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Efficacy of Mesotherapy and Trigger Point Injection in Post-Covid Pain Syndrome: A Randomized, Controlled Study

***(Running Title:** Mesotherapy and Trigger Point Injection in Post-Covid Pain Syndrome)*

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Abstract

Background: *Neuromuscular involvements are frequently reported after COVID-19 infection. The aim of this study is to investigate the efficacy of mesotherapy and combination of mesotherapy and trigger point injection in patients with chronic pain after COVID-19 infection.*
Materials And Methods: *62 patients with post-COVID pain syndrome were included in the study. They were divided into three groups. Oral diclofenac potassium, thiocolchicoside and cyanocobalamin treatment were given to the first group (n:23), intradermal mesotherapy containing 2% lidocaine + cyanocobalamin to the second group (n:17) and intradermal mesotherapy with intramuscular trigger point injection containing 2% lidocaine to the third group (n:22). Pain level was evaluated with visual analog scale (VAS) and neuropathic pain level was evaluated with The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) before and after treatment at 1 week.*
Results: *There was no significant difference between the pre-treatment VAS and LANSS scores of the cases. After treatment, significant response to treatment was recorded in all three groups. However, a more significant improvement in scores was observed in both groups, compared to the oral treatment group, respectively. When the VAS and LANSS scores before and after treatment were compared, a significant response was observed in both groups compared to the oral treatment group. However, there was no significant difference in response to treatment between the mesotherapy and combined group.*
Conclusion: *In post-COVID pain syndrome, both mesotherapy and trigger point injection combined with mesotherapy are effective treatments that are well tolerated in reducing pain and improving functions.*

Keywords: *COVID-19, pain, neuropathic pain, mesotherapy, post-COVID syndromes, trigger point injection.*

Background

The COVID-19 pandemic, which has been spreading around the world for almost 3 years, has affected more than 200 million people and resulted in the death of more than 4 million people (1).

Neuromuscular effects of this virus have begun to be defined, which can affect many organs and systems as well as cause severe acute respiratory tract infection. Acute COVID-19 infection includes the symptoms in the first 4 weeks, while prolonged COVID-19 infection includes the 4-12 weeks after acute COVID-19 infection (2). Post-COVID syndrome is characterized by fatigue, weakness, shortness of breath, chest pain, cough, joint pain, decreased exercise capacity, muscle pain, headache, palpitation, prolonged smell and taste disorders, sleep problems, poor concentration, mood changes, extreme forgetfulness, brain fog, depression, anxiety, lasting longer than 12 weeks and not due to any other cause (2). Post-COVID pain syndrome is also a component of this.

Chronic pain is defined as persistent or recurrent pain lasting more than 3 months or exceeding normal tissue healing (3). It is divided into three groups as nociceptive, neuropathic and nosiplastic pain. Nociceptive pain is the pain that develops with the stimulation of primary

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nociceptive nerve endings after tissue damage. Neuropathic pain is that occurs with damage or dysfunction of the central or peripheral nervous system. Nosiplastic pain is that results from nociception that changes without tissue or somatosensory damage caused by peripheral nociceptor activation (4). The coexistence of more than one type of pain is called as mixed type pain (4). Chronic pain causes a significant personal and socioeconomic burden when considering the disability, emotional instability and social isolation it causes. Therefore, early diagnosis and treatment is extremely important.

In previous studies, myalgia symptom was reported at a rate of 22-63% during COVID-19 infection (5,6). Persistent chronic pain reports are being made with increasing frequency after COVID-19 (7). Chronic pain seen after COVID-19 infection may develop due to direct invasion of nerve and muscle tissue by the virus, accumulation of immune complex and immune similarity mechanism, or it may develop due to tissue hypoxia secondary to increased hypercoagulability as a result of endothelial damage (5, 8).

When we evaluated patients with post-COVID chronic pain, we encountered a pain that did not show dermatomal spread, was innervated by many spinal nerves, usually spread to the back, neck or waist region and sometimes to the legs and arms, accompanied by neuropathic symptoms such as burning, tingling, numbness. These patients also had one or more accompanying latent and active trigger points.

