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The Clinical Effects of Laser Acupuncture on Hospitalized Patients With Severe COVID-19: A Randomized Clinical Trial

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Abstract

Introduction: The coronavirus disease (COVID-19) was extended to the entire population in China and around the world, and its mortality rate was about 3.4%. The impact of laser therapy on chronic respiratory diseases has been shown in previous studies. This study was aimed at examining the effects of laser acupuncture (LA) on patients with severe COVID-19.

Methods: In the present study, 60 patients with a positive reverse transcription-polymerase chain reaction (RT-PCR) test were assigned to the intervention and control groups (30 patients in each group). The intervention group was treated with LA, that is, laser light with low energy on acupuncture points, once a day for five consecutive days.

Results: The participants' mean age in the intervention and control groups was 48.96±12.65 and 53.16±12.28 respectively; 70% of the patients were male and 30% of them were female. IL6 had a significant reduction in the intervention group (*P* value=0.038) in comparison with the control group (*P* value=0.535). Furthermore, the mean admission time in the control group was significantly higher than that in the intervention group (*P* value=0.047). However, the mortality rate in the intervention group was zero, but three patients in the control group died.

Conclusion: Our study showed that LA can be used as supportive therapy for routine treatment in patients with severe COVID-19. Moreover, due to LA safety and it's low cost, it could be recommended as an adjuvant to conventional therapy in patients interested in treating their disease with such a method.

Keywords: Laser acupuncture; Laser therapy; COVID-19; Severity.

Introduction

COVID-19 was first reported in Wuhan, China, in December 2019 and then gradually extended to the entire population in China and around the world.[1] According to the World Health Organization, until February 2021, there were about 110 million confirmed cases of COVID-19 and the case mortality rate was about 3.4%.[2] As scientists have not been able to find an effective treatment for this disease yet, various methods have been used to reduce the mortality or severity of the disease.[3,4]

Low-level laser therapy (LLLT) is a rapidly developing area of clinical medicine. The number of studies on the biomodulating possibilities of LLLT and it's effects in various fields of medicine has been growing continuously.[5] LLLT is a noninvasive and safe technology accepted and approved by the US Food and Drug Administration (FDA) for anti-inflammatory[6] and analgesic effects,[7] treating tendinopathy[8], tissue healing[9], and improving lymphedema.[10] In LLLT, the light source touches the skin and the photon energy penetrates tissue. In addition, several different intracellular biomolecules restore normal cell function and improve the healing processes of the body.[11] In such human respiratory diseases as pneumonia, asthma, and chronic obstructive pulmonary disease (COPD), it has been shown that LLLT reduces respiratory symptoms, shortens recovery times, and normalizes respiratory function, immunological systems, and radiological parameters.[12-14]

COVID-19 is categorized as an "epidemic" disease in traditional Chinese medicine (TCM). To date, TCM has gained rich experience in combating epidemic diseases. Further, related records of acupuncture and moxibustion

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for preventing and treating an epidemic exist in the classical literature of TCM.

Recent clinical and experimental investigations have revealed that acupuncture-moxibustion can control immune function in humans and produce anti-inflammatory and anti-infection effects. It has a part in the treatment and prevention of infectious diseases. Furthermore, this Chinese therapy has played a major role in the control and prevention of COVID-19 and achieved good results.[15]

Having been used since 1970, laser acupuncture (LA) is utilized on the skin, and it can replace needles by means of laser-emitting devices, involving focused irradiation at specific points. These specific points in LA have been the most common traditional acupuncture points used over the past 35 years with a low-intensity laser.[16,17] LA treatment is deemed to be a discrete method of treatment; however, it is a subgroup of LLLT. In this treatment, rather than employing the direct effect of light on tissues to induce a physiological reaction, a diagnostic and therapeutic paradigm which has been defined by acupuncture theories is used to choose acupoints.[18,19] LA treatment is impacted by various wavelengths, energy doses, and acupoints.[16,20,21]

The impact of laser therapy on chronic respiratory diseases has been shown in previous studies, but it has not been specifically studied in the case of COVID-19. Therefore, due to the importance of treatment in patients with COVID-19, this study was done to examine the effect of LA on COVID-19 severity.

