BJUI
BJU INTERNATIONAL

Limited shock wave therapy vs sham treatment in men with Peyronie's disease: results of a prospective randomized controlled double-blind trial

Sudhanshu Chitale, Mohammed Morsey, Louise Swift* and Krishna Sethia

*Department of Urology, Norfolk & Norwich University Hospitals NHS Foundation Trust, and *Department of Medical Statistics, School of Medicine Health Policy and Practice, University of East Anglia, Norwich, UK*

Accepted for publication 22 December 2009

Study Type – Therapy (RCT)
Level of Evidence 1b

OBJECTIVE

To assess the role of extracorporeal shock wave therapy (SWT), in a prospective randomized controlled trial, comparing limited SWT vs sham therapy in men with Peyronie's disease.

PATIENTS AND METHODS

In all, 36 men were randomized to six sessions of SWT or sham treatment. Geometrical measurements of penile length and deformity, and the abridged International Index of Erectile Function (IIEF) score and visual analogue score (VAS) were recorded and re-evaluated at 6 months. The patient and assessor were unaware of the treatment type. Standard nonparametric tests were used for the statistical analysis.

RESULTS

A full set of outcome data was obtained for 16 patients in the intervention group and 20 in the sham/control group (mean age 58 and 60 years, respectively, mean duration of symptoms 15 and 33 months). There was no significant difference in the mean change between the control and intervention groups on any outcome measure. There were improvements in the mean (SD) dorsal and lateral angle, of 5.3 (11.66)° and 3.5 (17.38)° in the control group, and a deterioration of 0.9 (16.01)° and 0.9 (15.56)° in SWT group. Mean improvements in curved and straight lengths were 0.2 (0.58) and 0.1 (0.8) cm in the control and mean reductions of 0.1 (0.9) and 0.1 (1.49) cm in the SWT group. The mean changes in the IIEF and VAS scores were 0.1 (3.32) and −0.8 (1.77) for control and 0.56 (2.6) and −1.05 (1.79) for SWT group.

CONCLUSION

There were no significant differences in changes of variables in Peyronie's disease treated with short-term SWT.

KEYWORDS

Peyronie's disease, shock wave therapy, randomized controlled trial

INTRODUCTION

Shock wave therapy (SWT) has been used to treat Peyronie's disease (PD) since 1989, but the role and duration of SWT in men with PD remains unclear. The results have been favourable, with overall improvements reported of 54–72% [1–5]. However, there have been no controlled trials to provide robust evidence for or against the role of SWT, and only one case-control study with positive results [6]. Despite several published reports of men with PD benefiting from SWT, 15–20% of patients report spontaneous resolution/improvement of the disease without treatment. These latter data is derived from historical studies [7–9], which included no objective measurement of disease severity.

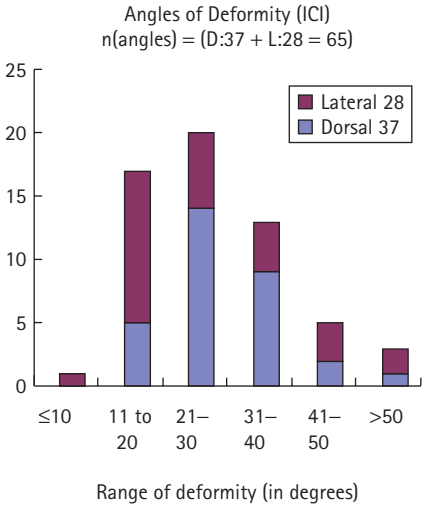
PD can affect men of any age and results in angulation on erection, with an unsightly appearance and which can also make sexual intercourse difficult, painful or almost impossible. Consequently, it has a significant negative impact on psychological status of these men, with up to half showing clinically meaningful depression requiring medical therapy [10].

Various medical and surgical treatment options have been described, with varying success rates, but none of the studies has compared treatment outcomes with the natural course of the disease. We present the results of the first prospective randomized controlled trial (RCT) comparing SWT with sham therapy.

