

Conference Paper Androtherm Application for the Peyronie's Disease

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Peyronie's disease is characterized by a scarring fibrosis within the tunica albuginea of the penis that could lead to penile length loss, narrowing, curvature, erectile dysfunction, or pain with erection. This problem has recently no appropriate treatment. Our objective is to treat this kind of disease by a new kind of hyperthermia method.

1. Introduction

1.1. Prevalence. The Peyronie's disease (induratio penis plastic) is a developmental condition with acquired fibrotic changes and development of a fibrous plaque (fibrous inelastic scar) on the tunica albuginea of the penis. The Peyronie's disease is mostly observable at men in their middle ages (50– 60 years) in Caucasian race [1]. The prevalence, commonly reported, is about 3%–9% [2], but according to the autopsy statistics the disease would be present in more than 20% of men [3]. It can also be an asymptomatic finding in almost 4% of male population seeking medical attention [4, 5]. In general the men, aged 40–60, are affected by Peyronie's disease in 2%–3% [6].

Actually we think that shame, fear, and poor possibilities of healing [7] are the main causes of reduced demand for medical consultation, although it also causes unpleasant side effects such as not agreeing to the modifications of the penis, reduction of self-esteem, impaired job performances, increased interpersonal conflicts, and depression.

Now, thanks to the many sources of information, the patient is aware of the limited possibilities of therapy and knows perfectly well that there is little chance of spontaneous recovery (15% of second Mulhall) [8].

1.2. Pathophysiology. Relatively little is known about the source of the disease, but nowadays there is growing

consensus on the possibility of an external stress received, most likely in the erect state, during sexual intercourse or masturbation.

Trauma during sexual activity can occur for several reasons: vehement and prolonged masturbation, instinctive and sudden movement of the penis, accidental contrast of the penis against the female perineum, difficulty in penetration due to lack of lubrication of the vagina, and lack of penile erection.

The abrupt penis deformation during sexual intercourse may disrupt small vessels within the tunica albuginea with blood trapped between the layers of the tunica.

The hematoma is responsible for excessive release of cytokines, of transforming growth factor (TGF betal), as a reaction to an autoimmune response. It is followed by an overproduction of collagen, high production of extracellular matrix, accumulation of fibroblasts and myofibroblasts, and decrease of elastic fibers [9].

This process, characterized by an abnormal healing of hematoma with the occurrence of scar, implies the coexistence of an autoimmune process probably leading to a genetic factor.

In 75% of patients affected by Peyronie's disease, high levels of antielastin antibodies [10] and a higher incidence of histocompatibility antigens HLA-27 are shown [11]. The autoimmune reaction may have, in some individuals, a certain degree of genetic predisposition.



FIGURE 1: Androtherm device (Treat-therm trademark).

Some searches have demonstrated in fact, on cultured cells derived from plaques from Peyronie's disease, chromosomal abnormality, during metaphase, in which the chromosome Y seems to be more involved.

The actual trauma could lead to inflammation, bleeding, and releasing a number of chemicals that lead to inflammation [12]. The closed, layered structure of the tunica may limit the ability to drain the produced inflammatory mediators away from the site of injury, leading to prolonged inflammation (when the inflammation became chronic it could block the healing process) [13, 14].

Nowadays, no effective therapy exists for this disease, although there are continuous and ever new attempts. There are many nonsurgical treatments for Peyronie's disease like Vitamin E, Carnitine, Colchicine, Pentoxyphilline, and various herbal and complementary remedies like Acetyl-L-Carnitine (ALC) and Dymethyl Sulfoxide (DMSO), or the "Tracker formula"; enzymes like Wobenzym, Fibrozym, Vitalzym, and Neprinol; as well as the minimally invasive (local in situ injection) treatments of Verapamil, Interferon, Collagenase, and various steroids (e.g., Glucocorticoids) could be applied.

All the treatments applied have no or poor efficacy. There are various surgical options to solve this problem [15]. There is huge interest in treating this disease worldwide [16] and there are also comprehensive books published on the topic [17, 18].

The transdermal electrophoresis [19] could be effective for the treatment combined with definite drug-therapy called "trasdermal electromotive drug-therapy" (EMDTA) [20].

This placebo controlled, double-blind study used Orgotein (8 mg), Dexamethasone (8 mg), and Lydocaine (120 mg) for 20 min three times a week for three weeks. The plaque reduction was 79%, the curvature improvement 62%, and the pain reduction 100%.

Others had also used EMDA with Dexamethasone + Verapamil combination [21], also compared to the Lidocain effect alone [22].