Methods

This randomized clinical trial was conducted on COVID-19 hospitalized patients at Shohada-e Tajrish Hospital, Shahid Beheshti University of medical sciences, Tehran.

Patients

We included 60 patients (30 patients in the intervention group receiving the laser and 30 patients in the control group) with severe COVID-19 physical symptoms, admitted to the hospital from September to December 2020. COVID-19 patients were diagnosed with a positive RT-PCR test and radiological signs of COVID-19 on a CT scan.

Inclusion and Exclusion Criteria

Patients with severe COVID-19 were hospitalized, and those who met the following criteria were included in this study: saturation of peripheral oxygen (SpO2) < 93% at sea level at room temperature, a ratio of arterial Oxygen partial/pressure PaO2 (in mm Hg) to fractional inspired oxygen (PaO2/FiO2) < 300 mm Hg, a respiratory rate of > 30 breaths per minute, or lung infiltrates > 50%.[22] Patients under 30 years or over 70 years, patients with cancer or tumor comorbidities, and pregnant patients were not included in the study.

The study was registered at the Iranian Registry of Clinical Trials website (identifier: IRCT20111121008146N34). This trial adhered to CONSORT (Consolidated Standards of Reporting Trials) and SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.

Randomization and Blinding

Eligible participants who consented to participate in this study were randomized into either the intervention group or the control group by the block randomization method. Block randomization was conducted to randomize the sequence. All possible patterns of blocks were written and selected randomly, and in the next step, four patients were assigned to each block (two patients in the intervention group and two patients in the control group). However, there was no possibility of blinding the therapist due to the obvious type of treatment. Finally, to prevent information bias, the analyzer was blinded about the kind of treatment.

Intervention

The participants were treated with LA once a day for 5 consecutive days. To choose acupoints, we not only drew on the evidence from ancient literature and modern clinical and basic pieces of research but also incorporated the results of the previous acupuncture research studies on lung function improvement, innate immunity regulation, anti-inflammatory and pro-inflammatory factors, vagal-cholinergic anti-inflammatory pathway activation, respiratory system regulation, and lung inflammation damage control.

The acupuncture points exposed to the low-power laser in this study included Hegu (LI4), Taichong (LR3), Tiantu (CV22), Chize (LU5), Kongzui (LU6), Zusanli (ST36), Sanyinjiao (SP6), Dazhu (BLll), Fengmen (BL12), Feishu (BL13), Xinshu (BL15), Geshu (BL17), Zhongfu (LU1), Danzhong (CV17), Qihai (CV6), Guanyuan (CV4), and Zhongwan (CV12)[23] that are shown in Figure 1. The participants' body acupuncture points were selected and irradiated with the gallium aluminum arsenide laser with a wavelength of 810 nm, power of 400 mW, and energy of 6 joules per point (6 J/point) with Nogier A (292 Hz) frequency.

Both the intervention group and the control group were treated with conventional drugs and antibiotics according to the national guideline of Iran.

Outcome Measurement

Patient demographic data, smoking status, alcohol abuse, comorbidity of chronic diseases, and body mass index (BMI) were collected at the beginning of the study. The number of breaths per minute, blood pressure, body

