

## IONTOPHORESIS FOR TREATMENT OF PEYRONIE'S DISEASE

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### ABSTRACT

**Purpose:** We evaluate the efficacy of iontophoresis of dexamethasone, lidocaine and verapamil to treat Peyronie's disease.

**Materials and Methods:** In an uncontrolled prospective study 100 unselected patients with Peyronie's disease were treated with 3 weekly courses of iontophoresis. The drug mixture was administered by an electrical current of 5 mA. and a self-adhesive receptacle fixed to the penile skin overlying the plaque.

**Results:** Resolution of pain was observed in 96% of patients, plaque diminution in 53% and improvement of penile deviation in 37%. Impaired sexual function was improved in 19 of 43 patients (44%). The benefit of iontophoresis therapy was more pronounced in patients with a short history of disease. Because of lack of side effects and painless administration iontophoresis was well tolerated and accepted by all patients.

**Conclusions:** Iontophoresis of dexamethasone, lidocaine and verapamil may be regarded as first line nonsurgical treatment for Peyronie's disease.

KEY WORDS: penile induration, iontophoresis

Peyronie's disease is a complex of symptoms due to structural alterations of the penile corpora cavernosa. The typical lesion (plaque) is a circumscribed induration of the tunica albuginea that can be painful or indolent and is usually dorsal in the area of the intercavernous septum. Loss of elasticity at the plaque site causes penile deviation and/or deformation, and may interfere with normal veno-occlusive function responsible for erection. A common course of Peyronie's disease is initial penile pain followed by development of a plaque, penile deviation, plaque calcification, penile deformation and erectile dysfunction. However, in a considerable number of patients penile deviation without pain is the initial presentation.

Therapy for Peyronie's disease is closely related to the predominant symptoms and patient primary concerns. Pain at the site of the lesion is mainly present during erections and, with pronounced penile curvature, interferes with sexual activity and prompts patients to consult a urologist. In contrast, painless plaques and minor penile deviation may not be recognized and/or reported. Thus, only a relatively small number of patients receive treatment for Peyronie's disease, despite the reported high prevalence of 1%.<sup>1,2</sup>

While surgical correction is the treatment of choice for major penile angulation and deformation, a variety of medical regimens have been used to resolve pain, plaques and minor deviation. Oral vitamin E, potassium para-aminobenzoate and tamoxifen, and intralesional injection steroids, orgotein, collagenase, verapamil and interferon- $\alpha$  have shown differing grades of efficacy to reduce the symptoms of Peyronie's disease.<sup>3–11</sup> However, except for vitamin E, they have considerable side effects, for example gastrointestinal symptoms often lead to premature termination of para-aminobenzoate therapy and local injections are extremely painful, requiring local anesthesia.

The use of iontophoresis, the electrokinetic transport of charged (ionic) molecules, for enhancement of transdermal drug transport into diseased tissues, has a long tradition in medicine,<sup>12,13</sup> with demonstrated efficacy in the treatment of arthritis and soft tissue diseases.<sup>14,15</sup> Anecdotal reports suggested that iontophoretic delivery of steroids was beneficial in some patients with Peyronie's disease.<sup>16–18</sup> More recently,

a placebo controlled study confirmed these preliminary results, and showed efficacy and tolerability of iontophoretic dexamethasone and verapamil for Peyronie's disease.<sup>19</sup> We evaluate the ability of iontophoresis of various drugs to resolve symptoms of Peyronie's disease in a larger number of unselected patients.

### MATERIALS AND METHODS

Between 1994 and 1998, 100 patients from 28 to 70 years old (mean age 53.6) with Peyronie's disease were treated with iontophoresis of dexamethasone, verapamil and lidocaine in a prospective, uncontrolled study. Mean duration of disease at presentation was 14.9 months (range 1 to 300). Prior therapy consisted of para-aminobenzoate in 18 cases, radiation in 5, orgotein in 4, orgotein and para-aminobenzoate in 4, radiation and para-aminobenzoate in 3, and surgery in 1.

