

Role of the informed consent, from mesotherapy to opioid therapy

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Abstract. – Informed consent is part of a process of communication useful to obtain an agreement (conscious, voluntary and free) between doctors and patients.

Mesotherapy is based on the introduction of drugs by intradermal route in order to obtain a dose-sparing effect with respect to deeper administration. Opioids are the most appropriate therapy for patients who do not respond to other therapies. Proper communication between doctor and patient, including an explanation of the potential benefits, limitations and risks (even mild), is recommended both in clinical practice and research. Active participation of the patient has the advantage of better control of adverse events, both of mesotherapy and opioid-based therapy. This information-education process returns to the fundamental concept of “first do no harm” and set a “therapeutic partnership” with patients.

Key Words:

Informed consent, Mesotherapy, Opioid therapy.

Introduction

Over the years the informed consent has become important from a philosophical, ethical and legal point of view. While it is debated whether the consent should be part of every medical and surgery decision, in clinical research it is rightly considered an essential condition.

There are some advantages in making the patient aware of the therapeutic choice. We emphasize the importance of informed consent through two different situations: the intradermal administration of drugs (mesotherapy), and the opioid-based therapy.

In these situations, the process that allows reaching the informed consent is also useful to increase adherence to therapy.

Notes on the History of Informed Consent

In ancient Greek and Latin culture the doctor had the power to decide for patients with a consequent asymmetric relationship between doctors and patients¹. This dominance of the physician, based upon the principle “first do no harm”, and on the authority to decide for the unconscious patient, slowed down the subject’s right to take part in the therapeutic decision. However, Plato from Kos suggested to “convince” the patients to perform the care and also Hippocrates proposed a “therapeutic alliance” between doctors and patients because it allowed a better understanding of the disease¹. Sometimes in the past the consent was required to implement a defensive medicine as in the case of the two doctors who treated Alessandro Magno: Filippo from Arcarnania required explicit consent to administer a drug suspected of being a poison. Critobulo requested express permission to remove an arrow from the right eye of Alessandro Magno because surgery was at high risk¹.

In the recent past some dramatic circumstances raised the ethical demand of informed consent. In fact, in 1946, a military court sentenced 23 Nazi doctors for crimes against humanity. They had carried out experiments on thousands of prisoners without the consent and the freedom to choose^{2,3}. As a result of this process has been published the Nuremberg Code (1948) which stresses the obligation of the voluntary consent of the human being to participate in experiments⁴. It represents the first international proposal to points out that the benefits of research must be greater than the estimated risks.

In 1948, the World Medical Association produced the Geneva’s Declaration (1948) to prohibit the use of medical knowledge against humani-

ty, and to inform about human beings research and treatment. This document (and its amendments) is still valid^{5,6}.

The disaster induced by thalidomide has participated to accelerate the need for a critical review of the patient's informed consent to include in research. In 1956, thalidomide was used for the treatment of influenza, but also for sedation, anti-nausea and anti-vomiting in pregnancy. Only a few years later, the damage teratogens have been associated with thalidomide^{7,8}, especially if the drug was taken during the first three months of pregnancy⁹.

In the case of thalidomide can be identified two major problems, on the one hand that the lack of clinical research prior to marketing, on the other hand that the patients had not been informed about the lack of definitive data on pregnant women.

This incident led to the publication of a document (Keufauver Amendments, 1962) by the FDA. The regulatory authority of the U.S. obliged companies that produce drugs to prove drug efficacy before marketing, to observe safety through controlled studies conducted in compliance with the consent of the patient, and allowing inspections to verify the good research practice.

In 1964 the World Medical Association published the Declaration of Helsinki, which emphasized the standards for conducting trials and (with periodic updates) it requires to enrol in clinical trials only individuals who give their informed consent^{10,11}. Over the last years international and national institutions have published many papers that indicate how to conduct clinical research, providing patients with the obligation to obtain informed consent (ethical codes, guidelines, national legislation, national ethics committees, etc.)¹²⁻¹⁶.