There is no study in the literature about the treatment of chronic pain after COVID. In the management of chronic pain, nonsteroidal anti-inflammatory drugs (NSAIDs) still constitute the first line of treatment. However, the lack of an adequate response to NSAIDs in chronic pain seen after COVID-19 and the concerns of gastrointestinal, renal and cardiovascular side effects that may be seen in long-term use lead clinicians to look for alternative treatment options.

Local anesthetic injection is a method that has been used for many years in trigger point treatment (9). Mesotherapy is a micro-invasive treatment method in which pharmacological substances are applied locally to the dermis layer of the skin. Its main advantages are to create a pharmacological effect directly on the target tissue, to apply low doses and to have a low risk of side effects (10). There are studies reporting that mesotherapy is effective in chronic back pain (11, 12).

Based on the promising results of these studies, we aimed to evaluate the efficacy of intradermal mesotherapy with local anesthetic + cyanocobalamin mixture and combination of mesotherapy+trigger point injection with local anesthetic in the treatment of post-COVID chronic pain and whether there is a difference compared to oral treatment. Our main goal is to raise awareness among clinicians by defining an effective treatment protocol with low potential for side effects in patients with chronic pain after COVID-19.

Materials and Methods

Study design

This study was designed as a randomized controlled trial in Istanbul Medipol University Hospital.

Population

The inclusion criteria were to be confirmed diagnosed of COVID-19 (positive diagnosis of severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2] with real-time reverse transcription polymerase chain reaction and/or positive SARS-CoV-2 antibodies testing), to be diagnosed with post-COVID regional pain syndrome and to be between the ages of 18-65. Patients who had contraindications for mesotherapy and trigger point injection, had concomitant fibromyalgia syndrome, rheumatologic, psychiatric or neurological diseases and pregnant women were excluded from the study.

Sample

We defined post-COVID pain syndrome in patients who did not have any previous muscle pain, started at the time of COVID-19 infection and persisted 3 months after COVID-19 infection.

Between January 2022 and June 2022, 70 patients were evaluated who were diagnosed with post-COVID pain syndrome. After exclusion criteria, 62 patients were included in the study (Figure 1).

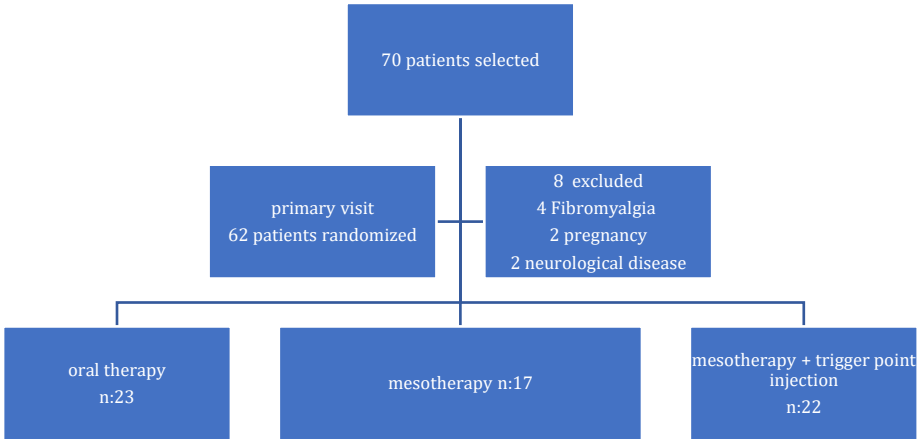

Figure 1: Flowchart

4 patients with fibromyalgia, 2 patients with neurological disease and 2 patients who were pregnant were excluded from the study. Demographic data of the patients, comorbidities, smoking, duration of pain, region of pain and presence of accompanying neuropathic symptoms were questioned. The clinical symptoms of the patients during the COVID-19 infection were recorded. Patients randomized according to the order of arrival to the outpatient clinic and were divided into three groups. Patients in the first group (n: 23) were given oral diclofenac potassium, thiocolchicoside and cyanocobalamin treatment and patients in the second group (n: 17) were given intradermal mesotherapy containing 2% lidocaine + cyanocobalamin (figure 2).

Figure 2: The sample photos showing intracutaneous injections in affected areas.

The third group (n: 22), a mesotherapy mixture containing 2% lidocaine + cyanocobalamin was applied to the painful area intradermally and 2% lidocaine injection to the trigger points intramuscularly.

Pain levels of the patients before and in the first week after treatment were evaluated with the Visual Analog Scale (VAS) and neuropathic pain levels were evaluated with The Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS).

