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Evidence based recommendations on mesotherapy: an update from the Italian society of Mesotherapy

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Abstract

Introduction. Mesotherapy, also known as local intradermal therapy, widely used all over the world, is a technique used to inject substances into the surface layer of the skin. There are no international guidelines for the correct use of this technique and in many countries, it is still applied empirically without valid patient consent. The Italian society of mesotherapy has planned a study to assess the rationale and clinical applications based on current evidence.

Methods. An independent steering committee, based on the available scientific literature, has formulated a series of clinical questions. 21 experts responded by writing an evidence-based document. From this document 30 statements were obtained which were presented to 114 experts using the Delphi method.

Results. 28 statements reached a broad agreement on definition, technique, pharmacological rationale, indications and some crucial ethical aspects.

Conclusions. Although further studies are needed to establish the clinical role of this technique in each field of application, our statements recommend the correct application according to the needs of the individual patient in full respect of ethics. ***Clin Ter 2021; 172 (1):e37-45. doi: 10.7417/CT.2021.2278***

Key words: *mesotherapy, intradermal therapy, recommendations*

Introduction

Mesotherapy (local intradermal therapy - LIT) is known as a technique which, through multiple micro-dermal deposits of a substance, allows its slow diffusion in the underlying tissues and a prolonged effect (1). However, despite being widely known and applied in a large number of clinical conditions, an international standard has not yet been established in every area of application (2). In fact, some authors have reported different methods of application and a non-rational use of products that have induced adverse events and consequently criticism on the mesotherapy technique (3,4). Although the LIT has been defined as a medical act and the choice of the products to be injected must be made on the basis of a clinical rationale (1, 5), a guideline is essential to apply this technique in the real practice. Many questions need to be considered to properly select patients for this type of administration. In this regard, the Italian Mesotherapy Society designed a scientific review with the aim of approving the definition of LIT and establishing the standard for performing the technique, the reasons for considering it in clinical practice, clinical conditions in which it can be considered and, last but not least, the ethical issues. This review process aimed to produce recommendations for the

expert panel**

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safe application of mesotherapy in the individual patient's therapeutic path and to provide a correct interpretation of the technique to the decision maker of the health authorities. To achieve these goals, we assessed the available evidence through a process based on scientific integrity.

Materials and methods

A bibliographic research was conducted by an independent committee (ALA, CK, AT) with the keywords "mesotherapy" and "intradermal therapy" on Medline and Embase (last literature check April, 2020). Based on the literature and previous national and international consensus (1, 3, 5) the steering committee (MM, RD, PT, ME, DMR, TD) produced several questions. All questions were asked to a writing commission (21 experts) who replied with an evidence-based document. The document was discussed and corrected through multiple rounds with each author and when the final agreement was reached, the steering committee developed a series of statements. The statements were submitted to the writing committee, and after reaching full agreement, have been submitted to a vote of all the experts involved in the review process. We have involved experts in various disciplines (prevention, treatment, rehabilitation, clinical research), and coming from different care settings (university, hospital, home care, public or private assistance). The experts came from different geographical areas and foreign experts were also involved to get a wider international sharing.

To reach a global agreement we used the Delphi method. This method is a widely accepted and widespread process for reaching consensus of a large number of experts (6,7). It allows to eliminate the prejudice of personal conviction by using repeated exchanges of a recommendation until a broad consensus is reached (8). All the experts were invited to vote on the statements and the results were examined anonymously by the steering committee to eliminate group or interpersonal dynamics (9).

After reaching global consensus, an independent committee (GR, PEF, BB, FG) verified this final paper. Each member of the steering committee was selected on the basis of previous experience in clinical research and the ability to organize national and international consensus. All the experts involved in the process were selected based on the level of clinical experience, scientific recognition and geographical distribution. All participants declared any conflict of interest (even potential). The approval process lasted 12 months: two for the search and selection of the literature, one for the selection of experts; three to select the main questions and fill in the answers, 4 for approvals, 1 for voting and 1 for reviewing the final document. All process of approval is summarized in figure 1.

