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Original Research

Effectiveness of Mesotherapy in Post-COVID Pain Syndrome: Retrospective Cohort Study of 96 Patients

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ABSTRACT

Purpose: Musculoskeletal pain may occur after becoming infected with SARS-Cov2. This study was designed to evaluate the efficacy of mesotherapy in treating chronic pain following COVID-19 infection.
Methods: A retrospective review was conducted of the records of 96 patients with post-COVID pain syndrome. Those who were eligible for oral therapy or mesotherapy, included in the study. Patients receiving oral treatment with diclofenac potassium, thiocolchicoside and cyanocobalamin were included in one group (n = 46), and patients receiving intradermal mesotherapy with 2% lidocaine + cyanocobalamin were included in another group (n = 50). The results of the Visual Analogue Scale (VAS) and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) were individually assessed before and one week after the treatment.
Findings: The participants were 40.2 ± 11.1 years old on average. Of the participants, 35.4% (n = 34) were male and 64.6% (n = 62) were female. Before treatment, there was no statistically significant difference between the patients in terms of VAS and LANSS scores. Following the treatment, a notable positive response was observed in both groups. Nevertheless, when compared to the oral treatment group, the mesotherapy group exhibited a more pronounced enhancement in VAS and LANSS scores ($P < 0.001$, $P < 0.001$, respectively).
Implications: While both mesotherapy and oral therapy offer benefits in reducing pain and alleviating neuropathic symptoms in post-COVID pain syndrome, mesotherapy stands out as an especially effective and well-tolerated treatment method, surpassing the efficacy of the oral alternative.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), defined as a new viral pneumonia in Wuhan, China in December 2019, spread rapidly around the world and was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020.[1]

SARS-CoV-2, which can invade tissues using angiotensin-converting enzyme-2 (ACE-2) and cellular transmembrane protein serine-2 (TMPRSS-2) receptors, can cause neurologic involvement such as headache, anosmia, loss of sense of taste, stroke, encephalitis, acute disseminated encephalomyelitis (ADEM), meningitis, Guillain–Barré syndrome (GBS), Miller–Fisher syndrome (MFS), Bell's palsy, critical illness polyneuropathy, neuropathic pain and paresthesia, and neuromuscular involvement such as arthritis, myopathy, myositis, rhabdomyolysis, and sarcopenia.[2–5]

Chronic pain is characterized by pain that persists for more than 3 months or extends beyond the expected timeframe for normal tissue healing, either as recurring pain or continuous discomfort.[6] Pain is categorized as nociceptive, neuropathic, nociplastic, or mixed type based on its pathophysiology.[7] COVID-19, which is a neurotropic virus, is capable of direct tissue invasion and has the potential to cause chronic pain as a result of tissue damage secondary to the severe inflammation it causes and the release of various pain mediators and tissue hypoxia associated with hypercoagulability.[8] While myalgia symptoms are reported in 22–63% of cases during COVID-19 infection, some studies have also documented the presence of persistent localized pain.[9-12]

As of now, there is no established treatment protocol for chronic pain following COVID-19, and the available information in the literature remains inadequate. Most of the reported data are at the case level.[13] Mesotherapy is a micro-invasive treatment technique that involves the local application of pharmaceutical substances to the dermal layer of the skin. There are research studies that indicate the effectiveness of mesotherapy in treating chronic back pain.[14,15] This technique allows for the creation of a pharmacological effect with low-dose direct application to the target tissue, resulting in a lower risk of side effects compared to oral treatment.[16]

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In our study, we sought to retrospectively analyze treatment outcomes in patients diagnosed with post-COVID pain syndrome who received either oral therapy or mesotherapy. Our goal was to define an effective treatment protocol with a minimal risk of side effects for this patient group.

Materials and Methods

Study Design

This study was designed retrospectively to investigate the effects of mesotherapy on individuals diagnosed with post-COVID pain syndrome. The research aimed to examine changes in pain perception and neuropathic pain levels following mesotherapy intervention.

Sample Selection

The research population consists of the medical records of 96 patients who were diagnosed with post-COVID pain syndrome in our hospital's physical therapy clinic between 2020 and 2023. These patients did not have a history of pain complaints before experiencing SARS-CoV-2 infection and subsequently developed chronic neuropathic pain. They received either oral treatment or mesotherapy as part of their management.

