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Intradermal therapy (mesotherapy): the lower the better

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Abstract

Background. Intradermal therapy (mesotherapy) is a technique used to inject drugs into the surface layer of the skin. The intradermal micro deposit allows to modulate the kinetics of drugs, slowing down its absorption and prolonging the local mechanism of action. This technique is applied in the treatment of some forms of localized pain when a systemic drug-saving effect is useful, when it is necessary to synergize with other pharmacological or non-pharmacological therapies, when other therapies have failed or cannot be used.

Aim. The purpose of our study was to evaluate the effect of a mixture with respect to its lower concentration. We also wanted to evaluate the number of sessions needed to reach the therapeutic goal (50% reduction in pain from baseline) in patients with acute or chronic neck pain.

Method. We analyzed retrospectively data from 62 patients with cervicobrachial pain treated with intradermal drugs. Group A received a mixture of drugs; group B received half the dose of drugs.

Results. Patients who received a lower concentration of drugs achieved similar results to those who received a higher dose. The therapeutic goal was achieved on average with 3.5 + 1.7 sessions on a weekly basis (min 1; max 9). Subjects in group A required 4±1.7 treatments (min 1; max 9), while subjects in group B required 3±1.5 treatments (min 1; max 7).

Conclusions. Our study confirms that even a lower dose of drugs can induce a clinically useful result. This study confirms that the useful effect of mesotherapy is only partly due to the pharmacological action. Further randomized prospective studies are needed to standardize the technique in the various pain syndromes, but it is recommended to follow the guidelines of the Italian Society of Mesotherapy to ensure patients receive appropriate treatment. ***Clin Ter 2022; 173 (1):79-83. doi: 10.7417/CT.2022.2396***

Key words: *mesotherapy, intradermal therapy, cervicobrachial pain, drug dose, recommendations*

Introduction

Mesotherapy, also described as local intradermal therapy (LIT), is a technique by which drugs are infiltrated into the thickness of the skin. Drugs in the dermis produce a micro deposit from which they slowly diffuse into the underlying tissues (1,2). With this technique, a drug-sparing effect is obtained with respect to the systemic route, with a reduction in the total drug dose (3). Indeed, an intradermally inoculated drug can diffuse into underlying tissues while maintaining tissue concentrations for longer periods of time than intramuscular administration (1,2). Many localized pain syndromes benefit from the mesotherapy technique (4). In fact, mesotherapy has been used to manage different types of localized pain with both, pain control and quality of life improvement (5-7). This technique is based on the inoculation of drugs (multiple micro-injections) on the pain site, but it is not possible to exclude that the effectiveness is also due to the action of the needle. In addition, dermal reactions have been hypothesized that may potentially have an increased analgesic effect (8). In fact, a randomized study designed to compare the effects of systemic therapy with respect to mesotherapy, highlighted a non-inferiority of localized treatment but with significant drug saving in subjects with acute low back pain (9). Other studies have also highlighted the lower consumption of the drug compared to the systemic route to obtain the reduction of pain in patients with pain (5,10,11). Finally, also the comparison between intradermal therapy and intravenous therapy showed a no inferiority of mesotherapy in patients who needed a pain reliever treatment for acute pain (12). However, some data reported that subjects treated with dry mesotherapy both obtained analgesic benefit (13).

These data suggest a synergistic effect between the local pharmacological action and a reflex analgesic action stimulated by the needle. In addition, three studies reported that intradermal injection of saline can reduce pain, although to

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a lesser extent and for less time than infiltrating analgesic drugs (14-16). For these reasons it has been hypothesized that the mesotherapy technique can induce an analgesic effect through three mechanisms: the pharmacological action, the micro traumatic effect induced by the needle and the injected liquid, and the endocrine neuro-immune reactions indicated by the term mesodermal modulation (8). The Italian society of mesotherapy recommends not mixing multiple active ingredients in the same syringe as it is not possible to establish which of the different active ingredients actually acted; it is not possible to predict physico-chemical interactions between mixed drugs; in the event of an adverse reaction it will not be possible to establish which of the inoculated principles to attribute responsibility for the adverse event (1,5). However, the efficacy of some drug mixtures has been reported by some authors but it is not possible to establish what is the minimum effective dose for the management of localized pain (5-7, 10, 11, 13-18). In fact, if the principle of mesodermal modulation is correct, we should reach the therapeutic goal even with a lower dose of drug than the one we would use systemically.

