

TRANSDERMAL TREATMENT OF EPF BY MEANS OF DERMOELECTROPORATION

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Summary

One of the ways of treating EPF (edematofibrosclerotic panniculitis) is to carry out cycles of intradermal mesotherapy involving the injection of simple drug cocktails with lipolytic and vaso-protective action. The authors decided to verify the possibility of administering the same drugs transcutaneously by means of dermoelectroporation. This method consists of the application to the skin of special-designed drug-delivery units that emit controlled, low-intensity electrical impulses, thus causing the opening of particular intercellular cutaneous channels (hydroelectric pores) through which the active molecules are transmitted. The following report provides the history of 23 cases chosen for EPF treatment of the lower limbs (trochanteric areas) with weekly application of a lipolytic and vaso-protective drug cocktail. The final results confirm the effectiveness of dermoelectroporation for the transcutaneous administration of drugs used for the local reduction of EPF and of localized adiposity.

Riassunto

Una delle strategie per trattare l' EPF (pannicolite edematofibrosclerotica) è di impostare cicli di mesoterapia intradermica somministrando miscele farmacologiche di sostanze con azione lipolitica e vasoprotettiva. Gli autori hanno deciso di verificare la possibilità di somministrare gli stessi identici farmaci attraverso la via transcutanea con l'uso della dermoelettroporazione.

Questo metodo consiste nell'applicazione sulla cute di uno strumento veicolante farmaci, appositamente progettato, che emette impulsi elettrici controllati e a bassa intensità, procurando l'apertura di particolari canali cutanei intercellulari (pori idroelettrici) attraverso i quali le molecole vengono trasportate.

Lo studio che segue raccoglie la storia clinica di 23 casi selezionati per il trattamento dell' EPF degli arti inferiori (area trocanterica) con applicazione settimanale di un cocktail a base di sostanze lipoli-

tiche e vasoprotettive.

I risultati finali confermano l'efficacia della dermoelettroporazione per la veicolazione transcutanea di farmaci utilizzati nel trattamento localizzato della EPF e delle adiposità localizzate.

INTRODUCTION

Edematofibrosclerotic panniculitis (EPF) is a degenerative process of the subcutaneous adipose panniculitis that results in a structural alteration of connective tissue. In addition to lymphatic venous insufficiency in the lower limbs, this condition is characterized by stasis of microcirculation in subcutaneous connective tissue, with the formation of intracellular edema. The presence of the latter leads to hypertrophy and hyperplasia of the collagen fibres that normally surround adipocytes, with subsequent vessel strangulation, alteration of metabolic exchanges and tissue suffering, as well as stasis of toxic catabolites. This process evolves into a fibrosis that soon becomes a fibrosclerosis, involving the formation of micro- and macronodules responsible for the generalized skin roughness known as "orange peel". Although there is a hereditary component in the etiopathogenesis of EPF, it is undeniable that conditions such as postural alterations, endocrine dysfunctions, weight increase, smoking, estroprogestogenic treatment, improper diet, etc., encourage its manifestation. One therapeutic approach to EPF that has proven effective is local intradermal treatment (LIT) (mesotherapy) with lipolytic, vaso-active, anti-edemagenic substances. This technique involves numerous microinjections with 4-mm long, 30-G needles in affected areas, with inevitable discomfort, such as: pain, redness, burning, possible microinfections, itchy red swelling lasting several days and micro-haematomas. With a view to eliminating and/or reducing these side effects, an alternative method was considered involving the non-injective transcutaneous passage of molecules, a technique known as dermoelectroporation (1). This technique derives from the well-known electroporation technique developed by American dermatologists in 1970. Since then, it has been significantly improved and, recently, biotechnologically refined, to the

extent that it has received FDA approval.

Method used for the administration of the drug cocktail

The transdermal administration of drugs is done by means of a preventive microdermoabrasion, the purpose of which is to lower the impedance of the skin, and by means of pulsed iontophoresis, with a waveform similar to that used in electroporation but with controlled, lower intensity in order to ensure penetration of the drug cocktail. It causes intercellular channels (known as hydroelectric pores) to open and remain open for a few seconds, enabling the passage of chemical substances and drugs.

The medical device using this method is the Ultrapeel Transderm Meso System (MATTIOLI ENGINEERING), which consists of three components:

- a disposable tip for the microdermoabrasion of pre-sterilized corundum crystals;
- a precision liquid-dispenser that distributes the drug cocktail at variable speeds (the dispenser we used distributed 0.5 ml/min.);
- a tip equipped with vibrating electrodes that emit electrical impulses from 1 to 5 mA (the impulse level we used was 4/5 mA).

