Rehabilitation of COVID-19 Patients with Cognitive, Autonomic and Sleep Disorders Using Medicinal Leech Therapy

Saltanat SERİKBAYEVA [1] (iD), Namazbay ORMANOV [2] (iD), Talgat ORMANOV [3] (iD),

Ibragim ISHİGOV [4] (iD), Murat ZHUNUSSOV [5] (iD), Gulnaz KAYSHİBAYEVA [6] (iD),

Ferruh YÜCEL [7*] (iD)

[1]Department of Neurology, Faculty of Medicine, Khoja Akhmet Yassawi International Kazakh-Turkish University
[2]South Kazakhstan Medical Academy, Shymkent-Kazakhstan
[3]Department of General Practitioner, Faculty of Medicine, Khoja Akhmet Yassawi International Kazakh-Turkish University
[4]Department of Physiology, Faculty of Medicine, Khoja Akhmet Yassawi International Kazakh-Turkish University
[5]Department of General Surgery, Faculty of Medicine, Khoja Akhmet Yassawi International Kazakh-Turkish University
[6]Department of Neurology, Faculty of Medicine, Khoja Akhmet Yassawi International Kazakh-Turkish University
[7]Department of Anatomy, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir-Türkiye

*Sorumlu Yazar / Corresponding Author: Ferruh YÜCEL, e-mail: yferruh@gmail.com

ABSTRACT

New coronavirus disease (COVID-19) pandemic is a historical and urgent issue worldwide. The long-term consequences of the disease are neurological disorders, which need further investigation in terms of treatment and prevention. Apart from the traditional medical approach, management of cognitive, autonomic and sleep complications may be rehabilitated using medicinal leeches. The purpose of this study is to compare the neurological condition of COVID-19 patients before and after hirudotherapy. This cross-sectional study was conducted from January to December 2021 at the medical centre of the Khoja Akhmet Yassawi International Kazakh-Turkish University. The research population consisted of 83 patients with mild and severe forms of COVID-19 (more than 6 months), who underwent medicinal leech therapy (MLT). MLT was applied to the patients on the 6th and 11th days and their assessment of cognitive, autonomic and sleep disorders were carried out. Statistical analysis was carried out using SPSS Statistics (version 20.0, IBM, USA). The results of studies indicate a progressive neurological deterioration in COVID-19 patients. Neuropsychological observations in patients taking a full course of MLT showed an objective improvement in their cognitive, autonomic and sleep disorders. In particular, the Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Montreal Cognitive Assessment (MoCA) Scale, Schulte Tables, Spielberger-Khanin Anxiety Scale (SKAS), Beck depression inventory (BDI), Study scheme to identify signs of autonomic disorders, Epworth Sleepiness Scale (ESS), Index of Severity of Sleep Disorders (ISSD) values improved after the MLT procedures.

Key words: COVID-19, Hirudotherapy, Medicinal Leech Therapy, Cognitive Disorders, Autonomic Disorders, Sleep Disorders

Bilişsel, Otonomik ve Uyku Bozuklukları Olan COVID-19 Hastalarının Tıbbi Sülük Tedavisi Kullanılarak Rehabilitasyonu

ÖZET

Yeni coronavirus (COVID-19) hastalığı pandemisi, dünya çapında tarihi ve acil bir sorundur. Hastalığın uzun vadeli sonuçları, tedavi ve önleme açısından daha fazla araştırmaya gereksinim duyan nörolojik bozukluklardır. Geleneksel tıbbın dışında bilişsel, otonomik ve uyku komplikasyonlarının yönetimi tıbbi sülükler kullanılarak rehabilite edilebilir. Bu çalışmanın amacı COVID-19 hastalarının hirudoterapi öncesi ve sonrası nörolojik durumlarını karşılaştırmaktır. Bu kesitsel çalışma Ocak-Aralık 2021 tarihleri arasında Hoca Ahmet Yesevi Uluslararası Türk-Kazak Üniversitesi Tıp Merkezinde gerçekleştirildi. Araştırma populasyonu tıbbi sülük tedavisi (MLT) uygulanan hafif ve şiddetli COVID-19 (6 aydan fazla) formları olan 83 hastadan oluşuyordu. Hastalara 6. ve 11. günlerde MLT uygulandı ve onların kognitif, otonomik ve uyku bozuklukları değerlendirildi. İstatistiksel analizler SPSS İstatistik (Sürüm 20.0, IBM, USA) kullanılarak yapıldı. Çalışmaların sonuçları COVID-19 hastalarında ilerleyici bir nörolojik bozulma olduğunu göstermektedir. Tam bir MLT kürü alan hastalardaki nöropsikolojik gözlemler bilişsel, otonomik ve uyku bozukluklarında nesnel bir iyileşme olduğunu gösterdi. Özellikle, Pittsburgh Uyku Kalitesi İndeksi (PSQI), Uykusuzluk Şiddeti İndeksi (ISI), Montreal Bilişsel Değerlendirme (MoCA) Ölçeği, Schulte Tabloları, Spielberger-Khanin Anksiyete Ölçeği (SKAS), Beck Depresyon Envanteri (BDI), Otonomik bozukluk belirtilerini teşhis etme çalışma şeması, Epworth Uykulu olma Ölçeği (ESS), Uyku Bozuklukları Şiddeti İndexi (ISSD) değerleri MLT uygulamalarından sonra düzeldi.