For this reason we wanted to investigate the effects of two different drug concentrations in the treatment of localized pain. We designed a retrospective study to evaluate whether a lower concentration of locally injected drugs can effectively control patients attending a pain therapy center. At the same time, we wanted to evaluate whether the reduction in drug concentration leads to an increase in the number of sessions necessary to obtain a 50% reduction in pain. To this end, patients with acute and chronic cervicobrachial pain were retrospectively studied.

Materials and methods

We designed a pilot retospective study to evaluate patients who were treated with a low dose versus those who received a higher dose of intradermal drugs. We have selected the clinical records of consecutive patients of both genders and over 18 years of age, suffering from acute or chronic cervicobrachial pain who are referred to our pain therapy clinic. The diagnosis had to be radiologically documented; the pain had to be greater than 8 points on the NRS scale (Number rate scale: 0 = no pain; 10 = worst possible pain). In our clinical practice we do not treat with intradermal therapy subjects with allergy to NSAIDs, and who take anticoagulants. In the analyzes we excluded patients who were taking other therapies, or with pathologies that could interfere with the purpose of our investigation. The studied population was divided into two groups. In group A we included patients who had previously been treated with a full dose of medication: ketorolac (30 mg), thiocolchicoside (4 mg), mepivacaine 1% (1 ml equivalent to 10 mg), and 1 ml of physiological solution (NaCl 0.9%) to achieve a total of 5 ml of injected solution. In group B we included patients who had previously been treated with ketorolac (15 mg), thiocolchicoside (2 mg), mepivacaine 1% (1 ml equivalent to 10 mg), and 2.5 ml of saline to arrive at a total of 5 ml of injected solution. The infiltration technique was performed through a mesotherapy needle (4 mm, 27 Gouge) by means of which about 0.2 ml was injected for each micro infiltration into the skin surface where the pain was located (along the course of the paravertebral muscles and on the cutaneous projection of the vertebral spinous processes). Both groups were also given an oral muscle relaxant (eperisone 100 mg twice daily). Patients were treated weekly until pain reached a 50% reduction from baseline.

Results

We examined 62 consecutive patients with a mean age of 57.2±13.9 years. All patients reported pain equal to or greater than 8 points (NRS mean 8.1±0.3) as reported in Table 1. No significant differences were detected in the two groups in terms of baseline pain severity (Group A: 8.1±0.3; group B: 8.0±0.2). 30 subjects in group A achieved a 50% reduction in pain from baseline. Only one patient did not reach the endpoint (he received only one session). 28 patients in group B achieved a 50% reduction in pain at baseline. The population studied received an average of 3.5±1.7 sessions per week. However, subjects in group A required 4±1.7 treatments (min 1; max 9), while subjects in group B required 3±1.5 treatments (min 1; max 7). We report that 6 patients of group A (patient number 2,5,18,19,20,21) and 5 of group B (pt 14,17,19,22,30) reported clinical symptoms attributable to sacroiliitis and were also treated with ultrasound-guided intra-articular infiltration with 40 mg of methylprednisolone and 2 ml of 1% mepivacaine (equivalent to 20 mg) via a spinal needle (25 Gouge) every week. This subgroup of patients achieved a reduction of at least 50% from baseline in sacroiliitis pain (table 2). No patient in the study reported adverse events related to the treatments received.

Statistical analysis

In our study, we calculated weighted averages for the number of treatments received. The average values, weighted with the number of treatments administered, are 1.1 (group A) and 0.8 (group B) and the average number of treatments was higher in group A, respectively 4±1.7 and 3±1.5. Patients treated with full dose (group A) and those treated with half dose (group B) achieved an average pain reduction of 3.9±0.7 and 3.9±1.1 points, respectively. Therefore, the empirical "effect size" is comparable but with the advantage that Group A received more treatment than Group B. Taking into account that the common variance in pain reduction calculated in the two groups was equal to 0.637, it is possible to calculate that a greater number of patients (92 patients for each group) would allow to obtain, with a probability of 90%, a level of statistical significance equal to or less than 5% (p value ≤ 0.05). As regards the statistical significance of the above comparison, the adopted test gave the following results: t-Student = 0.565; degrees of freedom = 60; p-value = 0.569.