Patients judged pain according to a pain scale. Plaques were measured with a measuring tape or ultrasound if not easily palpable. Penile deviation was photographically documented in 2 planes if the patients agreed or they were asked to sketch the curved erect penis. If erectile dysfunction was present intracavernous papaverine or prostaglandin E1 was injected for diagnostic evaluation, and the grade of deviation was judged by the investigator. In addition, any impairment of sexual activity caused by Peyronie's disease was recorded.

A 5 or 7 cc plastic self-adhesive receptacle was fixed to the penile skin overlying the plaque (fig. 1) The receptacle was filled with a solution of 8 mg. dexamethasone and 40 mg. lidocaine for painful plaques, and a combination of 8 mg. dexamethasone and 5 mg. verapamil was used for painless lesions. The positive electrode (anode) of the Physionizer 30\* current generator was connected to the receptacle and the cathode was connected to a skin electrode fixed to the lower abdomen. Iontophoresis with a pulsed direct 2,500 Hz. current of 5 mA. was performed for 20 minutes. In cases with a distal (subcoronal) location of the plaque a beaker electrode may be used instead of the receptacle.

Initially 3 weekly treatments to a total of 10 were performed. If symptoms were reduced by this course but the patient judged the outcome still unsatisfactory, iontophoresis

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FIG. 1. Self-adhesive receptacle for iontophoresis therapy in Peyronie's disease.

was continued. Treatment was terminated when symptoms resolved, patients were satisfied with the outcome or if no improvement was achieved. At the final examination changes in the initial symptoms were assessed, and alternative medical or surgical therapy was recommended if the outcome was unsatisfactory.

#### RESULTS

A defined cavernous plaque was palpable in 79 of 100 patients, diffuse induration and enlargement of the intercavernous septum only were noted in 19 and 2 presented without a plaque. Penile deviation was documented in 77 patients and 60 reported pain at the plaque site. Presenting symptoms are listed in table 1. In 5 patients a history of intracavernous self-injection with papaverine or prostaglandin (range 1 to 15 injections) and in 11 a history of penile trauma before the onset of disease were noted. In 7 patients signs of Dupuytren's contracture were evident on 1 or both hands.

A total of 1,137 iontophoresis treatments were performed (range 3 to 53 per patient). Dexamethasone and lidocaine were used in 559 treatments, dexamethasone and verapamil were given in 578. In 5 patients therapy was discontinued after 3 to 6 treatments as the outcome was subjectively unsatisfactory. Pain was eliminated by iontophoresis treatment in 38 of 60 patients (63%) and significantly improved (greater than 90% on the pain scale) in 20 of 60 (33%). Pain

TABLE 1. Severity of Peyronie's disease symptoms at initial presentation

	No. Pts.
Pain:	
None	40
Mild to moderate	37
Moderate to severe	23
Plaque:	
Less than 1 cm. <sup>2</sup>	22
Less than 2 cm. <sup>2</sup>	24
Greater than 2 cm. <sup>2</sup>	33
Induration of intercavernous septum	19
None	2
Multiple	7
Penile deviation:	
Less than 30 degrees	35
30-50 Degrees	24
Greater than 50 degrees	18
None	23
Dorsal	41
Ventral	7
Lt./rt.	8/4
2-dimensional	17
Erectile dysfunction:	
Mild to moderate	11
Moderate to severe	12
Sexual activity impairment	43
Dupuytren's contracture	7
Penile trauma history	11
Intracavernous injection history	5

at the plaque site disappeared as early as 1 week after initiation of therapy and was maximally reduced after 2 to 3 weeks. Only 2 patients reported that pain had remained unchanged, including 1 with pain at the site of prior surgery (plaque excision and venous grafting) and 1 with neurological disease that may have been the origin of constant pain.