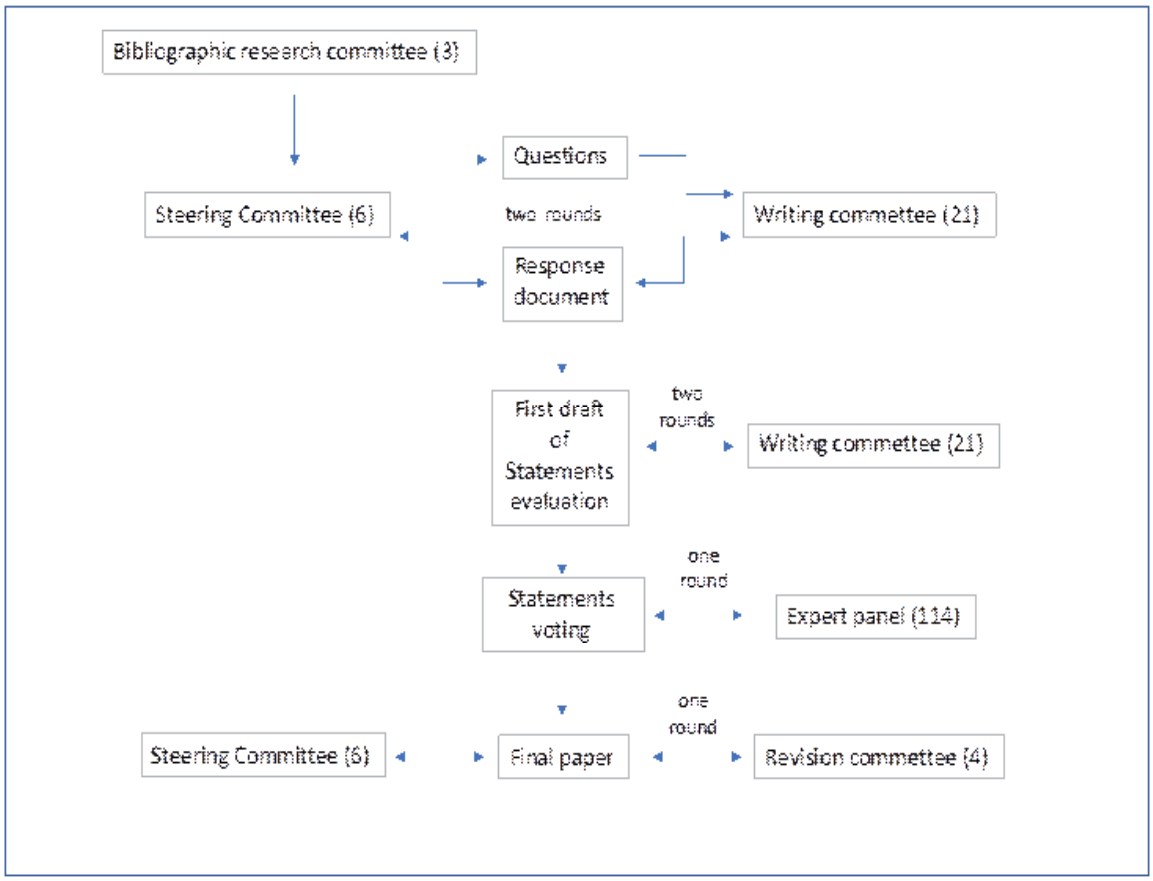

Fig. 1. The figure shows the statement making process according to the Delphi process.

The number of experts involved is indicated in parentheses.

Statistical analysis

The results of the analysis obtained using the Delphi method were expressed as a percentage of experts who voted on a 5-point Likert scale (1 = disagreement; 2 = somehow disagree; 3 = neither agree nor disagree; 4 = somehow agree; 5 = agree).

Agreement on each statement was reached if the percentage was > 70% established before the vote (10, 11). Consensus was considered if either the sum of answers 1 and 2 (negative agreement), or 4 and 5 (positive agreement) exceeded 70%, as described in previous studies with this method (12). If a statement exceeds 70% of negative agreement is rejected. Statements that exceed 70% of agreement will be classified as strong (level 1), those that do not reach the cut off will be considered weak (level 2), or will be rejected if the percentage of negative votes will be greater than 70% (level 3). Mean ± SD for the rating of each recommendation was also calculated. Italian experts assessed the statements in Italian, while experts from other countries assessed them in English (the English translation was validated by the task force to avoid different linguistic interpretations). The term "we recommend" has been used only for the level 1 if the benefit of the statement balances the risk.