Finally, over the years informed consent has become a form of protection to the patient and best practices essential in the field of medical research.

First cases of Jurisprudence

For the courts of the U.S. the informed consent has taken legal value already in the nineteenth century. The doctor cannot operate without explicit consent of the patient (case Slater, 1767)¹⁷ and he cannot provide incomplete information (case Carpenter, 1871)¹⁸. When the patient's consent is omitted the person is violated (case Mohr, 1905)¹⁹ and deprived of autonomy to decide for himself (case Schloendorff, 1914)²⁰. When the risks of a

surgical procedure are omitted, is missing the "intelligent consent", and this becomes malpractice (case Salgo, 1957)²¹. The knowledge of the risks of surgery allows the patient a complete decision (case Canterbury, 1972)²². The consent, even if signed, received without full awareness is invalid (case Demers, 1973)²³. In US the informed consent became legal before the current laws, and the judges wanted to promote the self-determination of patients (human dignity) and the ability to decide for themselves.

However, a valid consent must be obtained from patients with understanding, decision-making ability and voluntariness. In clinical practice there are many difficulties related with the patient's ability to understand the risks and treatment options²⁴. Patients with cognitive diseases, children, emergencies, are all critical and sometimes even elderly people with a low cultural level have difficulty to give informed consent if the doctor does not take adequate communication²⁵. The therapeutic relationship is based on a dual concept, the physician must fully inform the patient and the patient has the right to accept (or reject) the treatment. This involves communication skills and we underlined the role of the general practitioner who is often invited to answer the question whether there is an alternative therapy than proposed by specialist.

In several cases general practitioners should also argue the complementary medicine as an alternative²⁶ and they should be prepared to communicate with patients in order to make them aware and able to give the informed consent²⁷. For example in the case of herbal therapies, professional should inform about the effectiveness, compared to standard care, and about risks of drug interactions. In fact, several interactions between drugs herbal therapies (ginkgo biloba, garlic, ginger, sage, ginseng, etc.) have been described^{28,29}. In practice, to discuss with the patient the difference between alternative medicine and standard medicine requires knowledge of both disciplines and communications skills to properly inform the patient³⁰.

What is Mesotherapy?

Mesotherapy is a minimally invasive technique based on the introduction of pharmacologically active compounds in the superficial layers of the skin³¹⁻³⁶.

The intradermal injection (ID) of a small amount of drug allows a prolongation of the local pharmacological effect due to a slower and sustained diffu-

sion into the underlying tissues compared to intramuscular administration^{35,37}. Mesotherapy is useful when no other treatments can be applied or when other therapy options have failed, when there is a possible synergistic benefit with other therapies (systemic or local, pharmacological or non-pharmacological), when a drug-sparing effect can be obtained and whenever there is reasonable utility and tolerability for the patient³⁵.

Mesotherapy can be considered in different clinical situations. Several studies conducted on painful conditions of the musculoskeletal system (both, degenerative and traumatic) confirmed a relative tolerability and clinical efficacy of mesotherapy alone or in combination with other analgesic techniques^{35,36}. It can also be useful for symptoms caused by disorders of the peripheral microcirculation³⁸ or by chronic venous (or lymphatic) insufficiency of the lower limbs³⁹⁻⁴¹.

The ID was already known at the beginning of the twentieth century for the ability to induce the activation of the immune system^{42,43}. An antigen, inoculated by this route, stimulates the immune system more than the intramuscular administration⁴⁴. Actually, the ID vaccination is commonly used in order to reduce the amount of antigen and to avoid adjuvants in the flu vaccination^{45,46}.

Even some changes in microcirculation, such as the subcutaneous panniculitis (cellulitis)^{47,48}, seem to benefit from the use of active substances by ID injection⁴⁹⁻⁵². In many countries the success of mesotherapy has led the cosmetic operators to apply this technique for the treatment of skin aging.

