Neuromusculoskeletal Medicine (OMT) Clinical Practice

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Potential therapeutic effects of adjunct osteopathic manipulative treatments in SARS-CoV-2 patients

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Abstract: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) affects various human organ systems, including the lymphatic, pulmonary, gastrointestinal, and neurologic systems. The utilization of osteopathic manipulative treatment (OMT) techniques has been clinically effective in the alleviation of various upper respiratory infection symptoms. Consequently, the use of osteopathic manipulative medicine (OMM) in SARS-CoV-2 patients as adjunct treatment can be beneficial in promoting overall recovery. This paper attempts to address the pathophysiology of SARS-CoV-2 infection at the cellular level and its downstream effects. Subsequently, osteopathic principles were investigated to evaluate potential therapeutic effects, providing a holistic approach in the SARS-CoV-2 treatment. Although the association between the benefits of OMT on clinical improvement during the 1918 Spanish influenza pandemic can be seen, further investigation is required to establish a direct correlation between OMT and symptom management in SARS-CoV-2.

Keywords: COVID-19; infectious disease; lymphatic pump; osteopathic manipulative manipulation; SARS-CoV-2.

The SARS-CoV-2 outbreak started in December 2019 in Wuhan, China and quickly became a global health emergency across the world in early 2020. Coronaviruses are enveloped, positive single-stranded RNA viruses that infect humans and animals [1]. SARS-CoV-2 disrupts normal immune responses in the body, leading to impaired and uncontrolled inflammatory responses [2]. Severe cases of SARS-CoV-2 cause a sharp increase in cytokines, leading to a cytokine storm [2].

SARS-CoV-2 can invade many different organ systems and commonly affects the respiratory system [3]. Symptoms generally start after a mean incubation period of 5 days [1], and include fever, dry cough, dyspnea, nasal congestion, fatigue, headache, dizziness, generalized weakness, vomiting, diarrhea, loss of appetite, and anosmia (loss of smell) [3]. Ultimately, the infection can progress to severe disease leading to hypoxia, pneumonia, and the development of acute respiratory distress syndrome (ARDS) [3]. Patients ≥60 years of age are at higher risk of complications than the younger population, who are less likely to become infected and tend to present with milder symptoms or asymptomatic infection [1].

Various treatment methods have been considered for the management of SARS-CoV-2. One key modality is osteopathic manipulative treatment (OMT). This method encompasses the idea of unity between the body function and structure in relation to both health and disease [1]. OMT takes a holistic approach and utilizes palpatory diagnosis and manipulation to treat somatic dysfunctions [4]. OMT goals include restoring muscle movement, enhancing function, and improving biomechanical balance [4]. Ultimately, OMT modulates various systems including inflammatory, respiratory, neurological, and gastrointestinal systems. This paper considers the updates related to the therapeutic effects that OMT has on these body systems in relation to the management of SARS-CoV-2.

Clinical summary

Inflammatory pathways in SARS-CoV-2

SARS-CoV-2's initiation of inflammatory signaling pathways leading to cytokine storm is essential in the pathogenesis of

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ARDS in patients with SARS-CoV-2 [5]. The spike proteins bind to the angiotensin converting enzyme (ACE2) receptor [6]. This interaction forms angiotensin II, which causes cytokine production, local inflammation, fibrosis, and oxidative stress [7]. The ACE2 enzyme converts angiotensin II into angiotensin [1–7], an anti-inflammatory and anti-fibrotic mediator that releases nitric oxide (NO) and induces vasodilation [6]. SARS-CoV-2 utilizes the ACE2 receptor to gain entry into host cells, leading to a downregulation of the receptor and reduced activity of the enzyme [5, 8]. Consequently, there is an excess in angiotensin II due to a reduction in the hydrolysis of angiotensin II into angiotensin [1–7] via ACE2 [9]. This mechanism is central in the viral hyper-inflammatory states seen in patients with SARS-CoV-2, and it is a key contributor to the initiation of the cytokine storm. The immune system recognizes and processes viral antigens via antigen-presenting cells, and subsequently presents them to natural killer and CD8-positive cytotoxic T-cells utilizing the major tissue histocompatibility complex (MHC) [10]. This presentation initiates the production of abundant proinflammatory chemokines and cytokines through the innate and adaptive immune response. The innate immune system becomes dysregulated via the exaggerated secretion of pro-inflammatory cytokines and chemokines. In patients with severe disease, this activation is so excessive that it leads to a cytokine storm, which can result in multi-organ failure, thrombosis, and death [10].

