Original article

What is mesotherapy? Recommendations from an international consensus

Summary
The Italian society of mesotherapy, after a national consensus, carried out an international web-based consensus by the Delphi method. Our objective was to clarify the role of mesotherapy, its advantages, limitations, and correct use in clinical practice with multidisciplinary experts. All the experts approved the final recommendations and mesotherapy has been redefined as a minimally invasive technique that consists of the introduction of small amounts of pharmaceutical substances with micro deposits in the surface layer of the skin. The slowly injected compounds diffuse into the underlying tissues and produce a drug-sparing effect compared to the parenteral route. Used properly, this technique can be useful in some clinical indications.

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In 1975 the Italian Society of Mesotherapy began to validate mesotherapy with preclinical studies to establish the pharmacokinetics of active compounds injected intradermally[1-3]. Numerous clinical trials were conducted to verify the efficacy and tolerability in several clinical conditions with localized pain[4-35]. In the field of analgesia it was assumed that mesotherapy could act through two action mechanisms, the first generated by the local pharmacological activity of the drugs used, the second, supported by mechanical stimulation produced by the needles, with activation of local receptors and segmental reflex effects[36]. On the basis of these results, patient-selection criteria have been developed with algorithms for managing localized pain[37]. The possibility of administering drugs that act locally with mesotherapy has also stimulated studies to assess the effects on the signs and symptoms of chronic venous and lymphatic insufficiency[38-42]. Now defined as a minimally invasive technique, mesotherapy is based on microinjections of active ingredients into the surface layer of the skin corresponding to the area to be treated. This "micro deposit" gives rise to a slower release of the drug into the surrounding tissues compared to parenteral administration,[43] therefore with the possibility of obtaining two advantages. On one hand, a lower dose of active compound can be used, on the other, a rapid onset and prolonged action duration can be achieved.[43] These benefits are now also well

exploited by intradermal vaccines that use smaller amounts of antigens than with subcutaneous administration[3,44-46].

Over the last decade in several countries there has been a growing interest in mesotherapy applied to aesthetic medicine, as highlighted in publications worldwide[47-64]. However at the same time some adverse events have also been reported, many caused by incorrect application of the technique (often it is not possible to trace the compounds used), application by non-qualified personnel or lack of compliance with the minimum asepsis standards[65-92]. For these reasons many Authors have suggested the need for greater scientific evidence[93-97]. In order to facilitate a broad international agreement, the Italian Society of Mesotherapy have therefore suggested that international experts reassess their official position as a new starting point for a global standing on mesotherapy.

Methods

A web-based questionnaire was available from 20 December 2013 to 31 January, 2014, both for national and international experts. Each expert was asked to answer the questionnaire and attach scientific documents to support their position. All replies were collected and sent to an independent steering committee for validation, with a second discussion in the case of further clarification being necessary. The recommendations that have already been approved in Italy were proposed for a new validation at an international level; however the worldwide experts were also free to propose new recommendations.

The steering committee has submitted the final document to impartial experts for a final review and publication of the recommendations.

Results of the international consensus

The steering committee decided to divide the indications of mesotherapy into two main areas. The first included those based on relatively broad findings, where it was possible to suggest their use in clinical practice. A second area included those based on weak scientific findings where the large-scale use is not yet recommended. Rational, technique, and indications were discussed by all experts.

During the discussion it was stressed how contraindications for mesotherapy exist in some subgroups of patients, such as those under the age of 18. Despite previous preliminary clinical data suggesting some benefits[98-100], these patients have not been included in large clinical trials and therefore they cannot be considered for a routine treatment. It should also be noted that pregnant women are not enrolled in drug trials. Therefore, in these cases mesotherapy cannot be recommended in clinical practice with drugs not yet approved for this technique.