Visual Analog Scale (VAS): This test is evaluated on the scale of 10 points. 0 indicates no pain and 10 points indicates unbearable pain. 1-3 indicates mild, 4-7 moderate, 8-10 severe pain (13).

LANSS Pain Scale: Central neuropathic pain assessment was performed with the LANSS pain scale to determine the presence of neuropathic pain. This scale was first applied by Bennet (14) to differentiate neuropathic pain from nociceptive pain. The highest score is 24. It is thought that neuropathic mechanisms play a role in pain with scores of 12 and above.

Primary outcome: To evaluate the efficacy of treatment methods on VAS and LANSS scores applied to patients with chronic pain after COVID-19.

Secondary outcome: Evaluation of the efficacy difference of treatment methods applied to patients with chronic pain after COVID-19, between oral therapy and each other using VAS and LANSS scores.

Regulations and ethics

Ethical approval for the study was obtained from the ethics committee of Istanbul Medipol University (Approval number: E-95961207-604.01.01-3412). All patients who agreed to participate in the study were informed and signed informed consent.

Statistical analysis

The behavior of quantitative variables was indicated using centralization and measures of variance: Mean ± Standard deviation. The Ki-square test was used to identify differences in ratios or relationships between categorical variables. One-way Anova test was used to show the behavioral differences of the group averages. The Bonferroni post hoc correction method was used for multiple comparisons between groups. Statistical significance was determined as p=0.05 for all cases. Statistical analyzes were performed with the IBM SPSS (Statistics Package for Social Sciences for Windows, Version 21.0, Armonk, NY, IBM Corp.) package program.

Results

62 patients diagnosed with post-COVID pain syndrome were included in the study. The mean age of the participants was 41.4±10.8. 32.3% (n: 20) of the participants were male and 67.7% (n: 42) were female. 22.5% (n: 14) of the participants were smokers and 21% (n: 13) had any comorbidities. There was a history of hospitalization in 29% (n:18) of the cases. The mean duration of pain onset was 6.9±3.6 months.

There was no significant difference between the groups in terms of demographic data (Table 1). Among the randomly selected groups, the hospitalization rate of the group who were applied trigger point injection + mesotherapy combination was lower than the other groups (p: 0.002*).

Table 1: Comparison of demographic data between groups.

		Oral Therapy (N:23)	Mesotherapy (N:17)	Mesotherapy + Trigger Point Injection (N: 22)	p
Age		40,5±11,2	41,8,8±9,4	41,9±11,7	0,896
Height		168,7±9,1	170,0±9,1	165,0±8,6	0,202
Weight		74,3±9,3	78,7±7,9	72,2±9,0	0,78
Duration		6,6±3,6	6,1±2,8	7,8±4,1	0,330
Gender	Male	7	9	4	0,211
		41,2%	39,1%	18,2%	
	Female	10	14	18	
		58,8%	60,9%	81,8%	
Hospitalization	No	11	12	21	0,002*
		64,7%	52,2%	95,5%	
	Yes	6	11	1	
		35,3%	47,8%	4,5%	
Smoking	No	12	16	20	0,169
		70,6%	69,6%	90,9%	
	Yes	5	7	2	
		29,4%	30,4%	9,1%	
Comorbidity	No	12	20	17	0,440
		70,6%	87,0%	77,3%	
	Yes	5	3	5	
		29,4%	13,0%	22,7%	

During COVID-19, loss of taste and smell was observed in 59.72% (n: 37) of the cases, fever in 48.4% (n: 30), cough in 66.1% (n: 41), fatigue in 83,9% (n: 52) and headache in 62.9% (n: 39). When the symptoms during the COVID-19 infection were evaluated, there was no significant difference between the groups (Table 2).

Table 2: Comparison of symptoms during COVID-19 infection between groups.