Anahtar kelimeler: COVID-19, Hirudoterapi, Tıbbi Sülük Tedavisi, Kognitif Bozukluklar, Otonomik Bozukluklar, Uyku Bozuklukları

1. INTRODUCTION

World Health Organization declared the novel coronavirus disease (COVID-19) caused by SARS-CoV-2 as a pandemic in 2020 (Guan et al., 2019; Rothan, Byrareddy, 2020). Nowadays, the number of infected people reached 610,467,768, whereas the lethal cases from COVID-19 amount to more than 6.5 million. Among the main clinical manifestations of COVID-19, the progressive loss of neuronal condition is the urgent situation in the long-term management. This issue was not been fully investigated yet, although there were reported in multiple cases (Paterson et al., 2020; Kotfis et al., 2020; Moriguchi et al.,

2020; Varatharaj et al., 2020; Meier et al., 2021). Neuronal manifestations mainly include cognitive, autonomic and insomniac symptoms (Kumar, Veldhuis, Malhotra, 2021; Shouman et al., 2021; Partinen, 2021). The latter is called "coronasomnia".

Cognitive functions are usually understood as the most complex functions of the brain, providing rational knowledge of the world and purposeful interaction with it. (Chater et al., 2018). These functions include gnosis, memory, speech, praxis, attention, and thinking each of them is associated with one of four interacting components necessary in the process of cognition and interaction with the

world (Chater et al., 2018). Neurological disorders associated with COVID-19 had clinical manifestations of damage to various structures of the nervous system, including the central nervous system, peripheral nervous system and cranial nerves, as well as mental disorders (Guerrero et al., 2021; Taquet et al., 2021).

Insomnia occurs in people of all ages and races, and it is observed in all cultures and countries (Chater et al., 2018). Serious risk factors for the development of coronasomnia include age, female gender, comorbid disorders, shift work, possibly unemployment, and low socioeconomic status as well as psychosocial factors and confinements (Partinen, 2021; Altena et al., 2020). Excessive daytime sleepiness was noted in more than 2000 patients in the study of Sánchez-de-la-Torre et al. according to Epworth Sleepiness Scale (ESS) score being less than 10 (Sánchez-de-la-Torre et al., 2020).

Despite numerous publications on damage to the nervous system, in the context of COVID-19, the issues of pathogenesis, the presence of risk factors, and a reasoned connection between neurological disorders and coronavirus infection remain unclear. Undoubtedly, it is necessary to systematize the accumulated data on damage to the nervous system during COVID-19 for use in the practical work of a neurologist, further

developing an optimal treatment strategy and implementing effective preventive measures.

Hirudotherapy or medicinal leech therapy (MLT) is one of the options to treat COVID-19 patients. Thrombosis may be at the onset of the pathogenesis of the above-mentioned disorders. The neurotrophic effect of hirudotherapy is confirmed by numerous examples of the treatment of peripheral neuritis, "tunnel syndromes", etc (Apfel, 1999; Kulbida R, Mathes A, Loeser J., 2019). Experiments on organotypic cultures of the spinal ganglia showed that native destabilase, bdellin B-3, bellastezin, and eglin C stimulate the growth of neurons (Sig, Guney, Uskudar Guclu, Ozmen, 2017; Lemke, Vilcinskas, 2020). At the moment, a large theoretical and practical basis for the pathogenetic substantiation of the effective use of MLT in the treatment of patients with various forms of cerebrovascular diseases has been accumulated (Lemke & Vilcinskas, 2020; Le Marrec-Croq et al, 2013).