Participant Inclusion and Exclusion Criteria

The inclusion criteria for this study were individuals aged 18-65 who had regional pain lasting for more than 3 months after recovering from SARS-CoV-2 infection. Patients' medical records confirmed the COVID-19 diagnosis (either through real-time reverse transcription polymerase chain reaction with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or positive SARS-CoV-2 antibody testing). Patients over 18 and under 65, as well as those with chronic pain before experiencing SARS-CoV-2, were excluded from the study.

Participant Recruitment

The G*Power program[17] was used to calculate the sample size. Although identical parameters from reference studies could not be found, when VAS and LANSS parameters, similarly constructed, were compared, an effect size of 0.5 was observed. This corresponds to a moderate effect size according to Cohen's Effect Size Classification.[18] With an effect size of 0.5 and a significance level of 0.05, a minimum of 80 participants were decided to be included in the study to achieve an 80% power. As a result of the evaluation, a total of 96 eligible individuals meeting the specified criteria were included in the study.

Intervention Protocol

Patients receiving oral diclofenac potassium, thiocolchicoside, and cyanocobalamin treatment were assigned to the first group (n:46), while patients receiving intradermal mesotherapy containing 2% lidocaine and cyanocobalamin were included in the second group (n:50).

Oral treatment application method: Diclofenac potassium and thiocolchicoside, supplemented with cyanocobalamin due to its neuropathic pain nature, were applied orally for one week.

Mesotherapy application protocol: Administered as a single session. The mesotherapy mixture was prepared by mixing 2% lidocaine and cyanocobalamin in equal parts to prepare a 5 mL syringe. Using a 13 mm, 27-gauge needle tip, the mixture was applied intradermally to the painful area using the papule formation technique (Figure 1).

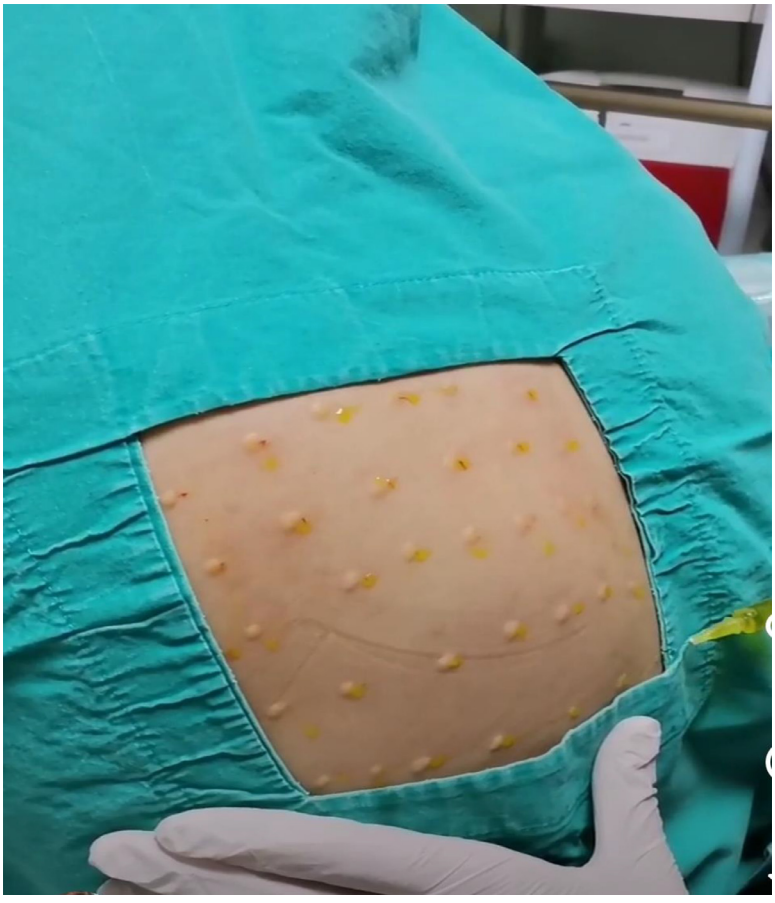

Figure 1. Sample photos showing intracutaneous injections in the affected areas.

