



Mesotherapy: a bibliographical review

Mesoterapia: uma revisão bibliográfica

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Abstract: Intradermotherapy is a medical procedure introduced by Pistor in 1958 that consists in the application of intradermal injections of diluted pharmacological substances that are given directly into the region to be treated. There are reports of the use of intradermotherapy to treat painful diseases, skin diseases and unaesthetic conditions. Medical clinics have been recently offering the treatment of intradermotherapy, using the more popular name for this practice - mesotherapy.

There is only scant scientific information about this subject published in periodicals indexed on MedLine. Only a few states rigorously pursue this method. Most indexed publications about this subject deal with the complications of this technique.

Unaesthetic dermatoses have been a common complaint in dermatologic clinics, and it has become necessary to have scientific evidence to give to patients. Therefore, well-researched scientific studies about this technique are necessary to offer data to medical professionals that will clearly explain to patients both the benefits and the risks of these procedures.

A bibliographical review was conducted and we verified the need for new studies with adequate methods to confirm the benefits of intradermotherapy as used in dermatologic treatment.

Keywords: Injections, intradermal; Review; Skin; Therapeutics

Resumo: A intradermoterapia é um procedimento médico introduzido por Pistor, em 1958, e consiste na aplicação, diretamente na região a ser tratada, de injeções intradérmicas de substâncias farmacológicas muito diluídas. Esse método é capaz de estimular o tecido que recebe os medicamentos tanto pela ação da punctura quanto pela ação dos fármacos, e apregoa-se que sua vantagem é evitar o uso de medicação sistêmica. Há relatos da utilização da intradermoterapia para tratamento de doenças dolorosas, dermatoses e condições consideradas inestéticas. Atualmente, clínicas médicas oferecem esse tratamento, utilizando, porém, o nome mais popular para essa prática, mesoterapia. Há escassa informação científica sobre o tema publicada em periódicos indexados no MedLine e poucos estudos com metodologia mais rigorosa sobre a eficácia e o mecanismo de ação da via intradérmica. A maioria das publicações indexadas sobre esse tema versa sobre as complicações dessa técnica. As dermatoses inestéticas têm se tornado queixas frequentes nos consultórios dermatológicos, sendo necessário um embasamento científico para lidar com tais pacientes, os quais, muitas vezes, estão em busca das novidades mostradas através da mídia. Assim, há necessidade de estudos cientificamente bem conduzidos sobre essa técnica. Estes estudos deverão oferecer aos médicos elementos para esclarecer os pacientes sobre quais benefícios esperar e quais os riscos de tal abordagem. Desse modo, realizou-se uma revisão bibliográfica sobre o assunto e constatou-se a necessidade de novos estudos com metodologia adequada para a confirmação dos benefícios da intradermoterapia como ferramenta útil no tratamento dermatológico.

Palavras-chave: Injeções intradérmicas; Pele; Revisão; Terapêutica

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INTRODUCTION

Intradermotherapy is a medical procedure introduced by Pistor in 1958 which consists in the application of intradermal injections of pharmacological substances that have been diluted and which are given directly into the region to be treated.^{1,2}

The event that introduced the intradermotherapy technique is well-known. Pistor saw a patient with an asthma attack and administered intravenous procaine, hoping to obtain bronchodilation. Besides asthma, the patient had chronic hearing loss. The following day, the patient returned and told the doctor that after forty years of deafness, he was again able to hear the church bell, which was attributed to the injection he had received. The patient requested a repeat injection of the same substance, since his hearing had improved for only a short period. The doctor re-administered intradermal injections of this product into the mastoid region and the patient once again experienced temporary hearing gain. The doctor continued with injections of procaine in various patients and, in 1958, he published his conclusions in "La Presse Medicale," an article entitled "Exposé sommaire des propriétés nouvelles de la procaine local en pathologie humaine" (Review of new properties of topical procaine in human pathology).¹

In this article he described his experience in treating deafness, tinnitus, vertigo, presbyopia and headaches by using local injections of procaine. He supposed that the effects stood to reason because of the neurosensory stimulation caused by procaine, even though it had a short duration. Pistor believed that this therapy model based on intradermal injections was so important that it deserved its own name – mesotherapy – in view of the embryologic origin of the skin.