PATIENTS AND METHODS

Ethics committee approval for the study was granted in January 2005. Men with symptomatic PD were seen in the Andrology outpatients' clinic. A preliminary assessment involved a clinical history, focused physical examination followed by artificial induction of erection using an intracavernous injection with prostaglandin E1. Systematic geometric measurements of penile deformity, including angle/angles (dorsal/ventral/lateral) of deformity and penile lengths (straight and curved) were conducted, using an angle measure and a ruler. A flexible pipe cleaner was used to record actual shortening or lengthening. The penile deformity was documented with a clinical photograph. We

FIG. 1. Distribution of the angles of deformity (before treatment).



used the abridged version of the International Index of Erectile Function (IIEF) to assess concomitant erectile dysfunction (ED), a visual analogue scale (VAS) for pain, and the Global Assessment Questionnaire (GAQ) for the effect of penile deformity on quality of sexual life. The pre-treatment GAQ posed to the patient was as follows: 'Has the overall quality of your sex life been significantly affected by the quality of erections and the penile deformity?', and the GAQ after treatment was: 'Has there been any significant change in the overall quality of sex life pertaining to the quality of erections and penile deformity?'

Patients were given a patient information sheet to read for a week before they would agree/disagree to participate in the trial. After obtaining informed consent for the trial, they were randomized using computer generated numbers to receive SWT or sham treatment (control group) and were invited to participate in the trial if they fulfilled the following criteria: Stable penile deformity secondary to PD affecting their ability to perform sexual intercourse and/or quality of life due to penile angulation; recent onset of painless deformity of the penis on erection, and stable for >6 months; pain and/or angulation of the penis on erection; difficult intercourse due to penile curvature, and partner dissatisfaction; a degree of ED (partial) associated with penile deformity; palpable plaque along the penis with penile deformity; aged >18 years. The exclusion criteria were: congenital curvature of the penis; previous treatment for PD (surgical/medical); patient on warfarin; patient with total ED in need of therapy for ED.

Treatment was commenced a week after randomization. Six treatment sessions of either SWT or sham therapy were delivered at one per week for 6 weeks. Each session lasted for 12 min when 3000 SWs were delivered at level 25 (38 MPa) for the SWT group and same number of SW were delivered to those in the sham group but at level 0, with the SW generator still making the same clicking noise as during real SWT. It was clearly explained to the patients in the information sheet that they would hear the noise irrespective of which group they were in, and as such were unaware of the type of treatment they received, as the treatment procedure otherwise was exactly the same. All patients were fully evaluated at 6 months after treatment using the same objective and subjective tools. The assessor was also unaware of the type of treatment rendered until after completing the assessment. Only the technician operating the SW generator was aware of the type of treatment an individual patient had, after opening the envelope containing the random number indicting real or sham treatment.

The primary outcome measures were the difference in the angle of deformity (mean change from before to after treatment, dorsal and/or lateral), and the difference in IIEF score before and after treatment. The secondary outcome measures were the difference in VAS before and after treatment and the difference in the response to the GAQ.

It was hypothesized that SWT (active treatment) might lead to some alterations in the various physical aspects of the penile deformity, i.e. the angle of deformity, penile length and plaque size. Sexual function was expected to show some change (reflected in the IIEF score and response to the GAQ), and in those with persistent pain on erection, a possible reduction in the VAS, as described in previous studies, was expected after SWT.

None of these changes were expected in the sham treatment arm, based on the natural history of the disease; the physical deformities were expected to remain unchanged after they had been stable for >6 months. Those patients with their disease process still not stable were excluded from the study, as per the exclusion criteria, thereby eliminating the chance of spontaneous resolution/improvement in the sham group.

The study sample size was determined to detect a between-group difference in the mean change in angle of deformity of 5.8° and a difference in the means of 4 on the IIEF score (assuming a SD of an individual's change in IIEF of 5 and normal data) with 80% power, hence 50 patients were needed in each treatment arm.

A *t*-test (for normally distributed data) or Wilcoxon Mann–Whitney test were used to compare outcomes between groups and provide a sensitivity analysis, as the available data were insufficient to make an assumption that the changes would be normally distributed. Fisher's exact test was used to compare the outcome measures between groups.

RESULTS

In all, 39 men were recruited over 18 months; 36 were randomized to six sessions of SWT or sham treatment, with three withdrawals after recruitment (one before randomization and two afterward). Sixteen men received SWT and 20 acted as controls. The mean (range) age was 59 (28–77) years and the mean duration of symptoms was 24 (6–120) months; 19, 11 and eight men had symptoms for <1, 1–2 and >2 years. All men had a palpable plaque, visible on ultrasonography but none of the plaques were calcified. Plaque size varied from 5 to 45 mm in maximum dimension. Thirteen men had distal flaccidity. Sixteen men were on phosphodiesterase-5 inhibitors (PDE-5i) for partial ED. Fourteen men had some pain on erection despite a long-standing stable deformity. Varying degrees of dorsal, lateral and combined dorso-lateral (18) deformities were recorded before SWT (Fig. 1) but there was no ventral deformity.

