Opinion

Pro: does shockwave therapy have a place in the treatment of Peyronie's disease?

Eric Chung[1,2]

[1]Department of Urology, Princess Alexandra Hospital, University of Queensland, Brisbane, QLD, Australia; [2]AndroUrology Centre, St Andrew's War Memorial Hospital, Brisbane, QLD, Australia

Correspondence to: Eric Chung. Associate Professor, AndroUrology Centre, St Andrew's War Memorial Hospital, 530 Boundary St,Brisbane, QLD 4000, Australia. Email: ericchg@hotmail.com.

Submitted Mar 19, 2016. Accepted for publication Mar 24, 2016.
doi: 10.21037/tau.2016.03.26
View this article at: http://dx.doi.org/10.21037/tau.2016.03.26

Introduction

Peyronie's disease (PD) is an often debilitating psychosexual condition characterized by the presence of penile pain, deformity and plaque(s), with ensuing erectile dysfunction (ED) (1). While the natural history of PD remains controversial, and no one truly knows the underlying pathophysiology of PD (2,3), it is accepted that in 50% of men with PD, the disorder is progressive (1,4).

The PD process is divided into two distinct phases, an initial acute (inflammatory) response and the subsequent chronic fibrotic stage with the formation of a penile plaque that signifies a stable disease (2). Patients usually describes a new onset of penile pain in the acute phase of PD, and penile deformities such as curvature, indentation, hinge effect or hourglass deformity may not be fully developed at the initial stage (2). It is possible that the optimal time to intervene is during the active disease phase when the inflammatory plaque is treatable (1). Surgery should be reserved in men who do not respond to conservative treatment, have a stable disease (at least 6 to 12 months of onset) or want the most definitive clinical outcome (1).

Why low intensity extracorporeal shock wave therapy (LiESWT) in PD?

The use of extracorporeal-generated electrohydraulic, electromagnetic or piezoelectric shock waves for the treatment of renal calculi has fundamentally changed the way urinary stones is managed (5). Since shock wave technology has become established in the field of urology, the modification to a lower energy source, that of LiESWT, soon has come to be of use in the orthopaedic field for treating degenerative and painful joint conditions (6). Furthermore, positive results have been achieved, particularly for the treatment of pain and wound healing (7). The application of LiESWT to target organs can induce a cascade of biological reactions that promote angiogenesis and tissue revascularisation (8,9).

Given that LiESWT has been established as an effective treatment option in various calcified and non-calcified orthopaedic disease, it is therefore possible that LiESWT could be effective in treating Peyronie's plaque. Since the PD process continues to evolve in the early phase, it is likely that the use of non-invasive therapy to halt and/or alter disease progression may be effective and appealing to many patients. Furthermore, when the remodelling of the plaque becomes complete, pain also tends to disappear. The dissolution of the plaque may result in resolution of penile curvature and/or deformity.

In fact, the use of LiESWT in PD has been reported since the late 1980s (10). Electron microscopy study demonstrated actual histological changes within the Peyronie's plaque following LiESWT (11). While clinical outcomes of LiESWT for the treatment of PD has been mixed, in recent years there has been a renewed interest in its use (1,12-18). Published studies also found that LiESWT generates a significant improvement in erectile function and penile hemodynamics without any adverse effect (19,20).

Penile pain

The initial exploratory meta-analysis showed a decrease

in penile pain from 56% to 100% following LiESWT in men with PD (12). Palmieri reported that a significantly lower pain score based on the visual analog scale (VAS) in those who received LiESWT compared to placebo group with pain disappearance (53% *vs.* 7%) and pain reduction (30% *vs.* 36%) (16). The mean VAS score was significantly lower when compared with baseline values in the LiESWT, while no statistically significant differences were found in the placebo group. Similarly, Hatzichristodoulou reported an 85% reduction in penile pain in the LiESWT group compared to 48% in the placebo group (P=0.013) with 4% of patients actually reporting worsening of penile pain in the placebo group. Importantly no patient received analgesia at the time of LiESWT administration (14).

Penile pain is frequently regarded as indicative of an active, inflammatory stage of PD. While pain seems to resolve faster with LiESWT than during the natural disease course, the question arises whether penile pain should be treated, as most patients will experience spontaneous improvement with time (4). In some instances, pain can be effectively treated with anti-inflammatory or intralesional therapy (1,2).