Moreover, due to the antioxidant, anti-ischemic, antihypoxic, and detoxification effects of MLT, as well as the neuroreparative action of cytokinesis and prevention of microthrombi formation, the application of hirudotherapy can be one of the methods of long-term rehabilitation from COVID-19. In this paper, we present the results of the neurorehabilitation of patients with cognitive, autonomic and sleep disorders after a

coronavirus infection with medicinal leech therapy.

2. Materials and Methods

83 patients with mild to severe forms of COVID-19 were studied. The average age of patients was 57.5, ranging from 45 to 70 years. 53 (63%) of the participants were female, whereas the rest 30 (37%) were male. Duration of a post-COVID-19period of more than 6 months was the main inclusion criteria as well as the presence of complaints of sleep quality and anxiety, whereas among the exclusion criteria were the presence of severe or unstable concomitant somatic pathology, stroke and transient ischemic attacks, traumatic brain injury, CNS tumours and diseases (inflammatory, degenerative, epilepsy, cerebral palsy), as well as mental disorders, depression, dementia, alcoholism, or drug addiction.

Considering the population of Shymkent city (south of Kazakhstan), which is around 900 thousand people, the number of COVID-19 cases in the region (approximately 50,000), and the willingness of patients to undergo the MLT, the sample size was considered satisfactory for this region.

To study the effect of medicinal leech therapy on the state of the cognitive sphere, we distinguished 2 comparison groups: the control group – healthy individuals without pathology from the central nervous system and the main group – COVID-19 patients. Patients were administered to the medical centre "Hirudomed" in Shymkent for the day of inpatient treatment. All patients signed informed consent to participate in the study. Study design: case-control.

This study was approved by the institutional review board – Clinical Ethics Commission of the School of Medicine of the Khoja Akhmet Yassawi International Kazakh-Turkish University (Certificate number: УЕ-ХҚТУ-104-2021) and the methods were in agreement with the ethical standards of the Declaration of Helsinki (October 2008 revision). Before the study, the participants were provided with personal explanations regarding the purpose and method of the study, as well as information regarding the processing of the results. The study was conducted with written consent.

Statistical processing of the data obtained during the study of the results was carried out using SPSS Statistics (version 20.0, IBM, USA). Qualitative characteristics are described using absolute and relative (%) values. Quantitative features are demonstrated in the form of Mean ± Standard Deviation (M±SD). The statistical significance of the differences between groups and the difference between two variables for the same group was determined by the paired t-test.

Medicinal leech therapy

Certified medical leeches, *Hirudo medicinalis,* are purchased at biofactories that have permission to produce and sell them was used for the MLT. Prior to the application of MLT, the points of leech application were cleaned with sterile water and a 5 ml syringe with the removed plunger was used to place the leeches. After the initiation of leech feeding, the syringe was removed. The exposition time was 1-2 hours until the auto-detachment of the animals. Then, the treatment area was cleaned with a sodium chloride solution. Depending on the severity of the cognitive functions of the central nervous system 5, 7, 10 leeches with an average size of 60.0 mm were used for mild, moderate and severe degrees, respectively.

Medical leeches are placed on the biologically active energy channels of the body depending on the pathologies. Points of staging medical leeches according to the method of Serikbaeva S. ZH., taking into account the energy regulation of the body 1 point Yin-tang, WB -20 feng-chi, 20th point back middle meridian Bai-hui, pp. 110-118 (Serikbaeva, 2022).

In addition to the fact that the impact on them has its reflex effect, during the work of the leech, a biologically active secret enters the patient's body. Medical leech normalizes the volume of circulating blood, unloads the lymphatic system, and evenly distributes blood throughout the body. The total duration of the MLT was 11 days with one session per day.

Assessment of cognitive disorders

The study of the neurological status was carried out according to the generally accepted method. To assess the state of sleep, Pittsburgh Sleep Quality Index (PSQI) questionnaire (Buysse et al, 1989) and Insomnia Severity Index (ISI) (Morin, Belleville, Bélanger, Ivers, 2011) were used (Table 1), as recommended by the Clinical guideline for the evaluation and management of chronic insomnia in adults (Schutte-Rodin, Broch, Buysse, Dorsey, Sateia, 2008).

