TRANSDERMAL IONTOPHORESIS WITH VERAPAMIL AND DEXAMETHASONE IN THE ACUTE PHASE OF PEYRONIE’S DISEASE. OUR EXPERIENCE

Pablo Garrido Abad, Almudena Coloma, Luis Miguel Herranz, Milagros Jimenez, Carlos Suarez, Maria Dolores Prieto, Teresa Formoso and Manuel Fernandez Arjona.


Summary.- OBJECTIVES: To evaluate the treatment of Peyronie’s disease (PD) with verapamil and dexamethasone iontophoresis.

METHODS: Twenty nine patients with PD were treated by means of a Miniphysionizer® dispositive 3 sessions a week during 4 consecutive weeks. 5mL of a combination of verapamil (10mg.) and dexamethasone (4mg.) were transdermally administered with a 2.5 mA current during 20 min. The aim is to evaluate treatment efficacy in correcting penile curvature (Kelami test), plaque size (penis ultrasound (US)) improvement of pain and, other parameters like erectile function (EF), intercourse capacity or adverse effects of the treatment, which were evaluated with questionnaires.

RESULTS: All patients completed the treatment protocol (12 sessions) and a total number of 348 sessions of iontophoresis were performed. After treatment, 3 patients (10.7%) continued with pain, but it disappeared in 25 of them (89.3%). A decrease of the size of the plaque was observed in 13 patients (44.8%), even disappearance in 4 patients (13.8%). No patient had curvature decrease after treatment. However, EF (IIEF score) and ability for intercourse improved in 3 (10.3%) and 4 patients (13.8%) respectively.

CONCLUSION: Verapamil and dexamethasone iontophoresis is a safe and reliable treatment resolving painful erections in the acute phase of PD. However its efficacy in solving penile curvature and erectile dysfunction (ED) is more limited.

Keywords: Penis. Iontophoresis. Peyronie´s disease. Erectile Dysfunction.

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Resumen.- OBJETIVO: Evaluar el resultado del tratamiento de la Enfermedad de Peyronie (EP) mediante iontoforesis de verapamilo y dexametasona.

MÉTODOS: Tratamiento de 29 pacientes con EP en 3 sesiones semanales durante cuatro semanas consecutivas mediante un dispositive Miniphysionizer®. Administando 5 mL de una combinación de 10mg de verapamilo y 4mg de dexametasona, aplicado transdérmico a través de una corriente de 2.5 mA durante ciclos de 20 min. Se evaluó la eficacia del tratamiento mediante corrección de curvatura peneana (test de Kelami), tamaño de la placa (ecografía peneana), mejora del dolor...
y otros parámetros, como, la función eréctil, capacidad de penetración o efectos secundarios del tratamiento, que fueron valorados mediante cuestionarios.

RESULTADO: Todos los pacientes completaron el protocolo de tratamiento (12 sesiones) y se efectuaron un total de 348 sesiones de iontoforesis. Tras finalizar el tratamiento completo, 3 pacientes (10.7%) continuaron presentando dolor, mientras que remitió en 25 de ellos (89.3%). En 13 pacientes (44.8%) se observó una disminución del tamaño de la placa, desapareciendo incluso totalmente en 4 pacientes (13.8%). La curvatura no se disminuyó en ninguno de los pacientes tras el tratamiento.

CONCLUSIONES: La iontoforesis con verapamilo y dexametasona es un tratamiento seguro y eficaz en la resolución del dolor con las erecciones en la fase aguda de la EP. Sin embargo la eficacia en la resolución de la curvatura y la DE es más limitado.


INTRODUCTION

In 1743 François de La Peyronie described for the first time the concept induration penis plastica. Since then, is named Peyronie’s disease (PD) (1).

PD is a complex of symptoms due to structural modifications in penile corpora cavernosum, that can result in penile deviation, painful erections, and difficulties during intercourse.

The cause of penile curvature is the presence of fibrotic plaques involving tunica albuginea.