However, the use of this method without a standard has resulted in some reports of adverse drug reactions⁵³⁻⁶⁵. These reports suggest that problems were related to the operators (non-medical staff), the technique (lack of asepsis or mixtures of multiple drugs in the same syringe), and many adverse events seem to be based on speculation rather than on scientific evidence. However, many of them could have been avoided if there had been a proper use of the informed consent. For these reasons, the Italian Society of Mesotherapy suggests the requirement for informed consent for many years, and it was also stated in the current recommendations for the proper use of intradermal therapy³⁵.

Why an Informed Consent in Mesotherapy?

There are many reasons to consider the interactive communication process between doctor

and patient. As all other therapies, ID should be suggested only after a clinical diagnosis, and a careful pharmacological anamnesis³⁵. Even when the patient has given an informed consent, he/she must continuously participate in the outcome evaluation to assess the clinical response and adverse events^{35,36}.

In pain-medicine the doctor-patient relationship and the informed consent are fundamental principles. Indeed, pain is a subjective sensation and everyone responds to the treatment in a different way (not always predictable). The patient will be invited to a constantly conscious and knowledgeable relationship with the doctor to reassess the risk/benefit ratio throughout the course of therapy. Applying the ID therapy, further critical issues will be present, such as those relating to the use of off-label drugs. For example, in Italy there is a packaging of ketoprofen, which reports the intradermal route while others do not. It is tricky if in these cases it is necessary an explanation to patient in order to inform him that the use of this drug is off-label, and whether there are or not evidences of efficacy and tolerability to achieve complete informed consent.

The ID route was tested for a long time in the field of vaccination to demonstrate the effectiveness compared with other routes and to evaluate the effect dose sparing⁶⁶⁻⁷². Even in the case of vaccination, purposes and risks must be shared with the patient. In addition, during the ID therapy, local reactions (redness, burning, itching, pain at the site of inoculation, etc.) may occur, so it is worth discussing this possibility with the patient in the information process⁷³⁻⁷⁵.

The treatment of chronic venous insufficiency is suggested in international recommendations^{76,77}, but also the ID has reported some benefits^{35,49-52}. Therefore, before applying a mesotherapy treatment the patient should be well informed about the advantages and limitations, as well as the differences with other therapies. This will allow a shared therapeutic plan between doctor and patient. It is interesting to underline that venous insufficiency is cause of localized imperfections of lower limbs, and many patients may be more attracted by the potential aesthetic benefits of ID treatment rather than by real clinical need. If informed consent is usually applied in clinical practice, it must be considered even more in matters of aesthetic medicine.

In addition, some patients may underestimate the risks of cosmetic procedures, convinced that a more youthful appearance may have positive

consequences (psychological and social)⁷⁸. Moreover, the possibility that the patient has a psychological disorder (such as a distortion of body image) should be evaluated^{79,80}. Therefore, informed consent in aesthetic medicine, not only confirms its utility to ensure the autonomy of the patient, but it becomes an indispensable tool for patient's education.

The interaction process between doctor and patient need time in order to explain the diagnosis and the most appropriate treatment. During the informative phase all clarifications should be given using a simple language.

The information sheet should contain general information about mesotherapy, and specific details depending on the protocol in case of clinical research (Table I). During the interview, the physician should simplify the contents adapting them to

patient's culture and age. The form must be a referenced document and it should not be given to the patient without a properly explanation.

What is Opioid Therapy?

The estimated prevalence of chronic pain as great as 25% of the general population⁸¹ while the prevalence of pain is 64% in cancer patients with metastatic and advanced disease⁸¹⁻⁸³. A careful diagnosis of pain (aetiology and characteristics), evolution of symptoms and physical tests, allows to choose the most appropriate analgesic therapy. Currently, opioids represent the appropriate treatment for chronic moderate-severe pain, in cancer and non-cancer patients⁸²⁻⁸⁶. Nevertheless, approximately 43% of cancer patients are undertreated⁸⁷. Reticence in the use of opioids may be due to an irrational fear to adverse

Table I. The table lists some essential topics that should be included in the informative form for ID therapy when it is used in the clinical practice or when it is proposed as clinical research.

