Effect of Low Level Laser Therapy on Hypercoagulability in Patients with COVID-19

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ABSTRACT

Background : COVID-19 is one of the sever acute respiratory syndrome, it can have an impact on a person's physical, psychological, and social well-being Along with respiratory illness , profound pro thrombotic milieu leading to both arterial and venous thrombosis .These patients are primarily managed with anti-coagulant drugs combined with circulatory exercises. **Purpose:** Finding out if there is effect of low level laser therapy on hypercoagulability in patients with COVID-19. **Subjects & Methods:** Sixty patients with COVID-19 both gender, their ages ranged from 35 to 45 years. The participants selected from ELMenshawy general hospital, Tanta governorate, Egypt randomly assigned into two groups equal in number. The experimental group received a program of low intensity laser therapy three times per week for two months, circulatory exercises, and medical treatment, and the control group received circulatory exercises and medical treatment. Demographic data will be collected as marital status, level of income, level of education, and occupation. **Subject and Conclusion** It was concouled from the study that LLLT combined with circulatory exercises is beneficial for protection from hypercoagulability in patients with COVID-19.

Keywords: COVID-19;lowlevel laser ; circulatory exercise; hypercoagulability.

INTRODUCTION

The coronavirus disease 2019 (COVID-19), a global pandemic caused by SARS-CoV-2, has become a challenge for all mankind, primarily for scholars and doctors, who are tasked with finding possible ways for disease control, effective treatment of patients with minimization of mortality and development of complications, and the rehabilitation of patients. In humans, this viral infection can cause a number of diseases, including severe acute respiratory syndrome (1).

Activation of blood coagulation has rapidly emerged as a distinctive clinical feature in patients with the most severe forms of the disease poor prognosis(2) Furthermore, numerous reports have shown a high incidence of venous thromboembolic events in COVID-19 patients (3,4). However, the reported incidence of thrombotic events varies depending on the severity of disease and thrombo- prophylaxis strategies. Based primarily on anecdotical observations, the use of low molecular weight heparin (LMWH) at therapeutic doses has been initially suggested in specific subsets of patients (5), although caution has been recommended in view of the inevitable hemorrhagic risk associated with such practice (6)

Pancani (7)showed that COVID-19 has been associated with an increased risk of thrombotic events; however, the reported incidence of deep vein thrombosis varies depending, at least in part, on the severity of the disease. Some studies suggest that inflammation-induced endothelial cell injury could lead to an activation of the fibrinolytic system (8,9), which may justify the elevated D-dimer levels in patients with severe COVID-19. Furthermore, it should be noted that a hyperfibrinolyic state and elevated levels of plasminogen activator inhibitor-1 (PAI-1) were observed in the SARS-CoV epidemics in 2002. (10) and similar alterations have been recently reported regarding SARS-CoV-2.28. Therefore, a complete evaluation of the fibrinolytic system could provide further information about COVID-19-associated coagulopathy. In addition, other possible underlying mechanisms of COVID-19 coagulopathy have been recently suggested. Elevated antiphospholipid antibodies have been observed in some patients (11;12), which could explain the endothelial damage that occurs in this disease and, thus, the coagulation abnormalities observed in these patients. The coagulation alterations observed in antiphospholipid syndrome are similar to those of COVID-19 coagulopathy, and they probably share some pathogenic mechanisms (13). Current research suggests that lymphopenia, defined as a low lymphocyte count, is commonly present in patients with COVID-19 (14;15)

The effect of low level laser therapy (LLLT) is due to its absorption by tissues through photoreceptors, facilitating events such as mitochondrial respiration, calcium transport—which results in more significant cell proliferation—repairing, and regenerating tissues. LLLT has to assist in the recovery process from nerve, bone, respiratory tract, and other injuries involved in functional rehabilitation, favoring the patient's recovery. LLLT can be used with the ILIB technique (Intravascular Laser Irradiation of Blood), which increases immunity, inducing positive effects on the expression of immunoglobulins (IgA, IgM and IgG) and modulation of inflammation. Therefore, this technique can be used to treat various pathogens such as infectious diseases, bronchitis, and pneumonia (16;17).

The long-term effects of LLLT are thought to be due to the activation of various transcription factors by the immediate chemical signaling molecules produce from mitochondrial stimulation by LLLT. The most important of these

signaling molecules are thought to be ATP, cyclic-AMP, NO and ROS (18). LLLT at low doses has been shown to enhance cell proliferation of fibroblasts (19), endothelial cells (20) and lymphocytes (21;22).