The cavernous plaque was reduced in 31 of 79 patients (39%), and plaques totally disappeared in 11 of 79 (14%). In 33 of 79 patients (42%) the plaques remained unchanged, whereas an increase in plaque size was observed in 4 (5%). When induration and enlargement of the intercavernous septum (and no distinct plaque) were present 14 of 19 patients (74%) showed no improvement, while a measurable reduction in size was observed in 4 (21%) and growth was noted in 1 (5%). In 1 patient an approximate 20% reduction in plaque calcification after iontophoresis therapy was observed (fig. 2).

Penile deviation significantly improved with complete straightening or more than a 30-degree reduction in deviation after iontophoresis treatment in 12 of 77 patients (16%) and less pronounced reduction in curvature was observed in 16 of 77 (21%). No change in deviation occurred in 43 of 77 patients (55%) while angulation increased in 6 of 77 (8%). Of 15 patients without a defined plaque and induration of the intercavernous septum deviation 4 (27%) had improvement but the condition was unchanged in the remaining 11 (73%). Restoration of erectile function was reported by 7 of 23 patients (30%) and 16 of 23 were further treated with self-injection of papaverine or prostaglandin E1, since all refused implantation of a penile prosthesis. Sexual activity improved in 19 of 43 patients (44%) and worsened in 1 with an increase in penile deviation during therapy.

Table 2 shows post-therapeutic changes in Peyronie's symptoms in regard to duration of disease. Rates for plaque size reduction decreased from 63.3% with duration of less than 3 months to 26.9% with duration of more than 12. Similarly, the highest rate of improvement in deviation occurred with a duration of less than 3 months (36.4%) compared to 27% after more than 12 months. Of the patients who had previously undergone other therapies 43.3% had improvement in deviation after iontophoresis. Pain was eliminated in all patients with a history of self-injection therapy or trauma but deviation improved more in those after self-injection (60% versus 25%).

Peyronie's symptoms recurred in 15 of 100 patients after a mean of 5.5 months (range 2 to 10) following successful initial iontophoresis therapy, and in 10 a second treatment course was given which again improved symptoms. In the remaining 5 patients surgery was recommended since a penile deviation of more than 45 degrees had developed. Surgery was also recommended to 5 patients who had an increase in initially

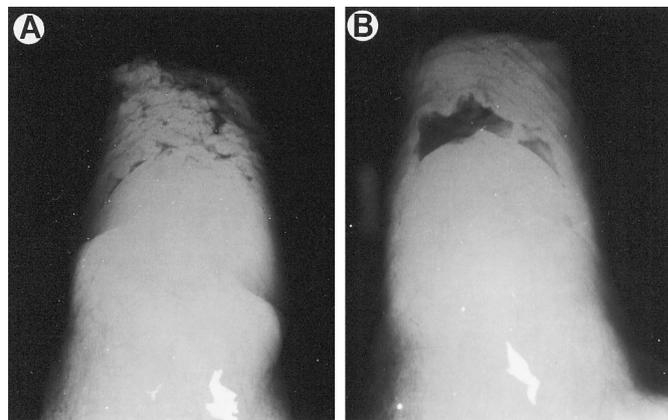


FIG. 2. A, calcifications of Peyronie's plaque before iontophoresis therapy. B, radiological reduction in calcifications with smoothing of plaque and improvement in penile deviation.

TABLE 2. Presence of and/or change in Peyronie's disease symptoms correlated to disease duration

	Less Than 3 Mos.	3-6 Mos.	6-9 Mos.	9-12 Mos.	Greater Than 12 Mos.
Total No. pts.	22	30	10	12	26
% Pain before therapy:	54.5	63.3	90	66.6	42.3
% Plaque:					
Improved	63.6	46.7	40	58.3	26.9
Unchanged	31.8	36.7	50	41.7	65.4
Increased	4.5	27.3	10	0	0
% Deviation:					
Improved	36.4	30	20	16.7	27
Unchanged	31.8	33.3	70	66.7	61.5
Increased	9.1	13.3	0	0	0
No deviation	22.7	23.3	10	16.7	11.5

moderate penile curvature after unsuccessful iontophoresis treatment, and to 10 whose severe initial penile deviation and impaired sexual function did not improve. Only 6 of 20 patients underwent surgical correction, while the remainder tolerated the final stage of Peyronie's disease. Except for occasional (about 1%) transient erythema and edema at the site of the penile or abdominal electrodes, no side effects occurred.