Is a relatively common disorder among men (40-70 year old), with a reported prevalence of 3.2-8.9%. However the actual prevalence of PD may be even higher because many men are embarrassed to complain about it (2,3).

Treatment for EP presents several approaches with different results. Due to relatively high number of patients in our daily andrology consultation, we think is interesting to evaluate one of the most unknown therapy for PD, the transdermal iontophoresis.

Transdermal drug delivery has been suggested to have advantages over oral or injection therapy by eliminating first pass metabolism and minimizing the pain of injection.

Transdermal iontophoresis is the transport of ions through the skin by an electric current, to reach higher concentrations of drugs in the site of action.

METHODS

The study design was a one-center retrospective serie of cases.

A total of 29 patients were treated, with a mean age of 62.7 year old (34-78), with PD in last 3 months. All treatments were completed between February 2010 and September 2011.

Inclusion criteria were clinical evidence of primary Peyronie’s disease including plaque, deformity of the penis and pain on erection or non-specific genital pain. Exclusion criteria were recent treatment with calcium channel blockers or corticosteroids, therapies interfering with these 2 drugs, and erectile dysfunction due to causes other than Peyronie’s disease.

During study, patients were not allowed to treat ED with pills or other treatments.

Electromotive drug administration treatment was performed under the established protocol, including thorough degreasing of the skin under the active and dispersive electrodes with rubbing alcohol. This step is important to decrease irregularities in skin impedance to electric current and drug transfer. Then a 5 cc plastic self-adhesive receptacle was filled with of 4 mg. dexamethasone and 10mg. verapamil and fixed to penis skin over plaque. The positive electrode (anode) of the Miniphionizer® (model MP 2.0, Physion, Italy) was connected to the receptacle and the cathode was connected to a skin electrode fixed to the thigh (Figure 1). A pulsed direct 2,500 Hz. current of 2.5 mA. was performed for 20 minutes. Complete treatment consisted of 3 weekly sessions during 4 weeks (total of 12 weeks).

According to Cabello et al (4), following parameters were assessed: penile deviation, plaque size, curvature severity, erectile function, ability for intercourse and presence of painful erections.

Penile deviation was classified in lateral or dorsal/ventral, plaque size (cm.) was measured by penis ultrasound before and after treatment (Figure 2). Grade of deviation by means of Kelami test (autophotos in three different planes during complete
erection) stratified in (<30º, 30-60º and >60º). Erectile function was measured by means of score of 1-5 and 15 International Index of Erectile Function questionnaire (IIEF). Ability for intercourse was classified in possible, difficult and impossible, after a questionnaire, just as presence or absence of painful erections, according to a pain scale from 0 to 10 and stratified (Absence:0; Mild:1 a 3, Moderate:4 a 7, Severe: 8 a 10).

All patients were assessed 1 month after treatment.

None of them have received any other treatment before for PD.

Penis ultrasound were not all performed by same radiologist, but all by urology-specialized radiologist into the department.

During treatment adverse effects were assessed. All patients completed 12 sessions.

RESULTS

All patients completed treatment (12 sessions) and a total of 348 iontophoresis sessions were administered (Table I).

Most frequent deviation in our serie was dorsal, in 19 patients (65.5%), and the rest 10 patients (34.5%) had lateral deviation.

Plaque presence was confirmed in all patients. Proximal plaque location was the most prevalent, 16 patients (55.2%), medium in 10 patients (34.5%), and distal in 3 patients (10.3%). After treatment reduced plaque size was evidenced. Mean plaque size before treatment measured by penis ultrasound was 2.37 cm. (0.1-3.1), and 1.78 cm. (0.0-3.3) after treatment. (p<0.001)

13 patients (44.8%) had a reduction in plaque size, and totally disappear in 4 patients (13.8%). All of this 4 patients had an initial plaque size < 0.8 cm.