OMT in the alleviation of immune processes and inflammation

Proper lymphatic fluid flow and drainage is essential in reducing inflammation via cytokine regulation, inhibition of macrophage activity, and neutrophil apoptosis. In particular, pump techniques are geared toward influencing lymphatic circulation. Infections that promote lymphatic congestion and prevent proper lymph circulation can inhibit leukocyte recirculation and worsen disease [11]. The flow of lymphatic fluid differs from the circulation of blood in that flow is not maintained by a heart pump. Drainage and circulation of lymphatic fluid occurs via rhythmic and phasic contraction of lymphatic vessels. External forces on lymph vessels through respiration, intestinal peristalsis, and muscle contraction aid in lymphatic flow [11]. Pump techniques that increase lymph flow also can cause an increase in the total leukocyte count in the thoracic and mesenteric ducts. Pumps increase leukocyte mobilization and the release of immunoglobulins from gut-associated lymphoid tissues (GALT), the largest mass of lymphoid tissue in the body [11]. Studies have shown that in patients with chronic back pain, OMT resulted in an attenuation of tumor necrosis factor alpha (TNF-α) levels posttreatment [11]. These techniques also resulted in a significant decrease in monocytes and in particular NO, which plays an active role in the propagation of inflammation [11].

Lymphatic pumps in COVID-19 patients

Lymphatic pump techniques (LPTs) including the thoracic and abdominal pump increase lymphatic flow through the thoracic duct [12]. Specifically, the abdominal lymphatic pump greatly improved lymph flow and mobilization of immune cells. LPTs can temporarily increase the influx of immune modulators such as chemokines, cytokines, and reactive oxygen species in lymph. In animal studies, LPTs have been shown to amplify the immune response by promoting the circulation of leukocytes and other inflammatory modulators into lymphatic circulation [12].

The thoracic pump and thoracic diaphragm release mechanically improve pulmonary lymphatic flow back to central circulation and drainage once restrictions to outflow have been relieved [12]. One major contributing cause of mortality in patients affected with SARS-CoV-2 infection is the accumulation of lymph in the lung's interstitium. The thoracic pump utilizes the body's own physiological system–respiratory expansion of the chest cavity to aid in pulmonary lymphatic drainage [12]. Patients who develop ARDS have strained respirations that consequently contribute to the inhibition of chest cavity expansion. This inhibition leads to lymphatic fluid accumulation in the lung interstitium. Reestablishing and aiding in normal respirations via thoracic pumps can aid in the body's ability to develop an adequate immune response against SARS-CoV-2 and can potentially help delay the need for mechanical ventilation [12]. The use of thoracic inlet release is performed first to remove any restrictions at drainage sites so that optimal lymphatic flow can be achieved when implementing LPTs. In patients with pneumonia, osteopathic manipulative medicine (OMM) has been shown to reduce mortality and even hospital stay when utilized as an adjunct treatment [13]. Similarly, the abdominal lymphatic pump can aid in the delivery of immune cells to lung tissue and can assist in the body's immune response.

Respiratory effects of SARS-CoV-2

SARS-CoV-2 infection suggests a dominant lung tropism [14]. SARS-CoV-2 enters the hosts' airway via its spike protein and targets the ACE2 receptors at the alveolar epithelial cells, alveolar macrophages, and vascular endothelial cells [14]. The expression of transmembrane protease serine 2 aids viral entry at the plasma membrane surface [14]. Thus, SARS-CoV-2 is able to infect the upper respiratory tract (URT), specifically the basal epithelium in nasopharyngeal/oropharyngeal tissues [14, 15].