We conducted neuropsychological testing according to the Montreal Cognitive Assessment (MoCA) scale (Nasreddine et al., 2005). which was developed as a rapid assessment tool for moderate cognitive dysfunction. It assesses various cognitive domains: attention and concentration, executive function, memory, language, visual constructive skills, abstract thinking, counting and orientation (Mahendran, Chua, Feng, Kua, Preedy. 2015). The time exposition for the MoCA is approximately 10 minutes. The maximum possible number of points is 30; 26 points or more is considered normal. Currently, the MoCA scale is considered the most appropriate for detecting moderate to mild cognitive impairment.

Table 1. Tests and questionnaires used for the assessment of cognitive, autonomic and insomnia disorders

Assessment of …	Tests and questionnaires
Cognitive disorders	Pittsburgh Sleep Quality Index (PSQI)
	Insomnia Severity Index (ISI)
	Montreal Cognitive Assessment (MoCA) scale
	Schulte tables
	Spielberger-Khanin anxiety scale (SKAS)
	Beck depression inventory (BDI)
Autonomic disorders	Study Scheme to identify signs of autonomic disorders
Insomnia disorders	Epworth Sleepiness Scale (ESS)
	Pittsburgh Sleep Quality Index (PSQI)
	Insomnia Severity Index (ISI)
	Index of Severity of Sleep Disorders (ISSD)

Schulte tables to study the speed of switching attention and working capacity in conditions of active selection of useful information; the scale of general deterioration, to assess the severity of not only cognitive impairment but also other (behavioural, emotional, functional) symptoms of the disease.

The state of emotional status was assessed according to psychometric scales: Spielberger – Khanin anxiety scale (SKAS) and Beck depression inventory (BDI). The test results of SKAS were interpreted as follows: up to 30 points - low; 31-44 points - moderate; 45 or more - high. The scale was adapted in Russian by Yu. L. Khanin (Budkevich, Budkevich, 2018). BDI included 21 categories of symptoms and complaints, each of them consisting of 5 statements that correspond to specific manifestations of depression, ranked according to the increase in the specific contribution of the symptom to the overall severity of depression. The score for each category is calculated as follows: each point on the scale is scored from 0 to 4 in accordance with the increase in symptom severity. The total score ranges from 0 to 62, and the test results are interpreted as follows: 0-9 – no depressive symptoms; 10-15 – mildde pression; 16-19 - moderate depression; 20-29 –moderate depression; 30-63 - severe depression (Butcher, Taylor, Cynthia Fekken, 1998).

Assessment of autonomic disorders
To identify signs of autonomic dysfunction, we used the Study Scheme to identify signs of autonomic disorders – a screening

questionnaire proposed by the Department of Pathology of the Autonomic System at the Sechenov Russian Medical Academy (Table 1). Emotional autonomic disorders were assessed on a point scale: a score exceeding 25 was regarded as a syndrome of autonomic dystonia. By the severity of the syndrome: the sum of points in the range of 25-30 corresponded to weak severity; 31-35 points - moderate; over 35 - a severe degree of Autonomic dysfunction syndrome (Magzhanov, 2017; Korchounov et al., 2005).

Assessment of insomnia disorders
Epworth Sleepiness Scale (ESS), PSQI questionnaire and ISI tests were used to assess insomnia disorders. ESS measures daytime sleepiness and consists of 7 components. The sum of points corresponding to 10 points, or more is regarded as pathological drowsiness, 6-10 points are moderate drowsiness, and the sum is not more than 5 points as normal (Johns, 1991; Manzar et al., 2019).

The scale of the PSQI questionnaire consists of 7 components that allow assessing the subjective assessment of sleep quality, sleep latency, duration and effectiveness of sleep, intrasomnical disorders, the use of sleeping pills, and disturbances in daytime activities. Component scores greater than 5 are considered insomnia (Snyder, Cai, DeMuro, Morrison,

Ball, 2018; Pilz, Keller, Lenssen, Roenneberg, 2018).

The ISI test consists of 7 components that allow for assessing the sleep problems of patients over the past 2 weeks. The sum of the results corresponding to 0-7 points was regarded as the norm, the sum of 8-14 points was mild sleep disturbances, the sum of 15-21 points as moderate sleep disturbances, and the sum of 22-28 points as pronounced sleep disturbances (Morin, Belleville, Bélanger, Ivers, 2011).

The index of severity of sleep disorders (ISSD) was identified using the following equation.

$$ISSD = \frac{PSQI+ISI+ESS}{3},$$

Where PSQI – Pittsburgh Sleep Quality Index, ISI – Index of the severity of insomnia and ESS – Epworth Sleepiness Scale

3. Results
Rehabilitation of cognitive disorders
To identify impairments in visual-constructive and executive skills, patients were asked to perform the "clock drawing" test, the "cube" test, and the "alternate path creation" test. The MoCA test results and the neuropsychological profile of the control and main groups are presented in Table 2.