		Oral Therapy (N:23)	Mesotherapy (N:17)	Mesotherapy + Trigger Point Injection (N: 22)	p
Smell And Taste Loss	No	12	7	6	0,234
		52,2%	41,2%	27,3%	
	Yes	11	10	16	
		47,8%	58,8%	72,7%	
Fever	No	12	10	10	0,708
		52,2%	58,8%	45,5%	
	Yes	11	7	12	
		47,8%	41,2%	54,5%	
Cough	No	6	5	10	0,352
		26,1%	29,4%	45,5%	
	Yes	17	12	12	
		73,9%	70,6%	54,5%	
Fatigue	No	3	1	6	0,174
		13,0%	5,9%	27,3%	
	Yes	20	16	16	
		87,0%	94,1%	72,7%	
Headache	No	6	7	4	0,309
		26,1%	41,2%	19,0%	
	Yes	17	10	17	
		73,9%	58, 8%	81,0%	

Pain was located in the back with a rate of 40.3% (n: 25), neck with 35.5% (n: 22), neck + back with 19.4% (n: 12) and lumbar region with 4.8% (n: 3). 74.2% (n: 46) of the cases had burning, 71% (n: 44) had numbness, 69.4% (n: 43) had tingling, 67.7% (n: 42) had stinging and % 54.82 had hypoesthesia. There was no difference in neuropathic pain symptoms between the groups (Table 3).

Table 3: Comparison of neuropathic pain symptoms between groups.

		Oral Therapy (N:23)	Mesotherapy (N:17)	Mesotherapy + Trigger Point Injection (N: 22)	p
Burning	No	9	3	4	0,183
		39,1%	17,6%	18,2%	
	Yes	14	14	18	
		60,9%	82,4%	81,8%	
Hypoesthesia	No	11	7	10	0,916
		47,8%	41,2%	45,5%	
	Yes	12	10	12	
		52,2%	58,8%	54,5%	
Stinging	No	9	3	8	0,312
		39,1%	17,6%	36,4%	
	Yes	14	14	14	
		60,9%	82,4%	63,6%	
Tingling	No	6	5	8	0,750
		26,1%	29,4%	36,4%	
	Yes	17	12	14	
		73,9%	70,6%	63,6%	
Numbness	No	9	5	4	0,302
		39,1%	29,4%	18,2%	
	Yes	14	12	18	
		60,9%	70,6%	81,8%	

There was no significant difference between the pre-treatment VAS and LANSS scores of the cases. In all three groups, significant response was recorded after treatment. However, a more significant improvement in scores was observed in both groups, compared to the oral treatment group, respectively (p: <0.001**, p: <0.001**) (Table 4).

Table 4: Comparison of VAS and LANSS scores between groups before and after treatment.

	Oral Therapy (N:23)	Mesotherapy (N:17)	Mesotherapy + Trigger Point Injection (N: 22)	p
LANSS	14,1±3,0	16,3±3,8	15,7±4,2	0,166
VAS	7,4±1,2	6,8±1,7	7,4±2,2	0,433
VAS TS	4,6±2,2	2,1±1,1	2,0±1,1	<0,001**
LANSS TS	9,2±4,6	4,7±3,2	2,6±2,1	<0,001**

When the VAS and LANSS scores before and after treatment were compared, a significant response was observed in both groups compared to the oral treatment group (Tables 5, 6). However, there was no significant difference in response to treatment between the mesotherapy and combined group (VAS difference p: 0.471, LANSS difference p: 0.99).

Table 5: Difference in VAS and LANSS scores before and after treatment.

Group	Oral Therapy (N:23)	Mesotherapy (N:17)	Mesotherapy+ Trigger Point Injection (N: 22)	p
LANSS differance	4.91 ± 3.73	11.65 ± 4.44	13.05 ± 4.13	**<0.001**
VAS differance	2.83 ± 1.99	4.71 ± 2.17	5.45 ± 1.77	**<0.001**

Table 6: Comparison of groups with differences according to VAS and LANSS score response.

		p
VAS differance	Mesotherapy vs. Oral Therapy	**0.011**
VAS differance	Trigger Point Injectıon + Mesotherapy vs. Oral Therapy	**<0.001**
VAS differance	Mesotherapy vs. Trigger Point Injectıon + Mesotherapy	0.471
LANSS differance	Oral Therapy vs. Mesotherapy	**<0.001**
LANSS differance	Oral Therapy vs. Trigger Point Injectıon + Mesotherapy	**<0.001**
LANSS differance	Mesotherapy vs. Trigger Point Injectıon + Mesotherapy	0.99

Discussion

The main findings of our study are as follows; firstly, significant response to treatment was observed in all three groups. Secondly, there was a significantly more pronounced response in the VAS and LANSS scores in the mesotherapy and combined treatment group, compared to the oral treatment group, respectively (p: <0.001**, p: <0.001**). When the pre-treatment and post-treatment VAS and LANSS scores were compared, there were better results in the mesotherapy and combined group compared to the control group but there was no significant difference in response to treatment between these two groups (VAS difference p: 0.471, LANSS difference p: 0.99).