Results

Overall process

114 experts, of which 15 from other Countries (Austria, Belgium, Colombia, France, Germany, India, Israel, Mexico, Spain, Switzerland, Tunisia, Turkey, Venezuela) were involved. The experts involved in the review process represent several areas of medicine (anesthesiology, clinical pharmacology, dentistry, dermatology, endocrinology, esthetic, forensic medicine, general medicine, immunology, internal medicine, neurology, oncology, orthopedics, pain medicine, palliative medicine, pediatrics, physiatry and rehabilitation, psychiatry, rheumatology, sports medicine, surgery, urology). Based on the responses received from the writing commission the steering committee identified 30 statements divided into 5 main areas: definition (1-4), rationale (5-6), technique (7-10), clinical pharmacology (11-16), areas of application (17-23), and ethics (24-30) as shown in table 1. The average total score for the recommendations was 4.5±0.7. We recorded a large overlap between the results recorded by the Italian experts and those received from other Countries, in fact the recommendations obtained an average score of 4.4±0.6 and 4.5±0.7 in the group of national and international experts, respectively. On average, we registered 89.4% of the agreement, but 28 out of 30 statements exceeded the level of significance established by the task force (> 70% of the agreement).

Definition and Rational

The area of definition reached an overall agreement of 86.6% although statement 1 registered 13,3% of disagreement. 78.1% of experts agree that the clinical effect of LIT depends on both local pharmacological action and mesodermal modulation (statement 3). There are no differences in the definition of mesotherapy between experts of various nationalities, the average score is 4.4±0.8 for national experts and 4.3±0.9 for international experts. The rationale for applying the techniques received an average score not different between Italy and other Countries 4.4±0.8 and 4.5±0.6 respectively.

The technique

A global agreement of experts was recorded on the technique (94.1% of agreement, with an average score of 4.7±0.6). However, a lower percentage of the agreement was recorded among experts from different countries for statements 7. In fact, this statement was voted favorably by 91.9% of the Italian experts against 66,7% of the others. However, both Italians and experts from other Countries reached significant agreement rates 97.8% and 83.3%, respectively. Full agreement on compliance with hygiene rules has been reached (statement 9).

Clinical Pharmacology

Regarding the pharmacological area 90.8% of agreement was reached. However, it was recorded that 7% of experts did not agree with the choice of drugs based on the authorized indications (statement 11). The use of mixtures was rejected, in fact 88.6 agree with the statement 13. On average, both Italian and foreign experts performed the same score for the pharmacological area (4.5±0,7).

Application areas

As expected, consensus was reached on the use of the technique in pain medicine, for localized pain and rehabilitation (statement 17 and 18). An agreement was also reached for the management of the symptoms of chronic venous disease (statement 20) with agreement percentages of 86%. In addition, both in the management of dermatological diseases (declaration 21) and in the field of skin aging (declaration 22), the level of agreement 72.8% and 84.2% were reached, respectively.

The limit of 70% of agreement was not reached in immunoprophylaxis and in dentistry (65.8% and 46.5%, respectively). In fact, in these two areas of application we recorded the score number of 3 (indecision): 29.8% for inradermal vaccination and 45.6% for dentistry.

Ethics

In the area of ethical declarations, the broadest general consensus (97%) and the lowest disagreement (0.8%) was achieved. This area also got the highest score from both Italian and other experts, 4.9 ± 0.4 and 4.7 ± 0.5 respectively.

Table 1. The table shows the statements divided by area. The level of agreement (%), score and the degree of evidence are reported. A (availability of randomized clinical trials and previous consensus), B (availability of clinical studies with case studies of large size or a series of studies with some methodological limitations and the presence of a previous expert consensus), C (series of cases with limitations).