28 patients (96.5%) have complained painful erections before treatment. After 12 iontophoresis sessions, 3 patients (10.7%) continued referring
pain, but disappeared in 25 of them (89.3%). 23 of these patients with pain disappearance, showed this improvement after third treatment session. This resolution of pain was registered in patients with dorsal (16) as lateral (9), and in all groups of plaque size, <1 cm (5), 1-2 cm (2) and >2 cm (18).

After Kelami test, patients were stratified in <30° (11), 30-60° (15) and >60° (3). Curvature did not decrease after treatment in any patient, if it is true that neither progressed. Erectile function (IIEF score) improved only in 3 patients (10.3%), and ability for intercourse in 4 patients (13.8%).

Mean patient follow-up was 14.1 months (3-22)

No adverse events related to iontophoresis were observed, except mild ecchymosis in skin electrode site.

**DISCUSSION**

The true nature of PD is almost unknown, but usually occurs after a penis trauma, autoimmune mechanisms, genetic anomalies or abnormal activity of fibroblasts (5).

The pathophysiology of PD and the mechanism of plaque formation are largely unknown. One paradigm is that PD begins with an inflammatory process that leads to a progressive fibrosis, although exact mechanism is still not well known. Several inflammatory mediators, growing factors and matrix proteins responsible of plaque formation: transforming growth factor beta 1 (TGF-β1), matrix metalloproteinases, plasminogen 1 activator inhibitor and growing factor for platelets A and B. (6-9)

Loss of elasticity in plaque site cause deviation and/or penis deformity, and may interfere with venous occlusion responsible of erection. (10)

Final result may be penile deformity, pain, difficulties for intercourse and erectile dysfunction. Clinically two well defined different phases: acute and chronic. In acute phase, 12-18 months, patients present painful erections, curvature or penile deformity, palpable plaque, and often erectile dysfunction. Whereas in chronic phase, penile deformity stabilizes and pain goes down. However,

**TABLE I.**

<table>
<thead>
<tr>
<th>Deviation</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td><strong>Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal</td>
<td>19</td>
<td>65.5%</td>
</tr>
<tr>
<td>Lateral</td>
<td>10</td>
<td>34.5%</td>
</tr>
<tr>
<td>Ventral</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30°</td>
<td>11</td>
<td>37.9%</td>
</tr>
<tr>
<td>30-60°</td>
<td>15</td>
<td>51.7%</td>
</tr>
<tr>
<td>&gt;60°</td>
<td>3</td>
<td>10.3%</td>
</tr>
<tr>
<td><strong>Plaque</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>16</td>
<td>55.2%</td>
</tr>
<tr>
<td>Medium</td>
<td>10</td>
<td>34.5%</td>
</tr>
<tr>
<td>Distal</td>
<td>3</td>
<td>10.3%</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1cm</td>
<td>5</td>
<td>17.2%</td>
</tr>
<tr>
<td>1-2 cm</td>
<td>2</td>
<td>6.9%</td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>22</td>
<td>75.9%</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28</td>
<td>96.5%</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>3.5%</td>
</tr>
</tbody>
</table>
exists a high variability in the PD development (5).

Natural evolution of PD is to progress in 30.3-48% of cases without treatment, but only 3.2-12% have a spontaneous resolution (11,12).

Despite a myriad of treatment options, PD remains a considerable therapeutic dilemma because of the paucity of randomized, placebo-controlled trials.

Iontophoresis is the electrokinetic transport of charged ionic molecules by a electric source, to overcome limitations of topical therapies. It is placed into the non surgical therapies for PD.

Stancik et al recently demonstrated the decreased expression of bFGF mRNA and bFGF protein, as well as overexpression of TGF-β protein and TGF-β receptor, in excised Peyronie’s plaques after having undergone electromotive drug therapy with dexamethasone, verapamil, and lidocaine when compared with therapy naive plaques (13).

It has been applied with different drugs and dosages since several years ago.

Most used medications are: verapamil, dexamethasone, lidocaine and orgotein.

Levine et al described in 2003 the presence of verapamil in the tunica albuginea during plaque surgery in PD patients after they have been treated with EMDA (14).

