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Original Research Article

The Effect of Vitamin B12, Magnesium and Vitamin D in COVID-19 among Geriatric Patients

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Abstract

Introduction: The pandemic hit caused a high prevalence of COVID-19 and fatalities globally. This disease has affected various organ systems and caused systemic inflammation, other than respiratory symptoms. The pathophysiological mechanism also showed that lower levels of vitamin B12 caused disruption in gut microbiota and increased oxidative stress. Reduced levels of vitamins and magnesium, which resulted from the infection of this disease, have led to further deterioration of the health status.

Aims and Objectives: This study is intended to evaluate the effect of combination therapy of vitamin D, magnesium, and vitamin B12 in COVID-19 patients by analyzing the outcomes of the disease when this combination therapy is applied.

Materials and Methods: This current study is a cohort observational prospective, in which 30 patients were given a combination of cholecalciferol (vitamin D3) of 1000 IU, magnesium oxide at 150 mg dose and methylcobalamin (Vitamin B12) of 500 µg, referred to as Intervention group. Another 25 patients were taken for comparison and referred to as the Control group. The baseline data was collected and the outcomes were observed and compared between the two groups.

Results: The study also found that the duration required to run the management of COVID-19 is significantly less in the Intervention group than the control group ($p<0.05$). The study further added that the group which received the combination therapy required less oxygen therapy with or without ICU support ($p<0.05$).

Conclusion: The study concluded that this combination therapy can improve the health status of COVID-19 patients by decreasing the probability to require oxygen therapy and ICU support. The study also concluded that this combined therapy can reduce the duration of hospitalization of COVID-19 patients.

Keywords: Covid, coronavirus, pandemic, nutrition, vitamin D, vitamin B12

Introduction

Since its start in late 2019, the coronavirus (COVID)-19 pandemic has ravaged the world, resulting in more than 20 million illnesses and 700,000 fatalities. Uncontrolled immune response has been proposed as a pathophysiologic element in disease severity, and immunological hyper inflammation has emerged as a major factor in patient prognosis. Immunomodulation seems like a promising prospective

therapeutic approach. Gastrointestinal symptoms are frequent and have a worse prognosis than lung involvement [1]. Because COVID-19 affects multiple organ systems, it is becoming clear that effective systemic inflammatory management is essential for overall survival. Other recognized patient variables linked to higher severity and fatality include age >50 years old, hypertension, diabetes, and coronary artery disease [2].

Low levels of vitamin B12 raise homocysteine and methylmalonic acid, which causes an increase in inflammation, reactive oxygen species, and oxidative stress [3]. Vitamin B12 also modulates the gut microbiota. Megaloblastic anemia, disruption of myelin sheath integrity, endothelial dysfunction, activation of platelet and coagulation cascades, and diminished immunological responses are all consequences of hyperhomocysteinemia [4]. SARS-CoV-2, however, might obstruct the metabolism of vitamin B12, preventing the growth of gut microbial populations. Given this, it is conceivable that symptoms of vitamin B12 insufficiency, such as increased oxidative stress and lactate dehydrogenase, hyperhomocysteinemia, and activation of the coagulation cascade, vasoconstriction, and renal and pulmonary vasculopathy, are similar to those of COVID-19 infection [3, 4].

Vitamin D is crucial for the immune system because it keeps cells physically protected and boosts cellular immunological responses, which lowers the risk of microbial and viral illnesses [5]. Vitamin D regulates the generation of pro-inflammatory cytokines and aids in humeral defence. In patients with severe COVID-19, vitamin D can lower cytokine storm and enhance cellular immunity [5].

As a cofactor for immunoglobulin synthesis, C'3 convertase, immune cell adhesion, antibody-dependent cytolysis, IgM lymphocyte binding, macrophage response to lymphokines, T helper-B cell adhesion, binding of substance P to lymphoblasts, and antigen binding to macrophage RNA, Mg participates in immune responses in a variety of ways. Rodents with a magnesium deficit experience problems with cell-mediated immunity and IgG synthesis, as well as thymus shrinkage, increased IgE, hypereosinophilia, histaminosis, and lymphoma. Human Mg shortage has subtle immunologic consequences that may be influenced by genetic factors that regulate blood cell Mg content. There have been reports of abnormal “C” activation, excessive antibody production, allergy susceptibility, and chronic fungal and viral infections. In severe allergic reactions, magnesium seems to have a protective effect [6].