Main Areas	N	Statements	% of agreement	Score (mean+SD)	Grading	Ref
Definition	1	The term mesotherapy means the infiltration into the superficial layer of the skin for preventive, curative or rehabilitative purposes	78,1	4.1 ±1.1	1B	1, 5, 13
	2	The term *local intradermal therapy* refers to a series of dermal micro deposits of products that result in its slow diffusion into the underlying tissues	97,4	4.7 ±0.5	1B	1, 5, 13
	3	The term *meso dermal modulation* is used to refer to the potential mechanisms of action of mesotherapy	78,1	4.1 ±0.8	1C	13,14
	4	Mesotherapy is a technique that can be used, in an individualized treatment path, in combination with other therapies, pharmacological or non-pharmacological, to obtain benefit with lower doses of the drug; or when other proven options have failed, or cannot be used; or there are no other treatment options	93,0	4.5 ±0.7	1A	1, 5, 13
Rational	5	The effect of mesotherapy depends on the local action of the product, but needle-induced reactions and tissue relaxation due to the injected liquid, dermo-immune reactions and systemic absorption of the priduct may also contribute to its clinical effect	94,7	4.6 ±0.6	1C	13,14
	6	Compared to subcutaneous delivery, the intradermal pathway is recommended to achieve a clinical effect with a lower dose of the product	90,4	4.3 ±0.8	1A	1, 15
Mesotherapy technique	7	To achieve correct intradermal injection, the needle must be inclined according to the anatomical site and the thickness of the skin layers. Usually an inclination of about 30° is suitable	90,4	4.4 ±0.8	1B	1, 13
	8	Syringe and needle, sterile and single use, are mandatory and manual technique is preferable to any electrical or mechanical device	94,7	4.8 ±0.6	1B	1, 5, 15
	9	Mesotherapy must be used in accordance with asepsis rules	100,0	4.9 ±0.2	1A	1, 5, 13, 16
	10	Immediately after intradermal infiltration local techniques that can accelerate the absorption of the injected drug should be avoided	91,2	4.6 ±0.8	1C	1, 5
Clinical pharmacology	11	By mesotherapy, products may be administered drugs with local effect and according to the authorised indications	80,7	4.2 ±0.9	1A	1, 5
	12	With the mesotherapy technique, only products authorised for the injection pathway shall be used	99,1	4.7 ±0.5	1A	1, 5
	13	The use of mixtures without validated scientific evidence in favour of compatibility, stability and tolerability is strongly discouraged; the use of single drugs in different syringes and at different inoculation point should be preferred	88,6	4.5 ±0.8	1A	1, 5, 13
	14	After an accurate diagnosis, mesotherapy, in the suggested indications, can be applied according to the pathophysiology of the sign/symptom/problem to be treated. The frequency and duration of treatment should be determined according to the clinical response	93,9	4.5 ±0.6	1B	1, 5, 13
	15	Absolute contraindications must be excluded before the application of the mesotherapy technique	99,1	4.9 ±0.3	1A	1, 5, 13
	16	Mesotherapy can have an effect comparable to systemic treatment but with lower doses of the same drug	83,3	4.3 ±0.9	1B	17 - 23
Localazed Pain	17	Mesotherapy is an option in the localized musculoskeletal pain management pathway	100,0	4.8 ±0.4	1A	24, 25
Rehabilitation and sports medicine	18	Mesotherapy can be considered in the individual path of rehabilitation and in sports trauma	95,6	4.6 ±0.6	1B	14, 24
Immuno prophylaxis	19	In the administration of vaccines the intradermal pathway may have a clinical role comparable to that obtained with deep injection, but with lower doses	65,8	4.0 ±1.0	2B	1, 15, 26
Chronic venous disease	20	Mesotherapy can be considered as one of the techniques that can be used to manage the symptoms and signs of chronic venous disease	86,0	4.3 ±0.8	1B	27
Dermatology	21	Mesotherapy is a local treatment option for dermatological diseases	72,8	4.1 ±0.9	1B	28
Skin correction	22	The mesotherapeutic technique can be considered in the treatment of skin imperfections if the goal, shared with the patient, is rationally achievable	84,2	4.3 ±0.8	1C	29
Dentistry	23	Mesotherapeutic technique in dental medicine is a possible experimental treatment strategy	46,5	3.6 ±1.0	2B	30
Ethics	24	Medical records with diagnosis, treatment, including products used by mesotherapy and results obtained, are strongly recommended	98,2	4.8 ±0.5	1C	31
	25	For the administration of mesotherapy, written informed consent is mandatory	94,7	4.8 ±0.6	1C	31
	26	Like any other medical act, mesotherapy may not be applied to a minor, although consenting, without the informed consent of his or her parents or legal representative	97,4	4.9 ±0.5	1C	31
	27	The time needed to inform and share the role of mesotherapy with the patient is an essential part of the medical examination	99,1	4.9 ±0.3	1C	31
	28	Mesotherapy should only be carried out by appropriately trained and up-to-date doctors	98,2	4.8 ±0.5	1C	31
	29	The training and updating of mesotherapy should be carried out by institutions based solely on scientific evidence	93,9	4.8 ±0.6	1C	31
	30	Any adverse reaction induced by the product injected with mesotherapy must be reported to the competent health authorities in accordance with current regulations	97,4	4.9 ±0.4	1C	31