Di Stasi in 2004 reported a prospective, randomized study including 96 patients with PD treated with 5mg. of verapamil + 8 mg. dexamethasone iontophoresis versus a group treated with iontophoresis of lidocaine 2%. 43% of patients of the verapamil + dexamethasone group showed reductions in plaque size or penile deviation, meanwhile lidocaine group did not show significative changes (15).

In 2003, Di Stasi (16) reported a serie of 49 patients treated by iontophoresis with 5mg. of verapamil and 8 mg. of dexamethasone with an amazing results. He reported 73% of plaque reduction, and 8% of total disappearance. Moreover describes a deviation reduction in 84% of patients, and 59% of improv in erectile function.

In 2007, Greenfield published his experience with iontophoresis of verapamil 10mg. versus saline. 65% and 58% of them, respectively, showed a reduction in deviation (9.1° vs 7.6°), without significative differences between both treatments.

Authors conclude that electric current, by itself, may cause beneficial effects (17).

In Spain few series of patients with PD treated by iontophoresis have been reported. In 2003 Pérez Espejo et al (18) reported a serie of 61 patients treated by iontophoresis with orgotein. 17 patients (27.9%) showed improv in pain, while 4 patients (6.5%) reduced penile deviation. In 2005 Cabello et al (4) reported a retrospective serie of cases, with a reduction in painful erections and plaque size in 80% and 60% of patients, improv of erectile function in 10%, without reduction in penile deviation in any patient.

Our results showed reduction in pain in 89% of patients, as high as previously reported in other series (28-96%) (10,15,16,18), and reduction of plaque size in 45%, softly lower than reported by other authors (53-100%) (10,15,16). It is surprising the null response in penile curvature reduction in our serie, according to Cabello et al (4), not seen in any patient, meanwhile reaches up to 84% in other reports.(16) In the same way, the mild improvement of erectile function in our patients (10%), does not belong with other series reported, with improvements up to 60% (16).

This results may be due to a lower number of patients included in our serie, or to a shorter follow-up.

Other non-surgical treatments for PD include oral therapies, topical therapy, intralesional therapies, local penile electroshock wave therapy [ESWT] and penile traction devices.

Different oral therapies are used for PD treatment, including vitamin E (tocopherol), potassium aminobenzoate (potaba), colchicine, tamoxifen citrate, acetyl esters of carnitine, phosphodiesterase type 5 inhibitors, and pentoxifyline (5,19). All of them fail to demonstrate efficacy in randomized trials, except potassium aminobenzoate (potaba) that demonstrated establish progression of penile deviation in Weidner et al (20).

Topical therapies include among others: verapamil, hydrocortisone and aminopropionitrile (19), although results are poor in nearly all of cases.

Several intralesional therapies have been used: corticosteroids, verapamil, orgotein, collagenase and interferons (α-β). Among them, corticosteroids are not recommended and verapamil has not demonstrate efficacy in randomized, controlled trials (21). Orgotein is forbidden in USA
and its use is not well recommended. Collagenase, however, in a recent phase II trial (not yet published) have demonstrated significative improv of painful erections and curvature (22), while interferon treatment have demonstrated efficacy in resolution of curvature, plaque size and pain, without effect in erectile function (23).

ESWL have not demonstrated benefical effect. Currently ESWL has no current place in PD treatment (24).

Penile traction devices and vacuum devices have suggested benefits in PD treatment, but not yet in RCT’s (25-27).

In severe cases of PD, treatment may include penile surgical procedures, like tunical shortening procedures (plication), tunical lengthening procedures (grafting) or penile prosthesis implantation.

CONCLUSION

Iontophoresis with verapamil and dexametasone is a safe and reliable treatment in resolving painful erections in acute phase of PD. However its efficacy in resolving curvature and ED is more limited.

This treatment should be recommended to patients whose main symptom is pain and to patients with mild curvature and those who do not want to perform an intralesional injection or surgical procedures.

REFERENCES AND RECOMMENDED READINGS

(*of special interest, **of outstanding interest)


