NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of extracorporeal shockwave therapy for Peyronie's disease

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and Specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in March 2003

Procedure name

Extracorporeal shockwave therapy (ESWT) for Peyronie's disease

Specialty society

Specialist advice was sought from the British Association of Urological Surgeons

Description

Indications:

Peyronie's disease is a localised connective tissue disorder of unknown cause. It affects around 1% of men, and in a significant minority (13%), the disorder will improve or resolve spontaneously [1].

Peyronie's disease is characterised by the formation of inelastic fibrous plaques within the erectile tissue of the penis (tunica albuginea).

The hardened plaque reduces flexibility, causing pain and forcing the penis to bend or arc during erection. Pain on erection and palpable nodule on the shaft of the penis are typical clinical features of the acute phase, which lasts about 12 to 18 months. The chronic phase commences when the deformity stabilises and pain diminishes.

For many patients, Peyronie's disease results in sexual problems due to the difficulty in attaining and/or maintaining erections.

Current Treatment and Alternatives

Suggested treatment for Peyronie's disease includes pharmacological interventions, radiation and surgery. The goal of treatment is not to cure the disease but to alleviate the symptoms.

Numerous surgical techniques have been developed for Peyronie's disease, these are typically reserved for those with more severe symptoms or patients who have failed to respond to conservative treatment. Surgery however has been associated with complications including penile shortening and impotence [1].

What the procedure involves

The procedure involves the use of shockwave lithotripsy technology to treat Peyronie's disease. Extracorporeal shockwaves are high pressure, low frequency sound waves, generated by a device outside the body and applied to the affected tissue in a site-specific manner. In Peyronie's disease the penile plaque is the target of these shockwaves and is generally localised using an ultrasound scanner.

There is a lack of standardisation regarding issues such as shockwave dosage, energy levels and number of sessions required for a therapeutic effect in patients with Peyronie's disease. Shockwaves per session range from 2000-3000, with the average person receiving around 3-5 treatment sessions. In terms of energy levels there are three basic levels:

1. low density energy around of 0.04 and 0.12 mJ/mm^2 .
2. average density of energy varying between 0.12 and 0.28 mJ/mm^2
3. high density of energy generally between 0.28 and 1.5 mJ/mm^2 per impulse.

Efficacy

- Based on the results from the comparative studies, the main benefits of extracorporeal shock therapy were alleviation of pain and reduction of angulation. In one comparative study, 50% (10/20) of patients receiving extracorporeal shockwave therapy experienced a 30% decrease in curvature Case series evidence also suggested some improvement in sexual performance from extracorporeal shock therapy.

- Caution should be exercised in interpreting these results, given the natural history of the disease, the lack of objective and valid outcome measures and the shortage of good quality comparative data.

- Specialist Advisors commented on the difficulty in evaluating efficacy given the lack of controlled data and agreement regarding relevant end points. Advisors also noted that placebo response, interpatient variability and the natural history of the disease were potential problems in evaluating the evidence.

Safety

- In the studies identified relatively few complications were reported as a result of treatment. Complications were mostly of a transient nature and included urethral bleeding, bruising, skin discolouration (petechiae) and haematoma. It is unclear at this stage what relationship the energy level used in the treatment has on reported complications.

- Specialist Advisors did not note any particular safety concerns of this procedure. Superficial bruising and moderate local pain were noted as potential adverse events.

Literature review
Rapid Review

The medical literature was searched to identify studies and reviews relevant to extracorporeal shockwave therapy for Peyronie's disease. Searches were conducted via the following databases from commencement to February 2003: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

Table 1 lists the selection criteria applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts, the full paper was retrieved

Table 1 Inclusion/criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Emphasis was placed on identifying good quality comparative studies. Abstracts were excluded where no clinical outcomes were reported; the paper was a review, editorial, technical or animal study
Patient	Peyronie's disease
Intervention/test	Extracorporeal shockwave therapy
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy
Language	Non-English language articles will be excluded unless they are thought to add substantively to the English language evidence base.

List of studies found

The literature search identified

- Three (3) studies with a comparative group [2] [3;4].
- Five (5) case series papers [5] [6-9]

This list includes two studies published in non-English journals.