Material & Methods:

Study design: This study randomized controlled prospective study.

Participants: Sixty patients with COVID-19 both gender, their ages will range from 35 to 45 years. The participants selected from ELMenshawy general hospital, Tanta governorate ,Egypt was randomly assigned into two groups equal in number, Experimental group, and control group. The experimental group received a program of low intensity laser therapy three times per week for two months, circulatory exercises, and medical treatment, and the control group received circulatory exercises and medical treatment. Demographic data collected as marital status, level of income, level of education, and occupation.

Measurement procedures:

1. Patient's medical history was carefully taken to collect data about her general condition.

2. The basic vital signs monitored (BP, temperature, respiratory rate, heart rate) before and during the application.

- The participants taught to stop the application and notify the researcher if they feel or complain from any of discontinuations of the device such as: dizziness, hypotension, fainting, heading, palpitation, arrhythmia, nausea, vomiting, anxiety, dyspnea, chest pain, Coughing or coughing up blood, sweating, and any other adverse effects.

Treatment procedures:

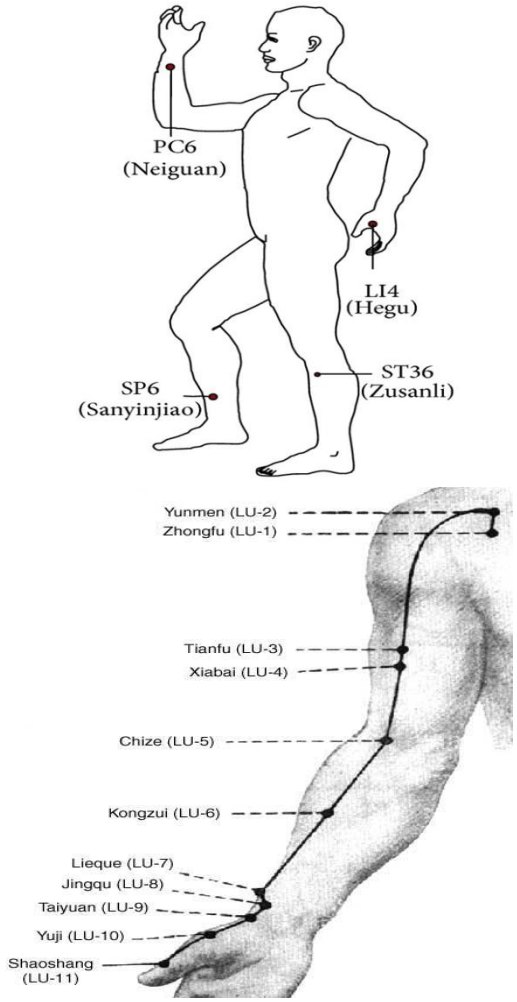
1. Experimental group: The 30 patients in this group performed application of low intensity pointed laser therapy with medication according to parameters shown in table 1.

Table 1. Specifications for Laser Parameters

Device information	
Manufacturer	International Electro Medical Company
Emitter type	GaAs
Code	PRO200
Irradiation parameters	
Center wavelength (nm)	808 nm
Operating mode	Pulsed
Frequency (Hz)	100 Hz
Beam shape	Circular
Treatment parameters	
Beam spot size at target (cm2)	Diameter = 1 cm, area = 0.78 cm2
Exposure duration (sec)	60 sec
Radiant exposure (J/cm2)	36 J/cm2
Radiant energy (J)	28 J
Number of points irradiated	15
Application technique	Without skin contact
Number and frequency of treatment sessions	24sessions, performed 3 sessions/ 2 months
Total radiant energy (J)	28 J per session, 672 J over all sessions
Output power	200mw

Acupuncture points: Laser acupuncture device applied on the lung acupuncture points that will be determined

according to the anatomical landmark shown as in (Fig. 1) (23).



II) Circulatory exercises:

Active assisted or against mild resistance. Supine with Leg up position 18 degrees measured by the bed water balance in the side rails. If patient was not comfortable according to the modified Borg scale or contra-indicated for the position then assume the supine position.

The subjects had a 3-min rest period to acclimatize themselves to each position. The ankle pumping exercises consisted of simple repetitions of dorsi flexion for 1 sec and plantar flexion for 1 sec with three different exercise intervals:

- Repeated dorsiflexion and plantar flexion with no rest (no-rest exercise)
- Repeated dorsiflexion and plantar flexion with a 2-sec rest period (2-sec rest exercise)
- Repeated dorsiflexion and plantar flexion with a 4-sec rest period (4-sec rest exercise).