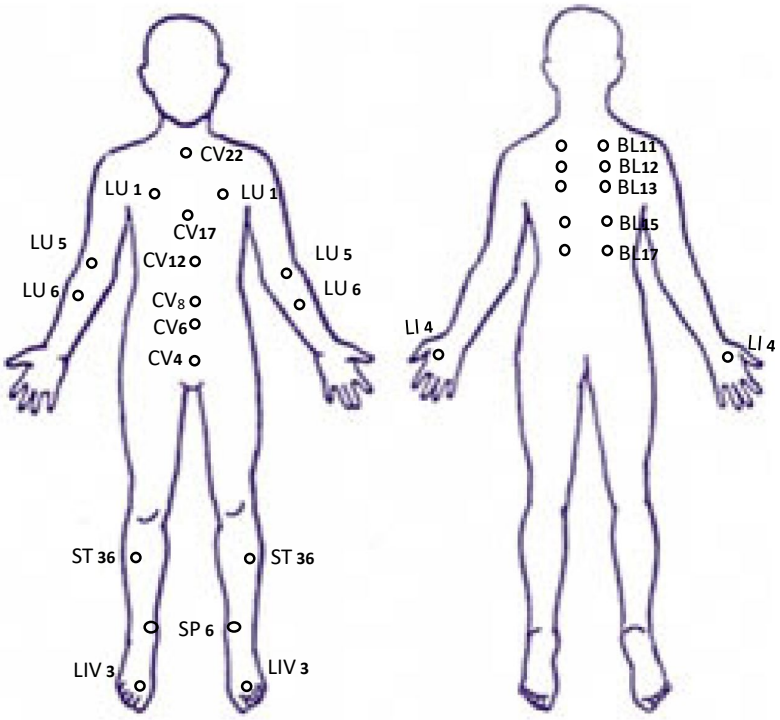

Figure 1. Place of Acupoints Used in the Present Research

temperature, percentage of oxygen saturation at rest, clinical symptoms, time of hospitalization, mortality, need for respiratory equipment, ICU hospitalization rate, and laboratory tests (CBC, lymphocytes, interleukin-6 [IL-6]) were assessed before and after the intervention.

Statistical Analysis

Frequency, percentage, and 95% confidence interval (CI) were used to describe the categorical variables; also, mean ± standard deviation (SD), and 95% CI were employed to describe the quantitative variables which were almost normally distributed. The normality of quantitative variables was tested with the Shapiro-Wilks test.

The paired-samples t-test and the independent-samples t-test were utilized to compare the mean differences in quantitative outcomes within and between the groups. Furthermore, the chi-square test was employed to examine the relationship between the categorical outcome and the independent characteristics. The analysis was based on completed data (without any missing data); all *P* values were based on two-tailed tests, and a $P < 0.05$ was deemed to be statistically significant. Data analysis was done with SPSS version 26 (IBM Corp Released 2016, NY, USA).

Ethical Considerations

We assured the patients that the collected data would remain confidential and they would receive a study information sheet. A signed and fully informed consent form was obtained from each participant, and each participant could leave the study at any time in case of dissatisfaction. In addition, laser therapy was the additional treatment; the intervention group did not receive less care than the conventional treatment group, and the participants did not pay for extra services.

Results

In this randomized clinical trial study, 60 participants were included. The randomization was conducted well and the measured variables were well distributed in the intervention and control groups. In this study, the ratio of males to females was 25 (83.3%)/5(16.7%) in the intervention group and 16 (53.3%)/14 (46.7%) in the control group ($P = 0.012$), and the mean age of the patients was virtually the same in the two groups, 48.96 ± 12.65 and 53.16 ± 12.28 years in the intervention group and the control group respectively ($P = 0.201$).

No patients had a history of cancer, benign or malignant mass, neurologic disease, epilepsy, and sensitivity to light. Clinical findings in each session of treatment are described in Table 1. The mean of the pulmonary involvement percentage was the same in the two groups (47.03 ± 13.17, 47.58 ± 12.72, $P = 0.980$). The pulmonary involvement percentage significantly decreased in each group ($P = 0.0001$ in the intervention group; $P = 0.001$ in the control group).

The mean admission time was 8.33 ± 3.45 days in the intervention group and it was 10.62 ± 5.63 days in the control group ($P = 0.047$).