Table 1. The table shows the baseline and final values of group A and B. It also shows the number of weekly sessions received by individual patients to reach the primary endpoint (pain reduction of 50% compared to baseline). Red numbers indicate patients who had cervicobrachial pain and sacroiliitis.

Group A: patients treated with full dose				Group B: patients treated with half the dose			
Pt	**basal NRS**	**final NRS**	**N. of treatments**	**Pt**	**basal NRS**	**final NRS**	**N. of treatments**
1	9	4	6	1	8	3	3
2	8	4	4	2	8	4	3
3	8	4	6	3	8	4	1
4	8	4	3	4	8	5	7
5	9	4	9	5	8	4	5
6	8	4	2	6	8	4	3
7	8	4	5	7	8	4	5
8	8	4	3	8	8	3	2
9	8	4	3	9	8	4	3
10	8	4	4	10	8	4	2
11	9	4	8	11	8	4	3
12	8	4	3	12	8	6	2
13	8	4	2	13	8	4	5
14	8	4	5	14	8	4	4
15	8	6	4	15	8	4	4
16	8	4	1	16	8	4	3
17	8	4	5	17	8	4	3
18	8	4	3	18	8	4	1
19	8	4	4	19	9	4	3
20	8	4	5	20	8	4	4
21	8	4	4	21	8	4	1
22	8	4	5	22	8	2	3
23	8	2	2	23	8	2	3
24	8	4	2	24	8	3	2
25	8	2	4	25	8	2	1
26	8	4	3	26	8	4	1
27	8	4	3	27	8	4	3
28	8	2	3	28	8	4	5
29	9	4	3	29	8	4	5
30	8	4	5	30	8	4	3
31	8	4	4	31	8	8	1

Table 2. The table shows patients who received ultrasound-guided spinal needle block (25 G) with 40 mg methylprednisolone + 20 mg mepivacaine 1% on a weekly basis.

Group A: patients with sacroiliitis				Group B: patiets with sacroiliitis			
Number of patients	**Basal (NRS)**	**Number of treatments**	**Final (NRS)**	**Number of patients**	**Basal (NRS)**	**Number of treatments**	**Final (NRS)**
1	8	4	4	1	8	4	4
2	9	9	4	2	9	3	4
3	8	3	4	3	8	3	2
4	8	4	4	4	8	3	4
5	8	5	4	5	8	3	4
6	8	4	4				

Discussion

In both groups, a 50% reduction in pain was achieved on average after 3.5±1.7 weekly sessions. However, we observed that patients who received a lower concentration of drugs showed a trend with fewer sessions. It should be emphasized that patients were managed with total doses much lower than those used by us systemically for the management of acute or chronic neck pain.

Some authors have in fact reported a number ranging from 1 to 9 weekly sessions for the management of low back pain (6). In our study we observed that the achievement of the endpoint in some patients occurs even after one or two sessions. This confirms the rapidity of action already reported by Kocak who experienced a greater effect of the single mesotherapy session compared to the intravenous route (12). Probably the number of sessions necessary to reach the goal varies according to the severity of the pain and the pathology that generates it. However, we cannot explain why some patients respond with a single mesotherapy session and others require multiple sessions.