SARS-CoV-2 commonly causes viral pneumonia and can exacerbate current respiratory comorbidities. SARS-CoV-2 can also cause parenchymal inflammation, diffuse alveolar epithelium destruction, alveolar septal fibrous proliferation, hyaline membrane formation, capillary damage, pulmonary consolidation, and altered diffusion capacity [15, 16]. Lung CT scan reports have shown pleural thickening and retraction, and bilateral multilobar peripheral lesions with vascular hypertrophy [17]. Comprehensive injury to alveolar epithelial cells and endothelial cells accompanying fibroproliferation can prompt alveolar remodeling. This remodeling can potentially cause pulmonary fibrosis or pulmonary hypertension [16]. These complications, along with lymphadenitis or pleural effusion, can progress to ARDS [17], an acute diffuse lung inflammatory injury that increases pulmonary vascular permeability due to the loss of barrier integrity [17]. Profibrotic processes trigger an increase in alveolar permeability, causing the leakage of plasma proteins into airspaces. This causes endothelial injury, which triggers recruitment of fibroblasts to the area of injury, forming fibrotic scars [18, 19]. This ultimately leads to interstitial pulmonary fibrosis (IPF), a type of restrictive lung disease that can affect pulmonary function [16]. Additionally, SARS-CoV-2 causes lymphatic fluid accumulation in the interstitium, impairing respiratory motion and increasing mortality in patients [13]. This respiratory decompensation can cause an imbalance in chest cavity expansion, increasing respiratory effort and potential progression to ARDS [13]. This mechanism can require the need for mechanical ventilation in SARS-CoV-2 patients [13]. OMT can serve as an adjunctive treatment to decrease mortality rates in ventilator-dependent respiratory failure in SARS-CoV-2 patients [13].

OMT in the improvement of respiratory processes

Retrospective data gathered shortly after the 1918 Spanish influenza pandemic has suggested that the use of distinctive OMT methods has significantly lowered morbidity and mortality among patients compared to just those treated with standard medical care [20]. A recent review paper discussed OMT procedures such as lymphatic pump, splenic pump, rib raising techniques, and sinus drainage procedures playing a role in the stimulation of the immune system and improvement of arterial, venous, and lymphatic circulation as part of the treatment protocol for avian influenza patients [20]. Reportedly, the use of OMT during the 1918 Spanish influenza pandemic showed evidence of a significant reduction in the mortality rate of up to 10% in pneumonia patients treated with OMT vs patients treated with standard medical care alone [13, 21]. However, the lower mortality rate cannot be definitively attributed to OMT and the osteopathic approach because of the lack of rigorous research methods at that time [22]. In a study of 406 pneumonia patients, Noll et al. [23, 24] demonstrated the effectiveness of OMT in reducing the length of hospital stay ($p=0.01$), duration of intravenous medications ($p=0.05$), and respiratory failure and mortality in patients hospitalized with pneumonia treated with OMT compared to patients receiving conventional care only after per protocol analysis.

In addition to pneumonia, chronic obstructive pulmonary disease (COPD) has similar clinical presentation to SARS-CoV-2 and presents with cough, shortness of breath (SOB), and sputum production [17]. The use of OMT in COPD patients has been shown to increase total lung capacity, decrease residual volume, and improve lung functionality [17]. This demonstrates that OMT has contributed to improved COPD symptoms and exercise capacity, which can be applied to SARS-CoV-2 patients.

Several OMT techniques improve lymphatic drainage, circulatory flow, thoracic cage compliance, and autonomic tone. Based on patient tolerance of OMT and response of tissue being treated, physicians can utilize a direct or indirect (gentler) technique [25]. The following OMT techniques can alleviate pulmonary symptoms, commonly seen in viral pneumonia patients with exacerbated respiratory illnesses [13, 15, 16, 21] (Table 1).

Gastrointestinal

The presence of SARS-CoV-2 nucleic acids in fecal matter demonstrates that the gastrointestinal tract is another entry point for SARS-CoV-2 [17]. It is shown that the ACE2 receptor can also be expressed in the upper esophagus and stratified epithelial cells and enterocytes of the ileum and colon [26]. TMPRSS2 and TMPRSS4, two transmembrane protease serines, can increase SARS-CoV-2 infection of human intestinal enteroids [26]. Additionally, the transcription and expression of ACE2 and TMPRSS2 is significantly increased in human intestinal organs. The ACE2 expression in enterocytes leads to the destruction of epithelial cells in the digestive tract, leading to inflammation [17]. Although the mechanism

Table 1: OMT for therapeutic management of respiratory manifestations in SARS-CoV-2.