DISCUSSION

Despite intense investigations, the etiology of Peyronie's disease remains obscure and the course of disease is unpredictable. Experimental studies, clinical observations and the recent elucidation of various traumatic events as a risk factor for the development of Peyronie's disease<sup>20</sup> led to the hypothesis that microtraumatic lesions to the aged and structurally altered tunica albuginea lead to formation of a hypertrophic scar (plaque), possibly on the basis of individual genetic predisposition.<sup>21</sup> This theory is supported by the microscopic findings of excessive and disorganized collagen deposits, and disordered and reduced elastic fibers and fibrin accumulation inside Peyronie's plaques, which are consequences of aberrant wound healing.<sup>22-25</sup>

Since multiple inflammatory mediators and cytokines are released by leukocytes at the trauma site to initiate wound healing,<sup>26,27</sup> anti-inflammatory drugs are supposed to restrict the overabundant tissue regeneration responsible for plaque formation. Corticosteroids were among the first drugs injected into plaques to reduce fibrous scars and related symptoms.<sup>7,8</sup> Williams and Green reported improvement in Peyronie's symptoms after steroid injections in 33% of men compared to 6.5% without treatment.<sup>28</sup> More recently Levine et al demonstrated that intralesional verapamil injections improved penile curvature in 42% and significantly reduced plaque volumes in 30% of patients.<sup>10</sup> These results were confirmed in a placebo controlled study by Rehman et al, who reported a decreased plaque volume in 57% of verapamil treated men compared to 28% of controls.<sup>29</sup> The efficacy of verapamil may arise from its known inhibition of extracellular matrix secretion and synthesis that results in a reduction in collagen, glycosaminoglycans and fibronectin, as well as from its increased collagenase and anti-transforming growth factor-β activity.<sup>10,29</sup>

Injections into Peyronie's plaques are painful and normally require local anesthesia. In addition, multiple injections into the fibrous hard plaques are difficult to perform and deliver the drug to distinct parts but not the entire lesion. In contrast, iontophoresis painlessly and homogeneously distributes drugs to the entire lesion underlying the receptacle. Enhanced transdermal penetration of dexamethasone and lidocaine by iontophoresis has been demonstrated.<sup>14, 15, 30, 31</sup> Verapamil hydrochloride with its positive charge implies adequate transcutaneous migration inside the electrical field. The combination of various drugs that are effective for Peyronie's disease was supposed to be superior to drug monotherapy. However, lidocaine, which is not effective in curing the lesion, provides temporary resolution of pain and, more importantly, the electrokinetic enhancement of dexamethasone transport.<sup>14, 19</sup>

We observed an appreciably prompt and almost complete (96%) rate of pain reduction and when combined with a 37% decrease in penile angulation, a 39% restitution of erectile function and a 44% improvement in sexual activity were noted. Restoration of erectile function was partly achieved by resolution of severe pain that interfered with complete erection. There may have been an additional effect by the iontophoretic drug delivery, since Montorsi et al reported significant improvement in penile hemodynamic parameters in 84% of patients.<sup>19</sup> Our results are compared to those of other conservative regimens in table 3.<sup>5, 6, 10, 19, 32-35</sup>

Our results confirm that the success of conservative therapy is an inverse function of disease duration. Improvement rates in plaque and deviation status decreased from 63.6% and 36.4%, respectively, for lesions of less than 3 months in duration to 26.9% and 27%, respectively, for disease duration of more than 1 year (table 2). Interestingly, patients experienced pain more frequently between 6 and 12 months of disease duration (90% at 6 months) than with early (54.5%) or long lasting (42.3%) disease. In addition, deterioration in symptoms only occurred during the first 6 to 9 months of disease. These data represent cogent arguments for early initiation of medical therapy and suggest that the best results are achieved when disease progression is most likely to occur.

