World Journal of Clinical Urology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5410/wjcu.v3.i1.31

World J Clin Urol 2014 March 24; 3(1): 31-37
ISSN 2219-2816 (online)
© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

MINIREVIEWS

Systematic review of the non surgical management of Peyronie's disease

Paolo Verze, Davide Arcaniolo, Tommaso Cai, Marco Franco, Roberto La Rocca, Mario Acquaviva, Lorenzo Spirito, Aleksandre Bochorishvili, Vincenzo Mirone

Paolo Verze, Davide Arcaniolo, Tommaso Cai, Marco Franco, Roberto La Rocca, Mario Acquaviva, Lorenzo Spirito, Vincenzo Mirone, Department of Neuroscience, Reproductive Sciences and Odontostomatology, Urology Unit, University of Naples Federico Ⅱ, 80131 Naples, Italy
Aleksandre Bochorishvili, National Centre of Urology, 00144 Tbilisi Georgia, Italy
Author contributions: Verze P, Arcaniolo D and Mirone V contributed to drafting manuscript; Verze P and Mirone V contributed to final review of the content; Cai T, Franco M, La Rocca R, Acquaviva M, Spirito L and Bochorishvili A contributed to selecting studies; Acquaviva M and Spirito L contributed to reference listing.
Correspondence to: Paolo Verze, MD, PhD, Department of Neuroscience, Reproductive Sciences and Odontostomatology, Urology Unit, University of Naples Federico Ⅱ, Via S. Pansini, 80131 Naples, Italy. pverze@gmail.com
Telephone: +39-081-7462611 Fax: +39-081-7462611
Received: December 24, 2013 Revised: February 3, 2014
Accepted: February 16, 2014
Published online: March 24, 2014

Abstract

This systematic review shows the "Status quo" on medical treatment for Peyronie's disease (PD). PD is a connective tissue disorder, characterised by the formation of a fibrotic lesion or plaque in the tunica albuginea, which leads to penile deformity. The aetiology of PD is unknown. Nowadays the most widely accepted hypothesis proposed by Gonzalez-Cadavid *et al*, is repetitive microvascular injury or trauma to the tunica albuginea. Physicians have proposed several medical alternatives for treatment of this disease with few effective results. Nevertheless, as of today nonsurgical options are currently available, and some of them are able to stabilize or even reduce deformity while improving pain relief and sexual function. A systematic literature search throughout the Medline database was carried out. The controlled vocabulary of the medical subject headings database employs the specific term "penile induratio" for PD. A total of 50 articles on PD were found. Studies were selected based on clinical relevance. The recommended standard of care for PD involves an initial treatment in the acute phase. Several non-operative treatment options have been used. Unfortunately no further substantial, quality evidence on the use of medical therapy currently exits. There is, however, an increasingly enhanced interest in this disorder and basic scientific and clinical research will eventually lead to a more effective methodology to study the disease.

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

Key words: Peyronie's disease; Non surgical; Dupuytren; Extracorporeal shockwave therapy

Core tip: Ince the first medical publication on Peyronie's Disease, physicians have proposed several medical alternatives for treatment of this disease. As of today nonsurgical options are currently available. A consistent number of non-surgical treatment options that offer some benefit with respect to disease stabilization, alleviation, as well as reduction of deformity and improved sexual function are available including oral treatment with potassium para-aminobenzoate, intralesional treatment with interferon, iontophoresis with verapamil 5 mg and dexamethasone 8 mg and extracorporeal shock-wave treatment.

Verze P, Arcaniolo D, Cai T, Franco M, La Rocca R, Acquaviva M, Spirito L, Bochorishvili A, Mirone V. Systematic review of the non surgical management of Peyronie's disease. *World J Clin Urol* 2014; 3(1): 31-37 Available from: URL: http://www.wjgnet.com/2219-2816/full/v3/i1/31.htm DOI: http://dx.doi.org/10.5410/wjcu.v3.i1.31

INTRODUCTION

Peyronie's disease (PD) is a connective tissue disorder, characterised by the formation of a fibrotic lesion or plaque in the tunica albuginea, which leads to penile deformity[1]. The true prevalence of PD is unknown. An evaluation of existing epidemiological data on PD revealed a prevalence rate of 3.2%. However the actual prevalence of PD may be even higher, considering many patients' reluctance to report this embarrassing condition to their physicians. The latest version of the European Association of Urology guidelines[1] reports a prevalence rate of 0.4%-9%.