OMT technique	Target	OMT effect
Rib muscle energy	Rib somatic dysfunctions, restricted inhalation/exhalation motion, asymmetric rib excursion, thoracic cage compliance [14, 20]	Increased and symmetric rib motion, increased thoracic cage motion, improved drainage of pulmonary lymphatic flow of neighboring thoracic inlet/outlet [14, 20]
Thoracic diaphragm doming	Diaphragm hypertonicity [20]	Improved lymphatic flow, decreased lymphatic flow impediments at cisterna chyli, improved rounded diaphragm shape [20]
Thoracic pump with respiratory assist	Pulmonary lymphatic outflow restrictions [14, 20]	Mechanical mobilization of lymphatic flow and allows for pulmonary lymphatic drainage into central venous circulation [14, 20]
Seated rib raising	Individual rib motion restrictions within the thoracic cage [14, 20]	Freer chest cavity motion, reduced sympathetic tone, decreased obstruction to lymphatic drainage, increased rib cage excursion [14, 20]

OMT, osteopathic manipulative treatment.

of injury is currently unclear, it is hypothesized to be related to the immune-mediated cytokine storm or hypoxic injury [27]. This inflammatory response can contribute to malabsorption, unbalanced intestinal secretions, and loss of immune responses by GALT [17]. These alterations in the digestive tract and disturbances of the intestinal microbiota can cause several gastrointestinal symptoms, similarly, seen in irritable bowel syndrome (IBS) patients, such as diarrhea, abdominal pain, nausea, vomiting, and GI bleeding [17, 28].

OMT in the improvement of gastrointestinal symptoms

Anorexia, nausea, vomiting, diarrhea, and abdominal pain are some of the frequently observed gastrointestinal manifestations in SARS-CoV-2 patients. Some of the symptoms described above including abdominal pain, nausea, and diarrhea, present very similarly to IBS [17]. A systematic review performed by Müller et al. [29] showed that OMT significantly improved the symptoms of IBS. These symptoms have improved via GALT stimulation, resulting in the production of leukocytes that aid in rebalancing local dysfunctions [29]. Thus, the use of OMT can ultimately relieve digestive symptoms that overlap in both SARS-CoV-2 and IBS [29]. A randomized, crossover placebo-controlled study of 31 patients that compared visceral manipulation and sacral articulation OMT with sham therapy for the treatment of IBS also demonstrated that OMT significantly decreased self-reported diarrhea, abdominal distention, abdominal pain, and rectal sensitivity [29, 30]. Moreover, Florance et al. [30] randomized 30 patients with IBS in a 2:1 distribution to OMT vs sham treatment groups. Patients in the OMT group were treated with abdominal visceral and spinal techniques and reported having significantly greater improvement in IBS symptoms than the control group at day 7. The potential therapeutic benefits of sacral and spinal articulations as well as abdominal visceral techniques in normalizing the balance between parasympathetics and sympathetics may prove beneficial as adjunct therapy in SARS-CoV-2 patients [31].

Neurology

The neurological symptoms of SARS-CoV-2 impact multiple different pathways, including gustation and olfaction [32]. Approximately one-third of individuals infected with SARS-CoV-2 reported anosmia (loss of smell), headaches, nausea, and vomiting [32]. In a study conducted by Mao et al. [33], the neurological implications of SARS-CoV-2 were classified into skeletal muscle injuries, central nervous system (CNS) indexes (cerebrovascular disease, headache, dizziness, ataxia), and peripheral nervous system indexes (nerve pain, impaired taste, and impaired smell). Their study found that neurological symptoms were more commonly seen in older patients, in patients with more severe symptoms, or in patients with comorbidities. These symptoms generally arose within the first two days of infection due to direct viral entry and infection of the CNS via ACE2 receptors [33]. In addition, the cytokine storm as a result of SARS-CoV-2 infection causes the release of IL- 6, IL-1β, TNF, and IL-17, which disrupts the blood-brain barrier, thus facilitating entry of the virus [34, 35].

Some postinfectious, long-term neurological effects include acute disseminating encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, and Guillain-Barre syndrome [36]. In addition, the early presentation of anosmia (loss of smell) and loss of taste can persist long after patients have been diagnosed with and have recovered from infection [37]. The prolonged effects of loss of taste and anosmia (loss of smell) lead to severe disruption in the daily life of infected individuals. Timely analysis of cerebrospinal fluid (CSF) and understanding of the neurological implications in patients' lives can aid in the prognosis of severely ill patients [38].