Table 2. Comparative characteristics of the neuropsychological profile before and after medicinal leech therapy of patients with COVID-19

Indicators	Control group, n=50	COVID-19 patients before MLT, n=83	COVID-19 patients after MLT, n=83	
			On the 6th day	*On the 11th day*
MoCA test	30±0.83	16.7±0.83*	21.7±1.08 **	26.7±1.33 **
Visual constructive and executive skills	5.0 ± 0.20	3.0 ± 0.18 *	3.9 ± 0.19 **	4.8 ± 0.24 **
Item naming	3.0 ± 0.09	3.0 ± 0.18	3.0 ± 0.18 **	3.0 ± 0.17 **
Attention	6.0 ± 0.18	3.5 ± 0.17 *	4.4 ± 0.21 **	5.7 ± 0.25 **
Speech, including fluency	3.0 ± 0.12	1.5 ± 0.07 *	2.0 ± 0.09 **	2.6 ± 0.12 **
Regulatory functions including thinking	2.0 ± 0.06	1.3 ± 0.06 *	1.5 ± 0.10 **	1.8 ± 0.08 **
Memory (delayed playback)	5.0 ± 0.15	2.1 ± 0.12 *	2.5 ± 0.11 **	4.7 ± 0.23 **
Orientation	6.0 ± 0.24	5.3 ± 0.26 *	5.5 ± 0.27 **	5.9 ± 0.26 **
Schulte test (sec.)	28.3 ± 1.4	54.8 + 14.8 *	37.7 ± 13.2 **	30.9 ± 2.8 **
Situational anxiety	20 ± 0.60	45.0 ± 2.6 *	33.7 ± 1.68 **	25.0 ± 1.25 **
Personal anxiety	20 ± 1.01	47.5 ± 2.5 *	37.5 ± 1.87 **	27.5 ± 1.37 **
Symptoms of Depression (Beck depression inventory)	1.1 ± 0.06	21.5 ± 1.07 *	12.9 ± 0.64 **	2.5 ± 0.32 **
Insomnia Severity Index (ISI)	5.4 ± 0.21	18.4 ± 1.40 *	11.5 ± 1.17 **	6.9 ± 1.17 **

* - coefficient of reliability ≤0.05 compared with the control group.

** - coefficient of reliability ≤0.05 compared with the group of COVID-19 patients before MLT.

In general, the results of the study of the cognitive sphere on the MoCA scale showed that 90.7% of patients with COVID-19 had a total score of fewer than 26 points, which corresponds to the level of moderate cognitive impairment (MCI). MoCA test results, as well as the "Visual constructive and executive skills" and the "Attention" function were reduced in most patients with COVID-19. Moreover, the absolute majority of the surveyed (50%) did not cope with the task "Speech, including fluency" mainly due to a decrease in phonetically mediated associations, this could be more indicative of subcortical dysfunction. Thinking and memory functions were reduced in COVID-19 patients. Partially the relative success of patients with COVID-19 patients was demonstrated in the functions "Orientation" and "Item naming". The resulting changes are more indicative of a dysregulation

defect associated mainly with dysfunction of the frontal lobes of the brain, which is consistent with literature data (Pensato et al. 2021).

Objective confirmation of emotional disorders revealed according to the questionnaire data was confirmed by psychometric testing. We studied the level of anxiety according to the SKAS, and depression according to the BDI and the Schulte test. The values of these tests were increased in patients with COVID-19 by 93% in the Schulte test, 131% in SKAS and 125% in BDI. The results of ISI show that 2/3 of patients with COVID-19 had sleep disorders, the degree of which varied from "Mild sleep disorders" to "Severe sleep disorders"in24.5% and 16.8%, respectively.

The results of neuropsychological testing in patients taking MLT showed an objective improvement in their cognitive functions, the average score on a short scale for assessing mental status in patients with moderate cognitive impairment significantly increased, and the average time for them to perform the Schulte test decreased. There was also a positive trend in the clock drawing test. In patients with moderate cognitive impairment, the indicators significantly improved when conducting tests of frontal dysfunction, and a significant increase in the speech activity of patients was recorded: the number of words increased when performing a test for associations.