Many studies have been reported in the literature for the administration of micro- (amino acid) and macromolecules such as hyaluronic acid (2) (3), collagen and lidocaine (4), heparin (5) (6) and even type-A botulin toxin (about to be published).

For this reason, it was our view that there were technical and scientific bases for using it in the treatment of EPF.

MATERIALS AND METHODS

23 female patients aged between 26 and 52 years (average age: 35) affected by second- and third-

degree EPF were selected. The exclusion criteria adopted were cigarette consumption (more than 10), current local or systemic pharmacological treatment and/or such treatment carried out within three months of the recruitment and other aesthetic treatments under way.

The patients were examined in upright posture to assess the presence of skin roughness, chromatic alterations (dyschromia, hyperpigmentation) of the skin, skin pallor, teleangiectasia and/or micro-varicosity or the presence of stretch marks. After palpation, in order to assess hypothermal variations in the areas concerned and the presence of fine granule micro-nodules at the lower levels, a thermographic examination was made of all the patients in order to determine the extent and seriousness of damage to cutaneous and hypodermal microcirculation and to determine precisely the extent of the EPF. All of the patients were found to be within second- and third-degree clinical and instrumental parameters. Digital photographs were taken in metrically graduated upright posture, anterior, posterior and lateral, pre- and post-treatment.

The areas treated were the trochanteric areas. The circumferences of these areas were measured in graduated centimetres in upright posture. The patients were subjected to LIT on the left side, with 4 -mm, 30-G needles, and to dermoelectroporation on the left side.

The drug cocktail, used on both sides, consisted of:

- in 11 patients: 1 ml aminophylline + 2 ml Lyndiaral + 2 ml Venon
- in 12 patients: 1 ml aminophylline + 1 ml L-carnitine + 2 ml Venon.

For the dermoelectroporation method, the drug cocktail, in 5-ml syringes, was released into the trochanteric cutaneous area by means of a variable-speed dispenser (0.5 ml/min.).

The patients were prohibited from having massages and/or lymph draining during the 72 hours following the treatment. They were also supplied

with a clinical diary in which they were asked to make note of any side effects or complications and to make a final assessment of the results.

RESULTS

The results were collated three months after the beginning of the treatment and were examined using subjective, objective and instrumental criteria.

From a subjective point of view, the patients did not refer to any complication or side effect from the treatment. They were provided with a quartile assessment scale (0 = no result, 1 from 0 to 25% improvement, 2 from 25 to 50% improvement, 3 from 50 to 75% improvement, and 4 from 75 to 100% improvement) to be completed independently by both the patients and the study personnel at the end of the treatment.

Overall, the results were satisfying: 13 4th level, 7 3rd level and 3 2nd level as far as the patients were concerned and slightly more critical as far as the study personnel were concerned (11 4th level, 9 3rd level and 3 2nd level). From an instrumental point of view, the final thermographic exam was repeated and showed a reduction in extent and seriousness of damage to the cutaneous and hypodermal microcirculation with a reduction of skin roughness and granularity on both visual inspection and palpation.

Comparative examination of the digital photographs showed reduction of skin blemishes, with improvement in the profile of the trochanteric line. The orthostatic measurements showed a metric reduction of approximately 3.8 cm in both areas, without significant statistical variation between the right side treated with dermoelectroporation and the left side treated with LIT.

Fig. 2 Before and After.

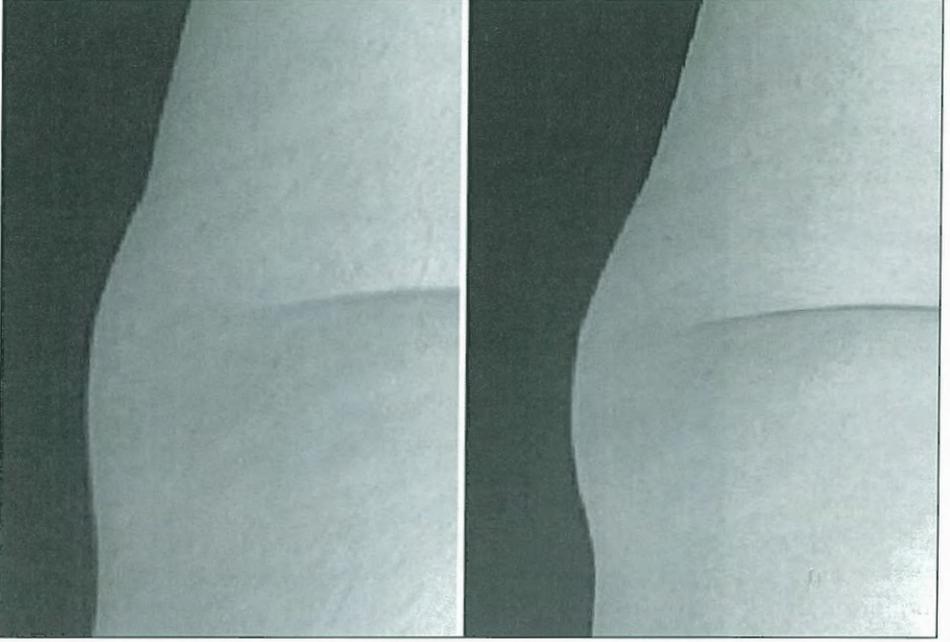


Fig. 1 Before and After.