Nonetheless the consensus from the 3rd and 4th International Consultation of Sexual Medicine (ICSM) (1) stated that LiESWT provided greater pain reduction in the LiESWT group compared to placebo. Possible therapeutic mechanisms of action of LiESWT include direct disturbance of pain receptors and hyperstimulation analgesia (21), as well as direct plaque damage and heat-induced increased vascularity of the area, leading to the induction of an inflammatory reaction with lysis of the plaque, calcification resorption, and removal of macrophages (22).

Penile curvature and plaque size

Early published literature reported that the decrease in penile curvature varies between 21% and 74%; with a reduction in plaque size between 0% to 68% among men who received LiESWT (12,13). However, the clinical outcomes in recent randomised controlled trials showed an actual change of less than 10° compared to the control group (14,15). Hatzichristodoulou reported an increase in penile deviation in 40% of patients following LiESWT although only five (10.9%) patients showed an increase in plaque size in this group (14). Similarly, Chitale reported deterioration in dorsal and lateral angle in LiESWT compared to control group, with no change in plaque size in most of the patients from both groups (15). In fact, most patients who showed an increased penile deviation after LiESWT also showed an increase in plaque size confirming that an increase in plaque size correlates with worsening of penile deviation.

On the other hand, Palmieri found that the mean plaque size and mean curvature degree were decreased in the LiESWT but increased in the placebo group (16). After 24 weeks, the mean plaque size and curvature degree were significantly higher in the placebo group when compared with both baseline and LiESWT values, leading to the assumption that LiESWT may have a protective effect on disease progression by stabilizing the deviation and plaques. In another recent single-arm, open-label prospective study, Chung reported that an improvement in penile curvature by more than 15° was observed in 33% of men with a corresponding decrease in penile plaque hardness in 60% of men, and a reduction in penile plaque by 2 cm^2 in 27% of men (23). There was correspondingly softening and reduction in penile plaque size in this successful group of LiESWT men. This change in penile plaque density is consistent with a previous study where electron microscopy of penile plaque tissue in patients with PD following LiESWT demonstrated a reduction in packing and clumping of the collagen fibres (11).

Sexual (erectile) function

In contrast to the published literature supporting the role of LiESWT in men with ED (17,18), the reported changes in erectile function following LiESWT for the treatment of PD has been mixed. While International Index of Erectile Function-5 (IIEF-5) score is frequently used to evaluate sexual function in men with PD, it has never been specifically validated for use in this disease state. Published meta-analysis in 2004 reported that the improvement in sexual function varies from 12% to 80% (12). However more recent studies have found no significant difference between LiESWT and control group (14-16).

Chitale did not identify any beneficial effect of LiESWT compared to placebo in terms of quality of erections based on the Global Assessment Questionnaire for the effect of penile deformity on quality of sexual life (15). Hatzichristodoulou reported no significant difference in successful intercourse between the LiESWT and control groups. He also reported that, in patients who were unable to perform intercourse before treatment, 61.5% of the LiESWT group reported an improvement, compared to 38.5% in placebo group (14). In contrast, Palmieri found a significant difference in terms

of men IIEF-5 score reported in the LiESWT group when compared with baseline values with no significant differences found in the placebo group (16). Chung also reported an increase in erectile function (23). This improvement in IIEF score, especially in men who reported mild to moderate ED prior to LiESWT, highlighted that the improvement in penile curvature resulted in easier sexual penetration. Perhaps an underlying neovascularization induced by LiESWT might play a role in the greater erectile function.

Controversy and unresolved issues

Despite the cellular basis of PD that points to distinct alterations in wound healing and propagation of fibrotic process as the underlying cause, PD remains a therapeutic challenge due to the lack of knowledge on the exact pathophysiology and the unpredictable natural course of the disease (1). Nonetheless, it is likely that treatment instituted during the active phase of PD will have the greatest impact and may alter the disease process.

Any treatment modality for PD should primarily focus on the reduction of penile curvature as this is the most important and bothersome symptom in affected patients and often leads to the inability of sexual intercourse and negative psychological effect. At present, Xiaflex is the only Food and Drug Administration-approved medical treatment for PD and can be associated with serious penile complications such as penile hematoma and fracture. While surgical therapy remains as the most effective treatment option in men with PD, it is associated with significant risks such as penile length loss, sensory alteration and ED. Among the minimally invasive therapies, LiESWT has been employed for treating symptomatic plaques in patients with PD, with controversial results (1,12-18,23). While the initial exploratory meta-analysis in the early 2000s showed that LiESWT could exert beneficial effects on painful erections and on sexual function with some effects on penile plaque size and curvature (12), recent published literature has largely failed to demonstrate a significant benefit in the use of LiESWT to treat both plaque size and penile curvature (14-16). In fact, the 3rd and 4th ICSM (1) stated that while there is evidence to support that LiESWT will improve penile pain, there is currently no strong evidence to suggest that its use will decrease penile curvature or plaque volume.