Table 2 Summary of key efficacy and safety findings for extracorporeal shockwave therapy from comparative studies

Authors, location, date, number of patients	Type of LT	Key Efficacy findings				Key safety findings	Comments
		Angulation	**Plaque**	**Pain**	**Sexual Improvement**		
Hauck et al (2000) [2] **Non randomised comparative study** **Group A:** Shock waves 22 pts (20 follow-up) Patients who did not respond to previous therapy **Group B:** 23 oral placebo. Patients without previous therapy of calcification *Follow-up:* Average 8.5 months in the ESWT groups; 6 months Group B	Storz Minilith SL1 lithotripter 2 sessions within 3 days If symptoms improved ESWT was repeated after 3 months Per session 2000 applied max level of 7 0.35mJ/mm^2 120 shocks/min	**Group A:** Decrease in curvature > 30% 10/20 (50%) 41.8 to 30.8^O (p=0.052)	**Group A:** Disappeared 2/20 (10%) Plaque size decrease	**Group A:** *Flaccidity* Pre: 3/20 (15%) Post: 1/20 (5%) *Erection* Pre: 9/20 (45%) Post: 4/20 (20%)	**Group A** *Pre* Possible 1/20 (5%) Impossible 5/20 (25%) *Post* Possible 4/20 (20%) Impossible 5/20 (25%)	Skin haemorrhage 4/57 sessions Urethral bleeding 12/57 sessions (explained by use of catheter)	Significant differences between the two groups noted: Average history, calcifications, quality of sexual intercourse. No information given as to how case matched controls were selected and from what setting No details given as to the 2 patients lost to follow-up in the ESWT group. They were not included in the analysis Safety reported in terms of sessions rather than patients Subjective and Objective measurement of outcomes. Lack of standisation. Penile curvature assessed pre treatment photography/injection. Post treatment photography Ruler/calliper (plaque)
		Group B: Decrease in curvature >30% 3/14 (21%) 45.9 to 45.0^O (p=0.513)	**Group B:** Disappeared 3/23 (13%) Plaque size decrease	**Group B:** *Flaccidity* Pre: 2/23 (9%) Post: 3/23 (13%) *Erection* Pre: 11/23 (48%) Post: 6/23 (26%)	**Group B** *Pre* Possible 9/23 (39%) Impossible 2/23 (9%) *Post* Possible 13/23 (56%) Impossible 2/23 (9%)	None reported	

Authors, location, date, number of patients	Type of LT	Key Efficacy findings					Key safety findings	Comments
		Angulation	**Reduction of plaque**	**Reduction in pain**	**Sexual Improvement**	**Positive Opinion**		
Mirone et al (2000) [3] **Non randomised comparative study** **Group A:** Shock waves 21 patients **Group B:** Shock waves/ verapamil 36 patients **Group C:** Verapamil 73 patients Duration of symptoms less than 12 months	Minilith SL1 Pts A/B 3 times a week for 20mins	**Group A:** 11/14 (78.5%)	**Group A:** 11/21 (52.3%)	**Group A:** 16/21 (76.1%)	**Group A:** 9/12 (74.9%)	_	Transient outcomes 11 petechiae were localised along the waves direction	Part of a larger study (see below) Description of patient characteristics and measurement of outcomes lacking Ultrasonography (plaque) No indication if any of the outcomes were significant or if analysis had been undertaken.
		Group B: 16/21 (76.2%)	**Group B:** 22/36 (61.1%)	**Group B:** 19/23 (82.6%)	**Group B:** 7/9 (77.7%)	_		
		Group C: 33/51 (64.7%)	**Group C:** 31/73 (42.4%)	**Group C:** 36/61 (59%)	**Group C:** 31/56 (55.3%)	_		

Table 3 Summary of key efficacy and safety findings for extracorporeal shockwave therapy from case series papers