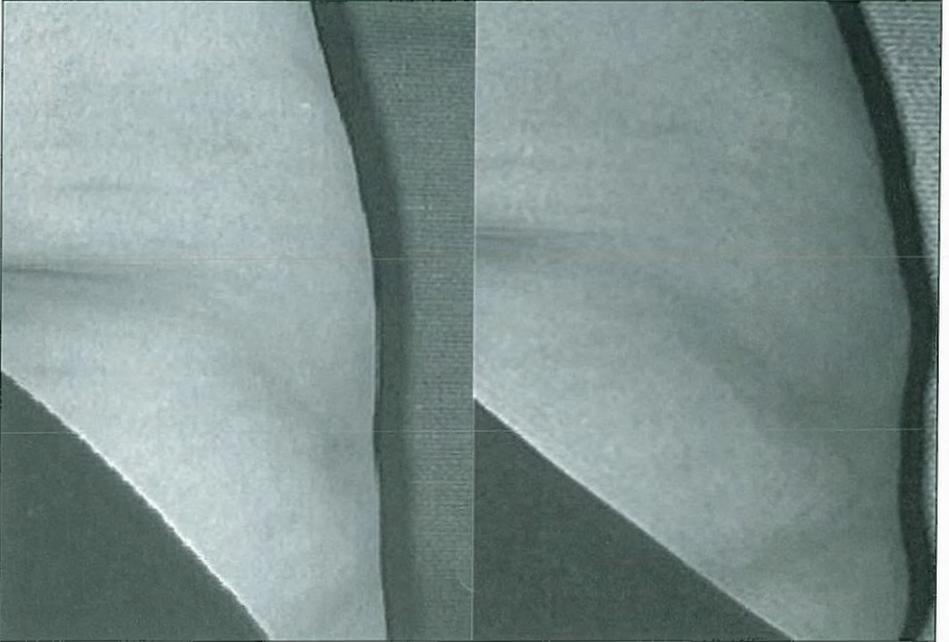


Fig. 4 Before and after.

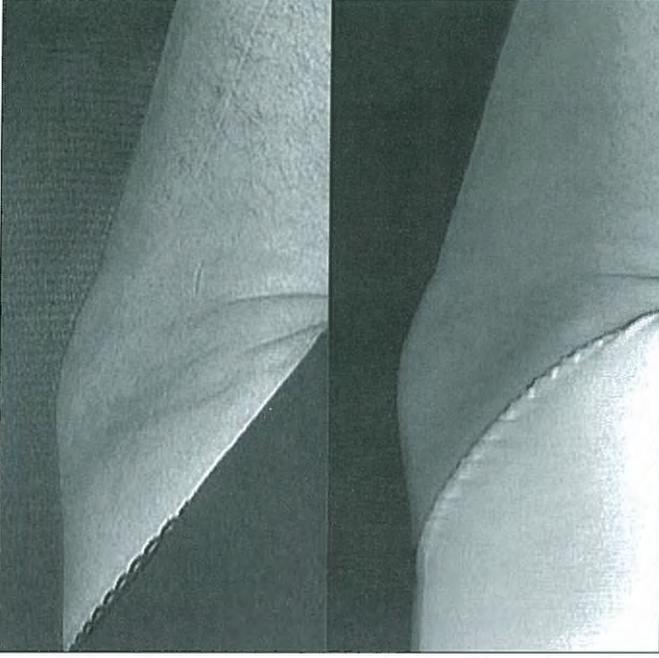
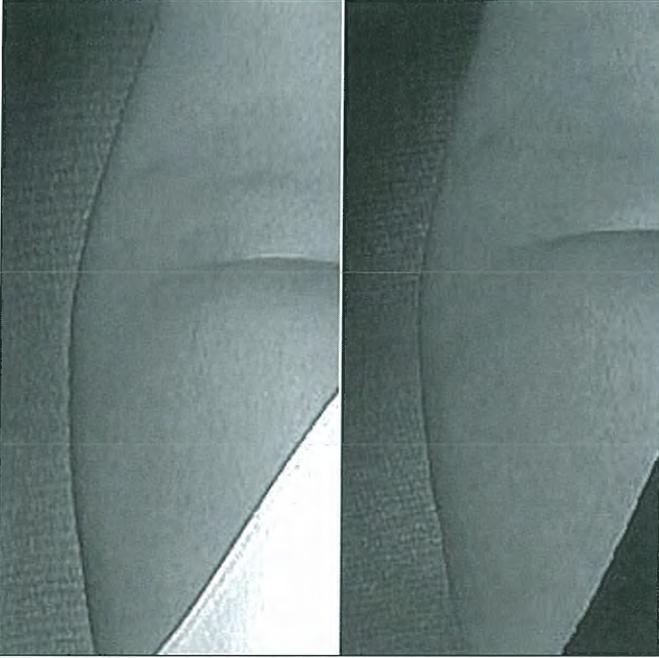