The mortality rate in the intervention group was zero, but three patients (10%) in the control group died

($P=0.076$).

As it is shown in Table 2, the main outcome of the patients was compared in the two groups.

O_2 saturation was matched in the two groups before LA ($P=0.644$), and there was no significant difference between the groups five days after the intervention ($P=0.969$). However, O_2 saturation significantly increased in the intervention group after the treatment ($P=0.036$). The reduction in the mean fever and respiratory rate in each group was not significant.

At the beginning of the study, the mean of IL-6 was 24.12 ± 50.57 in the intervention group and it was 24.26 ± 37.90 in the control group ($P=.991$). IL-6 had a significant reduction in the intervention group ($P=0.038$) in comparison with the control group ($P=0.535$).

The laboratory findings were compared within and between the two groups, as shown in Table 3. Patients' statement between the two groups was shown in Table 4.

Discussion

The current study was aimed at investigating the LA effects on the treatment of severe COVID-19. To our knowledge, this is the first study examining the effects of LA on COVID-19 treatment.

In the clinical course of COVID-19, dyspnea can commence five days after the infection. Coughing is the most important sign which represents an inflammatory reaction in the respiratory system. Although there have not been any standard treatment protocols for COVID-19 thus far, supportive care has played a significant role in COVID-19 management. Such treatment options as chloroquine, Kaletra,[24] and a combination of lopinavir and ritonavir can be administered in that regard. However, the definite effect of these medications on patients' survival has not been observed.[24] Due to a wide variety of adverse reactions, the use of corticosteroids in acute respiratory distress syndrome (ARDS) caused by COVID-19 is controversial.

As it was mentioned before, no definite treatment has been approved for COVID-19. Thus, every possible treatment method for reducing inflammation and improving the respiratory system or other impaired tissues can be adopted to manage COVID-19 progression.

COVID-19 is classified as one of the "five epidemics" and it is generally susceptible. All people are vulnerable to COVID-19 regardless of their age and experience similar symptoms. This epidemic goes into the human body via the mouth and nose, and according to TCM, it invades the lung first, then the spleen, stomach, and large intestine.[15]

There are a few reviews mentioning that LA, as an adjuvant treatment, is beneficial to COVID-19.[25] Although there is some suggestion of the beneficial effect of acupuncture on improving appetite, coughing,

Table 1. Patients' Medical History in the Two Groups

History	Intervention Group No. (%)	Control Group No. (%)	*P* Value
Smoking	4 (13.3)	3 (10)	0.688
alcohol consumption	4 (13.3)	3 (10)	0.688
Pulmonary disease	4 (13.3)	3 (10)	0.688
Cardiovascular disease	3 (10)	2 (6.7)	0.640
Hypertension	10 (33.3)	6 (20)	0.243
Diabetes	5 (16.7)	4 (13.3)	0.718
Renal disease	2 (6.7)	1 (3.3)	0.554
Thyroid function disorder	5 (16.7)	2 (6.7)	0.228
BMI>25	4 (13.3)	1 (3.3)	0.161
Surgery	15 (50)	4 (13.3)	0.161

Table 2. Comparison of the Primary Outcome Before and After Laser Acupuncture in the Two Groups

		Intervention Group	Control Group	*P* Value
O_2 saturation	Before treatment	90.17 ± 5.82	89.50 ± 5.31	0.644
	After 5 days	93.55 ± 4.48	92.17 ± 4.85	0.436
	P value	0.030	0.081	
Fever	Before treatment	36.90 ± 0.29	36.64 ± 0.38	0.064
	After 5 days	36.84 ± 0.96	36.59 ± 0.35	0.026
	P value	0.766	0.866	
Respiratory rate	Before treatment	19.42 ± 2.08	19.10 ± 1.65	0.186
	After 5 days	19.09 ± 1.57	18.61 ± 1.20	0.258
	P value	0.837	0.569	
IL-6	Before treatment	24.12 (0-150)	24.26 (0-178)	0.371
	After 5 days	15.37 (0-129)	22.37 (0-190)	0.478
	P value	0.038	0.535	