OMT in the alleviation of neurological symptoms

Studies have shown the effectiveness of OMT in patients with neurological symptoms. According to Schmid et al. [39], specific OMT could stimulate areas of the CNS and activate the descending inhibitory pathways. These techniques could lead to hypoalgesia, mitigating the symptoms of headache and neuralgia associated with SARS-CoV-2. Furthermore, OMT plays a role in the modification of cerebral blood flow [40]. As Hitscherich et al. [41] explain, the "glymphatic system" describes the connection between the lymphatic system of the body and the CSF and interstitial fluid. These connections, with OMT, influence different parts of the immune system that are affected by SARS-CoV-2 [41]. Of note, although limited research has been done on the influence of OMT on anosmia (loss of smell) and loss of taste, OMT has had an effect on both mechanical and inflammatory issues involving the respiratory system. To elaborate, such studies can confirm the benefits that OMT has on SARS-CoV-2 neurological symptoms.

The neurological implications of SARS-CoV-2 are common manifestations of other respiratory infections as well. For example, many experience headaches, musculoskeletal (MSK) complaints such as back pain and body weakness, and fatigue due to respiratory ailments [42]. Prior OMT research has been conducted to address headache concerns in patients. In the 2017 study by Ramezani and Arab [43], the suboccipital myofascial release (SMFR) technique was utilized to address cervical MSK dysfunction and muscle imbalance. The use of the SMFR technique resulted in improvement of cervical muscle strength after 10 treatment sessions via alleviation of pressure on nerves and blood vessels [43]. Furthermore, the use of OMT has been studied in the relief of back pain in patients with chronic disease [42]. Licciardone et al. [44] conducted a study in which participants were treated with different OMT (high-velocity low-amplitude [HVLA], muscle energy technique [MET], counterstrain) vs sham OMT and found that participants in the OMT group reported much greater improvement in lower back pain.

Nevertheless, the neurological implications of SARS-CoV-2 do not remain to be acute issues. According to Mehandru and Merad [45], in a study of 16 isolated patients, 60% of the patients reported symptoms persisting at 6 months postinfection. Common post–SARS-CoV-2 symptoms include fatigue, chronic headaches, brain fog, pain syndromes, and olfactory and gustatory impairments [45]. "Long-COVID" symptoms can persist beyond 12 weeks of disease onset, with the majority of the symptoms affecting the neuropsychiatric system [45], so understanding the benefits that OMT can provide for symptom alleviation will serve the infected population well. Although research still needs to be conducted on the effect of OMT on SARS-CoV-2 patients, the similarity in neurological symptoms that arise due to infection from SARS-CoV-2 and other respiratory illnesses shed light on the efficacy that OMT can have in the improvement of acute and chronic SARS-CoV-2 symptoms.

Discussion

This paper outlines some OMT approaches that can be applied in patients with acute and chronic SARS-CoV-2 symptoms. Severe complications of SARS-CoV-2 are often attributed to unregulated immune and inflammatory pathways, which can induce dysfunctions within many body systems: inflammatory, respiratory, gastrointestinal, and neurological. Biological and clinical evidence have supported the use of OMT as an adjunct in standard care against various pathologies. As discussed previously, OMT has proven to be beneficial in the alleviation of symptoms in patients with pneumonia, some of which overlap in SARS-CoV-2. Thus, parallels can potentially be drawn between upper respiratory illnesses and the effectiveness of OMT in symptom management. Specific studies that evaluate the therapeutic effects of OMT on acute symptoms and postresidual symptoms of SARS-CoV-2 are still being investigated. This paper is limited in its ability to accurately depict a correlation between the use of OMT in SARS-CoV-2 symptom management. Further research is warranted to elucidate the therapeutic effects of OMT on SARS-CoV-2 patients.

Conclusions

OMT can remove restrictions to improve our body's natural healing process and promote pain resolution. This paper attempted to address prior OMT research that has proven to be beneficial in alleviating symptoms of other illnesses that overlap with symptoms of SARS-CoV-2. The similarities in symptomatology can potentially serve as a rationale for the use of established manipulative treatment modalities that may aid and accelerate the resolution of post-COVID-19 conditions in patients. Overall, previous applications of OMT demonstrate that clinicians may possibly integrate OMT on SARS-CoV-2 safely and assist with managing symptoms and healing.

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