The MoCA scale at the 6th and after the 11th session of MLT increases from 16.7 ± 083 points to 21.7 ± 1.08 and 26.7 ± 1.33 points, respectively. The visual constructive and executive skills of COVID-19 patients after the 5th session of MLT increased by 18%, after the 11th day they increased by 36% and reached the indicators of the control group. The function "Attention" after the 5th and 11th courses of MLT was increased by 15% and 36.7%, respectively. The values of the test result for speech function were reduced, and under the influence of MLT, it increases at the 5th session by 16.7%, and by 36.6% after the full course of MLT. Reduced function "Thinking" in COVID-19 patients against the background of MLT after the 5th and 11th sessions increase by 10% and 35%, respectively. After 5 days of medicinal leech therapy, half of the patients coped with memory tests, and after a full course of MLT, complete memory recovery was established in 94%.

After the full course of MLT, the values of the Schulte test, SKAS and BDI decreased significantly: 83.9%, 44% and 70%, respectively, but remained higher compared with indicators of the control group by 25%, 37.5% and 40%, respectively. The results of the study of the severity of insomnia according to the ISI scale showed that after MLT, there are

positive changes in the area of insomnia, as evidenced by a decrease in the ISI by 67%.

Rehabilitation of autonomic disorders

Table 3 shows the clinical semiotics of autonomic disorders identified according to the screening questionnaire data. "Vascular necklace" is the hyperaemia on the neck, face and chest detected during external examination of patients. Five COVID-19 patients presented these "necklaces" and discolouration of hands and feet. Persistent white and red dermographism were diagnosed in 10 and 11 patients, respectively. Generalized hyperhidrosis was observed in 63 (75.9%) patients; the presence of hyperventilation syndrome was found in 59 (71%) patients; subfebrile condition (constant increase in body temperature) was observed in 42 (50.6%) COVID-19 patients before MLT.

According to the survey data, vegetative-vascular and vegetative-trophic changes were observed in most COVID-19 patients with a predominance of emotional disturbances (fear of death) in all participants before the therapy. Dysdynamic and dysrhythmic disorders manifested as the lability of blood pressure with a tendency to an increase in the lability of the heart rate with a tendency to tachycardia in 39 (46.9%) patients.

After the coronavirus infection, 40 (48.1%) of the surveyed showed impaired neuromuscular excitability (pain in the gastrocnemius muscles). The total number of points of symptoms of autonomic disorders after COVID-19 was 3159 and the index of severity of autonomic disorders was equal to 2.23 ± 0.11 (Table 4).

Table 3. Comparative characteristics of symptoms of autonomic disorders before and after medicinal leech therapy

Symptoms of autonomic disorders	COVID-19 patients before MLT, n=83		COVID-19 patients after MLT, n=83			
			On the 6th day		*On the 11th day*	
	Number of patients	*Total number of points*	*Number of patients*	*Total number of points*	*Number of patients*	*Total number of points*
"Vascular necklace" or hyperaemia on the neck, face and chest	5	25	4	20	-	
Changing the colour of the hands and feet	5	25	4	20	-	
Generalized hyperhidrosis	63	315	5	25	-	
Dermographism: white, resistant	10	50	2	10	-	
Dermographism: red, resistant	11	44	2	8	-	
Subfebrile condition (constant increase in body temperature)	42	252	2	12	-	
Temperature rises that occur suddenly in the absence of somatic diseases	21	147	2	14	-	
The presence of a deterioration in well-being when the weather changes	40	160	5	20	1	4
The presence of poor tolerance to cold, heat, stuffiness	39	156	6	24	1	4
Blood pressure lability	39	312	8	64	-	
Heart rate lability	39	312	8	64	-	
Presence of hyperventilation syndrome	59	472	19	152	-	
Dysfunction of the gastrointestinal tract (in the absence of organic pathology)	12	72	2	12	-	
The presence of vegetative-vascular crises, migraines, and the tendency to fainting	42	420	5	10	1	10
Emotional disturbances (fear of death)	83	581	8	56	1	7
Increased neuromuscular irritability (pain in the calf muscles)	40	240	6	36	1	6
Total	550	3159	88	557	5	31

Table 4. Comparative characteristics of changes in autonomic dysfunction before and after medicinal leech therapy

	Normal value	COVID-19 patients before MLT, n=83	COVID-19 patients after MLT, n=83	
			On the 6th day	*On the 11th day*
Index of the severity of autonomic disorders	0.00 ± 0.000	2.23 ± 0.11 *	0.39 ± 0.01	0.02 ± 0.001 **