A full set of outcome measures were obtained for 16 patients in the SWT and 20 in the control group. The mean (SD) age in the SWT group was 57.8 (8.0) years and in the control group was 60.0 (10.5) years. Patients in the SWT group had a mean duration of symptoms of 14.9 (8.4) months, vs 32.3 (28.0) months in the control group.

There were substantial mean differences in pretreatment dorsal and lateral angles

TABLE 1 Positive change indicates an improvement

Outcome	Pre-treatment Mean (SD) Control n = 20	Pre-treatment Mean (SD) Intervention n = 16	Post-treatment Mean (SD) Control n = 20	Post-treatment Mean (SD) Intervention n = 16	Change (SD) Control n = 20	Change (SD) Intervention n = 16	Difference (95% CI) I – C	p value (t test)	P value (WMW)
Dorsal*	33.3 (15.9)	24.9 (11.9)	28.0 (12.8)	25.8 (12.6)	5.3 (11.6)	–0.9 (16.0)	–6.2 (–15.6, 3.2)	0.190	0.539
Lateral*	23.7 (20.6)	20.0 (15.3)	20.2 (18.5)	20.9 (16.5)	3.5 (17.4)	–0.9 (17.4)	–4.4 (–15.7, 6.9)	0.438	0.648
Straight	11.3 (1.4)	11.1 (1.9)	11.4 (1.7)	11.0 (2.0)	0.1 (0.8)	0.0 (1.5)	–0.1 (–0.9, 0.7)	0.762	0.789
Curved	14.6 (2.3)	14.3 (2.3)	14.7 (2.0)	14.2 (2.2)	0.2 (0.6)	–0.1 (0.9)	–0.3 (–0.8, 0.2)	0.299	0.604
IIEF	15,6 (7.9)	19.3 (6.1)	15.7 (7.5)	**19.9** (4.8)	0.1 (3.3)	0.6 (2.6)	0.5 (–1.6, 2.5)	0.652	0.249
VAS*	1.2 (2.3)	1.5 (2.3)	0.4 (0.7)	0.5 (0.8)	0.8 (1.8)	1.1 (1.8)	0.3 (–1.0, 1.5)	0.679	0.539

**Dorsal, Lateral and VAS change calculated so that positive change is an improvement, and positive difference indicates Intervention better than Control.*

(Table 1) so changes before and after treatment were compared between groups for all outcome measures. There was no significant difference in the mean change between groups for any outcome measure using either the *t*-test (which assumes the data are normally distributed) or the nonparametric Wilcoxon-Mann–Whitney test (Table 1).

Six of 20 men (30%) in the control group and five of 16 (31%) in the SWT group ($P = 1.0$, Fisher's exact test) reported improvements on the GAQ questionnaire, although one of each group reported worsening; 13 from the control group described no change in their penile deformity or quality of erections, and 10 from the SWT group claimed no change.

There were improvements in the mean (SD) dorsal and lateral angle of 5.3 (11.66)° and 3.5 (17.38)° in the control (Fig. 2a, Table 1) and a deterioration of 0.9 (16.01)° and 0.9 (15.56)° in SWT group (Fig. 2b, Table 1), respectively. The overall distribution of change in the dorsal angles between the groups varied between +20 and –20°. Mean improvements in curved and straight lengths were 0.2 (0.58) and 0.1 (0.8) cm in the control and mean reductions of 0.1 (0.9) and 0.1 (1.49) cm in the SWT group. The mean changes in the IIEF and VAS scores were 0.1 (3.32) and –0.8 (1.77) for the control and 0.56 (2.6) (Figs 3a,4a) and –1.05 (1.79) for SWT group (Figs 3b,4b). Plaque size remained unchanged in most patients from both groups, worsened in two from the sham group, and one from each group developed a new plaque in place of the original one that had resolved. Four of 16 (25%) men from SWT group and three of 20

*FIG. 2. Changes in the dorsal angles after **a**, sham (control) therapy and **b**, SWT.*

