



The role of N-acetyl cysteine and some other clinical antidotes in the treatment of patients with COVID-19; review of the current evidence

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Abstract

Anti-viral and anti-cytokine drugs have been proven to be inadequate in ceasing the progression of the novel coronavirus disease, and severe cases are often associated with death or severe chronic injuries. In this respect, N-acetyl cysteine (NAC) has anti-oxidant, anti-inflammatory, and immune-modulating effects and has been revealed to be beneficial in the treatment and prevention of this virus. High-dose oral NAC (1200 mg) can improve adaptive immunity by increasing lymphocyte glutathione levels and regulating neutrophil function during the COVID-19 development. Given that the majority of these patients suffer from hypoxemic respiratory failure and require oxygen supplementation in hospitals, hyperbaric oxygen therapy (HBOT) appears to be an alternative treatment. In fact, HBOT can increase the circulation and delivery of oxygen under high pressures, making the tissue uptake more efficient and improving hypoxia in patients with COVID-19. In addition, low-doses of naltrexone can interact with angiotensin-converting enzyme 2 (ACE2), disrupt the binding of ACE2 to the receptor-binding domain, and have anti-inflammatory and suppressive properties of pro-inflammatory cytokines. Therefore, due to the ability of the low-dose of this drug in preventing the progression of this disease, it can be recommended as an adjunct drug with an immunomodulatory role in combination with other anti-viral drugs in patients with COVID-19. Finally, there appears to be a significant association between vitamin K and thiamine deficiency with the severity of COVID-19. These vitamins play an important role in the coagulation system and suppress inflammation. Therefore, they can be used as a supplement or treatment to improve the outcomes of COVID-19.

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Introduction

In late December 2019, cases of pneumonia of unknown cause were first reported to the World Health Organization (WHO) office in Wuhan, China. After examining the issue, the cause of these pneumonias was figured out to be a virus of the coronavirus family and recognized as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Due to the speed of the epidemic and its spread in the world, this disease was introduced as a pandemic by WHO. At first, patients infected with this virus had symptoms similar to the common cold including cough, shortness of breath, and fever; however, other complications such as multiple organ failure, pulmonary edema, pneumonia, and acute respiratory distress syndrome (ARDS) were observed in these patients over time (1).

In fact, it is an enveloped virus with a single-stranded ribonucleic acid (RNA) genome that uses the angiotensin-converting enzyme 2

Key point

The present study aimed at reviewing recent evidence on the effectiveness of N-acetyl cysteine (NAC) and vitamin B (thiamine), vitamin K, calcium, naltrexone, methyl blue, digoxin, silymarin, and hyperbaric oxygen therapy (HBOT) in the treatment of patients with COVID-19. It was found that N-acetyl cysteine and other antidotes examined in this review could significantly reduce the length of hospital stay, the need for mechanical ventilation, and the mortality rate of patients with COVID-19.

(ACE2) as a cellular receptor to enter target cells. ACE2 receptors are expressed in heart (coronary arterial endothelium, myocytes, fibroblasts, and epicardial fat), arteries (vascular smooth muscle cells and endothelial cells), intestine (intestinal epithelial cells), lungs (tracheal and bronchial epithelial cells, type II pneumocytes, and macrophages), kidney (surface of a lumen and tubular epithelial cells), testis, and brain (2).



When SARS-CoV-2 virus enters the respiratory tract, it means that it has been able to cross the body's first line of defense and enter the body. At this point, the non-specific innate immune system is activated. Immune system receptors can detect the genetic material of the virus, which is RNA. Once detected, the intracellular signaling pathways are activated, and cytokines are produced and secreted. In fact, cytokines can be considered as immune system hormones and inflammatory responses, which are the most effective innate (non-specific) defenses against viruses and can inhibit the virus in early stages (3).

Therefore, it seems that preventing the virus replication, reducing inflammation, and strengthening the immune system can be among the effective actions to be taken for patients with SARS-CoV-2. As anti-viral and anti-cytokine drugs are used extensively to control the disease progression, less attention has been paid to the use of N-acetyl cysteine (NAC) and other antidotes (4,5). Therefore, the present study aimed at reviewing recent evidence on the effectiveness of NAC and some other antidotes such as vitamin B (thiamine), vitamin K, calcium, naltrexone, methyl blue, digoxin, silymarin, and hyperbaric oxygen therapy (HBOT) in the treatment of patients with COVID-19.

N-acetyl cysteine

N-acetyl cysteine, as a glutathione anti-oxidant, is used to loosen thick mucus in lungs and prevent the overuse of acetaminophen. Moreover, it can strengthen the immune system, suppress virus replication, and reduce inflammation (4).

As the role of reactive oxygen species (ROS) and cytokine storms in the pathogenesis of COVID-19 has become more apparent and has been directly associated with COVID-19 mortality, several hypotheses in this epidemic have favored the administration of NAC in COVID-19 (6, 7).