Magnesium is an essential nutrient that can be utilized as a preventative approach to enhance patient outcomes in people with SARS-CoV2 infection and may even be able to lessen the severity of the infection by the virus by enhancing vitamin D functions. Magnesium insufficiency affects more than 50% of persons in the United States and is widespread throughout many other nations [7, 8]. People may be more susceptible to viral insults because of the low amount of magnesium in the general population.

Up-regulating T regulatory cells is a fundamental way that vitamin D lowers inflammatory cytokines. The improved immune function brought on by magnesium's role in vitamin D activation can lessen the severity of the cytokine storm during COVID-19 infection [9]. The cytokine storm consumes a lot of energy and causes ATP to be lost. Magnesium can assist refill energy reserves in the body to maintain and enhance immune system functioning since it and phosphate are necessary for the regeneration of ATP [10].

Instead of proactively controlling excessive inflammation, a large portion of current therapeutic efforts is focused on viral eradication. The latter function could be carried out by several immunomodulatory

drugs. For example, vitamin D protects against respiratory tract infections. Along with acting as a bronchodilator, antihypertensive, and antithrombotic, magnesium improves the action of vitamin D. The gut microbiota is significantly influenced by vitamin B12. Importantly, patients tolerate these substances well and they are generally safe [11]. Upon COVID-19 diagnosis, a brief course of vitamin D, magnesium, and vitamin B12 supplements (DMB) may have synergistic benefits to modify host immune response, lessen COVID-19 severity, and minimize negative outcomes. This investigation was carried out to assess the potential effectiveness of DMB on COVID-19 disease progression to severe disease.

Materials and Methods

Study Design

This current study is a cohort observational prospective one which was conducted during the period of five months. The study considered 55 COVID-19 patients who were administered with combination therapy of cholecalciferol (vitamin D3) of 1000 IU, magnesium oxide at 150 mg dose and methylcobalamin (Vitamin B12) of 500 µg. This combination was referred to as CMM. From 55 patients, 30 patients were given CMM combination therapy (intervention group) while the rest of the patients (25 patients) were not given this combination therapy and were referred to as the control group. Although, it was decided that if any patient would need oxygen therapy during the study period due to deterioration, the protocol was set to immediately provide oxygen therapy.

Cholecalciferol has a protective action on the respiratory system while magnesium supports and increases the positive effect of vitamin D and also has an anti-hypertensive effect and acts as bronchodilatory. Vitamin B12 has role in gut microbiota [10,11]. This combination therapy is well tolerated in COVID-19 patients which can also be said to have synergistic effects on immunity status and reduce the severity of COVID-19 and its adverse outcomes.

Inclusion and exclusion criteria

The patients aged more than 50 years, did not need oxygen therapy at the time of admission, and those who were willing to cooperate and gave consent to this study, were included to be the intervention group. More than 25 patients enrolled into this study who were not given the combination therapy but gave consent to this study, formed the control group.

The patients who had chronic nutritional and digestive abnormalities were excluded. The patients who did not cooperate till the end of the study were all excluded.

In total, the study considered 55 patients, of which 30 patients were included in the intervention group while 25 patients were included in the control group.

Data collection and sampling

The data was collected from the COVID-19 hospital where the study was done. As this study is of prospective type, the history of the patients was obtained, clinical features of the patients were obtained from the hospital records and the outcomes of the intervention group and control group were observed.

Ethical approval

This study was conducted according to the Declaration of Helsinki (World Medical Association). The consent from the patients were obtained and the study process was efficiently mentioned to each one of them.

Statistical analysis

The study conducted its statistical analysis using SPSS 25 and calculation in excel software. The binary data was used for analyzing the study outcomes. The baseline characteristics and other findings were evaluated with respect to the intervention and control group. The continuous variable was expressed as mean±standard deviation and categorical data was expressed in form of absolute values or percentages. The

study employed univariate logistic regression for effective analysis of associated risk factors with primary outcomes. The level of significance was considered to be $\alpha = 0.05$.