The Subjects had practiced ankle pumps before the exercise to get familiar and be educated about the procedures (24).

- Control group: The 30 patients in this group was only circulatory exercises with medical treatment.

Data analysis:

Presenting data:

Continuous data were assessed for normality using the Shapiro–Wilk test.According to normality testing, continuous data were described as medians and rangesfor not-normal data. Categorical data were described as numbers and percentages.

Data comparison:

Categorical data were compared using the chi-square test. Continuous data were compared between two study groups using Mann–Whitney U test. Additionally, within-group comparisons were made using the Friedman test, and the Wilcoxon signed-rank test further evaluated the post-hoc test comparison-adjusted by Bonferroni's corrections. All *p*-values less than 0.05 were considered significant.

Results :

Demographic characteristics

The present study included a total of 60 patients with covid 19, randomly assigned to two groups (30 patients per group). The median age was 39.00 years and ranged from 35.00 to 45.10 years.The median weight was 75.00 kg with a range of 59.00 to 95.00 kg, the median height was 169 cm with a range of 150 to 183 cm, and the median BMI was 27.05 kg/m2 with a range of 22.60 to 29.80 kg/m2. Thirty patients served as the experimental group and received low-intensity pointed laser therapy with medication, whereas the other 30 patients were served as a control group and received medical treatment only.

Baseline characteristics of both groups, including age, sex, weight, height, BMI, sepsis-induced coagulopathy (SIC) scores, D-dimer, fibrinogen, C-reactive protein, lymphocyte count, platelet count, prothrombin time, and activated partial thromboplastin time were not significantly different (all $P>0.05$)

Table1: Comparison of D-dimer in both groups across the follow-up period.

D-dimer(ng/ml)	Pre-intervention	Post-2 weeks	Post-2 months	P-value overall[a]	P-value within Time[b]
Experimental group (n=30)	500.00 (500.00-2000.00)	500.00 (500.00-1500.00)	230.00 (200.00-250.00)	<0.001*	P1=0.066 P2<0.001** P3<0.001**
Control group (n=30)	500.00 (500.00-2000.00)	492.50 (370.00-1650.00)	320.00 (200.00-360.00)	<0.001*	P1<0.001** P2<0.001** P3<0.001**
p-value[c]	0.554	0.001*	<0.001*		

Data presented as median (min-max)

[a]: Friedman Test. [b]: Wilcoxon's sign rank test. [c]: Mann-Whitney U-test.

P1: Difference between pre-intervention and post-2 weeks.

P2: Difference between pre-intervention and post-2 months.

P3: Difference between post-2 weeks and post-2 months.

*: Statistically significant at*p*-value<0.05.

**: Statistically significant at P <0.016 according to pairwise comparison adjusted by Bonferoni's corrections (p< 0.05/ 3 = 0.016).

Table 2: Comparison of lymphocyte count in both groups across the follow-up period.

Lymphocyte count ($x10^3$ /µl)	Pre-intervention	Post-2 weeks	Post-2 months	P-value overall[a]	P-value within Time[b]
Experimental group (n=30)	0.80 (0.10-1.40)	1.60 (1.50-2.00)	3.05 (3.00-4.70)	<0.001*	P1<0.001** P2<0.001** P3<0.001**
Control group (n=30)	1.10 (0.50-1.40)	2.35 (2.00-3.00)	2.35 (1.60-3.60)	<0.001*	P1<0.001** P2<0.001** P3=0.625
p-value[c]	0.071	<0.001*	<0.001*		

Data presented as median (min-max)

[a]: Friedman Test. [b]: Wilcoxon's sign rank test. [c]: Mann-Whitney U-test.

P1: Difference between pre-intervention and post-2 weeks.

P2: Difference between pre-intervention and post-2 months.

P3: Difference between post-2 weeks and post-2 months.

*: Statistically significant at *P*<0.05.

**: Statistically significant at P <0.016 according to pairwise comparison adjusted by Bonferoni's corrections (p< 0.05/ 3 = 0.016).