Authors, location, date, number of patients	Type of LT	Key Efficacy findings					Key safety findings	Comments
		Reduction in angulation	**Reduction of plaque**	**Reduction in pain**	**Sexual Improvement**	**Positive Opinion**		
Lebret et al (2002) [5] **Case Series** 54 patients. January 1999 to December 2000 Mean duration was 16 months, *Follow-up* at least 3 months.	Multiline Siemens lithotriptor 3000 shock waves 0.3mJ/mm^2 120 shocks/min 27 pts 1 session, 19pts, 2 sessions, 8pts 3 sessions.	29/51 (53.7%) decrease > 10^O Mean reduction 31 ^{O} P<0.001	23/54 (42.6%) 25/54 (46.3%) subjective improvement	31/35pts (88.6%) Mean reduction VAS 2.9 p<0.00001	6/24 (25%) Increase in erection quality and IIEF score	33/54 (61%) 9/54 pts requested surgery.	Transient outcomes Bruising, 7 buttock petechiae, 3 penile haematomas, 1 case of urethral bleeding	Angulation was calculated by auto-photography pre/post assessment Denominator re pain appears to be incorrect IIEF International Index of Erectile Function Injection (plaque)
Manikandan et al (2002) [6] **Case Series** 42 patients Mean duration was 16.57 months (18 less than 12 months) *Mean Follow-up:* 5.9 months (range 2-18 months)	Storz Minilith SL1 lithotripter 3000 shock waves 3 sessions 0.11-0.17mJ/mm^2 If symptoms improved 3 more sessions after 2 months	22/38 (57.8%)	Ultrasonography failed to pick up some palpable plaques.	21/25 (84%)	*Pre-treatment* Good 8/42 Moderate 17/42 Bad 17/42 *Post-treatment* Good 13/42 Moderate 17/42 Bad 17/42	27/42 (64%)	Transient outcomes 2 pts bruising, 8 pts pain, haematomas, dysuria	Angulation was calculated by auto-photography/injection pre treatment and photography post treatment Ultrasonography (plaque) Participants divided into two groups regarding interval of sessions
Husain et al (2000) [7] **Case series** 37 patients Duration of disease 19.43 months (4.0-60.0months) *Mean follow-up:* 7.5 months (5.0-11.00)	Storz Minilith SL1 lithotripter 3000 shock waves 3 sessions 0.11-0.17mJ/mm^2	15/32 (47%) Mean reduction was 12.8^O P<0.0001	–	12/20 (60%) Mean reduction VAS 1.9 p<0.0001	–	1 patient requested surgery	Transient outcomes 1 pt bruising; 19pts surface bleeding	Authors analysed whether difference between angulation/pain in those with acute/chronic disease – no difference reported. 3 pts did not complete the study Degree of erection calculated by vacuum device, angulation goniometer Ultrasonography (plaque)

Authors, location, date, number of patients	Type of LT	Key Efficacy findings					Key safety findings	Comments
		Reduction in angulation	**Reduction of plaque**	**Reduction in pain**	**Sexual Improvement**	**Positive Opinion**		
Hamm et al (2001) [8] **Case series** 28 patients All patients had disease > 1 year, considered stable	Storz Minilith SL1 lithotripter 3000 shock waves Patients underwent mean of 3.9 sessions 0.11-0.17mJ/mm^2	18/28 (64%)	Reported that measurements were unreliable 12/28 pts (42.9%) reported subjective improvement	13/16 (81%)	20/28 (71%) Pre-treatment 16pts unable to have intercourse, post treatment 11/16 recommenced IIEF P<0.001	20/28 (71%)	Transient outcomes 14pts penile bruising 1pts urethral haemorrhage, 1 pts blister	Angulation was calculated by auto-photography/injection pre treatment. Post treatment photography Ultrasonography (plaque) IIEF International Index of Erectile Function