Consensus on the rational and technique

Both, rational and recommendation on the technique listed in Tables 1 and 2 reached a level of firm agreement (100% of consent). It was pointed out that mesotherapy requires clinical and pharmacology experience, therefore it must only be performed by medical personnel able to make a diagnosis and evaluate the risk/benefit ratio. In selecting patients to be treated physicians must be aware of the advantages and disadvantages of mesotherapy compared to other therapies, and inform the patient of potential adverse events in order to obtain informed consent for the proposed treatment. Experts are all in agreement about how to perform the technique. In fact, they recommend only one drug in the syringe to prevent the risk of drug-drug interactions, unless clinical data are available confirming the safety achieved with ad hoc studies, or when active substances are already prepared in the same vial by the pharmaceutical industry and tested with trials performed in compliance with good clinical practice[42]. However, the practice of using different syringes (and injecting different drugs in separate locations) remains the safest technique. In addition, it is highly recommended to take every precaution to avoid bacterial contamination by performing mesotherapy in a medical environment and using single-use sterile materials.

Consensus on the pain area

Recommendations to apply mesotherapy to manage symptoms other than pain were also approved with >100% consensus (Table 2).

Experts in the pain area agreed that the administration of NSAIDs (or muscle relaxants or anesthetics) by mesotherapy represents an alternative therapeutic strategy to the systemic administration in obtaining pain reduction and facilitating rehabilitation.

When recommended in managing painful syndromes, mesotherapy should be part of a comprehen-

Table 1. The table shows rational and methods to apply the technique.

Rational and technique
Mesotherapy is a technique based on the administration of pharmaceutically active substances in the upper layers of the skin
It requires clinical and pharmacological expertise and must be initiated by physicians after a proper diagnosis
It can be proposed when there is a favorable risk-benefit ratio
It should be considered (in clinical practice and in clinical research) as a therapeutic option, in particular if others standard therapies are not available for the same indication
If it is used for indications without evidence of efficacy and tolerability it should be conducted in accordance with the rules of Good Clinical Practice (protocol, ethical committee, etc.)
Physicians should report on pros & cons of using this technique compared to other treatment options (if any) to allow the patient to make a valid decision (informed consent) in all indications mesotherapy is proposed
Potential adverse events should be reported to the patient and the measures that will be implemented to reduce the potential risk
Also injected substances must be disclosed to the patient because he can refer to other doctors when needed (occurrence of adverse effects, pharmacovigilance, etc.)
A single drug is recommended in the same syringe (unless there is documented evidence on the tolerability and efficacy) see muscle relaxants and anti-inflammatory compounds or some active substances already prepared in the same vial by the pharmaceutical industry
Mesotherapy should only be administered in a medical environment using sterile single-use syringes and needles, according to accepted standard hygiene precautions
Every precaution should be taken to avoid the contamination of the material used to apply mesotherapy. Gloves are mandatory

Table 2. The table shows recommendations to apply mesotherapy in pain medicine.

Specific recommendations for the use of mesotherapy in localised pain
Mesotherapy is indicated for the treatment of certain types of localized pain and must be integrated into a comprehensive plan of care for each patient (tailored therapy)
Before applying the mesotherapy, it is strongly recommended to diagnose the type, location, and possible causes of pain, and to measure the intensity by a validated scale
When mesotherapy is an option for the treatment of certain types of osteo-articular musculotendinous, and post-traumatic pain, it should not exclude the synergy with other therapies (physical, instrumental or pharmacological) and the patient's preference about the proposed plan of care
When the systemic route of a drug is not recommended and the painful symptoms is localized mesotherapy can be considered as the first choice to reduce the systemic impact of drugs, as in the case of NSAIDs (which can be administered by lower dose and less frequency with mesotherapy compared the systemic route)
Clinical report is strongly reccommended to collect data (diagnosis of pain, therapies, and results)

sive treatment plan, and its efficacy and tolerability should be assessed at every follow-up. Mesotherapy can provide clinical benefits in many painful conditions when other therapies are not effective or cannot be applied, or when we want to achieve a synergy between the various therapeutic strategies, or obtain a drug-sparing effect[37,43]. When the systemic route is not recommended and the painful symptoms are localized, mesotherapy can be evaluated as first choice to

Table 3. The table shows recommendations to apply mesotherapy in aesthetic medicine.

