PENILE EXTENDER DEVICE IN THE TREATMENT OF PENILE CURVATURE DUE TO PEYRONIE'S DISEASE

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Introduction

Peyronie's disease can be defined as an acquired penile deformity of the erect penis which is caused by a fibrous plaque. Men with Peyronie's disease may present with a combination of complaints, including penile curvature, painful erections, erectile dysfunctions and penile shortening leading to significant detrimental psychological effects (Hellstrom WJ, 2000; Gelbard MK, 1990). A conservative medical treatment is usually advocated as the first line therapy particularly in the early inflammatory phase although there is poor evidence that it might be effective (Russell S, 2007). If this management proves unsuccessful, a more invasive surgical approach may be contemplated once the disease has been stabilized, usually after 1 year from onset (Hellstrom WJ, 2000). The long term results of surgery have pointed out a significant patients' dissatisfaction, with erectile dysfunction, penile shortening and residual curvature being the chief complaints (Montorsi F, 2004; Kendirci M, 2004). The penile extender, a non-surgical device that employs progressive mechanical traction to the penis, has been claimed to produce significant improvement in penile length (Moncada I, 2005; Gontero P, 2007). A preliminary pilot experience has suggested that the tension forces exerted by a penile extender could also reduce penile curvature due to Peyronie's disease (Scroppo FI, 2001). The combination of these effects may provide an intriguing treatment option in selected Peyronie's disease patients. We tested this hypothesis in a phase II study designed to assess whether a penile extender may produce significant improvement in penile curvature due to Peyronie's disease.

Material and methods

Patients eligibility

Patients with a penile curvature due to Peyronie's disease were considered eligible for the study if they met the following inclusion criteria: a penile curvature not exceeding 50°, causing patient's complaint and sustained by fibrous plaques detectable through genital palpation or ultrasound; a history of the disease lasting at least 12 months; no penile pain in the flaccid state. Previous medical treatment did not contraindicate study participation. A history of major psychiatric disorder, a reduced manual dexterity that may prevent the correct use of the device, previous penile surgery and a severe erectile dysfunction based on the EF domain of the IIEF were exclusion criteria.

End points and sample size

Changes in penile curvature under erection over baseline after 6 months of treatment and durability of the response at 6 months after treatment discontinuation were considered the primary study end points. Given the objective difficulty to estimate the standard deviation of baseline penile curvature , the sample size was based on the "effect size" (Cohen J, 1988). It was assumed that with 15 evaluable patients the finding of "important" reduction in penile curvature, defined by an effect size ≥ 0.8, would have a statistical power of 80% and a probability of a false negative results of less than 5% (2-sided). Changes in flaccid and stretched penile length over baseline, plaque size, treatment tolerability, patient's compliance and satisfaction as well as changes in the IIEF EF domain scores at last follow up over baseline constituted secondary end points.

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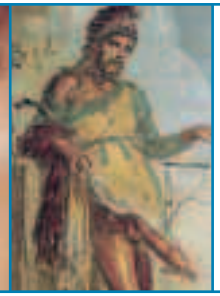
Baseline investigations

Baseline patients assessment included full medical and sexual history and physical examination. The EF domain of the IIEF was administered at baseline and at the end of the study (6 months after treatment discontinuation). Patients scoring severe abnormal values (IIEF EF ≤ 10) (Cappellieri JC, 1999) were excluded. A penile ultrasound was required for study entry in order to record the plaques size (determined as the product of length and width in mm2), the location and the sonographic appearance (calcified, hypoechoic, hyperechoic) of the plaques. Fibrous nodules undetectable sonographically were measured manually using a caliper. The degree of curvature was documented using photographic pictures taken by the patient from 3 angles (frontal, lateral and from above) during full erection or during an in-office intracavernous injection test with 20 mcg alprostadil. Penile measurements (t0) were obtained employing the standard technique validated by Wessells H et al (1996). Using a taper ruler to the nearest 0.5 cm, the penis was initially measured in the flaccid state and then while applying tension to maximally stretch it, from the pubopenile skin junction to the meatus. The circumference was measured at midshaft. Inter-operator agreement was assessed by performing a set of measurements on a small sample of young volunteers (N=8) with individual variability falling always below 0.5 cm.