While existing literature has largely failed to demonstrate any significant benefit in the use of LiESWT to treat penile curvature (1,12-18), these outcomes should be interpreted with some caution due to underlying methodological flaws (12-18,23) and perhaps the inappropriate use of shock wave energy flow density (12-18,23). At present, there is no agreeable treatment template and the existing treatment protocol is often based on manufacturer's guidelines and is likely derived from previous orthopedic literature. The conflicting study outcomes with regards to the change in penile curvature and plaque size may be attributed to several factors, such as inclusion of patients with complex PD: the presence of more than 1 axis of penile curvature, curvature greater than 90°, presence of hour-glass deformity, and men with two or more palpable Peyronie's plaques as well as longer duration of PD.

A variety of contributing factors will likely influence the outcome of LiESWT for PD. Prolonged history of PD and presence of plaque calcification, as a marker of chronicity, indicates unlikely history of spontaneous regression. It is also more likely that men who reported improvement in penile curvature had a PD history of less than 12 months, indicating likely active disease process, which is more susceptible to a mechanical effect. Furthermore, subgroup analysis of patients in the LiESWT group showed an overall better outcome in younger patients with a relatively milder degree of curvature (15,17). Comparative studies between LiESWT with other treatment modality showed that LiESWT is not superior to other options (1,11,12) and when used in combination with other therapeutic options such as intralesional injection or tadalafil for men with PD and ED, there were improvements in erectile function score and quality of life score while the plaque size and curvature were unchanged (24).

Published literature showed that LiESWT is safe and well tolerated in an outpatient setting without the need for anesthesia. In fact, most patients are satisfied and would recommend this treatment to other men, even when they did not obtain significant improvement in penile curvature and plaque size following LiESWT.

Conclusions

The current literature on the use of LiESWT in the PD population remains controversial. It may be possible that the newer generation of shock wave lithotripter has an improved technology that disrupts the tunical plaque without inducing further plaque formation or injuring the underlying cavernosal tissue. While the exact therapeutic mechanism remains unclear, it is postulated that LiESWT may play a role in plaque remodelling and improvement in consecutive resorption of calcification (12), resulting in

softer plaque and further correction and/or resolution of the penile curvature. Furthermore, LiESWT may have a protective effect on disease progression by stabilizing penile deviation and PD plaques (16). Therefore, it appears that LiESWT should ideally be offered and utilized in younger men during the active phase of PD, i.e., less than 6 months and with a milder degree of curvature and softer non-calcified plaque, and in the absence of hour-glass deformity. In a carefully selected group of men with PD, LiESWT appears to be safe, reduces penile pain, and has some efficacy in improving penile curvature and plaque, with high patient satisfaction rate. Many men are keen to pursue minimal invasive therapy such as LiESWT to preserve penile length, as the current surgical intervention is invariably associated with loss of penile length. Nonetheless, there is a need to define which subgroup of PD population is best suited, the LiESWT protocols (modality of shock wave energy, emission frequency and total energy delivery) and the role of combination therapy in PD such as concurrent penile remodelling and the use of penile traction device or intralesional therapy. Other important factors such as the actual physiological changes in the penile tissues and the long-term risk of shock waves have yet to be fully elucidated.