The aetiology of PD is unknown. Nowadays the most widely accepted hypothesis proposed by Gonzalez-Cadavid *et al*[2], is repetitive microvascular injury or trauma to the tunica albuginea. PD starts with an acute inflammatory process. The progression of inflammation causes a proliferation of the tunical fibroblasts, some of which differentiate into myofibroblasts with a disproportionate production of collagen, the persistence of fibrin, and resulting elastin fragmentation. This prolonged inflammatory reaction generates the remodelling of connective tissue into a dense fibrotic plaque. As a result of Penile plaque the penis develops a curvature which, in the case of severe bending, can prevent vaginal intercourse. Comorbidities and risk factors associated with the disease are diabetes, hypertension, lipid abnormalities, ischaemic cardiopathy, erectile dysfunction, smoking, and excessive consumption of alcohol[3]. An accompaniment with Dupuytren contracture is reported in 9%-39% of PD patients. Men experiencing sexual dysfunction after Radical Prostatectomy have a higher PD incidence rate then the general population and therefore should be routinely evaluated for PD. Younger men and Caucasian men are at increased risk for PD[4]. The natural course of PD indicates that penile curvature stabilizes in 47%-67% of patients or worsens in 30%-50% of patients. As well, spontaneous improvement is reported in only 3%-13% of patients[5]. In later phases, once the plaque becomes calcified the possibilities that penile curvature can be corrected are not as likely as in the early stage of the disease. Thirty-five percent to forty-five percent of patients can experience referred pain at early stages of the disease. However in 90% of men the pain tends to abate with time, usually during the first 12 mo after onset.

Nelson *et al*[6] reported that, besides the physiologic and functional alteration of the penis, 48% of men with PD experience mild-to-moderate depression as revealed through validated mental health questionnaires.

Since the first medical publication on PD, physicians have proposed several medical alternatives for treatment of this disease with few effective results. The most recent findings on the molecular pathophysiology of PD, though not conclusive, nonetheless give a bigger picture of the mechanisms underlying the evolution of the plaque formation and may one day guide to medical treatment. Nevertheless, as of today nonsurgical options are currently available, and some of them are able to stabilize or even reduce deformity while improving pain relief and sexual function. Unfortunately the studies found in literature, though providing evidence of the efficacy of these options, are compromised by the small size of the sample or the absence of a placebo control. Moreover, PD assessment lacks a validated questionnaire that allows for the interpretation of the data outcomes, and the analysis of the data is complicated by the fact that the spontaneous improvement rates reported are 5%-12%[7-10].

In light of existing Nonsurgical options for PD pain treatment and curvature including oral, intralesional, topical, and combination therapies, the aim of the current paper is to investigate, through a systematic review, the currently available Medical approaches for treating PD.

METHODOLOGY

A systematic literature search throughout the Medline database was carried out. The controlled vocabulary of the medical subject headings (MeSH) database employs the specific term "penile induratio" for PD. In order to identify relevant articles, the search included the MeSH terms, penis abnormalities, male, penile curvature and the terms "Peyronie's Disease" and "Induratio Penis Plastica". A total of 50 articles on PD were found. Relevant English-language articles were abstracted and reviewed using the reference list to identify additional potential articles for review. Studies were selected based on clinical relevance. If more than one article was published in the same study population, the study with the larger sample size was selected.

NON SURGICAL TREATMENT

The recommended standard of care for PD involves an initial treatment in the acute phase (first year) of this condition when symptoms are present and the plaque is not yet densely fibrotic or calcified[9]. Several non-operative treatment options have been used. Up to the present the European Medical Association has not approved any medication for the treatment of PD with the except of potassium para-aminobenzoate (Potaba) which has been classified as "possibly effective" for PD by the United States Food and Drug Administration.

The studies collected for this review showed contradictory results on conservative treatment for PD making it difficult to provide recommendations in an everyday real-life setting.

ORAL TREATMENT

Vitamin E

Vitamin E (tocopherol) is a fat-soluble compound that acts as a natural antioxidant to reduce the number of oxygen-free radicals produced in the energy metabolism. It has also been shown to play a role in DNA repair and in immune modulation[11]. The widely accepted use of tocopherol in the treatment of PD attests to the hypothesis that it inhibits fibrosis by acting as a scavenger of oxygen free radicals. *In vitro* studies examining the effect of free

radicals on human cavernosal cells have shown a direct association with increased collagen production[12]. Based upon these findings it is logical to conclude that inhibition of free radicals (*i.e.*, with use of tocopherol) should decrease the rate and degree of fibrosis. However, *in vivo* data has failed to reveal any concrete benefits in PD patients[13,14]. To date, tocopherol is commonly prescribed by most urologists in once- or twice-daily doses of 400 IU because of its wide availability, low cost, and safety. In 1983, Pryor *et al*[10] conducted a double-blind, placebo-controlled crossover study evaluating vitamin E for the treatment of PD in 40 patients. No significant improvements were noted in plaque size or penile curvature. The authors therefore did not recommend vitamin E for the treatment of PD as there was no meaningful evidence of its benefit in placebo-controlled trials.

Potassium para-aminobenzoate

Potassium paraaminobenzoate (Potaba, Glenwood) is a vitamin B complex and is believed to exert an antifibrotic effect through an increase in oxygen uptake by the tissues, a rise in the secretion of glycosaminoglycans, and enhancement of the monoamine oxidases activity in tissues thereby decreasing local levels of serotonin and, in turn, possibly decreasing fibrogenesis. A prospective double-blinded controlled study by Shah *et al*[15] analyzed 41 patients with PD and showed that, while penile pain was significantly improved by potassium para-aminobenzoate (12 g/d for 12 mo) neither penile curvature nor penile plaque size were affected. Weidner *et al*[16], in a prospective randomised double-blind placebo-controlled trial evaluating 103 patients with PD, found that potassium para-aminobenzoate (3 g/d four times daily for 12 mo) decreased penile plaque size significantly but had no effect on penile curvature or penile pain. The Treatment-emergent adverse events reported were: nausea, anorexia, pruritus, anxiety, chills, cold sweats, confusion, and difficulty concentrating and therefore no serious adverse events have been reported.