Comparison between Italy and other Countries

About the average scores obtained, only two statements showed a different value between Countries: statement 10 (4.7±0.6 Italy vs 3.9±1.2 other Countries) and statement 21 (4.2±0.9 Italy vs 3.9±1 other Countries). As expected, all experts reached full agreement on statements 9, 17.

Discussion and recommendations

Overall results

This study reached a wide consensus (28 out of 30 declarations) and no statements have been rejected. This result was achieved thanks to the fact that all statements were derived from the analysis of available clinical data. The involvement of experts in different disciplines, their origin from different care settings and a wide geographical distribution have allowed to obtain a representative result.

Definition and rational

In the light of our study, mesotherapy (local Intradermal Therapy - LIT), represents a technique that can be used in combination with other therapies, pharmacological or non-pharmacological, to obtain benefits with lower doses of the drug; or when other proven options have failed or cannot be used; or there are no other treatment options (1, 5).

Several mechanisms have recently been proposed to explain the local analgesic effect of LIT (13). The link between the drug and tissue receptors, the nerve stimulation induced by the needle, the mechanical relaxation of the tissues caused by the injected liquid, and the dermo-immune reactions have been identified as the main mechanisms (Figure 2). These mechanisms motivate the broad agreement of the experts on statements 3 and 4, and in particular on the emerging concept of a "meso dermal modulation" according to which the dermis can be considered a new target organ (13, 14). Further studies are needed to confirm the role of some mechanisms, in the meantime we recommend that LIT can be considered for preventive, curative or rehabilitative purposes according to the indications of the injected product.

The technique

Mesotherapy initially described the infiltration technique with potential benefits based on empirical observations (32). Studies available today show that the drug-saving effect, obtained with micro-skin deposits and the slow diffusion in the underlying tissues (1, 5), induces clinical results comparable to those obtained with the intravenous (17), intramuscular (18) or oral (19-21) administration. Although depth of administration is still a topic of clinical research, the needle with an average inclination of 30 degrees gathers a broad consensus of experts. Therefore, we recommend to perform the LIT with a variable degree of inclination of the needle, depending on the thickness of the dermis (which can vary according to the anatomical area, age, gender and race).

Safety

Based on the literature, the commission noted that some authors report adverse events caused by mesotherapy (3, 4, 33, 34). However, we observed that the adverse events were caused by the use of obsolete mixtures, by allergic reactions to the products used, by the use of the technique applied in skin areas where it is not recommended to practice LIT and especially by non-compliance with hygiene standards (16). Since the risk of infection during the intradermal administration is high, the practitioner must be extremely careful in preventing contamination of the treatment area. In our study, we observed that statement 8 did not reach full agreement as expected. This is probably due to the fact that today devices for the automatic administration of intradermal therapy are marketed. We do not recommend such instruments because they can carry infections if they are not sterilized after each use (16, 34). In addition, these tools, coming into contact with the points where the needle has penetrated the dermis, also become a risky source of contagion between one patient to another. Finally, we suggest preventing any self-administration for aesthetic purposes, precisely because dermal infiltration can also have severe consequences if not carried out in a suitable environment and in compliance with hygiene rules. For all these reasons we strongly recommend compliance with hygiene rules (statements 8 and 9).