EMDA application with Verapamil alone [23] was also effective.

Contrary to the new review of nonsurgical solutions to treat Peyronie's disease [24], hyperthermia was also applied with success for Peyronie's disease [25]. They studied 60 patients with Peyronie's disease, having a comparison between the application of Verapamil and Hyperthermia. The chosen cohort groups were identical in their main relevant parameters (Figure 1). Hyperthermia was applied for 20 minutes, twice a week for 5 weeks. A 2nd cycle was made after 1 month having 10 treatments. The control group received 10 mg injection of Verapamil once a week for 3 months. The Verapamil group had no real benefit of the treatment. There was significant relief of both subjective and objective symptoms in the Hyperthermia treated group, without any adverse side effects. The penil curvature decreased by 55.9% with Hyperthermia [25], while only 3.8% with Verapamil [22], and the plaque size decreased by 42.1% and by 2.2% with Hyperthermia and Verapamil, respectively (Table 2).

A similar controlled clinical study is in progress to repeat the results [26]. The clinical trial compares the only heat treatment and the treatment group is receiving a combination of Vitamin D and Testosterone injections additional to heat by infrared heating.

Learning from the failures of many applied conventional treatments and seeing the possible applicability of the heat and the electric field based on current knowledge of the pathophysiological mechanisms involved in the formation of plaque, we developed a new device for the treatment of the penis disorders, including Peyronie's disease.

The collected evidence based research data indicate inflammation processes, like the "primum movens" of the cascade process of healing that includes the inflow of platelets, macrophages, and mastcells.

Subsequently it releases numerous substances: interleukin, tubular necrosis factor (TNF α), platelet-derived growth factor (PDGF), and transforming growth factor (TGF β), which trigger the scarring process by means of the proliferation of fibroblasts, differentiation of myofibroblasts, the deposition of collagen tissue, and the transformation of "stem cells" of the tunica albuginea in osteoblasts [27, 28]. On this basis Peyronie's disease plaque is more similar to keloids than to scars. About the formation of keloids it is important to note that at the wound site there is a production of heat shock proteins in response to an inflammatory process in order to modulate the intensity of inflammation and the synthetic responses to stress toward the healing of the wound.

Overexpression of HSPs can, however, lead to an increase in the inflammatory process and an uncontrolled synthesis process.

In some cases, genetic factors, individual predisposition, and physical factors (a particularly aggressive inflammatory process) can play an important role in the formation of keloids.

Within the keloid tissue, compared to normal tissue, an high expression of HSPs 27,47 and 70 has been reported. This increased expression can induce an exaggerated proliferative effect (HSP 70) and a production and deposition of matrix (HSP 27, 47).

In Peyronie's disease, regulated expression of certain proteins such as the alpha-actin, beta-catenin, and heat shock proteins (Hsp47), which are established components of fibrosis and wound healing [30] have been noted/recognized.

It is a benign tumor [31], in which

- (1) plaque fibroblasts are immortalized cells;
- (2) plaques and normal tunica albuginea have chromosomal differences;

- (3) induced immune response by the plaque fibroblasts and their products;
- (4) mitochondrial dysfunction is observed in plaque fibroblasts;

In coherence of the above conditions it is not a surprise that apoptotic processes can play definite role in plaque formation and its elimination. There is a finding that apoptosis activation [32] albuginea plaques occur. This, at least, in part is realized via an extrinsic pathway [33].

Peyronie's disease is known to be associated with Dupuytren's disease [34]. Main characteristic of the Dupuytren's disease is palmar aponeurosis hyperplasy and contraction which leads to finger flexion contracture [35]. Peyronie's and Dupuytren's diseases have common pathophysiology [36].

The imbalance between proliferation and apoptosis, producing malignant growth, was thus confirmed for fibrosarcoma, but not the same form for Dupuytren's disease, [37], because this is benign as well, similar to Peyronie's disease.

However both can be regarded as system diseases, [38], because the immune system is involved.

It was a hypothesis that periostin, secreted by Dupuytren's disease cord myofibroblasts into the extracellular matrix, promotes the transition of resident fibroblasts in the palmar fascia toward a myofibroblast phenotype, thereby promoting disease progression [39].

2. Method

The traditional hyperthermia had good benefit in treatments of Peyronie's disease; however it was controlled with the only single thermodynamic intensive parameter, with the temperature.

Oncothermia is a special hyperthermia [40], working on the action of the modulated electric field in the locally treated lesion. It has long experience in the oncology [41]. Its idea to use the benefit of the electric field makes it feasible to apply it for Peyronie's disease, unify the effects of EMDA, and heat in a specialized treatment.