Fig. 3 Before and after.



DISCUSSION

At the treatment level, edematofibrosclerotic panniculitis (EPF), more commonly known as cellulitis, is a very demanding test-bench due to the multiple etiological factors. It must in fact be considered within the framework of complex metabolic disorder affecting the adipose tissue, the major defect of which is an increase in, and subsequent sclerosis of, the volume of adipocytes, associated with a cascade of combined, aggravating local complications. LIT is certainly the most common treatment used but it is not without side effects, including the pain of the microinjections and local erythema. Dermoelectroporation is an innovative technical alternative applicable to treating EPF. This study is the first observational study in the literature of its use. Dermoelectroporation is a method that exploits a discovery made by a number of American dermatologists in the early 1970s: an electrical impulse applied for a briefly over a sufficient period of time causes alteration of cellular-membrane polarization. The cellular membrane becomes more permeable to various molecules due to the opening of particular intercellular channels. The method has been perfected due to development of the technique and to further research, confirmed by more than 4500 international scientific studies published in the literature, and has led to the dermoelectroporation technique (Ultrapeel Transderm Meso System, developed by MATTIOLI ENGINEERING). This technique differs from other methods and from classical iontophoresis because of the characteristics of the electrical wave and of the low, controlled intensity (1-5 mA), which does not provoke the cellular lyses caused by high electrical intensity and which causes the opening of hydroelectric pores, that is, electrical "portals" through which biologically active substances can be made to penetrate. This is confirmed by recent studies, which have proven the passage of

micro- and macromolecules such as lidocaine (4), polydeoxyribonucleotide (7) and hyaluronic acid (2) (3).

The treatment strategy focused on aminophylline, given that it is recognized as the drug with the greatest lipolytic effectiveness, due to its ability to cause the breakdown of triglycerides into glycerol and fatty acids. Furthermore, phosphodiesterase inhibition promotes deactivation of cyclical adenosine monophosphate (cAMP) and prolongation of lipid hydrolytic activity. The addition of horse-chestnut extract (Venon) promotes microcirculation, which is often compromised due to the hypoxic reduction caused by adipomegaly. The innovative pharmacological approach was the use of L-carnitine, a substance identified in 1905 and synthesized from amino acids (methionine and lysine), and of which the RDA has not been established and the negative interactions of which with other drugs and vitamins is not known.

It is a natural constituent of cells, in which has a key role in the use of lipidic substrates occurs. The scientific premise for its use in this study is the fact that L-carnitine is the only vector by means of which fatty acids are able to cross the mitochondrial membrane and be sent for final beta-oxidation. In fact, in order for the fatty acids deriving from lipolysis induced by aminophylline to be demolished, they must move from the cytoplasm to the mitochondria.

This is favoured by the presence of L-carnitine, which enables the fatty acids activated (acylcoenzyme A) to cross the internal mitochondrial membrane and to be oxidized by means of the formation of acylCoA and insertion into the Krebs cycle. Normally, the L-carnitine added to the mesotherapeutic cocktail by means of LIT injection results in a marked burning sensation to the extent that the patient is unable to continue the treatment. With the DEP technique, this inconvenience is attenuated while the desired therapeutic effect is obtained. This is confirmed

by the clinical results obtained and which are essentially superimposable for the two techniques (LIT and DEP). DEP has been confirmed as a valid, alternative method for the transcutaneous passage of micro- and macromolecules and as an alternative to the injective method. It has been shown to be of particular value in pain treatment, physiotherapy, orthopaedics, rheumatology and sports medicine. But it is particularly its ability to cross the cutaneous and adipose layer that has opened up new possibilities for dermatological and aesthetic application, providing practitioners with a wide range of possibilities in the use of various molecules, including in association, as in the study presented.

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