LITERATURE REVIEW

Despite the fact that this is the most well-known event in the history of intradermotherapy, one must remember that experiments conducted earlier came before Pistor's experiment. These experiments were mentioned by Rotunda and Kolodney in 2006 in a review article: in 1884, Koller, an ophthalmologist, related his experience with the use of local cocaine to manage pain. In 1904, Einhorn discovered a new anesthetic with a low risk of drug dependence: procaine. In 1925, Lerich applied intradermal injections in the intercostal spaces. In 1937, Aron published a study about an intradermal injection of a histamine solution and concluded that intradermal injections of whatever product, when given into a painful location, would have an analgesic effect.³

However, it was with Pistor that intradermotherapy received more attention, when he found-

ed the French Society of Mesotherapy in 1964 and the technique became known throughout the world.

In 1976, Pistor succinctly defined this technique with the following words: "A little volume, a few times, and in the right place." The founder of mesotherapy realized that these recommendations were empirical and based on his personal clinical experience. He affirmed the belief that larger doses do not improve clinical results, and that multiple punctures seem to be better than fewer injections.¹

Intradermotherapy has always been described in articles as an intradermal injection of highly diluted drugs, making it more suitable to be used this way. The dermis, therefore, started to be viewed as a location where products could activate dermal receptors and which would diffuse them slowly using the micro-circulation unit. However, these explanations seem to be repetitious of the citations of his predecessor, although they are always referred to in the same way in subsequent articles.^{1,2,4,5,6,7} The basic course of action of intradermal injections greatly varies from one study to another, and this may reflect a lack of methodological patterns which sustain mesotherapy. The articles commonly describe mesotherapy as consisting of intradermal or subcutaneous injections of a medical substance or a mixture of various products, called "mélange." Views about the injection of the needle into the skin, however, vary from one author to the other and are described as either being perpendicular or forming an angle of 30-60 degrees.⁷⁻¹³ There is, however, agreement between these authors that the needle should penetrate no more than 4mm. To reach this depth, it is necessary to use a Lebel needle (bevel 4mm long). The injections should be contained within the area to be treated and the distance between them varies between 1cm (at the minimum) and 4cm (at the maximum). The applications reported in the articles are done weekly or monthly, and the number of sessions reported vary from four to ten.^{2,7,13,14} It is suggested that small amounts be given per puncture.^{1,4,8,11,13,15}

Besides the traditional needle-syringe combination, more sophisticated and more expensive instruments may be used, such as the mesotherapy gun. These guns electronically inject multiple points and allow a controlled amount and depth of application.⁶ The disadvantage of this system is the difficulty in sterilizing the complete apparatus, because only the needle is disposable.

Of all the parameters described, it appears that the only aspect that has been scientifically researched is the depth of injections in mesotherapy. It has been shown that the intradermal route contains its own pharmacokinetics and, for this reason, it is recom-

mended that injections not be given with a depth greater than 4mm.¹⁶

A theory has been suggested, through a study of cintilography, standardizing mesotherapy.¹⁶ The authors of this research studied sixty patients with neuralgia and used radioisotopes with a product to be injected. The injections were given manually, with a depth of 1.5 to 2 mm. The researchers concluded that, at this level, the local activity of the product would last longer. The authors affirmed that there is a persistent reservoir with weak local diffusion in the dermis, but that the products injected into the dermis reach great distances (passing progressively through the circulatory system). Because of this evidence, the researchers concluded that intradermotherapy functions with two factors: the activity occurs over short distances (by stimulating dermal receptors *in situ*) and the activity occurs over long distances (by reaching other organs by way of circulation). In this way, the diffusion of mesotherapy products has been demonstrated. There is empirical evidence that explains the mechanics of the process of mesotherapy by stimulating both near and far receptors. This is the running theory accepted by the French Society of Mesotherapy.

On the basis of this theory, a concept has been developed which is often cited in intradermotherapy: the concept of meso-interface, which is the surface of contact established between the injected products and the tissue injected. The more fragmented the substance injected (multiple punctures with the smallest possible quantity), the greater the meso-interface and the greater the number of dermal receptors activated.¹⁶

In addition to this study by Kaplan and Coutris, others also have been conducted, evaluating the importance of the depth of injection in the diffusion of pharmaceuticals in mesotherapy.