Table 3. Comparison of Laboratory Findings Before and After Laser Acupuncture in the Two Groups

		Intervention Group	Control Group	*P* Value
WBC count	Before treatment	8.31 ± 3.80	8.27 ± 4.48	0.975
	After 5 days	13.18 ± 4.63	9.86 ± 3.83	0.036
	P value	0.005	0.075	
Lymphocyte count	Before treatment	15.43 ± 9.27	19.17 ± 9.98	0.139
	After 5 days	11.00 ± 7.86	13.22 ± 7.70	0.456
	P value	0.672	0.088	
Platelet count	Before treatment	263.90 ± 108.64	217.80 ± 77.04	0.063
	After 5 days	325.81 ± 93.77	265.95 ± 110.44	0.132
	P value	0.046	0.068	

WBC, White blood cells

Table 4. Comparison of Patients' statement difference Between the Two Groups

	Intervention Group	Control Group	*P* Value
Dyspnea	5.56 ± 2.69	3.68 ± 3.48	0.160
Chest pain	4.56 ± 3.78	2.50 ± 2.20	0.203
feeling pressure on the chest	4.40 ± 3.44	2.86 ± 2.53	0.169

insomnia, and headaches in patients with COVID-19, there has been no report about the application of LA in COVID-19 patients until now.[26]

In the present study, the clinical examination and patients' declaration after LA in the intervention group demonstrated more improvements in respiratory symptoms like dyspnea, chest pain and feeling pressure on the chest, compared to the control group. Previous studies have shown the effective role of LLLT and LA in decreasing the swelling and diminishing pain associated with inflammation in respiratory diseases.[12-14]

Sigman et al reported the first severe COVID-19 patient treated with low-power laser therapy. They presented LLLT as an auxiliary treatment along with the usual treatment. Thereafter, several studies demonstrated LLLT outcomes in promoting lung tissue regeneration in COVID-19 patients.[27,28] In addition, there are pieces of evidence showing that acupuncture is an effective intervention in patients suffering from COVID-19.[29]

In this study, the mean platelet count increased in the group with LA intervention. The difference between the two groups was not significant. New studies have indicated that there is mild thrombocytopenia in hospitalized COVID-19 patients. This drop may be associated with systemic hypercoagulability.[30]

Thus, the frequency of venous thromboembolism in severe COVID-19 patients is high.[31,32] On the other hand, thromboembolism is connected with mortality in patients with COVID-19.[30] LLLT reduces platelet aggregation and destruction during damage and inflammation.[33] Consequently, it may possibly prevent arterial thrombotic events and venous thromboembolism. Güçlü et al suggested that the mean platelet could be used as an assisting investigation in calculating mortalities in COVID-19 patients.[34]

The mean length of stay (LOS) in hospital for patients with COVID-19 in the intervention group was 8.33 ± 3.45 days, whereas the median time in the control group was 10.62 ± 5.63 days, and this significant difference shows that a reduction in the length of hospital stay could play a role in decreasing treatment cost, accelerating recovery in patients, and preventing possible nosocomial infections. On the other hand, studies have shown that a prolonged hospital stay is related to a rise in creatinine levels and kidney failure.[35] Guo et al reported that the mean LOS in the hospital in COVID-19 patients was 17 days (13-22 days), and this was higher than the control group in the present study. There are multiple reports on this topic with different outcomes, and this differences may be due to the diversity in standards for hospital admission and discharge.[36]