	Mesotherapy		Notes
	Clinical practice	Clinical research	
Diagnosis	Pathology (or symptoms) and prognosis		Daignostic tests for free
Anamnesis	Exsclusion criteria for ID therapy (ex. Pregnancy, allergy, diathesis, etc.)	Exsclusion criteria for ID as per protocol	
Standard therapy	Report the therapeutic standard and/or alternative therapies, listing the differences about tolerability and efficacy (at long and short term)	Report differences between standard therapy and the proposed therapy in the study (differences between groups of treatment, etc)	Inform patient about non-treatment
Proposed treatment	Specify modalities of ID therapy, drug used, benefits and risks (even mild)		Inform patient about used drugs (off-label, experimental drugs, placebo, etc.)
Adverse reactions and their management	Specify the known adverse reactions (mild itch, sensitivity, discomfort, irritation at the injection site, allergic reactions, urticaria, bruise, etc.) and the possibility of ineffectiveness of therapy		
Follow up	Define the period of treatment and goals	Specify the duration of the study and the number of follow-up	Clarify whether the patient will have to fill diaries or other evaluation questionnaires. Indicate the referring physician
Time for the decision	Give the patient the appropriate time to decide		Deliver the informative form to the patient and answer patient's questions
Ethic aspects	Clarify whether the treatment has been previously tested and if there are international publications	Specify whether the ethics committee has approved the research protocol. specify that if the patient refuses to give consent, he will still receive the best care	Specify whether the clinical data (anonymously) will be used for scientific purpose. Specify whether adverse events will be reported to the health authorities

events. Opioids, as many other drugs, can cause gastrointestinal, cardiac, neurological, immunologic and hormonal effects. Among those, the cognitive effects, addiction, physical and psychological dependence, and risk of over dosage represent the most feared.

As concerns the unrelieved pain may be more prevalent in chronic non-cancer pain (CNCP) than in the malignant pain (CCP)⁸⁸. This under-treatment could depend on both, the dreaded adverse reactions, and the lack of consent for opioid-based therapy in CNCP⁸⁹.

Guidelines for CNCP suggest the use of strong opioids for short term, since most trials were performed for less than 4 weeks (⁸⁴). A prolonged use is considered, but that choice should be taken by a pain specialist and by considering the clinical response of each patient.

We believe that the opioid-based therapy, both in CCP and CNCP, could be improved through better information and patient education. This educational process can be achieved by applying the procedure for obtaining informed consent.

Why an Informed Consent in Opioid Therapy?

Barriers to the use of opioids include poor assessment of pain, inadequate training and education on the management of pain, greater attention toward cancer treatment rather than pain management, poor knowledge about opioids, and lack of adherence to the treatment regimens^{88,91,92}.

All these barriers are both, among patients/caregivers and professional, even in the hospitals⁹³.

The patient's information process toward opioid therapy is crucial. Indeed, people consider opioids a therapeutic approach for terminal stages of the disease⁸³. Therefore, there is the need to educate the cancer and non-cancer patient about their disease, highlighting both, benefits and potential adverse events (Table II).

The uncontrolled pain may delay or interrupt the treatment of cancer⁹² or radiotherapy⁹⁴. Several proposals of informed consent or "contracts" which patients have been proposed to improve the use of opiates^{89,93,95-99}.

However, we believe that the patient information-education process, including the procedure to collect the informed consent, allows a dual goal: to make the patient well informed and involved in the treatment plan. This process offers the advantage of providing a doctor-patient/caregiver partnership, which is useful to increase adherence to opioids.