Tamoxifen

Tamoxifen is a nonsteroidal oestrogen receptor antagonist. The action mechanism which should determines changes in PD is the modulation of the transforming growth factor (TGF)b1 secretion by fibroblasts. Teloken *et al*[17] published a placebo controlled randomised study performed in 25 patients in the late stages of PD with a mean disease duration of 20 mo. The results of this study showed that Tamoxifen 20 mg twice daily for 3 mo failed to demonstrate significant improvement in pain, curvature, or plaque size[17].

Colchicine

Colchicine is a medication that is commonly employed in the treatment of acute attacks of gout. Its anti-inflammatory effects suggested its possible use in treating PD. Kadioglu *et al*[18] reported on the results of a study on 24 men, half of whom were given colchicines (0.6-1.2 mg daily for 3-5 mo) and whose painful erections and penile curvature were shown to improve in 50% of them with penile plaque decreasing or disappearing completely. Akkus *et al*[19] presented the results of a study involving 60 men treated with colchicine 0.5-1 mg daily for 3-5 mo and subsequently increased to 2 mg twice daily. Following this treatment penile pain was resolved in 95% of the cases while penile curvature improved in 30%. The reported treatment-emergent adverse events from the use of colchicine were gastrointestinal effects (nausea, vomiting, diarrhea), which were improved by dose escalation.

Finally, Prieto Castro *et al*[20] investigated the combination of vitamin E and colchicine (600 mg/d and 1 mg every 12 h, respectively) in patients with early-stage PD for 6 mo. The results of this study showed a significant improvement in plaque size and curvature, but not in pain when compared with ibuprofen 400 mg/d for 6 mo.

Acetyl esters of carnitine

It has been suggested that carnitine can reduce intracellular calcium levels in endothelial cells which, in turn, may eventually suppress fibroblast proliferation and collagen production thereby reducing penile fibrosis. To date, only 1 randomised double-blind study evaluating the efficacy of acetyl-L-carnitine has been conducted by Biagiotti and Cavallini[21]. In 48 patients with early-stage PD, subjects were given either tamoxifen 20 mg twice daily or acetyl-L-carnitine 1 g twice daily for 3 mo. After 3 mo, acetyl-L-carnitine was significantly more effective than tamoxifen in reducing pain and curvature and in inhibiting disease progression, but not in reducing penile plaque size (both tamoxifen and carnitine significantly reduced plaque size.

Another study investigated the combination of propionyl-l-carnitine (2 g/d for 3 mo) with intralesional verapamil (10 mg weekly for 10 wk). The results showed that this combination therapy significantly reduced penile curvature, plaque size, and disease progression when compared with intralesional verapamil combined with tamoxifen (40 mg/d) for 3 mo[22].

Pentoxifylline

Pentoxifylline is a nonspecific phosphodiesterase inhibitor that downregulates TGFb1 and increases fibrinolytic activity. Valente *et al*[23] found that normal human and rat tunica albuginea as well as PD plaque tissue expresses phosphodiesterase (PDE)5A-3 and PDE4A, B and D. In their in vitro study, PD fibroblasts were cultured with pentoxifylline and found to have increased cyclic adenosine monophosphate levels and reduced collagen I levels as compared to controls. An increase of nitric oxide levels may be effective in preventing the progression of PD or reversing fibrosis. Brant *et al*[24] performed a study on 62 patients with PD, and showed that treatment with pentoxifylline for 6 mo appeared to stabilize or reduce calcium content in penile plaques and also tended to improve penile curvature.

Phosphodiesterase type 5 inhibitors

The rationale for the use of a phosphodiesterase type 5 (PDE5-I) in PD comes from animal studies which show

that PDE5- I can reduce the collagen/smooth muscle and collagen Ⅲ/ I ratios and increase the apoptotic index in PD like plaque[25]. In a recent retrospective controlled study Chung *et al*[26] investigated the role of daily tadalafil (2.5 mg for 6 mo) which resulted in a statistically significant ($P < 0.05$) resolution of the septal scar in 69% of patients compared with 10% in the control group (no treatment). However, this study included patients with isolated septal scars without evidence of penile deformity[26].

INTRALESIONAL TREATMENT

The injection of a medication directly into the penile plaque results in restricted delivery and higher drug concentrations inside the plaque.