LiESWT remains a useful and valid minimally invasive treatment option for men with PD who have failed conventional medical therapy and are not keen to undergo surgical intervention. In a carefully selected group of men with PD, LiESWT appears to be safe, has moderate efficacy in improving penile curvature and pain, and is associated with high level of acceptance and patient satisfaction rate.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Ralph D, Gonzalez-Cadavid N, Mirone V, et al. The management of Peyronie's disease: evidence-based 2010 guidelines. J Sex Med 2010;7:2359-74.
2. Smith JF, Walsh TJ, Lue TF. Peyronie's disease: a critical appraisal of current diagnosis and treatment. Int J Impot Res 2008;20:445-59.
3. Chung E, De Young L, Brock GB. Rat as an animal model for Peyronie's disease research: a review of current methods and the peer-reviewed literature. Int J Impot Res 2011;23:235-41.
4. Mulhall JP, Schiff J, Guhring P. An analysis of the natural history of Peyronie's disease. J Urol 2006;175:2115-8; discussion 2118.
5. Chaussy C, Brendel W, Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. Lancet 1980;2:1265-8.
6. Ioppolo F, Tattoli M, Di Sante L, et al. Clinical improvement and resorption of calcifications in calcific tendinitis of the shoulder after shock wave therapy at 6 months' follow-up: a systematic review and meta-analysis. Arch Phys Med Rehabil 2013;94:1699-706.
7. Mariotto S, de Prati AC, Cavalieri E, et al. Extracorporeal shock wave therapy in inflammatory diseases: molecular mechanism that triggers anti-inflammatory action. Curr Med Chem 2009;16:2366-72.
8. Mariotto S, Cavalieri E, Amelio E, et al. Extracorporeal shock waves: from lithotripsy to anti-inflammatory action by NO production. Nitric Oxide 2005;12:89-96.
9. Kikuchi Y, Ito K, Ito Y, et al. Double-blind and placebo-controlled study of the effectiveness and safety of extracorporeal cardiac shock wave therapy for severe angina pectoris. Circ J 2010;74:589-91.
10. Bellorofonte C, Ruoppolo M, Tura M, et al. Possibility of using the piezoelectric lithotriptor in the treatment of severe cavernous fibrosis. Arch Ital Urol Nefrol Androl 1989;61:417-22.
11. Mirone V, Imbimbo C, Palmieri A, et al. A new biopsy technique to investigate Peyronie's disease associated histologic alterations: results with two different forms of therapy. Eur Urol 2002;42:239-44; discussion 244.
12. Hauck EW, Mueller UO, Bschleipfer T, et al. Extracorporeal shock wave therapy for Peyronie's disease: exploratory meta-analysis of clinical trials. J Urol 2004;171:740-5.
13. Manikandan R, Islam W, Srinivasan V, et al. Evaluation of extracorporeal shock wave therapy in Peyronie's disease. Urology 2002;60:795-9; discussion 799-800.
14. Hatzichristodoulou G, Meisner C, Gschwend JE, et al. Extracorporeal shock wave therapy in Peyronie's disease: results of a placebo-controlled, prospective, randomized, single-blind study. J Sex Med 2013;10:2815-21.
15. Chitale S, Morsey M, Swift L, et al. Limited shock wave therapy vs sham treatment in men with Peyronie's disease:

results of a prospective randomized controlled double-blind trial. BJU Int 2010;106:1352-6.
16. Palmieri A, Imbimbo C, Longo N, et al. 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;56:363-9.
17. Taylor J, Forster JA, Browning AJ, et al. Extracorporeal shockwave therapy for Peyronie's disease: who benefits? J Endourol 2006;20:135-8.
18. Claro JA, Passerotti CC, Figueiredo Neto AC, et al. An alternative non-invasive treatment for Peyronie's disease. Int Braz J Urol 2004;30:199-204; discussion 204.
19. Gruenwald I, Appel B, Kitrey ND, et al. Shockwave treatment of erectile dysfunction. Ther Adv Urol 2013;5:95-9.
20. Lei H, Liu J, Li H, et al. Low-intensity shock wave therapy and its application to erectile dysfunction. World J Mens Health 2013;31:208-14.
21. Lingeman JE, McAteer JA, Kempson SA, et al. Bioeffects of extracorporeal shock-wave lithotripsy. Strategy for research and treatment. Urol Clin North Am 1988;15:507-14.
22. Wild C, Khene M, Wanke S. Extracorporeal shock wave therapy in orthopedics. Assessment of an emerging health technology. Int J Technol Assess Health Care 2000;16:199-209.
23. Chung E. Peyronie's disease and low intensity shock wave therapy: Clinical outcomes and patient satisfaction rate in an open-label single arm prospective study in Australian men. Korean J Urol 2015;56:775-80.
24. Palmieri A, Imbimbo C, Creta M, et al. 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;35:190-5.

Cite this article as: Chung E. Pro: does shockwave therapy have a place in the treatment of Peyronie's disease. Transl Androl Urol 2016;5(3):366-370. doi: 10.21037/tau.2016.03.26