Assessment Measures

From the patients' records, demographic data, duration of pain, pain intensity, neuropathic pain symptoms, and severity were determined. Patients' pain levels were assessed using the Visual Analog Scale (VAS) and neuropathic pain levels were evaluated using The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale. The VAS and LANSS assessments were conducted through patient interviews by the same physician before and after the treatment. The results before treatment and at the end of the first week of treatment were compared.

Visual Analogue Scale (VAS): This test is scored on a scale of 0 to 10, with 0 indicating no pain and 10 indicating severe pain. A score of 1 to 3 indicates mild pain, 4 to 7 indicates moderate pain, and 8 to 10 indicates severe pain.[19]

LANSS Pain Scale: It is a test that is used for the evaluation of the presence or absence of central neuropathic pain. It was initially utilized by Bennet to distinguish between neuropathic pain and nociceptive pain.[20] A diagnosis of neuropathic pain is established if a score of 12 or higher is recorded on the scale. The highest score on the scale is 24.

Regulations and Ethics

The study received ethical approval from the Ethics Committee at Istanbul Medipol University (Approval number: E-95961207-604.01.01-3412).

Statistical Analysis

Centralization and variance measurements were used to specify the attributes of quantitative variables: mean ± standard deviation. The chi-squared test was employed for the purpose of ascertaining discrepancies or associations among categorical variables. The one-way analysis of variance (ANOVA) test was employed to demonstrate distinctions among group means, while the Wilcoxon test was utilized for comparisons conducted before and after the treatment. A significance level of $P = 0.05$ was set for all statistical analyses. The statistical analysis was conducted using the IBM SPSS software package (IBM Corp., Armonk, NY, Version 21.0) for Windows.

Results

This study included 96 patients who had been diagnosed with post-COVID pain syndrome. The participants were 40.2 ± 11.1 years old on average. Among the participants, 35.4% (n = 34) were male and 64.6% (n = 62) were female. Of these, 25% (n = 24) were smokers and 20.8% (n = 20) had comorbid (diabetes mellitus, hypertension, Hashimoto's thyroiditis, Behçet's disease, and asthma) conditions. Among the cases, 35% (n = 34) had a history of hospitalization, and 12.5% (n = 12) had a history of intensive care unit (ICU) admission during their experience with COVID-19. The average duration of hospitalization for patients admitted to the general ward was 9.5 ± 4.7 days, whereas for those in the ICU, it was 4.8 ± 2.3 days. The average time from the onset of pain was 6.2 ± 4.1 months.

There was no significant difference in demographics between the groups (Table 1).

Among the cases, 41.7% (n = 40) experienced neck pain, 37.5% (n = 36) reported low back pain, 14.6% (n = 14) presented with both neck and back pain, and 6.3% (n = 6) described pain localized to the lumbar region. Before treatment, the mean VAS score of the patients was 7.6 ± 1.5. Neuropathic pain symptoms, including burning sensations in 66.7% (n = 64) of patients, tingling in 72.9% (n = 70), numbness in 70.8% (n = 68), stinging in 70.8% (n = 68), and anesthesia in 58.3% (n = 56), were observed. Before treatment, the mean LANSS score of the patients was 15.2 ± 3.5. The incidence of stinging and numbness symptoms was significantly higher in the mesotherapy group ($P = 0.046$ and $P = 0.046$, respectively) (Table 2).

Table 1
Comparison of demographic data between groups.

		Oral treatment (N = 46)	Mesotherapy (N = 50)	*P*
Age	40.5 ± 11.2	40 ± 11.2	0.804	
Height	168.7 ± 9.3	164.2 ± 7.9	0.527	
Weight	74.3 ± 9.3	72.6 ± 9	0.412	
Duration	6.6 ± 4	5.8 ± 4.2	0.412	
Hospitalization duration	4.3 ± 5.7	2.0 ± 4.6	0.123	
Gender	Male	18	16	0.525
		39.1%	32.0%	
	Female	28	34	
		60.9%	68.0%	
Hospitalization	No	28	34	0.525
		60.9%	68.0%	
	Yes	18	16	
		39.1%	32.0%	
Smoking	No	32	40	0.251
		69.6%	80.0%	
	Yes	14	10	
		30.4%	20.0%	
Comorbidity	No	40	36	0.083
		87.0%	72.0%	
	Yes	6	14	
		13.0%	28.0%	

The *P*-value of <0.05 is considered as the level of statistical significance.