Results

The study has found the baseline characteristics and analyzed them separately for the intervention group and control group. The study also considers to find out the significance between two groups with respect to the outcomes of the patients. Table 1 shows the detailed findings.

Table 1: The baseline characteristics of the study population and its result of significance with respect to the outcomes of the patients

	Intervention group (n=30)	Control group (n=25)	*p*-value
Age	57.6±5.9	59.3±4.4	$p>0.05$
Males, n (%)	20	16	$p>0.05$
Females, n (%)	10	9	$p>0.05$
Other conditions			
Diabetes Mellitus	0	0	$p>0.05$
Hypertension	3	2	$p>0.05$
Hyperlipidemia	4	3	$p>0.05$
Cardiovascular disease	1	2	$p>0.05$
COPD or asthma	3	2	$p>0.05$
Stroke	0	0	$p>0.05$

The quality of management depends on several factors but this current study considered some of the parameters for statistical analysis, that can contribute in the quality of managing the patient. The study also found that the duration required to run the management of COVID-19 is significantly less in the Intervention group than in the control group ($p<0.05$). Table 2 shows the detailed findings about the parameters of management quality.

Table 2: The parameters of management quality in intervention and control group

	Intervention group (n=30)	Control group (n=25)	*p*-value*
Normal chest X-Ray during the time of admission, n (%)	4 (13.33)	2 (8)	$p>0.05$
Duration between the admission and the onset of symptoms (days)	2.8±0.6	2.9±0.23	$p>0.05$
Duration between onset of symptom and beginning of therapy (days)	3.7±1.1	3.9±0.98	$p>0.05$
Duration between admission and initiation of therapy (days)	0.9±0.3	1.0±0.2	$p>0.05$
Duration of running therapy (days)	11.2±2.8	18.2±1.21	$p<0.05$**
Treatment with remdesivir or hydroxychloroquine, n (%)	2 (6.67)	16 (64)	$p>0.05$

*p-value is obtained by comparing the difference between the two groups (intervention and control) with that of the outcome of the patients

**This parameter is statistically significant when compared with the outcome.

The outcomes of the patients are analyzed in each group and there is a statistically significant difference between the two groups. The study found that the group which received the

combination therapy required less oxygen therapy with or without ICU support (p<0.05). Table 3 shows the detailed findings of the patients' outcomes in each group.

Table 3: The outcome of the patients in each group

	Intervention group (n=30)	**Control group (n=25)**	***p*-value***
Oxygen therapy is required with ICU, n (%)	1 (3.34)	7 (28)	p<0.05**
Oxygen therapy is required without ICU, n (%)	2 (6.67)	13 (52)	p<0.05**
Admitted to Intensive Care Unit (ICU)	0	3	P>0.05**
Death	0	0	P>0.05**

*p-value is obtained by comparing the difference between the two groups (intervention and control) with that of the outcome of the patients

**This parameter is statistically significant when compared with the outcome.

Discussion

It is now known that 20% of patients may experience a life-threatening reaction to COVID-19. The lack of a survival advantage significantly reduces the effectiveness of many antivirals as the world waits for a viable vaccine. Only the terminal events in severe cases may be addressed by targeted therapy against cytokines and antithrombotic medicines, with only modest results. When it came time to provide DMB to elderly patients, it was clear that preventing hyperinflammation with relatively safe medications was a desirable alternative course of action. This pairing was made in light of strong, albeit circumstantial evidence for their ability to control the inflammatory response to viral infections. Through its impact on nuclear factor-kB and other pathways, vitamin D can reduce the number of pro-inflammatory cytokines that are generating the uncontrollable cytokine storm seen in severe COVID-19, with insufficiency being related to severe COVID-19 [12].

As a cofactor in many of the enzymes involved in vitamin D metabolism, magnesium is essential for the production and activation of vitamin D. To maintain a healthy gut microbiome, which is crucial for the growth and operation of both the innate and adaptive immune systems, vitamin B12 is required. In COVID-19 patients with microbiota dysbiosis, which has been linked to severe illness, this may be crucial in limiting an overactive immune response [13].