COVID-19 virus enters cells using angiotensin converting enzyme-2 (ACE-2) and cellular transmembrane protein serine-2 (TMPRSS-2) receptors (15,16). ACE-2 receptors are commonly found in neuronal cells (15). At the same time, the virus can enter nerve tissue from vascular endothelial cells using the TMPRSS-2 pathway (16). In peripheral nervous system involvement, the molecular mimicry mechanism is more prominent (16). An immune-mediated response occurs against the myelin sheath or Schwann cells (16). The similarity between glycoproteins on the virus and human neuronal tissue proteins causes an autoimmune response. Direct invasion into the cell via ACE-2, immune complex deposition, immune similarity mechanism and the release of cytokines that cause myositis are responsible in the involvement of muscle cells (16). Hypercoagulability and endothelial dysfunction secondary to hyperinflammation in COVID-19 patients increase the risk of thrombosis (17). At the same time, vasodilation is impaired by decreasing nitric oxide release from endothelial cells (17). This can cause tissue hypoxia and initiating nociceptive pain in the muscles. At the same time, somatosensory damage secondary to thrombosis of the vase nervorums feeding the nerve may also cause neuropathic pain. All of these possible mechanisms may cause localized tissue hypoxia and lead to trigger point development.

Myofascial trigger point is a hyperirritable focus located within the taut band of skeletal muscle or muscle fascia, which is painful with compression and may cause characteristic referred pain, sensory, motor dysfunction and autonomic phenomena (9). The basis is the release of algogenic substances secondary to localized tissue hypoxia and as a result, there is an ongoing muscle contraction due to sensitization in autonomic and sensory nerve fibers (18). Local ischemia and hypoxia resulting from continuous contracture of taut bands reduce pH significantly (18). Low pH plays a role in mechanical hyperlagesia and central sensitization.

Viral infections may cause neuromuscular findings by affecting the central and peripheral nervous system (19). Many viruses including ebstein bar virus (EBV), varicella zoster virus (VZV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), influenza A and enteroviruses have been associated with neurological complications (19). Cases of unilateral vesicular lesions and long-lasting neuropathic pain and allodynia localized in a specific dermatome in herpes zoster infection, neuropathic pain accompanied by burning and mechanical allodynia in HIV infection, acute flaccid myelitis and chronic neuropathic pain cases associated with enteroviruses have been reported (19). Attal et al. (19) predicted that neuropathic pain may develop in the early period or within weeks related to COVID-19 considering the data analyzed after previous viral infections and stated that early diagnosis and treatment strategies should be developed in this regard. In early series, it has been reported that up to 2.3% of patients hospitalized for COVID-19 infection may develop probable neuropathic pain (8). Ocak et al. (20) reported that 65.4% of the patients evaluated with the diagnosis of COVID-19 had pain and 29.2% had a neuropathic pain component. In the study of Topal et al. (7) evaluating chronic pain in 501 patients with COVID-19 infection, the incidence of chronic pain was 13.7%. These patients had pain that did not show dermatomal spread, mostly localized in the back, neck and lumbar region and sometimes spread to the arm or leg. Some of the patients also had symptoms of burning and neuropathic pain at varying rates. In the study of Aksan et al. (21), in a case who was followed up with the diagnosis of COVID-19 and developed severe pain, burning and allodynia in the neck and back (C1-L5) involving the trapezius and paraspinal region on the second day of hospitalization, there was no response to a non-steroidal anti-inflammatory (NSAID) drug and gabapentin treatment was beneficial. In the case described by McWilliam et al. (22), it was reported that the patient who had neuropathic pain localized in the distal extremity during COVID-19, did not fully respond to pregabalin treatment but improved during steroid withdrawal regimen.

Although there are studies reporting chronic pain after COVID-19, there is no study in the literature about its treatment yet. NSAIDs are still the first line of treatment. On the other hand, the fact that post-COVID pain is chronic and localized, accompanied by neuropathic pain symptoms and

the presence of trigger points in the examination led us to search for alternative treatment options.