Steroids

The powerful anti-inflammatory effect of steroids makes them obvious agents for intralesional therapy of PD. Steroids operate by counteracting the inflammation responsible for Peyronie's plaque progression *via* inhibition of phospholipase A2 and suppression of the immune response and by diminishing collagen synthesis. In 1954, Bodner *et al*[27] reported improvement in 17 patients treated with intralesional hydrocortisone and cortisone. In 1975, Winter *et al*[28] showed no difference between patients treated with dexamethasone injections and the natural history of the disease. Cipollone *et al*[29], in a single-blind placebo-controlled study with intralesional administration of betamethasone, reported that no statistically significant changes were seen in penile deformity, penile plaque size, nor penile pain during erection. Adverse effects included tissue atrophy, thinning of the skin, and immune suppression.

Verapamil

Verapamil is a calcium channel antagonist that is thought to selectively inhibit calcium ion flux in both cardiac muscle and cells responsible for intracardiac conduction, as well as in coronary and systemic arteries. The rationale for its use in the intralesional treatment of patients with PD is based on in-vitro data that demonstrates transport of extracellular matrix molecules that include collagen, fibronectin, and GAGs as a calcium-dependent process[30]. A concomitant increase in collagenase activity, modification of the inflammatory response in the early phase of the disorder, and inhibition of fibroblast proliferation in the plaques are other proposed mechanisms. Shirazi *et al*[31] reported in a randomized placebo-controlled study that no statistically significant differences in plaque size, penile curvature, penile pain during erection, and plaque "softening" were seen.

Clostridial collagenase

Clostridial collagenase is a chromatographically purified bacterial enzyme that selectively attacks collagen and is known to be the primary component of the PD plaque. Collagenase was first studied *in vitro* by Gelbard *et al*[32] in 1982. A subsequent clinical trial by that group demonstrated subjective improvement in 64% of patients within 4 wk of treatment[33]. A decade after their initial study, the group published their findings of a double blind trial in 49 men[34]. In this study which compared the effects on plaque size and penile deformity of intralesional purified clostridial collagenase (6000-14000 U) and saline placebo, the overall response was 36% with clostridial collagenase compared with 4% with placebo ($P < 0.007$). Follow-up was only 3 mo. Response rates were even higher in patients with smaller plaques and curvature < 60°. The efficacy of intralesional collagenase injections (three injections of clostridial collagenase, 10000 U/0.25 cm^3 per injection, administered over 7-10 d and subsequently administered over 7-10 d at 3 mo) was assessed over a non-placebo-controlled short-term follow up study in a small population of men with PD[35]. This study showed a significant reduction from baseline in the deviation angle, plaque thickness, and plaque extension, but it was biased by an incorrect scientific approach. The most commonly reported side effects were penile pain, contusions, and ecchymosis.

Interferon

Duncan *et al*[36] reported in 1991 that interferons decrease the rate of proliferation of fibroblasts in Peyronie's plaques in vitro, reduce the production of extracellular collagen, and improve the activity of collagenase. Hellstrom *et al*[37], demonstrated that intralesional injections (5×10^6 units of interferon a-2b in 10 mL saline two times per week for 12 wk) improved average curvature in the treatment group by 13° *vs* 4° in the placebo arm, and that 27% of patients in the treatment group had measurable improvement *vs* 9% of the saline group. Pain resolution was noted in 67% of the treatment patients *vs* 28% for the placebo[37]. Side effects include myalgias, arthralgia, sinusitis, fever, and flulike symptoms which can be effectively treated with nonsteroidal anti-inflammatory drugs before interferon injection.

TOPICAL TREATMENTS

Topical verapamil

Fitch *et al*[38] presented the results of a small randomised placebo controlled study on topical verapamil applied as gel 15% to the penile shaft twice daily. The penile curvature, plaque size, and penile pain were significantly improved. After 9 mo of treatment better improvement was reported compared with the results at 3 mo, demonstrating that a prolonged treatment period may be important. However, a lack of evidence exists supporting that topical verapamil applied to the penile shaft produces adequate levels of active compound within the tunica albuginea.

Iontophoresis

To overcome limitations of topical therapies, emphasis has more recently been placed on testing modalities such as iontophoresis, which enhances the local uptake of drugs. Iontophoresis involves the application of an exter-

nal electric force to induce further (electromotive) penetration of topical medication. Di Stasi *et al*[39] presented their results of a randomised double blind controlled study, demonstrating that iontophoresis with verapamil 5 mg and dexamethasone 8 mg resulted in a statistically significant improvement in penile curvature and plaque size. On the other hand, Greenfield *et al*[40] with a randomized double-blind placebo controlled study showed that penile curvature was not statistically improved after iontophoresis with verapamil 10 mg. No significant events with Iontophoresis were reported.

Extracorporeal shock wave lithotripsy

The mechanism of action involved in extracorporeal shock wave lithotripsy (ESWL) for PD is still unclear, but there are two hypotheses. In the first hypothesis, ESWL may work by directly damaging and remodeling the penile plaque. In the second hypothesis, ESWL may increase the vascularity of the area by generating heat, resulting in an inflammatory reaction with increased macrophage activity causing plaque lysis and eventually leading to plaque reduction. Hauck *et al*[41] in an exploratory meta-analysis detected that ESWT seems to have an effect on penile pain during erection and on the improvement of sexual function. Pain seems to resolve faster after ESWT than during the course of the natural history. The effect on plaque size and penile curvature is less impressive. This result were confirmed by Palmieri *et al*[42] that published the only existing prospective randomised double-blind placebo-controlled study where they investigated four weekly treatment sessions of ESWL, with each session consisting of 2000 focused shock waves which resulted in significant improvement for penile pain only.