According to the results, an immunomodulator approach to reducing catastrophic outcomes in COVID-19 has already shown promising effects. Patients receiving DMB had a significantly lower need for oxygen therapy compared to controls. In an intention-to-treat study, two of the three DMB-treated patients who had clinical deterioration likely worsened within 24 hours due to their underlying infection. The benefits that have been shown might have been more significant had they been eliminated due to insufficient DMB exposure time. The final patient to deteriorate began taking DMB 7 days after first experiencing symptoms. Patients might need to be begun earlier in the infective cycle to benefit from its preventive effects. DMB should be simple to administer and should be started as soon as symptoms appear in the primary care context or as prophylactic among high-risk contacts during epidemics in identified clusters [11,14].

Within 24 hours of the start of DMB, two patients in the DMB group who needed oxygen therapy had their treatments begin. After 3 days of DMB supplementation, the third patient needed further oxygen therapy but did not need ICU assistance. Only one

patient needed oxygen therapy out of the nine patients who received DMB during the first week of the onset of symptoms. One of the two situations, when a patient's condition worsened within 24 hours of starting DMB, was this one. It should be noted that DMB had no side effects or negative consequences. Throughout the follow-up period, there were no deaths in either group [11].

According to the study, its observational approach raised concerns about bias risk. Directness was also downgraded because the trial did not examine the impact of the B vitamin alone. After all, it was administered along with magnesium and vitamin D. The quality was lowered in part due to the small sample size's impact on precision. At best, there is very little evidence to support the use of vitamin B as a supplement in the care of COVID-19 patients. Only when given in combination rather than alone can vitamin B12 be effective in treating COVID-19 [15].

Supplementing with vitamin D in SARS-CoV-2 positive individuals may benefit both those with mild and severe symptoms. Given that several excellent randomized control studies have shown a reduction in hospital mortality, vitamin D should be viewed as an additional therapeutic of great interest. The cost and benefit to worldwide pandemic mitigation efforts would be considerable if vitamin D were to lower hospitalization rates and symptoms outside of the hospital setting [7].

Data from throughout the world indicates that up to a quarter of COVID-19 patients encounter problems that put their lives in peril. In this case, addressing the late occurrences and being largely unsuccessful, IL-6 blockers and anti-thrombotic medicines could not be much better than a Band-Aid. The current investigation, nevertheless, aimed to apply pre-emptive immunoregulatory, secure, and well-tolerated medicines to lessen the cytokine storm connected to organ damage and death at the end of life [7, 9, 12, 15].

This approach may be implemented as a secure, simple to implement, and early intervention in the primary care context due to its apparent success. It might also be applied just as successfully to shield high-risk contact clusters identified during an outbreak from developing symptoms or serious illness [11,15]. It is suited for low- and middle-income countries even when vaccines or therapeutic medications may be too expensive to afford due to its extraordinarily high cost-effectiveness. Last but not least, the use of DMB may be as helpful in other viral infections that also generate a lot of cytokines and harm the body without causing direct tissue damage [12,14].

DMB can help a sizable portion of the world's population, especially in economically underdeveloped nations with slow or restricted access to vaccines and other treatments because all of the medicines in this combination are widely accessible, secure, and affordable. DMB might also be effective in general against viruses with similar pathogenic mechanisms [10-13]. Even so, this proof-of-concept study has shown encouraging findings that support the combination of vitamin D, magnesium, and vitamin B12's role in preventing clinical deterioration in patients at high risk. A well-designed randomized controlled trial will be needed to further validate recent findings [14-16].

Conclusion

The study has evaluated the effect of vitamin B12, Magnesium and Vitamin D in COVID-19 patients as compared to the control group who did not receive this combination. As discussed, this combination is well accepted in terms of nutritional status and contributes in the immunological advantage to COVID-19 patients. The study has concluded that the duration required to run the management of COVID-19 is significantly less in the Intervention group than the control group ($p<0.05$). Hence, the combination is seen to have contributed in the improvement of

COVID-19 management and prevented ICU support. Also, the study had shown that the hospitalization of COVID-19 patients can be reduced by including combination therapy as part of COVID-19 management. Moreover, the study has shown that the group which received the combination therapy required less oxygen therapy with or without ICU support ($p<0.05$). The study was done with 55 patients and so, the authors suggest that there is a need to conduct more studies which can further evaluate the effect of this combination on COVID-19 patients on varied populations.

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