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Device description and treatment schedule

After signing the informed consent, patients were instructed on the use of a common brand of penile extender, the Andro-Penis® (Andromedical, Madrid, Spain), a device designed to exert a continuous and gradually increasing traction force on the penis. The device consists of a plastic ring, where the penis is introduced and from where 2 dynamic metallic rods originate the traction. In the superior part there is a plastic support where a silicone band holds the glans in place. Detailed instructions on how to increase the traction force from 600 gr during the 1st month, 900 gr during 2nd month, up to 1200 gr during 5th y 6th month were provided following the manufacturer's leaflet. In case of concomitant untreated ED, patients were suggested to postpone the use of erectile aids until the end of study. Patients were suggested to wear the device up to 9 hours/day, explaining that, based on the little available evidence (Scroppo FI, 2000; Colpi GM, 2001; Gomez EA, 2001), the magnitude of both the straightening and the elongating effect would be proportional to the traction time. The minimum time of daily use for testing treatment efficacy was assumed to be 5 hours and this was the minimum requirement for entry the study.

Follow up visits

Follow up visits were scheduled at 1 (t1), 3(t3), 6 months (t6) and at 12 months (t12) (end of study, after a wash out period of 6 months) to record side effects, treatment compliance, calculations of curvature on fresh photographs and carry out genital examination and penile measurements.

At the end of study the EF domain of the IIEF and a satisfaction questionnaire were administered. The latter consists of a set of 5 questions designed by the investigators that ask to quote subjective improvements in penile curvature (Q1) in a 0 to 4 scale number (0=worsening, 1= unchanged, 2= mild improvement, 3= significant improvement, 4=complete resolution), as well as to refer about flaccid penile length (Q2), erect penile length (Q3), overall results (Q4) in a 0 to 3 scale number (0=no change/worsening, 3=optimal result). Lastly Q5 addresses overall results achieved in a 0 to 4 scale number (0=no result, 1=very mild, 2=acceptable, 3=good, 4=optimal results). Plaque size was also calculated at the end of study using a caliper or a penile ultrasound. The study protocol was granted Ethical Committee approval on February 2005.

Statistical analyses

Given the objective difficulty to estimate the standard deviation of the degree of penile curvature in a series of patients with Peyronie's disease patients, the sample size was based on the "effect size" method (Cohen J, 1988). Thus, 15 evaluable patients were required to have an 80% statistical power of detecting an important reduction of penile curvature (defined by an effect size ≥ 0.8), with an alpha-error of less than 5% (2-sided Wilcoxon test).

Results

Out of a set of 40 patients referring with a complaint of penile curvature between February 2005 and May 2006, nineteen met the inclusion criteria and entered the study. Reasons for exclusion were congenital curvature (N=2), concomitant penile pain (N=6), disease history lasting less than 12 months (N=6), a curvature exceeding 50° (N=4) and refusal to undergo the proposed treatment (N=3). Baseline characteristics of the sample for age, disease features, EF domain of the IIEF and penile measurements are listed in table 1. None of the eligible patients was taking ED therapy at study entry. One patient discontinued treatment with the penile stretcher after a few days due to discomfort for the device, three did not attend the scheduled follow up visits and were lost to follow up. Data on the 6 months treatment period and follow up were available for all the 15 remaining patients. Median time of daily use of the device was …. hours at 1 month, …. hours at 3 months, …. hours at 6 months respectively (p=….).