Scott and Scardino,<sup>36</sup> and Williams and Thomas<sup>37</sup> suggested that Peyronie's disease has the tendency for gradual

TABLE 3. Outcome of nonsurgical regimens for Peyronie's disease

References	Drug	No. Pts.	% Pain Reduction	% Plaque Reduction	% Deviation Improvement	% Sexual Function Improvement
Devine and Horton <sup>32</sup>	Vitamin E	30	66.3	53	53	—
Weidner et al <sup>5</sup>	Para-aminobenzoate, placebo	22, 24	68.4, 58.8	31.8, 12.5	36, 0	—
Ralph et al <sup>6</sup>	Tamoxifen	36	80	34	35	—
Koren et al <sup>33</sup>	Radiation	265	61.4	66.4	53	—
Williams and Green <sup>28</sup>	Corticosteroids	45	—	33	33	—
Primus <sup>34</sup>	Orgotein	18	100	—	39	83
Levine et al <sup>10</sup>	Verapamil	14	91	30	42	58
Judge and Wisniewski <sup>35</sup>	Interferon	13	67	30	60	—
Montorsi et al <sup>19</sup>	Iontophoresis	40	100	79	62	—
Present series	Iontophoresis	100	96	53	37	44

resolution with time and medical therapy is not necessary. Both groups only presented small series. Scott and Scardino reported that patients treated with vitamin E, which is supposed to be beneficial for Peyronie's disease, achieved a 78% rate of deviation improvement, which to our knowledge would be superior to all other reported medical treatments (table 3). More recently Devine reported on 200 patients, including 125 treated with vitamin E.<sup>2</sup> Of these patients 80 were satisfied with the outcome at 2 years of followup, which represents a success rate of 40% of the initial patient number, which included 75 advised to undergo primary surgical correction. Whereas pain disappeared in 99% of the patients during followup, only 16 (13% of the surveillance and 8% of the initial group) reported improvement in plaque or deviation and 66 (53% and 33%, respectively) considered function to be adequate. Gelbard et al reported that symptoms resolved in 13% of 97 men with disease duration of 3 months to 8 years but worsened in 40% with time.<sup>38</sup> There was no statistically significant difference in outcome between the 41% of patients treated and those not treated with vitamin E.

Generally, the comparison of studies concerning Peyronie's disease is difficult. A variety of etiological events may be responsible for tunica fibrosis which, may react differently to various regimens. Most reports do not include large numbers of patients and only a few studies have a controlled 2-arm design. In addition, the recording of plaques and penile deviation, and their changes during therapy is not standardized. However, several placebo controlled studies demonstrated a statistically significant beneficial effect of various medical regimens, including iontophoresis.<sup>5, 19, 28, 29</sup>

Concordant with Mira who demonstrated acceleration of symptom improvement with medical therapy compared to untreated patient groups in a meta-analysis,<sup>39</sup> our results argue strongly for iontophoresis therapy compared to watchful waiting. Even if pain disappears in almost all cases with time whether treated or not, a painless state is usually achieved after 2 weeks of iontophoresis therapy. A plaque reduction rate of 53% and improvement in penile curvature in 37% compare favorably to the 13% improvement rates reported for various no therapy groups.<sup>2, 38</sup> Furthermore, our data suggest that iontophoresis prevents deterioration of Peyronie's lesions (8% versus 40% in the no therapy group<sup>38</sup>) in early stage disease. The greatest advantages of iontophoresis compared to all other conservative standard therapies are the lack of side effects and painless procedure.

#### CONCLUSIONS

Iontophoresis of dexamethasone, verapamil and lidocaine is effective for Peyronie's disease and especially beneficial for painful lesions of less than 12 months in duration and for deviations less than 60 degrees. In our opinion this procedure should be regarded as first line noninvasive therapy for Peyronie's disease. In cases with greater penile curvature or a prolonged course of disease we primarily recommend surgery if erectile function is adequate. If erectile dysfunction is present, optimal treatment is probably implantation of a penile prosthesis.

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