Traction devices

The use of tissue expanders has long been a mainstay of treatment in the orthopedic, oral-maxillofacial and plastic surgical fields. A continuous traction in Dupuytren contracture increases the activity of degradative enzymes. This first leads to a loss of tensile strength and subsequently to solubilization. This is followed by an increase in newly synthesized collagen. Levine *et al*[43], in an uncontrolled study, applied this technique on 10 patients with PD whereby application of the the FastSize Penis Extender was the only treatment for 2-8 h/d for 6 mo. Penile curvature was reduced in all men from 10° to 45°, with an average reduction of 33% (range: 51°-34°). Stretched penile length increased to 0.5-2.0 cm, and erect girth increased to 0.5-1.0 cm, with a correction of the hinge effect in four of four men. No adverse events such as skin changes, ulcerations, hypoesthesia, or diminished rigidity were reported.

Vacuum devices

When it comes to vacuum devices the same principles as traction devices are followed. Raheem *et al*[44], evaluated the efficacy of vacuum devices in an uncontrolled study assessing 31 patients. The vacuum device was applied over a 12-wk period (Osbon ErecAid, MediPlus, High Wycombe, United Kingdom) for 10 min twice daily. Penile pain was reduced significantly ($P = 0.012$). Stretched penile length also increased significantly ($P = 0.029$) with a mean of 0.5 cm. Reduction of the curvature was reported in 67% of patients. 10% had worsening curvature and 23% showed no change. Half of the patients were satisfied with the outcome while the remainder had their curvature corrected surgically. Vacuum therapy can improve or stabilize PD curvature, is safe to use in all stages of the disease, and could reduce the number of patients requiring surgery.

COMBINATION THERAPIES

In 1999, Mirone *et al*[45] prospectively examined patients treated with ESWT or ESWT and perilesional verapamil injections. A 52% improvement in plaque size by ultrasound was noted in the ESWT-only group compared to 19% for the combination therapy. A follow-up study by the same investigators involving 481 patients demonstrated a 49% improvement in plaque size among those treated with combination therapy[46]. A recent study by Palmieri *et al*[47] investigated the effects of extracorporeal shock wave therapy (ESWT) plus tadalafil 5 mg once daily in the management of patients with PD and erectile dysfunction who had not not previously been treated. One hundred patients were randomly allocated to receive either ESWT alone for 4 wk ($n = 50$) or ESWT plus tadalafil 5 mg once daily for 4 wk ($n = 50$). They concluded that ESWT and tadalafil 5 mg once daily may represent a valid strategy for the conservative management of selected PD patients complaining of ED as it significantly improves erectile function and quality of life when compared to ESWT alone. However, ESWT plus tadalafil 5 mg once daily was not able to significantly improve plaque size and curvature degree in our subset of patients.

A placebo controlled study by Prieto Castro *et al*[20] randomized 45 patients to receive vitamin E and colchicine or ibuprofen. Statistically significant improvements in curvature and plaque size were noted in the group treated with vitamin E and colchicine as compared to the group receiving ibuprofen. Patients in the vitamin E and colchicine arm reported a greater decrease in pain, although this did not reach statistical significance.

In 2002, Cavallini *et al*[22] randomized 60 men to receive intralesional verapamil plus oral carnitine or intralesional verapamil plus oral tamoxifen. Statistically significant subjective improvements in curvature, plaque size and erectile function were found in the carnitine group. No difference in improvement of pain was noted between the two groups.

CONCLUSION

In our review we showed the "Status quo" on non-surgical treatment for PD (Table 1). Unfortunately no further substantial, quality evidence on the use of medical therapy currently exits. There is, however, an increasingly

Table 1 Efficacy of non surgical treatments on Peyronie's disease

Therapy	Therapeutic activity and indication
Oral treatment with potassium para-aminobenzoate	Reduction in penile plaque size and penile pain as well as penile curvature stabilization
Oral treatment with vitamin E and tamoxifen	Not associated with significant reduction in penile curvature, plaque size or penile pain
Other oral treatments (acetyl esters of carnitine, pentoxifylline)	Not recommended
Intralesional treatment with verapamil	No statistically significant differences in plaque size, penile curvature, penile pain
Intralesional treatment with steroids	Not associated with significant reduction in penile curvature, plaque size or penile pain
Intralesional treatment with interferon	Improve Penile curvature, plaque size and density, and pain
Intralesional treatment with clostridial collagenase	Significant decreases in the deviation angle, plaque width and plaque length
Iontophoresis with verapamil 5 mg and dexamethasone 8 mg	Improve penile curvature and plaque size
Extracorporeal shock-wave treatment	Beneficial for penile pain and stabilization of plaque
Topical verapamil gel 15%	Improve penile curvature and plaque size
Penile traction devices and vacuum devices	Reduce penile deformity and increase penile length
Combination therapies	Preliminary evidences to be clarified