Our study showed the efficacy of LA in the treatment of COVID-19. Likewise, previous studies, some of which are mentioned below, have shown a significant effect of LLLT on pulmonary function parameters, asthma, COPD, and bronchiectasis. Nejatifard et al systematically reviewed the positive effects of photobiomodulation on COVID-19 patients and showed that photobiomodulation could help to reduce lung inflammation, promote regeneration in damaged tissues, and increase oxygenation indirectly to rehabilitate the affected organs.[37] In a study, Mohamed et al showed that LLLT led to an improvement in 31 patients with a chronic respiratory illness (asthma, COPD, bronchiectasis, and interstitial lung disease (ILD) in forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), forced expiratory flow (FEF), and minute walk distance (MWD) after ten days of laser therapy as compared to the baseline data in the study group.[38]

In a study, Scheewe et al examined the effect of 12 acupuncture sessions in a 4-week period on bronchial asthma patients, and their results revealed that the lung function improved significantly ($P < 0.01$) in the peak expiratory flow (PEF) of the acupuncture group versus the control group.[39] In another study, Fung et al. investigated the efficacy of acupuncture and placebo acupuncture in mild to moderate exercise-induced asthma in an outpatient setting, and they concluded that acupuncture led to statistically significant improvements in lung function parameters FEV1, FVC, and PEF compared with the control group, $P < 0.02$.[40] In addition, the results of the study by Chow et al. who examined the impacts of acupuncture on asthma patients in two weeks showed a significant improvement in FEV1 in intervention patients.[41]

Several studies have shown an increase of IL-6 in COVID-19 patients in comparison with healthy individuals. This increase could be indicative of disease progression to severe disease and mortality.[42] In this study, we found that the level of IL-6 was reduced in the intervention group compared to the control group.

Therefore, the results of this study suggest that LA may cause an improvement in the prognosis of patients with COVID-19 by anti-inflammatory effects. The benefit and effects of LA observed in this study should be reinforced by functional and biologic plausibility. To explain the mechanism, it can be said that LA may activate the interferons (IFNs), enhance the micro- and macro-circulation, and decrease the expression of TNF-α mRNA and its production levels. PBM is able to lower the IL-6 levels during acute lung inflammation or ARDS, increase the generation of interleukin-10 (IL-10), and inhibit the generation of macrophage inflammatory protein-2 (MIP-2). Interferons (IFNs) have the main role in protecting cells against viruses and balancing the immune system; however, IFN-α and IFN-β increase the T lymphocytes and macrophages which can control the immune system reactions.[37,43-46] TNF-α can stimulate IL-6 generation. Moreover, TNF-α causes neutrophil adhesion and activation that cause an increase in coagulation and

edema in acute lung inflammation.[47,48] Interleukin-1beta (IL-1β) and IL-6 are other types of cytokines that increase inflammation, and a severe case of COPD with a poor prognosis shows a higher level of these cytokines; many studies have shown that LLLT decreases the production of IL-1β and IL-6.[44,49]

Conclusion

LLLT with coherent light of low energy in LA has photobiomodulation effects such as immunomodulatory and regulation of inflammation. Acupuncture as a part of TCM has different biological effects and can regulate Immune System and Inflammation, so the combination of photobiomodulation by laser light and acupuncture in LA can regulate inflammation in patients with severe COVID-19.

Our study showed that LA as a supportive therapy with conventional drugs may be useful in patients with severe COVID-19.

In addition, this treatment is safe and cost-effective and could be recommended as an adjuvant to conventional treatment for better and faster prognosis in patients who are interested in treating their disease with other methods.

Limitation

Due to the type of study (randomized control trial), appropriate randomization, blinding, data collection, monitoring, and quality control of data by members of the research project, the authors of this article believe that their findings have a high level of validity. However, the sample size of the present study was small, although it had sufficient power to assess the association and differences.

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Competing Interests

The authors of this manuscript have declared no conflict of interest.

Ethical Approval

The study protocol was approved by the Shahid Beheshti University of Medical Sciences Ethics Committee in Biomedical Research (registration code: IR.SBMU.RETECH.REC.1399.509) and registered in the Iranian registry of clinic trial (IRCT: IRCT20111121008146N34).

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