Specific recommendations for the use of mesotherapy in aesthetic medicine
Mesotherapy is a valid method to pharmacologically treat Chronic Venous Linfatic Insufficiency and its consequence edema fibro sclerotic pannicolopaty (cellulite)
Mesotherapy is a valid method to treat facial skin conditions (scars, aging)
A clinical/psychological profile of the patients is recommended before beginning mesotherapy for aesthetic treatment and patients should be clearly informed of the realistic benefits
Mesotherapy used for esthetical reasons should be applied by physicians with expertise in the aesthetic field

reduce the systemic impact of drugs and offer the benefit of a lower dose and a lower frequency compared to systemic therapies[37]. Experts in pain area have also suggested an algorithm that allows for evaluating the efficacy and tolerability at each follow-up and they strongly recommend recording all the parameters on the medical chart to enable a global assessment of pain, such as diagnosis, intensity, location and duration of pain, as well as the technique used to apply mesotherapy (figure 1).

Consensus on other indications

Agreement was also reached regarding the management of the signs and symptoms of chronic venous lymphatic insufficiency (CVLI), even when there are alterations in the subcutaneous tissue (cellulite) [38-42]. The inoculation of medical devices for aesthetic purposes also obtained consensus. In fact, the injected materials approved by the regulatory bodies in the US, including substances that are absorbable (collagen, hyaluronic acid, calcium hydroxylapatite, poly-L-lactic acid)

Figure 1. The figure shows an example of scheduled treatment for a localized pain. NRS=Numerical scale rate.