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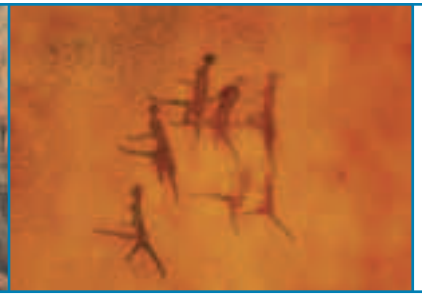
Penile curvature decreased from a mean baseline value of 31° (SD 1.55) to 27° (SD 2.79) after 6 months of treatment (p=0.059) (figure 1). The degree of curvature was worsened (+10°) in 1 patient, unchanged in 8 and decreased in 6 (-20° in 2/6, -10° in 2/6 and -5° in 2/6). Figures 2 and 3 report the box plots related to the changes occurred in the flaccid and stretched penile length respectively at 6 months. At the end of treatment (6 months), a significant (p=0.00? and p=….) overall mean gain in length of 1.3 cm and of 0.83 cm for the flaccid and stretched penile length respectively was observed. Table 2 reports the changes occurred across all time intervals in penile curvature and length. The gain in length was maximal in the t0 – t1 time interval and showed progressive declines in t1 – t3 and t3 – t6 intervals. Curvature degrees and penile length remained stable at 6 months follow up (t6 – t12). Changes in penile girth were negligible and not significant (mean value of 9.86 cm at baseline and of 9.96 cm at 6 months). Plaque size did not show significant changes during the study period (1.35 cm vs 1.30 cm, p=0.4). No patient requested treatment for ED during the study period. IIEF EF domain score showed only marginal improvements, from a mean baseline value of 23.8 (SD 4.07) to 24.7 (SD 4.11) at 12 months (p=0.23). Specifically, six months post treatment IIEF EF domain normalized in 3 out of 6 patients with mild ED at baseline, while 2 patients with normal pre treatment erectile function scored EF IIEF values consistent with mild ED. Mean patients satisfactions scores for the 5 items questionnaire are reported in table 3. The treatment was generally well tolerated with only 3 patients reporting bruising (N=2) or itching (N=1).

Discussion

Several treatment options, including oral compounds, intralesional and topical agents, have been proposed for the treatment of Peyronie's disease (Briganti A, 2003) but the evidence that any of these may be effective remains weak, such that observation alone is considered a viable option (Kendirci M, 2004). The lack of precise data on the pathogenesis of Peyronie's disease is probably one key element that prevents a step forward in treatment strategies for this disease. Some data suggest that the currently available non-surgical options may have a window of opportunity in the acute phase of the disease. Once the disease is stabilised, typically after 12 to 18 months, it is unlikely for any medical treatment to produce a beneficial effect (Riedel CR, 2000). At this stage, surgery may be contemplated as the last remaining option to restore successful sexual intercourse (Kendirci M, 2004). All the currently available surgical techniques are essentially unable to provide a curative effect of the disease, rather they aim to palliate its side effects by restoring a straight shape to the curved penis. Strict selection criteria (i.e. highly motivated patients with severe curvature impairing sexual intercourse) (Pryor J, 2004) are mandatory as surgery carries a significant risk of complications leading to a high patients' dissatisfaction rate (Montorsi F, 2004).

We selected a study population of patients with clinically stable Peyronie's disease and a mild to moderate degree of curvature (not exceeding 50°) and no severe erectile dysfunction as defined by the EF domain of the IIEF (Cappellieri JC, 1999). No specific treatment is currently available for this disease subgroup as surgery may probably turn out to be an over-treatment while non-surgical options are unlikely to be effective once the disease is stabilized (Gholami SS, 2003). Notably, the majority of our patients had previously failed medical treatment. Based on the preliminary evidence reported by Scroppo et al (2001) of a 50% reduction in the curvature of the shaft after the application of progressive mechanical traction forces on the penis over a 6 months period, these patients may be ideal candidates for a trial with a penile extender device. In our series the mean curvature of the shaft decreased of 4° (13% of the baseline value) following a 6 months treatment period using the same penile extender brand. Albeit of borderline significancy, the magnitude of improvement did not meet the expected "effect size" to state that the treatment was effective. Interestingly enough, these results were comparable to the average absolute improvement in penile curvature (13.5%) reported by a recent meta-analysis on intralesional injection therapy, one of the most popular treatment modality for Peyronie's disease (Russell S, 2007). Measurable reductions of the curvature ranging from 5° up to 20° were recorded in 6 out of 15 (40%) evaluable patients, the remaining having stable (8/15) or progressive (1/15) disease. Although spontaneous improvement in the degree of bending has been reported (Gelbard, 1990; Teloken C, 1999), this is less likely to occur when the disease is stabilized as in our series. Of note, no changes in penile curvature were detected after 6 months of treatment wash-out. If it seems reasonable to state that the