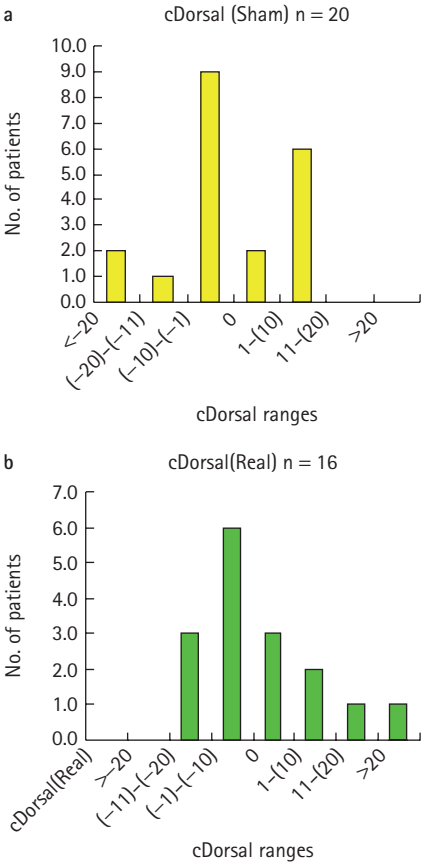
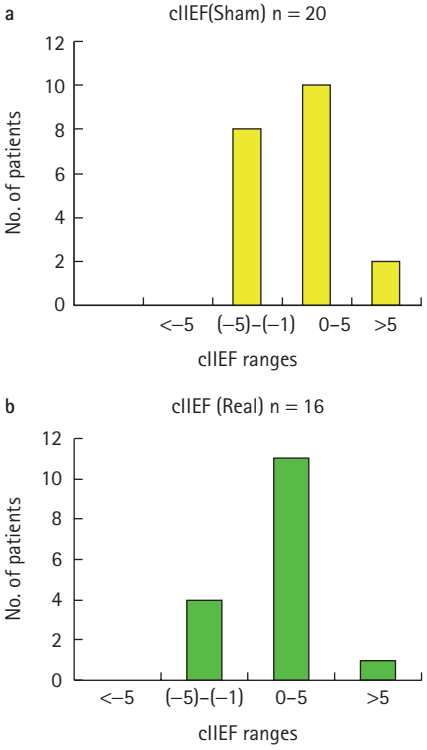


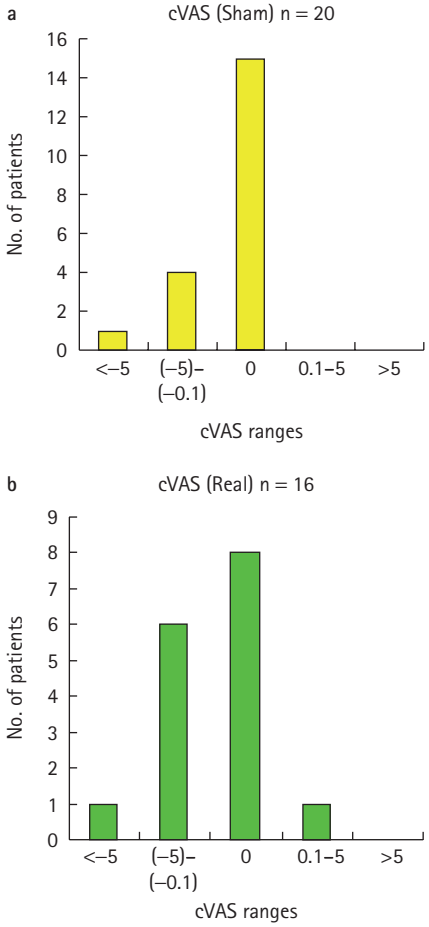
*FIG. 3. Changes in the IIEF in **a**, sham (control) therapy, and **b**, SWT.*



(15%) from sham group had a reduction in their plaque size on ultrasonography at the end of six treatment sessions. There were no significant complications of treatment in any patient. Two patients from the SWT group noticed superficial bruising at the site of SWT on the penile shaft, which was self-limiting and required no analgesia. All trial patients, once enrolled, completed their treatment with no withdrawals during the treatment period up to the 6 monthly follow-ups.