Clinical pharmacology

The use of mixed principles without a strong rationale led the committee to propose statements from 11 to 16. Overall, the pharmacological area obtained 90.8% agreement. Despite this, there was 7.1% of disagreement in the statement 11, probably due to the use of off label drugs in the real practice. In this regard, off label use for the intradermal route must take place in compliance with the pathophysiology of the sign / symptom to be treated (statement 14). As for the administration of mixtures, as already reported (1,5) it should be noted that some studies have adopted experimental protocols with multiple drugs for analgesic purposes (35-37). Therefore, in a safe environment, expert doctors can replicate the treatment protocols of which data in support of compatibility, efficacy and safety are available. Where such data are not available, the use of mixtures (not approved by the regulatory authorities) can be considered malpractice.

Application in pain medicine

A series of preclinical (1) and clinical studies (17-24) have highlighted the drug-sparing effect that today justifies the use of LIT in various localized pain syndromes. This advantage is particularly useful in some categories of patients, such as the elderly or patients in polytherapy who present a high risk of drug interactions or adverse events (38). Even in the field of rehabilitation, both in patients with osteoarticular pain and after a tendon muscle injury, LIT plays a positive role and is applied by many practitioners immediately before physiotherapy techniques to facilitate joint mobility and reduce pain. In some cases, when it is necessary to prolong the painkiller effect or local muscle relaxant it has been suggested to avoid massage, pressotherapy, lymphatic drainage,

ad physio-kinetic therapy immediately after the application of the LIT. In the area of pain medicine, mesotherapy must be applied after a correct diagnosis (type, location, duration and intensity of pain), in accordance with statement 14. In fact, different approaches can be considered based on the location and type of diagnosis (2, 24, 39, 40). We recommend taking the LIT into consideration for the management of localized pain syndromes, but always in accordance with the best therapeutic path for each patient.

Application in other clinical settings

LIT was also evaluated as remarkable in the management of the symptoms of chronic venous disease (pain and heaviness of the lower limbs). Although there is less clinical evidence in this field (1,5) the lack of effective therapeutic alternatives for the control of these symptoms justifies the consensus registered in favor of LIT (statement 20). We recommend considering LIT as an adjuvant for the treatment of chronic venous disease symptoms (27).

As expected, an agreement was signed for the application of LIT also in some dermatological conditions (statements 21 and 22). The greater agreement of the Italian experts in this area of application is explained by the fact that LIT, in the dermatological setting, is better known as local regional infiltration and is supported by many experimental data (28). During the evaluation of clinical trials, the steering committee also noted that many studies report frequent use of corticosteroids in dermatological application. We also found a deeper injection in the treatment of trigger points (2), and more superficial (and diluted) in the treatment of some dermatoses (28). However, more studies are needed to investigate the usefulness of the use of these off-label drugs.

The application of mesotherapy technique in the aesthetic field, although supported by a limited number of tests, some of which conflicting (41,42), has obtained a general agreement. According to the statement 22 the use of mesotherapy is rational only if the injected product has data in favor of tolerability and efficacy which justify its use for aesthetic purposes. For these reasons, we recommend to consider the use of LIT only if the therapeutic goal is rational and achievable. After applying LIT for aesthetic purposes, it is advisable to avoid massages, pressotherapy, lymphatic drainage, ultrasound, application of creams, sun exposure or any other maneuver that may increase the risk of infections. Statement 19 did not reach the minimum level established by the committee. However, it should be noted that 29.8% of experts expressed their indecision for this statement (3 points on the Likert scale) although intradermal vaccination has shown clinical and economic benefits and could represent a mass strategy for mass immunization if confirmed by current research (43). This suggests that the role of intradermal vaccination (clinical and economic benefits) are not yet widespread and that health institutions should invest in vaccination training.

The task force, examining the available literature, proposed to evaluate the application of the mesotherapy technique on oral mucous membranes with statement 23. However, due to the high number of undecided, statement 23 did not reach the 70% consensus limit. Therefore, the application of the technique on the oral mucosa remains an area of investigation (30,44, 45).