enhanced interest in this disorder and basic scientific and clinical research will eventually lead to a more effective methodology to study the disease. In the meantime, a consistent number of non-surgical treatment options that offer some benefit with respect to disease stabilization, alleviation, as well as reduction of deformity and improved sexual function are available. In conclusion the most beneficial treatment identified are: (1) oral treatment with potassium para-aminobenzoate (may result in a significant reduction in penile plaque size and penile pain as well as penile curvature stabilization); (2) Intralesional treatment with interferon (may improve penile curvature, plaque size and density, and pain); (3) iontophoresis with verapamil 5 mg and dexamethasone 8 mg (may improve penile curvature and plaque size); and (4) Extracorporeal shock-wave treatment (may be beneficial for penile pain and stabilization of plaque).

REFERENCES

1 **Hatzimouratidis K**, Eardley I, Giuliano F, Hatzichristou D, Moncada I, Salonia A, Vardi Y, Wespes E. EAU guidelines on penile curvature. *Eur Urol* 2012; **62**: 543-552 [PMID: 22658761 DOI: 10.1016/j.eururo.2012.05.040]

2 **Gonzalez-Cadavid NF**, Rajfer J. Mechanisms of Disease: new insights into the cellular and molecular pathology of Peyronie's disease. *Nat Clin Pract Urol* 2005; **2**: 291-297 [PMID: 16474811 DOI: 10.1038/ncpuro0201]

3 **Rhoden EL**, Riedner CE, Fuchs SC, Ribeiro EP, Halmenschlager G. A cross-sectional study for the analysis of clinical, sexual and laboratory conditions associated to Peyronie's disease. *J Sex Med* 2010; **7**: 1529-1537 [PMID: 19912489 DOI: 10.1111/j.1743-6109.2009.01584.x]

4 **Tal R**, Heck M, Teloken P, Siegrist T, Nelson CJ, Mulhall JP. Peyronie's disease following radical prostatectomy: incidence and predictors. *J Sex Med* 2010; **7**: 1254-1261 [PMID: 20500447 DOI: 10.1111/j.1743-6109.2009.01655.x]

5 **Bekos A**, Arvaniti M, Hatzimouratidis K, Moysidis K, Tzortzis V, Hatzichristou D. The natural history of Peyronie's disease: an ultrasonography-based study. *Eur Urol* 2008; **53**: 644-650 [PMID: 17673362 DOI: 10.1016/j.eururo.2007.07.013]

6 **Nelson CJ**, Diblasio C, Kendirci M, Hellstrom W, Guhring P, Mulhall JP. The chronology of depression and distress in men with Peyronie's disease. *J Sex Med* 2008; **5**: 1985-1990 [PMID: 18554257 DOI: 10.1111/j.1743-6109.2008.00895.x]

7 **Levine LA**, Greenfield JM. Establishing a standardized evaluation of the man with Peyronie's disease. *Int J Impot Res* 2003; **15** Suppl 5: S103-S112 [PMID: 14551586 DOI: 10.1038/sj.ijir.3901083]

8 **Greenfield JM**, Lucas S, Levine LA. Factors affecting the loss of length associated with tunica albuginea plication for correction of penile curvature. *J Urol* 2006; **175**: 238-241 [PMID: 16406919 DOI: 10.1016/S0022-5347(05)00063-7]

9 **Hellstrom WJ**. Medical management of Peyronie's disease. *J Androl* 2009; **30**: 397-405 [PMID: 18974422 DOI: 10.2164/jandrol.108.006221]

10 **Pryor JP**, Farell CF. Controlled clinical trial of vitamin E in Peyronie's disease. *Prog Reprod Biol* 1983; **9**: 41–45

11 **Traber MG**, Vitamin E. In: Shils ME, Olson JA, Shike M, & Ross AC eds. Modern Nutrition in Health and Disease. 10th ed. Baltimore, MD: Williams & Wilkins; 1999: 347–362

12 **Ahuja SK**, Sikka SC, Hellstrom WJ. Stimulation of collagen production in an in vitro model for Peyronie's disease. *Int J Impot Res* 1999; **11**: 207-212 [PMID: 10467520]

13 **Scardino PL**, Scott WW. The use of tocopherols in the treatment of Peyronie's disease. *Ann N Y Acad Sci* 1949; **52**: 390–401

14 **Hauck EW1**, Diemer T, Schmelz HU, Weidner W. A critical analysis of nonsurgical treatment of Peyronie's disease. *Eur Urol* 2006; 49: 987-997 [PMID: 16698449]

15 **Shah PJR**, Green NA, Adib RS, Hamilton Stewart PA, Smith P, Coxon R. A multicentre double-blind controlled clinical trial of potassium para-amino-benzoate (POTABA1) in Peyronie's disease. *Progr Reprod Biol Med J* 1983; **9**: 61–67