In 1992, Mrejen conducted research to establish if there was a difference between the diffusion of products injected into the dermis at up to 4 mm or at 10 mm of depth. He concluded that a product injected up to a depth of 10 mm diffuses more rapidly and reaches the circulatory system more quickly, while at the same time lasting shorter than when given at less than 4 mm. Because of this study, it has been suggested that injections in intradermotherapy be given at a depth of 4 mm (so that the product will remain longer in its location).¹⁷

The more superficial the injection, the slower the diffusion, resulting in increased time in the upper dermis. Fifty percent of the amount of the pharmaceutical injected at less than 4 mm of depth remains at the point of injection after ten minutes, while only sixteen percent of the pharmaceutical injected at more than 4 mm of depth remain at the point of injection

for the same amount of time. Thus, it has been concluded that the diffusion of a product in intradermotherapy depends upon the depth to which it is injected. This difference can be illustrated with elimination curves: the superficial intradermal path would have a monoexponential elimination curve, while the deeper intradermal path would have a biexponential curve (quicker initial elimination, corresponding to an intravenous injection, followed by slower elimination in the dermis reservoir).¹⁷

However, as mentioned earlier, most of the research done on intradermotherapy in indexed journals relates to complications. The most feared and most often reported complication is mycobacterial infection, which requires months of treatment with multiple drugs and generally results in unaesthetic scars.¹⁸⁻³² Apparently, secondary infections described in the aforementioned works can be explained by inadequate asepsis before the procedure or by contamination of the product being used.

Other complications reported are: lichenoid eruption,³³ induction of psoriasis,³⁴ urticaria,^{35,36} cutaneous necrosis, systemic lupus erythematosus,³⁷ panniculitis,³⁸ acromia, atrophy and others.^{2,39-43} These complications are attributed to poor techniques or to the effects of the medication itself.

Tennstedt and Lachapelle (1997) further reported that neither alcohol nor oil-based substances are recommended for mesotherapeutic use because of the great risk of cutaneous necrosis.²

Initially, mesotherapy research addressed the treatment of painful illnesses. Therefore, research indicates the use of intradermotherapy with benefits in the treatment of tendonitis,¹¹ cervicobraquialgia,⁴⁴ muscular-skeletal illnesses,¹⁵ and oral and periodontal pain.^{8,45} A random study has been conducted comparing the efficacy of mesotherapy and laser treatment for deep, sharp lumbar pain with dysfunctional sacroiliac, with positive results for the injections.⁴⁶ Another report indicates that pain was adequately controlled by substituting one session of mesotherapy for anti-inflammatory prescription for post-operative dental surgery.¹⁰ A review article cites mesotherapy as an alternative to treatment for joint pain.⁹ These studies have one fact in common - the presentation of intradermotherapy as an alternative to pain therapy - and this indicates the need for more research about this treatment.

In 2001, indexed studies began to appear in MedLine regarding the use of intradermotherapy for unaesthetic dermatoses.

There are reports of lipolytic injections (deoxycholate or phosphatidylcholine) being given subcutaneously, in the name of mesotherapy, to try to diminish the layer of fat in areas such as the abdomen, infe-

rior eyelids, neck, buttocks or thighs.⁴⁷⁻⁴⁹ Some studies have been revised regarding the role of mesotherapy in gynoid lipodystrophy⁵⁰ and others regarding the role of mesotherapy lipolysis.^{3,6,51} These revisions offer the conclusion that, theoretically, a subcutaneous injection of specified products can function, but they lack indexed scientific publications on which to base this technique.

In 2004, Rotunda *et al.* published a study in which researchers injected two main components of a lipolytic product (phosphatidylcholine and sodium desoxicholate) used for subcutaneous injections. With the use of pork fat tissue, they concluded that the active ingredient of the product is sodium desoxicholate and that this acts as a detergent, causing unspecified lise of adipocyte cell wall.⁵² In 2005, Rose and Morgan published a study demonstrating anatomical pathological exams of biopsies from one patient after treatment with phosphatidylcholine and sodium desoxicolato. Histology demonstrated inflammation and necrosis in the adipose tissue.⁵³

Conceptually, it is argued that if the technique is mesotherapy, then the number of punctures and the amount injected subcutaneously should not correspond to the traditionally recognized methods as specified by intradermotherapy. Even though subcutaneous injections fall under the definition of mesotherapy, as subcutaneous tissue is also derived from the mesoderm, larger doses and a smaller number of puncture points will not yield the same results as claimed by Pistor, the founder of this technique.³

In 1992, also in an unindexed publication, Aumjaud recommended organic silicon for intradermal use in age wrinkles and skin with rhytids and photoaging. The study used organic silicon associated with other substances, and the author did not mention any scientific study that supported his recommendation, but instead spoke of his own experience.¹²

Maya, in a review article published in 2007, cited organic silicon as an intradermal medication able to stimulate the synthesis of collagen.⁷

Food rich in fiber, such as vegetables and whole grains, is a major source of silicon in the diet. Doses up to 50 mg per day of organic silicon supplements did not show any collateral effects.⁵⁴