Ethics

The highest level of agreement of all of the experts has been recorded in the area of ethics. This area is crucial, since it alone would be enough to achieve an international standard in any application of mesotherapy practice. Given the results of our study, we recommend to suggest mesotherapy based on clinical diagnosis and after collecting a valid informed consent. It is necessary to dedicate the time necessary to inform the patient on the rationale for this choice, the reasons why a certain product is chosen (especially if off-label), and the expected difference compared to other routes of administration. We also recommend filling in the medical record, reporting the type of therapy and the results obtained. Furthermore, with declarations 28 and 29 we confirm the need for ad hoc professional training based on scientific evidence and no longer on personal beliefs transmitted from one doctor to another. For this purpose, the Italian Society of Mesotherapy has a code of ethics, respecting the patient's rights, which aims to disseminate only evidence-based data to avoid false expectations (46). We also recommend to report any adverse event to health authorities (statement 30) in order to prevent other patients from being exposed to unnecessary or underestimated risks.

Limits of the study

Our study has some weaknesses. We have involved a greater number of national experts, however experts from other countries are representatives of the scientific societies of their countries of origin.

All experts voted on the statements received from the steering committee, but they did not receive the level of scientific evidence for each recommendation according the GRADE System (47). This made it possible to evaluate any discrepancy between the opinion of each expert and the scientific evidence. Nevertheless, the strength of each statement obtained with the vote corresponds to the available evidence. The limit imposed by the steering committee (> 70% to obtain a meaningful agreement) could also be considered too restrictive. However, this limitation reduced the influence of personal opinions. Our study aims to evaluate the technique and not the role of individual products. However, our recommendations are useful for identifying patients to be treated with LIT and the most appropriate care pathways.

Conclusion

Our study did not aim to investigate the use of injectable products in each indication, but to evaluate the role of the intradermal administration technique (Mesotherapy, local intradermal therapy – LIT-, meso dermal modulation). As with other techniques, there are no predefined treatment schemes and its application depends on the diagnosis,

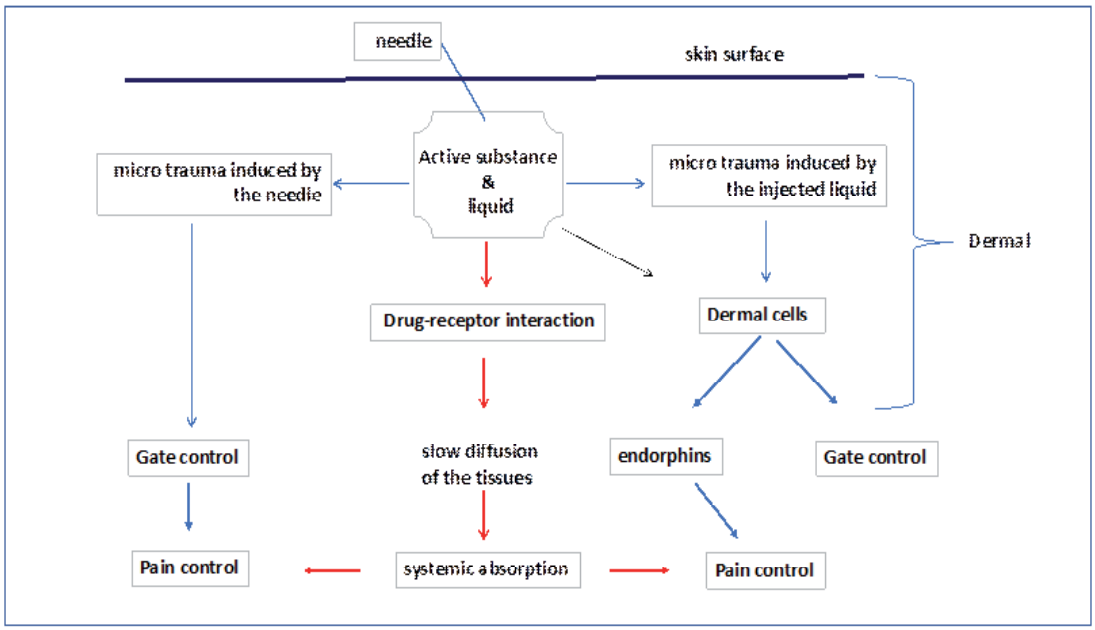

Fig. 2. The figure shows the potential analgesic mechanisms of action of LIT. In red the actions due to the drug; non-drug related actions in blue.