16 **Weidner W**, Hauck EW, Schnitker J. Potassium paraaminobenzoate (POTABA) in the treatment of Peyronie's disease: a prospective, placebo-controlled, randomized study. *Eur Urol* 2005; **47**: 530-535; discussion 535-536 [PMID: 15774254 DOI: 10.1016/j.eururo.2004.12.022]

17 **Teloken C**, Rhoden EL, Grazziotin TM, Ros CT, Sogari PR, Souto CA. Tamoxifen versus placebo in the treatment of Peyronie's disease. *J Urol* 1999; **162**: 2003-2005 [PMID: 10569556]

18 **Kadioglu A**, Tefekli A, Köksal T, Usta M, Erol H. Treatment of Peyronie's disease with oral colchicine: long-term results and predictive parameters of successful outcome. *Int J Impot Res* 2000; **12**: 169-175 [PMID: 11045911]

19 **Akkus E**, Carrier S, Rehman J, Breza J, Kadioglu A, Lue TF. Is colchicine effective in Peyronie's disease? A pilot study. *Urology* 1994; **44**: 291-295 [PMID: 8048212 DOI: 10.1016/S0090-4295(94)80155-X]

20 **Prieto Castro RM**, Leva Vallejo ME, Regueiro Lopez JC, Anglada Curado FJ, Alvarez Kindelan J, Requena Tapia MJ. Combined treatment with vitamin E and colchicine in the early stages of Peyronie's disease. *BJU Int* 2003; **91**: 522-524 [PMID: 12656907 DOI: 10.1046/j.1464-410X.2003.04134.x]

21 **Biagiotti G**, Cavallini G. Acetyl-L-carnitine vs tamoxifen in the oral therapy of Peyronie's disease: a preliminary report. *BJU Int* 2001; **88**: 63-67 [PMID: 11446848]

22 **Cavallini G**, Biagiotti G, Koverech A, Vitali G. Oral propionyl-l-carnitine and intraplaque verapamil in the therapy of advanced and resistant Peyronie's disease. *BJU Int* 2002; **89**: 895-900 [PMID: 12010235]

23 **Valente EG**, Vernet D, Ferrini MG, Qian A, Rajfer J, Gonzalez-Cadavid NF. L-arginine and phosphodiesterase (PDE) inhibitors counteract fibrosis in the Peyronie's fibrotic plaque