The SWT group were analysed to examine the effect of SWT; the duration of symptoms was ≤12 months in three and >12 months in 13. Only four patients were aged ≤59 years (mean

*FIG. 4. Changes in the VAS in **a**, sham (control) therapy, and **b** SWT.*



age) and 12 were >59 years. With up to 26 angles of deformity noted in 16 patients, 17 angles were ≤30° while nine were >30°. Of the 16 patients, three admitted to having PDE-5i therapy for ED, four had distal flaccidity, whereas seven had painful erections. SWT led to a marginal objective improvement with no subjective sense of well-being in nine of the 16 patients, a mixed response in two and deterioration in one. Four of the 16 patients noticed a significant improvement on both subjective and objective fronts; all of them were aged ≤59 years, three had symptoms for >12 months and four of five angles were ≤30°.

DISCUSSION

It is thought that in ≈20% of cases PD improves with no treatment, but in the remainder the disease is static or deteriorates with time. Apart from surgery, no treatment has been shown to definitely help the latter group of patients, except for evidence for some improvement after limited (6 weeks) of SWT [1,11–15]. There was no significant influence of SWT on plaque size [16] but benefits of SWT for pain in men with PD have been reported [17]. However, the effect of this treatment on the physical aspect of deformity (angulation/shortening) and its effect on sexual quality of life have not yet been studied.

Subgroup analysis from some of the previous case series [18] showed that the best outcomes after SWT were in relatively younger men (<55 years) with milder penile curvatures (<30°). A degree of success in improving pain and penile curvature has also been reported for the combination of SWT with peri-lesional injection of a calcio-antagonist [19,20] or high-dose oral vitamin E [21].

PD is not uncommon, with a reported prevalence of up to 3.2% [22], but we found that recruitment was slow and difficult, due to stringent inclusion/exclusion criteria, thereby avoiding patients in an early/unstable state when the natural history remains largely unclear and unpredictable. Most patients with chronic stable disease and deformity had an altered body image, leading to a compromised quality of life, in particular with their sex life; the general inclination was for a noninvasive non-surgical treatment option, and reluctance for surgery as the first option. Hence it was not difficult to persuade them to participate in the trial, with total compliance and willingness to continue with the SWT even after completing trial, hoping to achieve maximum satisfaction/improvement from this treatment.

The evidence available for the role of SWT in PD so far has been in the form of retrospective/prospective observational studies. To our knowledge, the present study is the first RCT comparing the outcome of limited SWT and sham therapy in PD, with outcome measures based on accurate geometrical measurements of the penile deformity, and its primary objective being to assess the outcome of SWT in PD.

We found no evidence that limited SWT over 6 weeks was effective in changing any of the outcome variables. One of the main limitations of this trial was the small sample size, which might be responsible for the negative results; however, none of the observed differences seemed to be in the 'right' direction, so it is unlikely that we have 'missed' a positive result. Improvements in the dorsal and lateral angles in the sham group could be attributed to the natural history of PD, showing resolution, albeit late, but the deterioration in the angles in the SWT group was too small to remotely suggest detrimental effects of SWT in these patients. The trial was not large enough to achieve the intended power, but showed no evidence that SWT was any better than sham treatment. The CIs were wide for the between-group difference for every outcome measure (Table 1), so this study cannot be totally conclusive and a larger, better powered study could possibly provide the statistical significance of what currently appear to be clinically significant changes in various outcome measures in individual cases from both groups. Subgroup analysis of the patients from the SWT group showed an overall better outcome in younger patients with a relatively milder degree of curvature. The sham group ironically had an improvement in the angle of deformity and penile length, but this is most likely to be an erroneous result. The mean changes in the IIEF and VAS were better in the SWT group but were not statistically significant. Based on our results, SWT cannot be recommended for treating PD, but a trial of longer-term treatment with SWT (12–18 weeks) using a larger sample in a randomized controlled setting might show positive results, and this might be worth exploring with a further study.

In conclusion, there was no significant change in variables in PD treated with short-term SWT. RCTs using longer-term SWT in more patients are needed to fully explore the role of SWT in men with PD. Until then, surgery will remain the mainstay of treatment for this desperate group of men.

ACKNOWLEDGEMENTS

We sincerely thank Mr Tony Dempster, Director, Focus Medical Services and his team for their immense help in conducting this trial.

CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Lebret T, Loison G, Herve J-M *et al.*** Extracorporeal shock wave therapy in the treatment of Peyronie's disease. Experience with a standard lithotripter (Siemens-Multiline). *Urology* 2002; **59**: 657–61

2 **Butz M, Teichert HM.** Treatment of Peyronie's disease by extracorporeal shock waves. *J Urol* 1998; **159** (Suppl.): 118 (Abstract 457)

3 **Colombo F, Mantovani F, Pateli E.** Shock wave therapy in la Peyronie's disease: two year's experience. *Eur Urol* 1999; **35** (Suppl. 2): 124 (Abstract)

4 **Gianneo E, Nespoli R, Conti G.** La Peyronie's disease and extracorporeal shock wave therapy: our experience. *J Urol* 1999; **161** (Suppl.): 205 (Abstract 786)

5 **Manikandan R, Islam W, Srinivasan V, Evans CM.** Evaluation of extracorporeal shock wave therapy in Peyronie's disease. *Urology* 2002; **60**: 795–9

6 **Hauck EW, Altinkilic BM, Ludwig M *et al.*** Extracorporeal shock wave therapy in the treatment of Peyronie's disease. *Eur Urol* 2000; **38**: 663–70

7 **Gholami SS, Lue TF.** Peyronie's disease. *Urol Clin North Am* 2001; **28**: 377–90

8 **Williams JL, Thomas GG.** The natural history of Peyronie's disease. *J Urol* 1970; **103**: 75–6

9 **Gelbard MK, Dorey F, James K.** The natural history of Peyronie's disease. *J Urol* 1990; **144**: 1376–9

10 **Nelson CJ, DiBlasio CJ, Kendirci M, Hellstrom WJG, Mulhall JP.** The chronology of depression and distress in men with Peyronie's disease. *J Urol* 2007; **177** (Suppl.): 253; Abstract

11 **Husain J, Lynn NN, Jones DK, Collins GN, O'Reilly PH.** Extracorporeal shock wave therapy in the management of Peyronie's disease: initial experience. *BJU Int* 2000; **86**: 466–8

12 **Kiyota H, Ohishi Y, Asano K *et al.*** Extracorporeal shock wave treatment for Peyronie's disease using EDAP LT 02; preliminary results. *Int J Urol* 2002; **9**: 110–3

13 **Seftel A.** Extracorporeal shock wave therapy in the treatment of Peyronie's disease: experience with standard lithotripter (Siemens Multiline). *J Urol* 2002; **168**: 2322

14 **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**: 327–30

15 **Abdel-Salam Y, Budair Z, Renner C *et al.*** Treatment of Peyronie's disease by extracorporeal shock wave therapy: evaluation of our preliminary results. *J Endourol* 1999; **13**: 549–52

16 **Hatzichristodoulou G, Meisner C, Stenzi A, Lahme S.** Efficacy of extracorporeal shock wave therapy on plaque size and sexual function in patients with Peyronie's disease – Results of a prospective, randomized, placebo-controlled study. *J Urol* 2007; **177** (Suppl.): 251. Abstract 747

17 **Hatzichristodoulou G, Meisner C, Liske P, Stenzl A, Lahme S.** Efficacy of extracorporeal shock wave therapy (ESWT) in patients with Peyronie's disease (PD) – First results of a prospective, randomized, placebo-controlled, single – blind study. *J Urol* 2006; **175** (Suppl.): 320. Abstract

18 **Taylor J, Forster JA, Browning AJ, Biyani CS.** Extracorporeal shockwave therapy for Peyronie's disease. Who benefits? *J Endourol* 2006; **20**: 135–8

19 **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**: 384–7

20 **Baumann M, Bohme H, Tauber R.** Extracorporal shock wave therapy (ESWT) in combination with local verapamil injections in the treatment of IPP (induratio penis plastica). *Aktuel Urol* 2001; **32**: 61–4

21 **Claro JA, Passerotti CC, Figueiredo Neto AC, Nardozza JRA, Ortiz V, Srougi M.** An alternative non-invasive treatment for Peyronie's disease. *Int Braz J Urol* 2004; **30**: 199–204

22 **Sommer F, Schwarzer U, Wassmer G *et al.*** Epidemiology of Peyronie's disease. *Int J Impotence Res* 2002; **14**: 379–83

Correspondence: Sudhanshu Chitale, Department of Urology, Norfolk & Norwich University Hospitals NHS Foundation Trust, Colney Lane, Norwich NR4 7UY, UK.
e-mail: chitalenorwich@aol.com

Abbreviations: **SWT**, shock wave therapy; **PD**, Peyronie's disease; **RCT**, randomized controlled trial; **IIEF**, International Index of Erectile Function; **ED**, erectile dysfunction; **VAS**, visual analogue scale; **GAQ**, Global Assessment Questionnaire; **PDE-5i**, phosphodiesterase-5 inhibitor.