* - coefficient of reliability ≤0.05 compared with the normal value

** - coefficient of reliability ≤0.05 compared with the COVID-19 patients before MLT

Under the influence of MLT, the objective and subjective indicators decreased in comparison with the indicators of patients before the therapy, particularly the "Vascular necklace" and the discolouration of the hands and feet. The presence of hyperventilation syndrome disappeared in 40 patients (67.7%), subfebrile condition in 40 (95.2%), the presence of vegetative-vascular crises, migraine, and the tendency to fainting was absent in 37 (88.8%). After the medicinal leech therapy, on the sixth day of the study, emotional disturbances (fear of death) were absent in 75 (90.3%) patients, dysdynamic and dysrhythmic disorders in 31 (79.4%) patients and the reaction to a change in the body to meta-conditions were absent in 35 (87.5%) patients.

After MLT on the sixth day of the study, pain in the gastrocnemius muscles disappeared in 34 (85%) and gastrointestinal dysfunction was absent in 10 (83.3%) patients. Under the influence of five sessions of MLT, the total number of points for symptoms of autonomic disorders was 557 points, which is 82.4% lower than without MLT; the index of severity of autonomic disorders decreased to 0.39 ± 0.01.

After a full course of MLT, "Vascular necklace", discolouration of hands and feet, generalized hyperhidrosis, presence of hyperventilation syndrome, subfebrile condition, dysfunction of the gastrointestinal tract, dysdynamic and dysrhythmic disorders were absent in all examined individuals. Deterioration of well-being with a change in weather remained only in one patient (2.5%), and the presence of vegetative-vascular crises, emotional disorders and pain in the gastrocnemius muscles was also noted in 1 patient. The total number of points for symptoms of autonomic disorders was 31

points and decreased by 99.1% compared to the indicators of COVID-19 patients before MLT. The index of the severity of autonomic disorders decreased from 2.23 ± 0.11 to 0.02 ± 0.001.

Rehabilitation of insomnia disorders

The clinical manifestations of the sleep disorders identified according to the screening questionnaires are presented in Table 5. According to the results of the PSQI questionnaire, only 2 COVID-19 patients did not suffer from insomnia, 81 (97.5%) respondents had scores of the sum of components more than 5 points. Subjectively, the quality of sleep was assessed as "Very good" by 1% of the respondents, "Quite good"

by 32.6%, "Rather bad" by 43.7% and "Very bad" by 22% of patients before MLT. Sleep latency up to 15 minutes was detected in 15.6% of cases; from 15 to 30 minutes in 25.2%; from 31 minutes to 1 hour in 27.4%; more than 1 hour was observed in 31.1% of patients.

Sleep duration of fewer than 5 hours was noted by 33.3% of the surveyed; 5-6 hours in 25.9% of patients; 6-7 hours of sleep in 24.4% of cases; more than 7 hours of sleep was detected in 15.6% of participants. Difficulties with maintaining the duration of sleep of varying severity from once a week to 3 or more times were observed in the vast majority of patients (94.8%). Daytime activity disorders of varying severity were noted in 69 (83.1%) patients.

Table 5. Comparative characteristics of changes in autonomic and insomniac dysfunctions after medicinal leech therapy

Indicators	Normal values	COVID-19 patients before MLT, n=83	COVID-19 patients after MLT, n=83	
			On the 6th day	*On the 11th day*
Pittsburgh Sleep Quality Index (PSQI)	4.5 ± 0.21	11.4 ± 0.57 *	8.6 ± 0.43 **	6.1 ± 0.30 **
Insomnia Severity Index (ISI)	5.4 ± 0.21	17.5 ± 1.05 *	13.1 ± 0.65 **	8.6 ± 0.43 **
Epworth Sleepiness Scale (ESS)	4.2 ± 0.19	11.8 ± 0.59 *	8.8 ± 0.44 **	6.8 ± 0.34 **
Index of the severity of sleep disorders (ISSD)	4.7 ± 0.33	13.5 ± 0.67 *	10.2 ± 0.62 **	7.16 ± 0.42 **

* - coefficient of reliability ≤0.05 compared with the normal values

** - coefficient of reliability ≤0.05 compared with the COVID-19 patients before MLT

According to the results of the PSQI questionnaire, the COVID-19 patients before MLT showed a more than two-fold (253.3%) increase compared to the normal values. ISI results demonstrated moderate drowsiness in 37 (44.5%) respondents, and pathological drowsiness was observed in 10 (12%) patients. The ISI scale, reflecting the severity of insomniac disorders, revealed a predominance of moderate and severe insomnia in patients with COVID-19. The Epworth sleepiness scale was 11.8 ± 0.59, with the normal values being 4.2 ± 0.19 points, and the increase was more than twofold (280.9%). The mean value of the ISSD in the group of COVID-19 patients before the treatment was 13.5 ± 0.67 points (normal: 4.7 ± 0.33 points).