In 2007, a study published in an indexed journal histologically compared the skin of women with moderate photoaging submitted to intradermal injections of salicylate silanol and physiological solution. The authors analyzed the density of collagen fibers and elasticity in the dermis injected with salicylate silanol in relation to the density of fibers in the dermis that received a physiological solution. They also evaluated the texture of the dermis that received salicylate

silanol in comparison with the dermis that received a physiological solution. Intradermotherapy with organic silicon increased the number of collagen and elastic fibers in the dermis and improved the texture of collagen on the side that received silicon.⁵⁵

The conclusions of the study on intradermotherapy are still pending. The study by Herreros *et al.* (2007) is, as far as the authors can tell, the first work with a rigorous method published in an indexed medical journal and which 1) evaluates the histological consequences of mesotherapy procedures, 2) demonstrates a significant increase in the number of collagen and elastic fibers, and 3) shows improvement of the dermal texture after intradermotherapy. In spite of using women with moderate photoaging, it was not the purpose of this study to evaluate intradermotherapy as a treatment for this condition. The decision to use skin with photoaging in this study was made because an earlier study had been published suggesting the use of intradermotherapy with organic silicon in women with this condition. Still, the results of this study suggested that women with only a small amount of elastic fibers were those who gained more fibers in the underarms that received silicon. This was further confirmed by Spearman's rank correlation coefficient - women with fewer elastic fibers in their underarms who received physiological solution showed an increase in the number of elastic fibers on the side with silicon. The authors were able to separate the effects of puncturing from the effects of mesotherapy medication. Traditionally, it had been declared that the therapeutic effect of this technique was a result of combined medication and stimulation by needles and that the effects of both could not be distinguished. Injecting organic silicon into one side and physiological solution into the other and obtaining an increase in the number of fibers on the side injected with silanol proves that the effect of silicon is more significant than that of puncture.⁵⁵

More than three years since this study was concluded, there have not been any complications in the volunteering women.⁵⁶

As mentioned before, a previous study has been published in an unindexed periodical describing the benefits of mesotherapy for gynoid lipodystrophy. However, the author used a mix of products and his criterion to evaluate improvement was the loss of measures (clinical evaluation and size), which makes a rigorous analysis difficult.¹⁵ One can question if the loss of measures is adequate to evaluate gynoid lipodystrophy and also the possibility of evaluating a treatment based on a combination of products, since it would be difficult to determine which product is responsible for the result. Park *et al.*, 2008, could not demonstrate the effectiveness of mesotherapy on body

contouring using computed tomography scans to measure the cross-sectional areas and thickness of fat injected with a specific solution.⁵⁷ Lacarrubba *et al.*, 2008, conducted a preliminary study to evaluate mesotherapy for skin rejuvenation and assessed the subepidermal low-echogenic band through ultrasound with cross-sectional B-mode scanning after multiple intradermal microinjections of hyaluronic acid salts weekly for four weeks. They showed that this could be an effective treatment for skin photoaging.⁵⁸

Brown, 2006, stressed that, to date, the effects of mesotherapy have not been scientifically evaluated. He pointed that there was no dosage standardization and no treatment protocol.⁵⁹

The only previous, more adequate, methodical work is the already cited study by Amin *et al.*, 2006.¹³ In this study, the authors discovered clinical benefits of mesotherapy for the treatment of facial photoaging in four monthly sessions and an increase in collagen in the treated area, which was evaluated through a zone of repair. However, there was not a statistically significant increase. Although the methodology for evaluating the results was good, the technique developed by the authors has been criticized. It is unknown what product was used, although they have declared to have applied a mixture of hyaluronic acid and "multivitamins." Besides this, the number of sessions

(four) and the time between the last application and the biopsy (two months) were different from those of the study by Herreros *et al.*, 2007 (10 weekly sessions and biopsy two weeks after the last session).⁵⁵

The conclusion of this study about silicon and intradermotherapy induced the use of silanol to treat atrophy scarring in a certain patient. She was treated with doxycycline for atypical mycobacteriosis that occurred in the locations of application of hydrolipoclasia by using ultrasound. From a clinical perspective, the results were partially satisfactory, and the patient was sufficiently satisfied as she chose not to undergo corrective surgery.⁶⁰

Similarly to Atiyeh *et al.*, 2008, we concluded that until further studies are conducted, patients considering mesotherapy for cosmetic purposes must be aware that the substances currently being injected have not been thoroughly evaluated for safety or efficacy.⁶¹

CONCLUSION

Since there are few indexed studies about the use of intradermotherapy and so many about its complications, it is only natural to distrust dermatologists in relation to this technique. More adequate methodological studies need to be conducted so that the true value of intradermotherapy with useful procedures in the practice of dermatology can be demonstrated. □

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