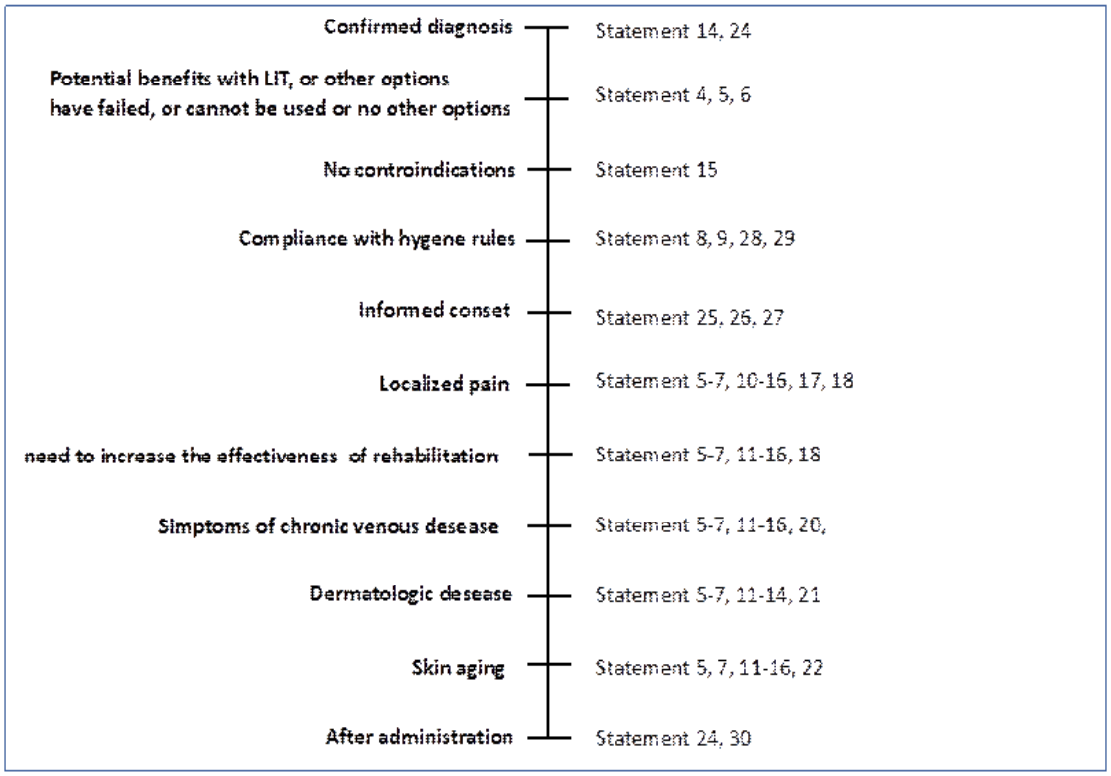

Fig. 3. The figure shows a top-down decision tree according to the recommendations.

contraindications, the patient's preference, and the clinical response obtained. An example of a top down decision tree is proposed in figure 3.

The intradermal route, has spread in clinical practice for its convenience: a lower dose of drug, injected where it is needed, when it is needed. Some recommendations may not be accepted by doctors who apply mesotherapy according to the suggestions of the pioneers of mesotherapy (32). However, the method we used to reach an agreement on the application of mesotherapy provides clinicians with a guideline to select patients to be treated with LIT, allows to avoid some errors that have raised criticisms on the intradermal route, and provide the decision maker more information on the potential benefits (including economic) of mesotherapy. Based on available clinical data and assessments on tolerability and efficacy, we proposed recommendations that

also represents a milestone for clinical practice. Finally, the proposed recommendations provide a basis for future clinical research useful for integrating our knowledge on meso-dermal modulation and on the role of the skin as a "target organ" in prevention and treatment.

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Authors' Contributions

MM has proposed the review and drafted the first manuscript, RD, PT, ME, DMR, TD discussed and shared the text; GR, PEF, BB, FG supervised the text.

Conflict of interests

The authors declare no conflicts of interest. No sponsorship has been received for the organization of the scientific review process and throughout the duration of the study. The complete report is published: "Standards of good clinical practice in mesotherapy - report 2020-2021" Ed. EMSI 2020 - Rome

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