The results of neuropsychological testing in patients taking medicinal leech therapy showed an objective improvement in their insomniac disorders, the mean score significantly decreased after five and 10 days of use. After initial and full MLT sessions, PSQI mean score and ISI scale decreased notably. Moreover, ESS value also decreased after five and ten days of MLT as well as ISSD on the 11th day.

4. Discussion

The results of studies indicate a progressive neurological deterioration in the indicators of the cognitive, autonomic and insomnia spheres in COVID-19 patients. Results of the MoCA test and various examinations of memory, speech, attention and orientation showed improvement in the intermediate and full MLT sessions. Also, the reduction of situational and personal anxiety values, as well as symptoms of depression were observed during and after therapy. We tend to substantiate the positive shifts in patients with cognitive disorders under the influence of medicinal leech therapy.

Changes in the neuro-cognitive characteristics potentially occurred due to the pharmacotherapeutic effect of biologically active substances contained in the saliva of a medicinal leech and numerous enzymes. The latter has antioxidant (Pteridines), anti-ischemic (Hirudin and Calin), antihypoxic (Acetylcholine and Carboxypeptidase-A inhibitors), detoxification (Bdellins, Eglins and Chloromycetyn), reparative action of cytokinesis (Hyaluronidase and Hirustasin), which prevents formed microthrombi and prevention of their formation (Destabilase) and improvement of microcirculation in the vessels of the central nervous system (Sig, Guney, Uskudar Guclu, Ozmen, 2017; Lemke, Vilcinskas, 2020; Le Marrec-Croq et al., 2013; Moosavian, Mirghazanfari, Moghaddam, 2014; Conforti, Connor, Heisey, Hartig, 2002; Koeppen, Aurich, Pasalar, Rampp, 2020).

In our study, vegetative-vascular and vegetative-trophic changes were observed in

the vast majority of patients with COVID-19 with a predominance of emotional disorders (fear of death), generalized hyperhidrosis, the presence of hyperventilation syndrome, subfebrile condition, the presence of vegetative-vascular crises, migraines, a tendency to fainting, pain in the calf muscles, and sensitivity to climatic changes. The use of a full course of MLT showed an objective improvement. Moreover, studies showed a significant increase in the PSQI, ISI indices, ESS scale in untreated individuals, whereas, after MLT, there was observed an improvement in sleep functions by 47%.

Although the use of medicinal leech therapy seems largely restricted, it may increase blood flow velocity, improve microcirculation and accelerate anastomosis (Moosavian, Mirghazanfari, Moghaddam, 2014; Conforti, Connor, Heisey, Hartig, 2002; Koeppen, Aurich, Pasalar, Rampp, 2020). Moreover, the dilution of thrombosis and the action of heparin and hormone are the other influential factors of leeching (Giglia et al., 2013). MLT is the subject of many studies determining its clinical application, efficacy and safety (Koeppen, Aurich, Pasalar, Rampp, 2020). Nevertheless, it should be noted its side effects: allergic reactions, bleeding and infections. Also, recent studies have suggested the role of vaccines in the induction of immune thrombotic thrombocytopenia and Guillain-Barré

syndrome, (Furie et al, 2021; Woo et al 2021) which needs further investigation into the neurological and autonomic dysfunction among COVID-19 patients. Thus, there is a demand for the complex treatment and rehabilitation of neurological disorders in patients with COVID-19.

5. Conclusion

All in all, all cognitive, autonomic and sleep disorders of COVID-19 patients were managed using MLT in a full 11-day course. Such indicators as the Pittsburgh Sleep Quality Index, Insomnia Severity Index, Epworth Sleepiness Scale and Index of the severity of sleep disorders showed promising outcomes for the neurorehabilitation of COVID-19 patients. Research findings might be included in the management of long-term consequences and complications of the disease as the rehabilitation of COVID-19 patients will be an issue for future medicine and we believe that MLT can be used to improve in their cognitive, autonomic and sleep disorders.

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