Acta Scientific Orthopaedics (ISSN: 2581-8635)

Volume 4 Issue 2 February 2021

Review Article

Systematic Review of Post Covid Myalgia Literature

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Received: December 16, 2020

Published: January 28, 2021

Abstract

Since the end of 2019, the whole world has been suffering through the pandemic of the new Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2). Pain is a most common symptom during Novel Coronavirus Disease 2019 (COVID-19). According to the World Health Organization, patients suffering from COVID-19 show symptoms of muscle pain (myalgia) and/or joint pain (arthralgia), sore throat and headache. We present a narrative review of musculoskeletal manifestation and available treatment options. Our aim is to update the pain physicians and physicians working with COVID-19 Patients about possible pathogenesis of myalgia and best proposed treatment available.

Research data for this article is based on literature search which has been referenced in the text. There was no preliminary data. A search of PubMed and Google Scholar was done. We found 15 scientific papers on the related topics. Based on the review we infer that in addition to the cytokine storm experienced by many COVID-19 patients, certain additional factors such as severity of COVID-19 infection contributes to post covid myalgia and fatigue.

Keywords: Coronavirus; Neuropathy; Myalgia; Arthralgia; Headache; Opioids

Introduction

The aim of this article is to collect currently available international literature on pathophysiology of covid myalgia and available treatment options.

Methods

A systematic literature search and critical review of collected studies were conducted. An electronic search was done with the help of search engines PubMed and Google Scholar. Search terms used were COVID-19, SARS-CoV-2, Myalgia and Post Viral Fatigue. Identified articles were read and cross referenced and relevant literature was identified. Study selection and extraction of data was used as data collection process. This was done by two investigators and verified by other two. The consensus was made. This study did not involve any living objects hence was exempt from institutional review board approval. Research papers published in English language were used as a reference.

Discussion

Patients suffering from viral infections including COVID-19 show myalgia as a common symptom. Myalgia shows generalized inflammation and cytokine response. This can be a primary symptom of about 36% of patients with COVID-19 [1]. Patients suffering from COVID-19 may exacerbate myalgia and fatigue for prolonged duration as compared to patients with other viral infections. They may be unresponsive to conventional painkillers.

In addition to classic mechanism of myalgia known in viral fever the mechanism of musculo skeletal pain could be completely dif-

ferent in COVID-19. At low cytosolic pH, COVID-19 can enter the cell by penetrating ACE2 and can cause infection in the pulmonary system [2,3]. As ACE2 receptors presence is also there the brain tissue, kidney and musculoskeletal system these organs are also at a risk [4,5]. It has been reported in a recent article that surplus cell damage during COVId-19 infection causes increase in lactate levels thereby causing hyperlactemia [6]. Due to hyperlactemia, erythrocytes lose oxygen carrying capacity to the tissues and the thus tissues remain hypoxic.

Figure 1: Mechanisms of Myalgia during viral infection.

The virus can infect all tissues containing ACE2 such as the heart, brain, kidney and also musculoskeletal system as it can spread through the bloodstream or vascular endothelium. Muscle involvement during COVID-19 infection is proven by increasing creatinine kinase levels.

Lactate begins to accumulate in the muscles, when muscle tissue cannot provide the necessary energy in aerobic ways during exercise. To prevent lactate accumulation there is an activation of Monocarboxylate transporter (MCT) (synonym, lactate/H+ ion symporter) [7]. MCT pumps lactate and H+ ion, both from the extracellular space to the intracellular space and also to the mitochondria. Lactate dehydrogenase (LDH) increases the lactate formation from pyruvate in anaerobic condition [7,8]. During exercise MCTs will increase between 32 and 76% and MCT capacities may increase 3 to 4 times during extensive exercise [7,8]. Cytosol pH decreases due to accumulation of lactate and H+ ion. This is due to exceeding the capacity of MCTs and other regulatory pumps [8]. Anaerobic glycolysis reduces ATP synthesis. As an end result pain and fatigue are due to decreased ATP synthesis and low intracellular pH [7,9].

Figure 2: Peripheral Mechanisms of Ischemic Myalgia.

Musculoskeletal system remains deoxygenated due to lack of oxygen transport to the tissue. This is due to erythrocytes losing the oxygen carrying capacity in hyperlactatemia Muscles may show ischemic changes during COVID-19 infection. There is an increase of growth factors and cytokine levels during hypoxic ischemia. Ischemic conditions, and microvascular changes can cause overexpression in the dorsal root ganglion triggering pain [10]. As the virus damages muscles and other tissues LDH levels will increase. This coupled with anaerobic glycolysis increases lactate level excessively.