Table 2
Comparison of neuropathic pain symptoms between groups.

		Oral treatment (N = 46)	Mesotherapy (N = 50)	*P*
Burning	No	18	14	0.283
		39.1%	28.0%	
	Yes	28	36	
		60.9%	72.0%	
Hypoesthesia	No	22	18	0.301
		47.8%	36.0%	
	Yes	24	32	
		52.2%	64.0%	
Stinging	No	18	10	0.046
		39.1%	20.0%	
	Yes	28	40	
		60.9%	80.0%	
Tingling	No	12	14	0.508
		26.1%	28.0%	
	Yes	34	36	
		73.9%	72.0%	
Numbness	No	18	10	0.046
		39.1%	20.0%	
	Yes	28	40	
		60.9%	80.0%	

The *P*-value of <0.05 is considered as the level of statistical significance.

Before treatment, there were no significant differences between the patients in terms of VAS and LANSS scores. However, after treatment, both groups showed a significant response to treatment (Table 3). Interestingly, the mesotherapy group displayed a notably greater improvement in VAS and LANSS scores before and after treatment when compared to the oral treatment group (VAS difference: $P < 0.001$, LANSS difference: $P < 0.001$) (Table 4). It is worth noting that 8 patients in the oral treatment group reported gastrointestinal system (GIS) complaints, while none of the patients in the mesotherapy group experienced any GIS side effects. Among the potential side effects of mesotherapy, 3 patients reported redness, and 2 reported itching, which resolved without the need for medical intervention within a few hours.

Discussion

The primary findings of our study can be summarized as follows: Firstly, there was a significant positive response to treatment in both study groups. Secondly, the mesotherapy group exhibited a notably

Table 3
The effectiveness of mesotherapy and oral therapy on pain and neuropathic pain.

		Mean ± Std. Deviation	*P*
Mesotherapy	VAS1	7.8 ± 1.8	<0.001
	VAS2	2.0 ± 1.1	
	LANSS1	16.2 ± 3.7	<0.001
	LANSS2	3.1 ± 2.8	
Oral treatment	VAS1	7.4 ± 1.2	<0.001
	VAS2	4.6 ± 2.2	
	LANSS1	14.1 ± 3.0	<0.001
	LANSS2	9.2 ± 4.6	

The *P*-value of <0.05 is considered as the level of statistical significance.
VAS = Visual Analog Scale; LANSS = Leeds Assessment of Neuropathic Symptoms and Signs; T1 = before treatment; T2 = after treatment.

Table 4
Comparison of the effectiveness of mesotherapy and oral treatment.

	Group	Mean ± Std. Deviation	*P*
VAS difference	Oral treatment	2.8 ± 1.9	<0.001
	Mesotherapy	5.8 ± 1.9	
LANSS difference	Oral treatment	4.9 ± 3.7	<0.001
	Mesotherapy	13.0 ± 4.7	

The *P*-value of <0.05 is considered as the level of statistical significance.
VAS = Visual Analog Scale; LANSS = Leeds Assessment of Neuropathic Symptoms and Signs.

more significant response in terms of VAS and LANSS scores when compared to the oral treatment group.

COVID-19 has been linked to various neurological symptoms. In a study conducted by Wang et al[21] that evaluated the clinical characteristics of hospitalized COVID-19 patients, arthralgia was reported in 15%, while myalgia was reported in 44% of the cases. In the meta-analysis conducted by Ciaffi et al,[22] arthralgia was reported in 32% of cases and myalgia in 19%. Attal et al[23] have suggested that neuropathic pain may emerge as a consequence of COVID-19, and they advocate for the establishment of early diagnosis and treatment strategies in response to this potential development. Another study has reported that up to 2.3% of patients hospitalized for COVID-19 infection have developed probable neuropathic pain.[24] In their study, Topal et al[11] documented a 13.7% incidence of chronic pain among COVID-19 patients and noted that neuropathic pain findings were concomitant in these individuals. Patients in our study also had neuropathic pain complaints. A significant benefit was achieved in LANSS scores with oral treatment and mesotherapy. However, a more substantial improvement was noted in the mesotherapy group.