Our objective is to perform a pilot study with the application of a special (adaptively modified) kind of oncothermia for Peyronie's disease, called Androtherm.

The method is based on the paradigm of the energydose control, replacing the single temperature concept [42– 44]. With this approach the oncothermia returned to the gold standards of the dose concepts in medicine: instead of the parameter, which cannot be regarded as dose (the temperature does not depend on the volume or mass), Oncothermia uses the energy dose, measured in kJ/kg, like Gy is used in the radiation oncology to characterize the dosing of the treatment. The requested job is to change the structure of the target, for which a definite energy dose is necessary [45].

The historical energy-dose-like control (temperature multiplied by its application time) is physically incorrect and operates with an overall energy average in the area, instead of a directed and well-measurable energy dose (measured in kJ). So these points are realized, and this procedure is



FIGURE 2: The electrode setup for penile treatment of Peyronie's disease.



FIGURE 3: The fit of the electrode on the penis during the treatment.

called modulated electrohyperthermia or oncothermia [46] and it is specialized now for andrology. It is a well-designed capacitive coupling on 13.56 MHz free frequency [47]. The presently applied radiative hyperthermia device is operating with a frequency one order of magnitudes higher than oncothermia does. The process is controlled by the changes of the impedance and by the absorbed energy, which are both accurately measured. It was developed for Peyronie's disease, concentrating the plaque dissolution, using all the experiences and achievements from the past 20 years. The Androtherm device is the product of Onchotherm GmbH, Troisdorf, Germany (Figure 1).

A set of special electrodes were developed for the best performance (Figure 2).

2.1. Protocol of Treatments. The proposed and tested protocol of treatment was made for 30 min two times a week, overall treatment number was 30 treatments/case in 3 cycles (10 sessions in each). One of the actual treatment setup is shown in Figure 3.

The treatments were used only as monotherapy, studying first the effect on the new method alone. All the patients were in advanced stages, and their symptoms were measured with standard methods.

The practical parameters to observe the expected changes were

- (i) size plaque,
- (ii) curvature of the penis,



FIGURE 4: Patient with an extreme curvature of the penis, before and after treatment.

TABLE 1: The plaque size reduction after Androtherm. The difference between the observed means is significant for P < 0.01.

Plaque size	Androtherm		
	Before	After	
Number of patients	22	22	
Average plaque size (mm)	12.3	6.2	
Standard deviation	7.2	4.3	
Significance level (P)	0.0016		

TABLE 2: Results on curvature. The difference between the observed means is significant for P < 0.05.

Penile curvature	Androtherm		
	Before	After	
Number of patients	15	15	
Average curvature (deg)	35.8	23.7	
Standard deviation	16.3	10.1	
Significance level (P)	0.021		

(iii) pain reduction at erection,

(iv) erection function.

3. Results

Thirty patients were studied: one of them was withdrawn; 5 patients have not completed the whole course of treatments; at present we have the final data of 22 Patients. The age distribution was shifted to elderly categories (between 65 and 70 years). The plaque size decreased, after the treatments, for about 50%; Table 1 shows the plaque size before and after Androtherm application.

We evaluated the extent of the plaques with ultrasound scans before and after the treatments.

TABLE 3: Improvement of the average IIEF score before and after
treatment. The difference between the observed means is significant
for $P < 0.05$.

Erectile dysfunction	Androtherm		
	Before	After	
Number of patients	10	10	
Average IIEF score	46.1	57.5	
Standard deviation	13.5	9.5	
Significance level (P)	0.043		

We estimated the curvature degree of the penis, during erection, before and after treatments, with a goniometer (Figure 4 shows our method of measurement in a patient with a curvature, very noticeable).

Only 15 patients had curvature of the penis during erection; Table 3 shows the average of curvature of the penis before and after Androtherm treatment.

Ten patients reported the coexistence of an erectile dysfunction which was evaluated by the administration of questionnaires IIIEF 5, 15, before and after the treatments. Table 3 shows the improvement of sexual performances obtained after treatments with Androtherm.

All patients who presented with pain during erection reported the complete disappearance of symptoms.

4. Conclusions

Based on the results obtained, we can say that the Androtherm can be considered a feasible promising new therapy for the treatment of Peyronie's disease. The study is still in progress and the results of new cases in treatment confirm the validity of the method.

The data until now obtained could pave the way for new therapeutic approaches for others diseases of the penis.

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