Post COVID-19 Syndrome, a long term state of chronic fatigue is experienced by some of the COVID-19 affected patients. This is

described by post-exertional neuroimmune exhaustion [11]. Interlukin 6 and Interlukin 10 are predictors of development of chronic fatigue as they are known to promote inflammatory changes in the body.

SAR's and MER's show similar long term respiratory musculoskeletal and neuro, psychiatric sequeale. These other coronaviruses also have similar pathophysiological findings to COVID-19.

Symptoms

- Persistent fatigue
- Diffused myalgia
- Depressive symptoms
- Non restorative sleep.

In post COVID myalgia symptoms of three most common muscular disorders such as Chronic Fatigue Syndrome, Polymyalgia Rheumatica and Fibromyalgia may exacerbate. In many cases arthralgia is also associated with myalgia.

Treatment

Presently very few clinical trials or specific guidelines are present for managing pain in COVID-19 patients [12,13]. The aim of this review is to discuss the problems associated with pain management during the COVID-19 pandemic.

NSAIDs and non-opioid analgesics

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are most commonly used drugs for managing pain. They are very popular due to easy accessibility and efficacy as anti-inflammatory and analgesic agents. There are higher chances of exacerbation of respiratory tract infections in COVID-19 patients after use of NSAID's [14]. Also NSAID's are known to have higher side effects. The WHO evaluated 73 studies in which adults and children treated with NSAIDs for respiratory tract infection but none of the studies showed the infection was caused by COVID-19, SARS or MERS [15]. There is no contraindication for using NSAID's. SARS-CoV-2 infections are constantly increasing worldwide. Mild and moderate clinical symptoms of COVID-19 patients are treated mainly with the supportive therapy. Overall, discontinuing the use of NSAID's for pain management in patients with suspected or diagnosed SARS-CoV2 infection is not recommended by EMA (European Medicines Agency) and WHO [16].

Opioids

Use of Opioids during COVID-19 pandemic for treating pain cannot be justified unambiguously as there are no clinical trials conducted. In patients with severe pulmonary disease Opioids have been found to increase both mortality and the risk of adverse clinical events [17-19]. Opioids is also known to cause immunosuppression. In an animal model (Flores., *et al*.) found that morphine induces adrenal-dependent lymphopenia and reduces the response to mitogenic stimulation (dose = 10 mg/kg) by nearly 70% [20,21].

Tramadol and buprenorphine are superior that other Opioid's. Both of them do not have any immunosuppressive properties, so, theoretically, they do not prolong viral shedding [22,23]. Buprenorphine is safe in multi-organ failure and it has a ceiling effect for respiratory depression [22,23].

Corticosteroids

Systemic corticosteroids have been shown to inhibit interferon (ifn) pathway of innate immunity. Some reports published recently also states that it may exacerbate symptoms of COVID-19 while others conflicting ones shows improvement in patients' symptoms. [24]. Based on these findings, WHO recommends cautious corticosteroid use for the pain management [25].

Neuropathic pain treatment in SARS-CoV-2 infection

Peripheral nervous system involvement, including painful neuropathies, was reported in many patients with SARS-CoV-1 and now with SARS-CoV-2 infection [26-29]. This may be a consequence of either viral invasion of the peripheral nerves (neurotropism) [30] or prolonged immobility during severe illness [31], or both. Gabapentin and pregabalin are commonly used in the treatment neuropathic pain. While the numbers needed to treat (NNT) for 50% pain relief for these therapeutic agents are similar (7.2-gabapentin; 7.7-pregabalin) [32,33] pregabalin acts quicker than gabapentin [34]. They are usually well tolerated and characterized by similar adverse effects [32-34]. Their potency in treating neuropathic pain in SARS-CoV2 patients cannot be predicted as no clinical sufficient clinical trials have been done.

Preventive measures

- Regular gentle stretching exercises
- Deep breathing exercises

- Small walks in house
- Positive optimistic outlook to reduce stress
- Endurance exercises involving light weights
- Hot fermentation and gentle massage for tight muscles
- Drinking lot of water and healthy well balanced diet.
- Regular change of posture and avoiding sitting in one position for long period.

Conclusion

Pain symptoms caused by the virus includes myalgia, arthralgia, sore throat, headache and peripheral neuropathies. For the treatment of pain, each patient requires an individual approach based on available knowledge and, more importantly, the patient's condition and comorbidities. The information provided is a cross-section of the available knowledge aimed at improving the patient's clinical condition. A structured prospective evaluation should be undertaken to analyse the probability, severity, sources and adequate treatment of pain in patients with COVID-19 infection and those suffering due to an unavailability of pain services during the COVID-19 pandemic.

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