and related fibroblast cultures. *Nitric Oxide* 2003; **9**: 229-244 [PMID: 14996430 DOI: 10.1016/j.niox.2003.12.002]
24 **Brant WO**, Dean RC, Lue TF. Treatment of Peyronie's disease with oral pentoxifylline. *Nat Clin Pract Urol* 2006; **3**: 111-115; quiz 116 [PMID: 16470210 DOI: 10.1038/ncpuro0409]
25 **Ferrini MG**, Kovanecz I, Nolazco G, Rajfer J, Gonzalez-Cadavid NF. Effects of long-term vardenafil treatment on the development of fibrotic plaques in a rat model of Peyronie' s disease. *BJU Int* 2006; **97**: 625-633 [PMID: 16469038 DOI: 10.1111/j.1464-410X.2006.05955.x]
26 **Chung E**, Deyoung L, Brock GB. The role of PDE5 inhibitors in penile septal scar remodeling: assessment of clinical and radiological outcomes. *J Sex Med* 2011; **8**: 1472-1477 [PMID: 21324095 DOI: 10.1111/j.1743-6109.2011.02217.x]
27 **Bodner H**, HOWARD AH, KAPLAN JH. Peyronle's disease: cortisone-hyaluronidase-hydrocortisone therapy. *J Urol* 1954; **72**: 400-403 [PMID: 13202225]
28 **Winter CC**, Khanna R. Peyronie's disease: results with dermo-jet injection of dexamethasone. *J Urol* 1975; **114**: 898-900 [PMID: 1195471]
29 **Cipollone G**, Nicolai M, Mastroprimiano G, Iantorno R, Longeri D, Tenaglia R. Betamethasone versus placebo in Peyronie's disease. *Arch Ital Urol Androl* 1998; **70**: 165-168 [PMID: 9823662]
30 **Roth M**, Eickelberg O, Kohler E, Erne P, Block LH. Ca2+ channel blockers modulate metabolism of collagens within the extracellular matrix. *Proc Natl Acad Sci USA* 1996; **93**: 5478-5482 [PMID: 8643600]
31 **Shirazi M**, Haghpanah AR, Badiee M, Afrasiabi MA, Haghpanah S. Effect of intralesional verapamil for treatment of Peyronie's disease: a randomized single-blind, placebo-controlled study. *Int Urol Nephrol* 2009; **41**: 467-471 [PMID: 19199072 DOI: 10.1007/s11255-009-9522-4]
32 **Gelbard MK**, Walsh R, Kaufman JJ. Collagenase for Peyronie's disease experimental studies. *Urol Res* 1982; **10**: 135-140 [PMID: 6291216]
33 **Gelbard MK**, Lindner A, Kaufman JJ. The use of collagenase in the treatment of Peyronie's disease. *J Urol* 1985; **134**: 280-283 [PMID: 2991611]
34 **Gelbard MK**, James K, Riach P, Dorey F. Collagenase vs. placebo in the treatment of Peyronie's disease: a double blind study. *J Urol* 1993; **149**: 56–58
35 **Jordan GH**. The use of intralesional clostridial collagenase injection therapy for Peyronie's disease: a prospective, single-center, non-placebo-controlled study. *J Sex Med* 2008; **5**: 180-187 [PMID: 18173766 DOI: 10.1111/j.1743-6109.2007.00651.x]
36 **Duncan MR**, Berman B, Nseyo UO. Regulation of the proliferation and biosynthetic activities of cultured human Peyronie's disease fibroblasts by interferons-alpha, -beta and -gamma. *Scand J Urol Nephrol* 1991; **25**: 89-94 [PMID: 1651559]
37 **Hellstrom WJ**, Kendirci M, Matern R, Cockerham Y, Myers L, Sikka SC, Venable D, Honig S, McCullough A, Hakim LS, Nehra A, Templeton LE, Pryor JL. Single-blind, multicenter, placebo controlled, parallel study to assess the safety and efficacy of intralesional interferon alpha-2B for minimally invasive treatment for Peyronie's disease. *J Urol* 2006; **176**: 394-398 [PMID: 16753449 DOI: 10.1016/S0022-5347(06)00517-9]
38 **Fitch WP**, Easterling WJ, Talbert RL, Bordovsky MJ, Mosier M. Topical verapamil HCl, topical trifluoperazine, and topical magnesium sulfate for the treatment of Peyronie's disease--a placebo-controlled pilot study. *J Sex Med* 2007; **4**: 477-484 [PMID: 17367443 DOI: 10.1111/j.1743-6109.2006.00417.x]
39 **Di Stasi SM**, Giannantoni A, Stephen RL, Capelli G, Giurioli A, Jannini EA, Vespasiani G. A prospective, randomized study using transdermal electromotive administration of verapamil and dexamethasone for Peyronie's disease. *J Urol* 2004; **171**: 1605-1608 [PMID: 15017231 DOI: 10.1097/01.ju.0000116450.82816.2c]
40 **Greenfield JM**, Shah SJ, Levine LA. Verapamil versus saline in electromotive drug administration for Peyronie's disease: a double-blind, placebo controlled trial. *J Urol* 2007; **177**: 972-975 [PMID: 17296390 DOI: 10.1016/j.juro.2006.10.065]
41 **Hauck EW**, Mueller UO, Bschleipfer T, Schmelz HU, Diemer T, Weidner W. Extracorporeal shock wave therapy for Peyronie's disease: exploratory meta-analysis of clinical trials. *J Urol* 2004; **171**: 740-745 [PMID: 14713800 DOI: 10.1097/01.ju.0000108060.30363.8d]
42 **Palmieri A**, Imbimbo C, Longo N, Fusco F, Verze P, Mangiapia F, Creta M, Mirone V. A first prospective, randomized, double-blind, placebo-controlled clinical trial evaluating extracorporeal shock wave therapy for the treatment of Peyronie's disease. *Eur Urol* 2009; **56**: 363-369 [PMID: 19473751 DOI: 10.1016/j.eururo.2009.05.012]
43 **Levine LA**, Newell M, Taylor FL. Penile traction therapy for treatment of Peyronie's disease: a single-center pilot study. *J Sex Med* 2008; **5**: 1468-1473 [PMID: 18373527 DOI: 10.1111/j.1743-6109.2008.00814.x]
44 **Raheem AA**, Garaffa G, Raheem TA, Dixon M, Kayes A, Christopher N, Ralph D. The role of vacuum pump therapy to mechanically straighten the penis in Peyronie's disease. *BJU Int* 2010; **106**: 1178-1180 [PMID: 20438558 DOI: 10.1111/j.1464-410X.2010.09365.x]
45 **Mirone V**, Palmieri A, Granata AM, Piscopo A, Verze P, Ranavolo R. Ultrasound-guided ESWT in Peyronie's disease plaques. *Arch Ital Urol Androl* 2000; **72**: 384-387 [PMID: 11221076]
46 **Mirone V**, Imbimbo C, Palmieri A, Fusco F. Our experience on the association of a new physical and medical therapy in patients suffering from induratio penis plastica. *Eur Urol* 1999; **36**: 327-330 [PMID: 10473993 DOI: 10.1159/000020013]
47 **Palmieri A**, Imbimbo C, Creta M, Verze P, Fusco F, Mirone V. Tadalafil once daily and extracorporeal shock wave therapy in the management of patients with Peyronie's disease and erectile dysfunction: results from a prospective randomized trial. *Int J Androl* 2012; **35**: 190-195 [PMID: 22085227 DOI: 10.1111/j.1365-2605.2011.01226.x]

P-Reviewers: Creta M, Pastore AL **S- Editor:** Song XX
L- Editor: A **E- Editor:** Wu HL

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Telephone: +852-6555-7188
Fax: +852-3177-9906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.