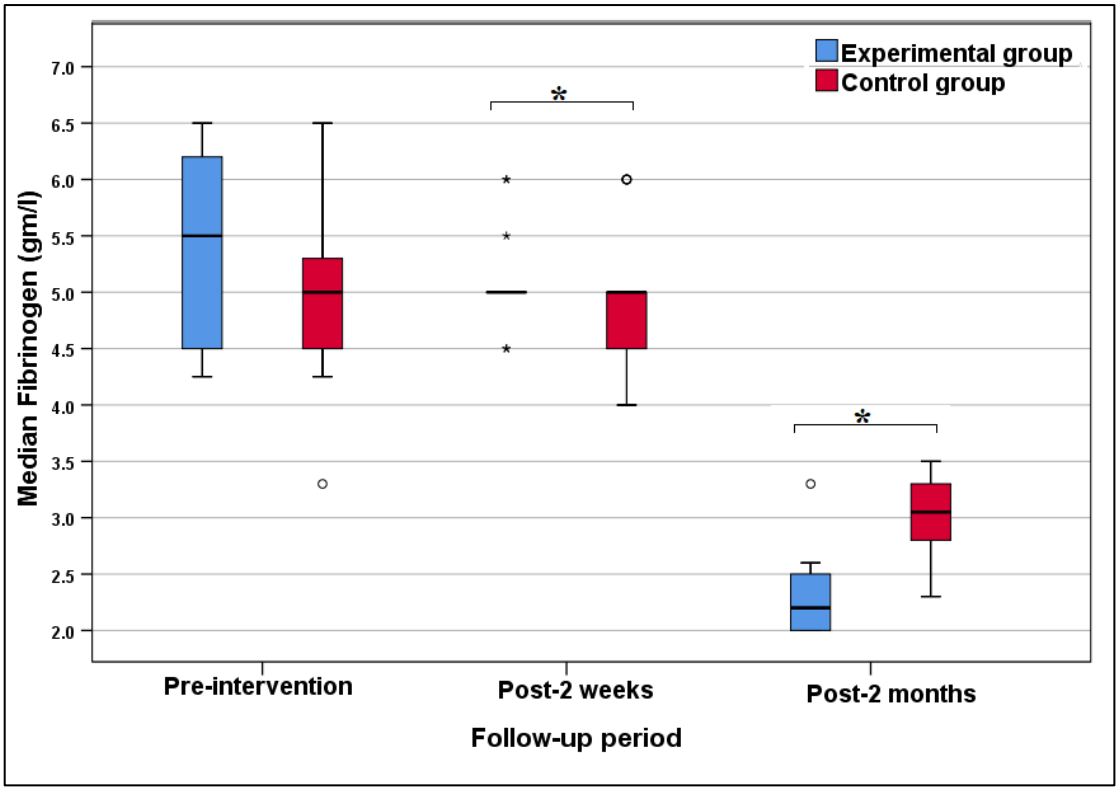


Fig.8: Box blot showing the median change of Fibrinogenbetween the two groups across the follow-up period.

*:Statistical significance at P<0.05.

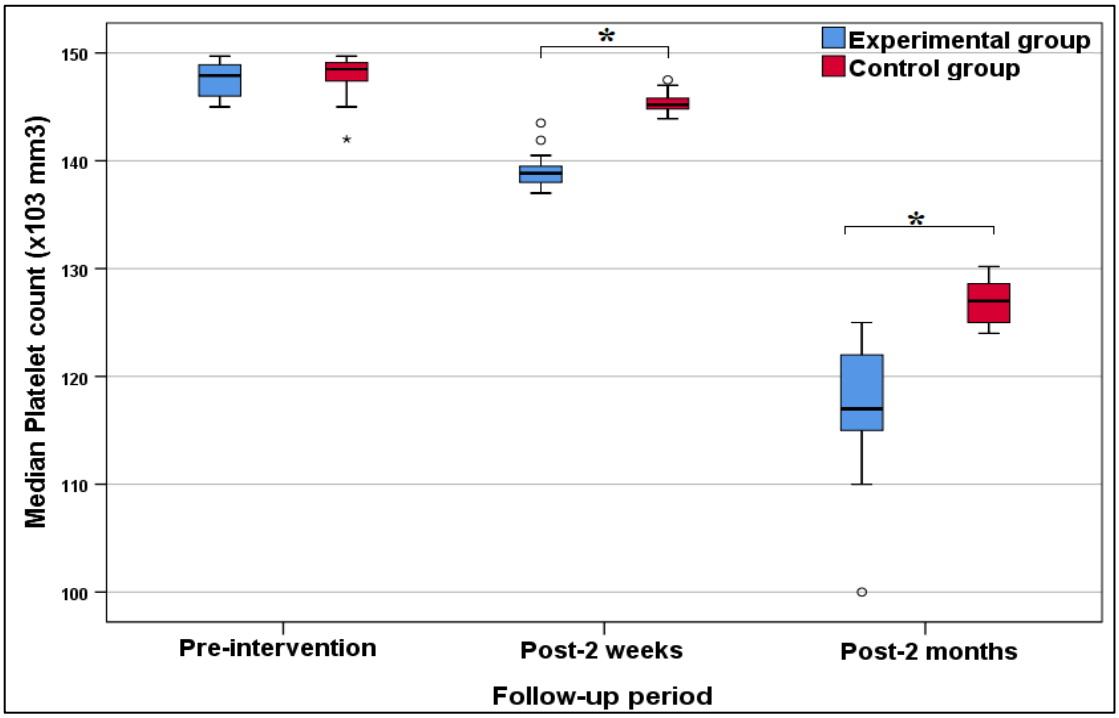


Fig.11: Box blot showing the median change of platelet count between the two groups across the follow-up period.

