studied the effect of CCH on PD from another point of view, as little was known about the consequences of PD or treatment on the sexual partners of affected men. Their result supported the safety and efficacy of CCH in the management of appropriate patients with PD and the potential benefits for patients' partners. These well-designed clinical trials confirmed the safety and effectiveness of CCH, which made intralesional CCH the only FDA-approved drug for PD. More researches on CCH treatment of PD are still ongoing.

Other Nonsurgical Treatments

Extracorporeal shock wave treatment (ESWT)

ESWT was introduced in the treatment of penile sclerosis in 1989 [35], and it has been reported that it is effective in reducing penile curvature and pain, as well as improving sexual function. The theoretical basis of its role is unclear and may be related to induration of revascularization and calcification. A study in 2002

[36] reported the use of Siemens lithotripsy in the treatment of 54 patients with PD, in which 91% of patients had penile pain relief, and 54% had penis curvature improved with an average reduction of 31°. A recent placebo-controlled RCT [37] evaluating ESWT for PD showed a modest decrease in pain associated with PD, but a slight trend towards increased curvature and plaque size in the ESWT group. In general, ESWT for the treatment of PD can be well tolerated by the patient, but its long-term efficacy is still needed to be observed.

Stem cell therapy

As a treatment for PD, stem cells therapy is still in the pre-clinical stage, but it is more and more widely concerned because of its potential to limit fibrosis in early acute phase. Lin and Lue [38] used adipose-derived stem cells (ADSCs) to treat PD, and Castiglione's group [39] used human ADSCs to assess the improvement of PD and ED in rat models, in which they noted a reduction in fibrosis and improvement in erectile function. The same work was done by Dellis and Papatsoris [40]. The research findings suggested that ADSCs was a feasible, safe and effective therapeutic modality for PD. They also give their views that several practical issues such as cost, ease of isolation and culturing, effectiveness and source along with ease of administration should be addressed before clinical application of stem cells. With the continuous progress of research, it is believed that stem cell therapy as a non-surgical treatment of PD will become a reality.

Penile traction therapy (PTT)

In recent years, penile traction therapy has gained considerable interest as a novel nonsurgical treatment option for men with PD and short penises [41]. PTT can increase the length of the penis and reduce penile deformity. Some studies have shown that penile curvature has decreased by 25°, sexual function has improved, and the risk of surgical indications has been greatly reduced [42]. PTT, as a method of treating PD, exhibits good tolerance, but the overall effect on PD is small when used alone. As part of the combined treatment of early PD, the PTT will play a more important role in the future.

Conclusion

Apart from physiological and functional alterations of the penis due to fibrotic tissue, PD lowers patients' self-esteem and has a considerable negative impact on patients' sexual and psychosocial life with almost half of the patients suffering from depression [43], which should not be underestimated. The precise etiology of PD is still unknown [44], therefore the current treatments are all symptomatic treatment. Currently, many data on non-surgical management is conflicting. However, there is no doubt that non-surgical treatment has received widespread attention and a great deal of effort is being devoted to non-surgical treatment of PD. Until today, the efficacy of various non-surgical treatments of PD is still not perfect. Maybe in the future, non-surgical treatment will replace surgery.

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