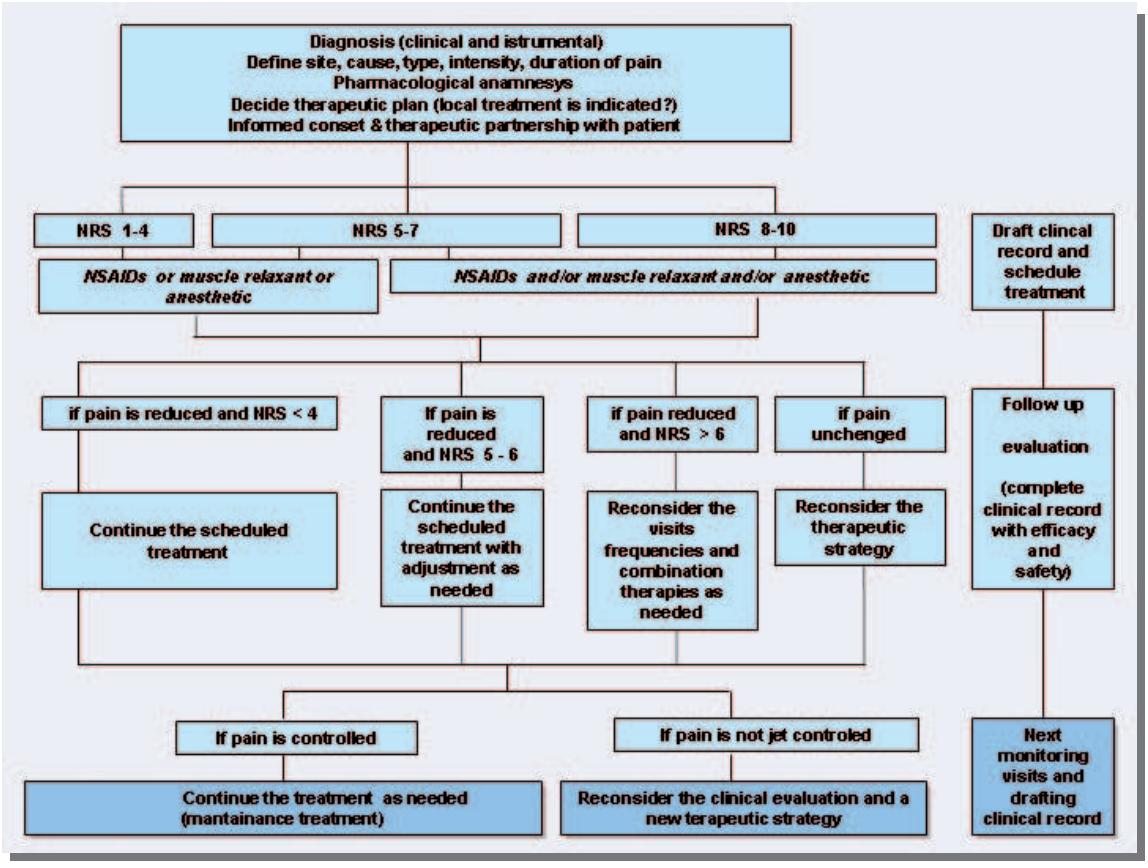
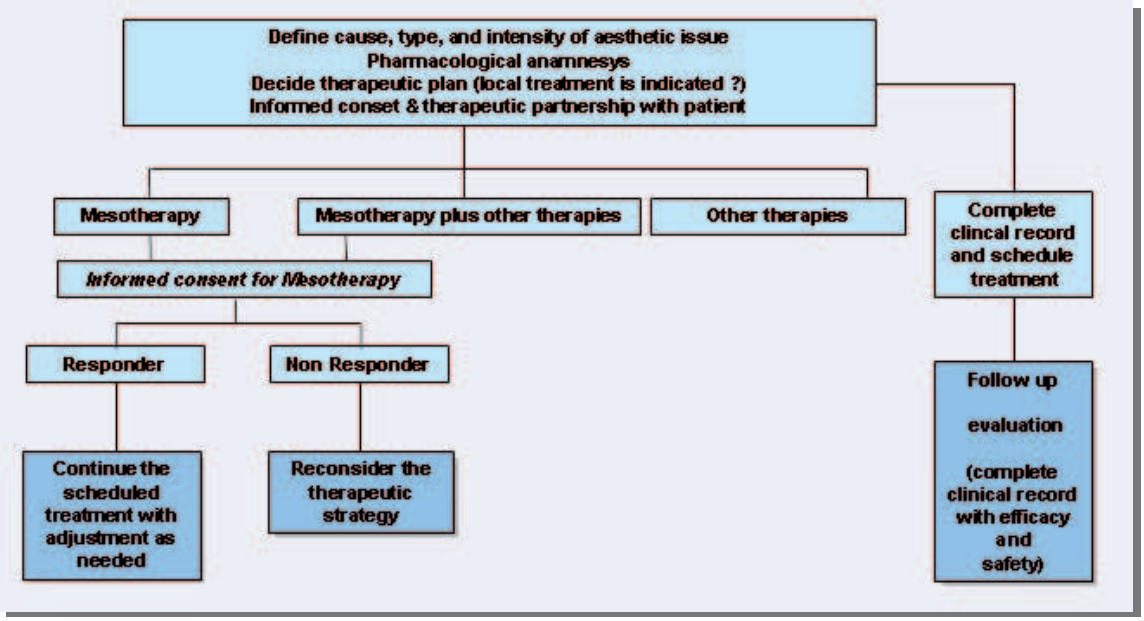


Figure 2. The figure shows an example of scheduled treatment for aesthetic clinical condition.



or non-absorbable (polymethylmethacrylate beads), are now commonly used in several countries[47]. However, some experts have suggested that the active ingredients available for this purpose should be adequately tested before being proposed for large-scale use. Experts have suggested an algorithm to approach patients with clinical problems with aesthetic aspects (figure 2).

Discussion

It has been pointed out how mesotherapy is a minimally invasive technique that consists of pharmaceutical products (or other bioactive substances) administered in small quantities through multi-skin punctures, where the injection site corresponds to the area of the pathological condition. The indications for mesotherapy (table 4) are therefore determined by the indications of the active ingredient used and not by the technique itself. In fact, regulatory agencies do not approve of the technique, just the drugs used via a particular administration route. If a drug (or medical device) used in mesotherapy has been approved for different purposes (or for an administration route other than mesotherapy) it is considered off-

Table 4. The table shows indications recommended by experts.