*:Statistical significance at P<0.05.

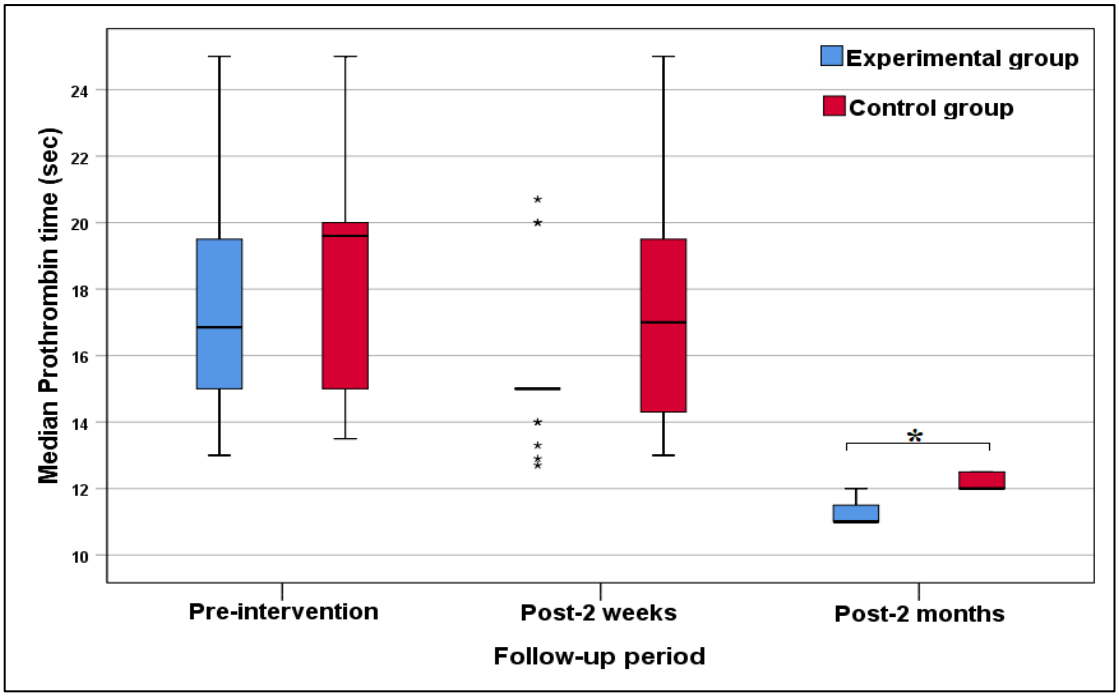


Fig.12: Box blot showing the median change of prothrombin time between the two groups across the follow-up period.

*:Statistical significance at P<0.05.

Discussion

The corona virus disease 2019(COVID-19),"The sever acute respiratory syndrome ''caused by SARS-COV-2 is a single stranded RNA corona virus that binding to angiotensin converting enzyme 2(ACE2),then enters The cell human, expressed in large amounts in alveolar cell of the lung , vascular endothelium ,cardiac myocytes and others cells(25),(6).

And pulmonary congestion by thrombosis and micro vascular occlusion , in addition to thrombosis of central lines and catheters and vascular occlusive events .

Covid19 patients common systemic inflammatory response syndrome is the presence of coagulopathy (2).

LLLT at low doses has been shown to cell proliferation of endothelial cells (20).and fibroblasts (19),and lymphocytes (21)(22). Lins RDAUconcluded that NO evidence that the LLLT has asignificant instant effect on the circulation or the oxygen saturation could be found .

In the study was carried out double –blind and placebo controlled in two batches of testing . the test subjects received one –off LLLT on adefined area of the arch of the foot simultaneously aplaccebo treatment(26).

Huang stated that LLLT represent deeply penetration through skin and achieve the muscles , for this reason , this study used an infrared wave length (808nm) that is inside of the best optical window to stimulate biological tissues(27).

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