Table 4 Large Non-English Full text published papers with English abstracts

Authors, location, date, number of patients	Key Efficacy findings	Key safety findings	Comments
Mirone et al (2000) [4] **Non randomised comparative study** Group A: Shock waves 56 patients Group B: Shock waves/ calcioantagonist 324 patients Group C: calcioantagonist 101 patients	**Reduction in angulation** Group A: Pre: 46° (10°-90°) post: 42° (15°-76°) Group B: Pre: 42° (10° - 80°) post 36° (1°-71°) Group C: Pre: 44° (15°-90°) post 43° (15°-85°) **Reduction in Plaque size** Group A: 27/56 (48%) Group B: 159/324 (49%) Group C: 39/101 (39%) **Sexual Improvement (reduction in painful erection)** Group A: 25/32 (78.1%) Group B: 163/178 (91.5%) Group C: 16/35 (45.7%)	Not reported in abstract	Data extracted are based on abstract information and text supplied in table. Therefore comment cannot be made regarding methodology. It would appear that a significant proportion of participants did not answer questions in relation to sexual improvement
Colombo et al (2000) [9] **Case Series** March 1998 to May 2000 82 patients aged 44-74 Duration of symptoms (3-120 months) 44 pts reported painful erections 78 showed bending of the penis 4 treatment sessions	37/82 (45%) pts reported stoppage/regression of the disease **Reduction in Angulation** 24/78 (30.7%) **Reduction in plaque (ultrasound)** 34/82 (41%) had a reduction in plaque, 32 (39%) patients had unchanged plaque, 16 (20%) patients had a larger plaque **Reduction in Pain** 31/44 (70.4%) reduction of pain **Reduction in disease (non-calcific pts)** 21/46 (46%) showed an improved disease, 25/46 (54%) plaque had worsened **Reduction in disease (calcific pts)** 13/36 (36%) improvement, 23/36 (64%) unchanged or worsened	Transient discolouration of the skin	Data extracted are based on abstract information and text supplied in table. Therefore comment cannot be made regarding methodology. Subjective and objective measurement of outcomes

Validity and generalisability of the studies

The validity and generalisability of the two non-English articles reported on in Table 3 will not be addressed below given the lack of available information.

- In general, the studies identified (two comparative and four case-series) reported on a small number of patients treated with extracorporeal shock therapy (total n=204).
- Patient selection varied among the studies. Some studies included patients in the early stages of the disease, while other studies reported on a broader spectrum of patients. Given the natural history of this disease this may have implications for the generalisability of results.
- In one case series paper an analysis was undertaken to assess whether the mean reduction in pain and angulation was related to duration of disease.
- In the two studies with control groups, one provided little information on patient characteristics while in the second study case history differed significantly between the two groups.
- There is a lack of objective and agreed measures in reporting outcomes. Many authors noted this as a limitation within their study, particularly in relation to the measurement of angulation.
- The majority of papers assessed pre-treatment angulation by autophotography and pharmacological injection, but only by autophotography post treatment. Two issues arise with this approach; namely the use of autophotography, a relatively non-objective measure, and secondly the bias introduced by using two different means to measure outcomes pre and post treatment.
- Three studies also reported a subjective measurement of sexual improvement, rather than using a validated inventory such as International Index of Erectile Function.
- A number of authors also identified issues with ultrasonography as a technique to localise and measure plaque. It is unclear at this stage what implication this has on reporting of outcomes or the efficacy of the procedure.
- It is also unclear how appropriate and useful pain is as an endpoint given the natural history of the disease and the issues around subjective measurement of outcomes in non-comparative studies.
- The energy levels used in the treatment of Peyronie's disease also varied among the studies from 0.11mj/mm^2, which might be considered low-density energy to 0.35mj/mm^2 defined as high-density energy. One study also used a different lithotripter.
- Follow-up in the studies ranged from 3 to 8.5 months.

Specialist advisor's opinion / advisors' opinions

- Peyronnie's disease is relatively uncommon and less than 10% of specialists are engaged in this area of work.
- There appear to be no uncertainties regarding the safety of this procedure.
- Uncertainties exits however regarding the efficacy of this procedure. This is based on the lack of controlled data, the natural history of the disease, inter-patient variability, outcome measurement and placebo response.

- An audit of patients is being undertaken by one of the Advisors.

Issues for consideration by IPAC

- Several papers identified referred to a number of abstracts (case-series) looking at extracorporeal shockwave therapy for Peyronie's disease. The largest abstract reports on a trial with 153 patients [5].

- A UK quality of life study for patients who have undergone extracorporeal shockwave treatment for Peyronie's disease is also listed on the National Research Register. However no publication has been produced.

References

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