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treatment proved effective in some patients, the low sample size did not allow us to identify predictors of response. It may be speculated that the shorter daily use of the device in our study in comparison to the study of Scroppo (2001) might account for the lower degree of curvature reduction. The mean time of daily use of the device in our study tended to be close to the minimum required for study entry. It is likely that a more strict protocol requiring a minimum of 8 or 9 hours of daily use (Scroppo, 2001; Gomez E, 2001) will greatly reduce patients' compliance.

The application of a penile extender in the current study caused only minimal and self resolving side effects, leading to discontinuation of treatment in only 1 case

Mean baseline IIEF EF domain score was consistent with mild ED as we deliberately excluded patients with severe ED that may be less amenable for conservative treatment of Peyronie's disease. Sexual dysfunction is a common complication in the presence of fibrous penile plaques with both psychological and organic factors contributing to its pathogenesis (Gholami SS, 2003). Currently there is no evidence that any medical treatment may exert beneficial effects on sexual function of Peyronie's disease patients (Russell S , 2007). Similarly, post-treatment IIEF EF domain in our study did not show significant changes compared with baseline, meaning that erectile function was at least unaffected by the device. If we failed to demonstrate a positive effect on sexual function as previously reported after employing the penile stretcher in cases of short penis (Gontero P, 2008), the finding corroborates the safety profile of this treatment option as opposed to the detrimental effect of surgery on sexual function (Montorsi F, 2004).

Andropenis® produced an effective and durable (over the 6 months off treatment period) lengthening of the penis both in the flaccid and the stretched state. The elongating effect was of a lower magnitude than that observed in our previous study where dysmorphophobic and post-surgery short penises underwent the same treatment protocol (Gontero P, 2008). A reduction in penile elasticity as a consequence of the reduced content in elastin within the fibrous plaques (Pryor JP, 2002) could explain why Peyronie's disease patients are less susceptible to the elongating effects of the penile extender. Albeit baseline penile size in our patients fall within the normal range based on the criteria outlined by Wessells et al (1996), penile lengthening was probably the most notable clinical finding of the current study. Penile shortening, a bothering symptom of Peyronie's disease, cannot be addressed as an end point by any medical treatment. Besides, it is usually significantly worsened by surgery, no matter the procedure employed, leading to a high dissatisfaction rate (Kendirci M, 2004). From this perspective the penile extender could play an essential role as part of a multimodal treatment strategy. In the absence of validated instruments to assess the patient's perception of efficacy of the device, we designed a specific post-treatment 5 items questionnaire. Average scores for the 2 questions addressing the flaccid and stretched penile length were consistent with "acceptable results". While improvement in sexual function and penile curvature were rated as intermediate between "no changes" and "acceptable", the overall results were surprisingly quoted as "acceptable". Our satisfaction assessment is limited by the absence of a comparative pre and post treatment analysis and lack of validation. Notwithstanding these limitations, it provides hints on a favourable acceptance of the device that warrants further study to explore the clinical utility of this non invasive treatment modality in Peyronie's disease.

Conclusions

In our study population the penile extender produced improvement in penile curvature of little clinical significance but comparable to that achieved with other commonly used treatment modalities such as intralesional injections. Notably, results were achieved in a selected population with stable disease, a condition where the existing treatment options are less likely to be effective. Significant lengthening of the penis both in the flaccid and in the stretched state was also recorded. The device caused negligible side effects. Overall results were self-reported as "acceptable", making this minimally invasive treatment modality a potential new treatment option in selected Peyronie's disease patients.