It has recently been shown that the analgesic effect can be induced not only by the inoculation of the drug, but also by the puncture of the needle, and by the tissue trauma induced by the liquid injected into the dermis (5). Furthermore, physiological solution has also been shown to have an analgesic effect in patients suffering from chronic spinal pain (16). In addition, it should be noted that in these studies, although saline solution reduced pain, only patients who received active drug treatment achieved a longer-lasting clinical outcome. In our study, it should be noted that group B received a greater amount of saline than group A and the analgesic effect of this liquid may have played an analgesic role. These data confirm a possible synergistic effect between the pharmacological action induced by drugs injected into the dermis and a reflex mechanism stimulated by the needle and saline solution. Furthermore, the greater dilution of drugs, compared to group A, constitutes a further confounding factor that makes it even more difficult to state that a lower dose of drugs is to be preferred over a higher dose. Several studies have been conducted with analgesics, anesthetics, muscle relaxants, vasodilators (1,2,4). However, few data are available to evaluate different drug treatments. It is reasonable to assume that the therapeutic response depends on the pharmacological potency played by the individual analgesics. Indeed, it has recently been shown that a direct comparison between two different drugs inoculated intradermally can induce a different analgesic effect in chronic neck pain or low back pain (17, 18). However, our study seems to confirm that some patients respond better than others with a lower quantity of active ingredients. Probably this result is due to a "mesodermal modulation" played by skin structures in response to mesotherapy (8). Therefore, increasing drug concentrations mixed in the same syringe could represent overtreatment.

To date, many data confirm the usefulness of the mesotherapy technique in particular in patients who cannot take systemic treatments or when it is necessary to use the minimum dose of drugs to reduce the risk of adverse effects, especially in subjects treated for other concomitant pathologies (20).

As expected, our preliminary study confirms that patients with cervicobrachial pain respond to mesotherapy treatment. We have observed that with relatively few sessions per week it is possible to achieve pain control. This is particularly relevant considering that patients who go to a pain therapy center have often already taken many drugs systemically without reaching the clinical goal. It should also be noted that some of our patients also had sacroiliitis and tolerated both ultrasound-guided deep infiltration therapy and mesotherapy treatment for cervicobrachial pain. This confirms the synergistic effect of mesotherapy with other analgesic strategies (21).

However, the recommendation of the Italian society of mesotherapy is confirmed: the use of several drugs in the same syringe does not allow to understand which of them allows the achievement of the clinical endpoint (22). Our data confirm that the use of drug mixtures does not make it possible to interpret which of the mixed drug is responsible for the results obtained although fewer sessions were required to reach the endpoint in the lower dose group. Therefore, mixtures based on different compounds used in some countries should be reviewed in the light of studies demonstrating the efficacy and tolerability of individual compounds before being offered to patients.

Our retrospective analysis confirms that local intradermal therapy allows pain control with a lower concentration of drug than the classic systemic route and that the treatment algorithm that provides weekly sessions seems to meet the needs of most patients. Some patients (rapid responders) benefit from fewer weekly sessions than others.

We are interested in a greater understanding of the mechanisms by which mesotherapy reduces pain. It will therefore be necessary to design prospective studies that compare individual drugs to define which of them can be really considered effective. Subsequently, studies will be designed comparing different dosages of the same drug to identify the lowest effective dose. Finally, it may be useful to compare the administration of single drugs with the administration of mixtures, to understand if the latter can really offer clinical advantages.

Study limits

Our pilot study was designed as a retrospective study and has some limitations. The number of people enrolled was not sufficient to highlight statistically significant differences between the two groups. The sample was not randomized and does not allow definitive conclusions. However, this pilot study allows us to calculate the statistical sample useful for designing a prospective study to investigate which minimum effective dose should be used locally to manage localized pain. This work clearly highlights the limits of the use of drug mixtures, which makes it very difficult to analyze the effectiveness or any adverse effects of its individual components.

Conclusions

Intradermal therapy induces a drug-sparing effect that can be useful when the patient needs a lower total dose of pain killers. It can be a useful therapeutic weapon when other therapies have failed or cannot be used. It also can synergize with other pharmacological or non-pharmacological therapies. More studies are needed to standardize the technique in the various forms of localized pain (21). According the recent guidelines the treatment must be adapted to the individual patient's response (22). The use of injected compounds must be the consequence of a clinical diagnosis, pathophysiological considerations and a careful pharmacological evaluation in order to choose the appropriate drug dose. Many studies indicate that mesotherapy can be considered in standard care pathways, but more studies are needed to identify treatment algorithms in individual patient subgroups (23). Mesotherapy represents a technique to combat pain and analgesic drugs are allies of the doctor (24).

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