The doctor-patient relationship is essential when chronic opioid therapy is scheduled, such as in non-cancer patients, because the data of long-term effectiveness and tolerability were achieved mainly in cancer patients. In our clinical experience, the implementation of this partnership has allowed the adherence to treatment with opioids, even for a long time in patients with chronic non-cancer pain¹⁰⁰⁻¹⁰².

Conclusions

Patients should be closely involved in the management of their treatment plan. The doctor-patient relationship has a therapeutic role and is essential in the management of risks associated with drugs. For the treatment of ID a doctor-patient relationship is necessary, as suggested by the Italian Society of Mesotherapy. Similarly, for opioid therapy informed consent is not only a legal act, but it is the proper way to get the "therapeutic alliance" between doctor and patient. Before mesotherapy, informed consent is proposed to educate the patient to reach a decision free and conscious. The consent may not be valid if he/she urges towards a treatment without considering alternatives and omitting the risks (even mild). The patient should be invited to a continuous communication to assess the effects of therapy. In the case of opioid therapy, consent is a dynamic process of patient education, and is a significant advantage to manage risks and prevent drug abuse.

The doctor, interacting with the patient, highlights the limitations of medical science and agrees treatment plan (therapeutic alliance), in order to manage the inefficacy, adverse events and risks related to the use of drugs.

The proposals of the doctor, driven by science and knowledge, are based on the fundamental principles: first "do no harm", and then establish a therapeutic collaboration with the patient.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

Appendix

Steering Committee of Italian Society of Mesotherapy (SIM): Giardini Manuela, Jacovitti Silvia, Dario Dorato, Trocchi Gloria, Salciccia PierLuigi, Laurenza Massimo, Massironi Alberto, Migliore Alberto, Rocchi Piergiovanni, Benedetto Vergari.

Table II. The table lists some essential topics that should be included in the informative form for opioid therapy when it is used in the clinical practice or when it is proposed as clinical research.

	Opioid based therapy		Notes
	Clinical practice	Clinical research	
Diagnosis	Pathology (or symptoms) and prognosis		Daignostic tests are borne by the sponsor of the study
Anamnesis	Criteria for opioid based therapy (ex. pregnancy, allergy, non responder to other drugs, etc.)	Criteria as per protocol	
Standard therapy	Report that there is no therapeutic dose, and that the response is subjective. Report alternative therapies, listing the differences of tolerability and efficacy, at long and short term	Explain the proposed study (differences between the groups of treatment, etc as per protocol)	Inform patient if the non-treatment can interfere with the diagnosed pathology/symptoms
Proposed treatment	Report the proposed treatment, modalities of execution, drug used (specify combination therapy and adjuvants), benefits and risks (even mild)		Inform patient about used drugs (off-label, experimental drugs, placebo, etc.)
Adverse reactions and their management	Report expected side effects (nausea, constipation, disorientation, etc.) and adverse events (even rare). Report about tolerance, addiction and opioid hyperalgesia. Specify strategy to manage adverse events (dose reduction, rotation of the route of administration, switch opioids, discontinuation of therapy). The dose should be changed only with the doctor's consent. Remind the patient that the opioid can interfere with the ability to drive. The opioids should be kept away from children. Advise patient how to dispose of unused drug		
Follow up	Define period of following visits and specify that follow up are needed to verify effects of treatment	Specify the duration of the study and number of follow-up	Clarify whether the patient have to fill diaries or other evaluation questionnaires. Indicate the referring physician
Time for the decision	Give the patient the appropriate time to reflect		Deliver the informative form to the patient and answer patient's questions
Ethic aspects	Clarify whether the treatment has been previously tested and if there are international publications	Specify whether the Ethics Committee has approved the research protocol and even if the patient does not agree to participate in the study, he will receive the best treatment	Specify whether the clinical data (anonymously) will be used for scientific purpose. Specify whether adverse events will be reported to the health authorities

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