Literature studies concerning pain that initiates and persists during COVID-19 infection suggest it is a component of the long COVID syndrome. Acute COVID-19 syndrome covers up to 4 weeks. The term "prolonged symptomatic period" refers to a period of 4–12 weeks, and "post-COVID-19 syndrome" refers to symptoms and signs that develop after infection, last for more than 12 weeks, and cannot be attributed to any other cause.[24] In a case series, Illéš et al[25] reported that among 9 patients with lumbar disc herniation, the mean VAS score increased from 5.6 ± 1.1 to 8.0 ± 1.3 during their COVID-19 infection and subsequently returned to pre-infection levels (5.8 ± 1.1) 4 weeks after recovery.

Currently, there are no established treatment recommendations for chronic localized pain following COVID-19. The literature predominantly consists of case-level studies, and there is a scarcity of comprehensive data.[26] While non-steroidal anti-inflammatory drugs (NSAIDs) are often the initial choice for treatment, their efficacy appears to be constrained. Džubera et al[27] presented 2 cases of lumbar disc herniation in which patients developed radicular pain in the lower back and leg during COVID-19 infection. Despite 6 months of treatment with conservative methods (including NSAIDs, exercise, and electrotherapy), there was no response, ultimately leading to surgical intervention. In a study conducted by Aksan et al,[28] a patient diagnosed with COVID-19 experienced severe neck and back pain, burning sensations, and allodynia shortly after being admitted to the hospital. Initially, there was no response to the primary treatment with NSAIDs; however, benefits were observed following gabapentin therapy. While experiencing COVID-19, a patient described by McWilliam et al[29] developed neuropathic pain that was localized to the distal extremity. Despite the patient's partial response to pregabalin treatment, the patient's clinical symptoms returned to normal on their own during a steroid withdrawal regimen. In our study, both oral therapy and mesotherapy demonstrated a positive response in VAS and LANNS scores among patients suffering from post-COVID chronic pain. However, the response to mesotherapy treatment was more substantial. Mesotherapy has gained popularity as a pain management method in recent years due to its ease of application, low likelihood of causing systemic side effects, and its proven effectiveness as a treatment method.

Brauneis et al[30] reported that in all 141 patients who received mesotherapy for spinal pain unresponsive to NSAIDs, there was a minimum of 50% reduction in pain compared to baseline. Additionally, they noted that the patients were able to tolerate the treatment without the need for increased systemic drug dosages. Viscito et al[31] demonstrated the effectiveness of mesotherapy, either with normal saline solution or a pharmaceutical cocktail, in reducing pain and disability in 100 spondylarthrosis patients with neck pain in the short term. Furthermore, they revealed that patients treated with the pharmaceutical cocktail continued to experience improvement 3 months after treatment. In their study involving 78 patients, Scaturro et al[32] reported that mesotherapy with diclofenac and thiocolchicoside was a safe and effective procedure in the short term for reducing pain, improving functionality, and enhancing quality of life in fibromyalgia patients with neck pain. In our study, we observed a more substantial improvement in VAS and LANNS scores within the mesotherapy group when compared to the oral therapy group.

Limitations and Strengths

Our study has certain limitations. It has a relatively small sample size, is conducted at a single center, and is retrospective in nature. Another limitation is the absence of a scale assessing the patients' psychological status.

Nevertheless, our study contributes to the limited body of research evaluating treatment methods for post-COVID pain syndrome, for which treatment guidelines have yet to be established. Our findings may provide valuable insights for clinicians in the development of treatment guidelines.

Conclusions

In post-COVID pain syndrome, mesotherapy represents an easily applicable, cost-effective, well-tolerated, and effective treatment modality with potentially low side effects for the relief of nociceptive and neuropathic pain. Nonetheless, there is a requirement for comprehensive, multi-center, prospective studies that also evaluate the enduring psychological impacts of chronic pain following COVID-19.

Author Contributions

İlknur Topal: Conception and design of study, data analysis, drafting manuscript. Onur Yılmaz: Data acquisition, data analysis, technical and material support.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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