Mesotherapy is an effective treatment method that has become increasingly popular in pain management in recent years. It's easy to apply and has a low probability of systemic side effects. Yang et al. (23) showed that intracutaneous injection mixture of a local anesthetic and steroid into the affected paravertebral area in patients with acute nonspecific neck pain was sufficient to relieve neck pain and the analgesic effect was stronger than oral ibuprofen. Ferrara et al. (24) examined the short and long-term effects of normal saline solution and lidocaine + acetylsalicylic acid mixture mesotherapy in chronic spinal pain (CSP) patients and they found that normal saline solution reduced the pain intensity at equal rates with the drug cocktail at short-term follow-up, but the drug cocktail showed a better outcome at long-term outcome improvement. Akbaş et al. (25) compared the effectiveness of mesotherapy application of a mixture of lidocaine + tenoxicam + thiocolchicoside and oral dexketoprofen treatment in patients with a diagnosis of lumbar disc herniation who applied to the emergency department due to acute low back pain and they found that while more effective results were obtained in those with mesotherapy, the need for analgesic use was found to be lower in one-week follow-up. There is a study in the literature reporting that mesotherapy is beneficial in the long term in carpal tunnel syndrome (CTS) in which neuropathic pain is the main component. In the study of Conforti et al. (26) in 25 patients with CTS, after intradermal mesotherapy injection with a mixture of lidocaine + ketoprophen lysine-acetylsalycilate + xantinol nicotinate + cyanocobalamine, all patients except four reported a significant reduction in pain and paresthesia. After 12 months, pain resolved completely in 17 patients and eight patients reported recurrence of pain and sensory symptoms. Our patients also had neuropathic pain symptoms so we added cyanocobalamin to the mesotherapy solution. Similar to previous studies, a more effective treatment response was observed in the VAS and LANSS pain scales in the mesotherapy group compared to oral treatment in our study.

Trigger point injection with lidocaine is a treatment method that has been used for many years. Kamanli et al. (27) evaluated the effectiveness of dry needling, lidocaine and botulinum-A (BTX-A) injection in patients with myofascial pain syndrome. At the end of the 4th week, pressure pain thresholds (PPT) and pain scores (PS) improved significantly in all three groups. PPT values were significantly higher in the lidocaine group than in the dry needling group. PS values were significantly lower than both BTX-A and dry needling groups. Finally, VAS scores were significantly reduced in the lidocaine injection and BTX-A groups and were not significantly changed in the dry needling group. As a result of the study, it was reported that lidocaine injection can be preferred in trigger point treatment because it causes less discomfort than dry needling and is more cost-effective than BTX-A injection. In our study, trigger point injection combined with mesotherapy provided a significant response in visual analog scale and neuropathic pain scores. It has shown more effective results compared to oral therapy. However, no significant difference was observed in the treatment results with the mesotherapy group alone.

Limitations and Strengths

Our study has some limitations. Our results are valid in the short term but are probably not sufficient to predict the long-term efficacy of mesotherapy and combined therapy of mesotherapy and trigger point injection on the control of post-COVID chronic pain. There are also other limitations regarding the lack of blinding due to the nature of the study's design and the need to protect patients from the potential side effects of the invasive procedure. Because the study had a relatively small sample size and was single-center, the results may not be generalizable to a larger population. Pain scale and neuropathic pain scores were used in the assessment as the study focused on pain relief, One of the limitations of the study is the lack of a scale assessing mental status. Studies are needed have larger sample sizes and evaluating the long-term psychological effects of chronic pain.

However, our study is the first to evaluate treatment in post-COVID chronic pain syndrome. Our results on this subject will guide clinicians in the management of post-COVID pain.

Conclusion

In post-COVID pain syndrome, both mesotherapy and trigger point injection combined with mesotherapy are effective and well tolerated treatments in reducing pain and improving functions. Both treatment methods are seen as a very good alternative treatment option in patients who have contraindications for systemic administration with NSAIDs or who do not respond to NSAIDs. However, mesotherapy alone or combined with trigger point injection has not been found to be superior to each other. Long-term follow-up of both methods, enlarging the sample size and multicenter further studies are required for a more objective evaluation of post-COVID chronic pain treatment.

Disclosure statement

All authors declare no conflict of interest.

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