Clinical indications	Consensus
Osteo-articular, musculotendinous, post-traumatic pain symdromes	S
Crhonic venous linphatic insufficiency (CVLI)	S
Edema fibro sclerotic pannicolopaty (cellulite)	S
Treatment of facial skin aging	S
Vaccination	S
Hair loss	W
Pregnancy	R
Lactation	R
Immunocompromised patients	R
Lipolysis	W
Obesity	R

S=Strong consensus due to clinical data available; W=Weak consensus due to lack of evidence even if some data suggests rational for local treatment; R=Rejected indication due to lack clinical studies in favour of safety and efficacy.

label. Therefore, we suggest studying the safety and effectiveness with a research protocol in GCP of an off-label compound before using it on a large scale.

Mesotherapy for lipolysis, for example, has not gained unanimous consent for a variety of reasons. In fact, the different compounds tested have produced preliminary results on small numbers of patients, none of which have been approved for this indication[101-105]. We are aware that in some countries many physicians (as well as non-medical personnel) use these substances (aminophylline, isoproterenol, forskolin, yohimbine phosphatidylcholine, deoxycholate and others, either alone or in combination) on the basis of a pathophysiological rationale, but we cannot fully judge how much we must inoculate, how deep, how often, for how long, and more importantly, the real benefit (medium-or long-term) and safety cannot be guaranteed for the patient. Also in the case of other indications, such as hair loss and alopecia, there are no studies that allow for defining a safe therapeutic value of the active ingredients proposed[106]. Some indications of mesotherapy have been tested since the seventies[43,96], while others have only recently been studied[38-42]. Therefore we cannot rule out that in the near future the number of drugs (and medical devices) to be used with this technique may increase. Some authors include both the intradermal and subcutaneous route of administration in the definition of mesotherapy[96]. However, the available evidence indicates that a more superficial administration produces a "micro-deposit" of the drug that is slowly released into the underlying tissues, as demonstrated in preclinical[1-3] and clinical studies[107,108]. More recently, it has also been demonstrated that the administration of a recombinant human FSH injected at a depth of 1-2 mm under the skin of the lower abdominal wall, instead of 10-13 mm, as in conventional subcutaneous injection, produced an extended absorption with persistently higher serum FSH levels for up to 360 hours[109].

Conclusion and final remarks from experts

This consensus was proposed to clarify the role of mesotherapy and to demonstrate that it is an inoculation technique of pharmacologically active compounds (and in some cases medical devices) that requires medical and pharmacological expertise. We consequently only suggest its application after a clinical diagnosis.

During the discussion, the scientific committee also identified a number of calls to action for health authorities, scientific societies, and physicians.

Health authorities should be aware that mesotherapy has a drug-sparing effect. In those countries where non-medical personnel use mesotherapy for aesthetic purposes, health authorities should alert citizens about the risks of accepting pharmacological techniques by non-medical personnel. In Italy, mesotherapy is recognized as a medical practice, this means that only a physician can perform it. We can argue as to whether a nurse can practice mesotherapy in the presence of a physician, but no more than that.

Scientific societies wishing to explore the use of mesotherapy in the field of aesthetics should offer algorithms for every area of application, in order to ensure standards to be evaluated over time. As already suggested, tools should also be proposed in local languages in order to ensure valid informed consent and facilitate physician-patient relationships[110-111]. This would avoid malpractice and, perhaps even some adverse events deriving from incorrect mesotherapy.

Physicians should be aware of the advantages and limitations of mesotherapy when selecting patients, and decide where and when not to suggest mesotherapy. We strongly recommend that if it is necessary to use off-label drugs, the choice should be made on the basis of previous scientific publications that demonstrate their safety and efficacy. As with any field of medicine, the physician must distinguish between clinical and scientific speculation. We could also argue that a patient who does not tolerate a cancer drug administered systemically, may experience benefits with mesotherapy (a lower dose administered locally, with a more prolonged effect and less side effects). However, decisions like this have to be screened by an ethics committee, according to the criteria of scientific research and medical science. As is always the case in pain medicine, this principle should also be applied in the field of aesthetics.

Author Disclosure Statement

The Authors declare that no conflicts of interest exist in relation to the contents of this article.

Compliance with ethics guidelines. This article in based on previously conducted studies. The Authors does not involve any new studies (on human or animal subjects).

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