In addition to secreting cytokines, neutrophils also produce ROS radicals. ROS are species containing chemically active oxygen such as superoxide, peroxide, hydroxyl radical, singlet oxygen, and alpha oxygen. Superoxide ion ($O_2^{\bullet-}$) can cause direct damage and can be converted into more harmful oxidant species such as hydroxyl radical (OH^{\bullet}) and hypochlorous acid (HOCl). Of these, OH^{\bullet} has been indicated to be a key ROS for pulmonary edema during acute lung injuries (8). In addition to the tissue damage, ROS can also activate the nuclear factor- κ B (NF- κ B) pathway to enhance inflammation by positively regulating the expression of multiple genes such as interleukin 6 (IL-6), tumour necrosis factor α (TNF α), and chemokines. NAC, as a powerful OH^{\bullet} scavenger, can effectively prevent cytokine storms, pulmonary edema and ROS-induced respiratory failure. Furthermore, NAC has been shown to inhibit the replication of human influenza viruses in lung epithelial cells, human immunodeficiency virus (HIV), and respiratory syncytial virus (RSV) and reduce the production of pro-inflammatory cytokines

including IL-8, CXCL10, CCL5, and IL-6 (4). This means that NAC can be an effective drug in inhibiting SARS-Cov-2 replication due to its structural properties and ability to negatively regulate NF- κ B. Consequently, many studies have indicated the effectiveness of intravenous, oral, or inhalation administration of this drug. For example, Lai et al revealed that oral NAC at a dose of 1200 mg/d as compared to 600 mg/d could significantly increase glutathione levels in lymphocytes during a chronic inflammatory disease (9). Oral NAC can be absorbed in the small intestine, interact with epithelial and immune cells, and potentially strengthen the immune system to fight off viral infections. Therefore, in addition to modulating the function of neutrophils during the development of COVID-19, it can be stated that this drug can increase the level of immunity by increasing the level of glutathione in lymphocytes.

In this regard, Horowitz et al reported two cases with COVID-19, both of whom, in addition to receiving the standard treatment, received NAC orally at doses of 600 and 1200 mg daily. They indicated promising results in achieving a complete cure of the disease (10).

In another study addressing patients with acute lung injuries, the intravenous administration of NAC at 40 mg/kg/d for three days had a significant effect on improving systemic oxygenation, reducing the need for a ventilator support, and decreasing the mortality rate (11). However, in one case report for a patient with septic shock due to influenza (H1N1) infection, intravenous infusion of a higher dose of NAC (100 mg/kg/d for three days) was performed, which still had acceptable results and was able to improve the rate of sepsis in the patient by eliminating pulmonary infiltrates and ultimately eradicate the virus (12).

A study conducted by Ibrahim et al on ten patients with COVID-19 found that the intravenous NAC administration (600 mg twice daily) significantly improved the liver function and reduced the oxygen need. Moreover, C-reactive protein and serum ferritin levels had a significant reduction in all patients after the treatment with intravenous NAC (600 mg twice daily) (13).

Andreou et al also reported the combination of NAC with remdesivir, copper, nitric oxide (NO), and colchicine as an effective combination therapy for COVID-19 (6).

Regarding its inhalation administration, FDA guidelines has suggested that 3-5 mL of a 20% NAC solution or 6-10 mL of a 10% NAC solution using a nebulizer can be inhaled three or four times a day to loosen the mucosa. High concentrations of NACs can effectively reduce viral replication and significantly reduce pneumocyte injury as well as excessive immune responses (4).

Therefore, it can be stated that the administration, concentration, and adequate time of NAC exposure are the main points in controlling the replication of virus and the development of pneumonia and other respiratory problems. Moreover, it can be useful for the treatment of

COVID-19 and reduction of the mortality rate.

In a general conclusion, it can be said that considering the potential therapeutic benefits of NAC (intravenous, oral, or inhalation administration) such as suppressing cytokine, protecting T cells, replenishing intracellular glutathione, eliminating extracellular scavenging ROS radicals, reducing inflammation and tissue damage, having very low toxicity, and being cost-effective, NAC in combination with other anti-viral drugs can reduce hospitalization, mechanical ventilation, and mortality rate in COVID-19 epidemic (1,4).

Methylene blue

Radicals and cytokines are directly involved in the development of endothelial dysfunction, which is a common cause of multiple organ failure in COVID-19. When ARDS occurs, the production of abundant free radicals such as ROS, reactive nitrogen species (RNS), and cytokines gets out of control, and attempts to control all three groups with one cytokine inhibitor are virtually impossible. Methylene blue prevents the formation of superoxide anion (ROS precursor) by blocking the xanthine oxidase pathway. It counteracts direct inhibition of NO-synthase by nitric oxide synthesis (RNS precursor) and regulates the cytokine expression by attenuating NF- κ B signaling (14).

In addition, the ability of methylene blue to inactivate bacteriophages and viruses has been declared for many years. The positively-charged methylene blue may be able to support the anti-viral effect against SARS-CoV-2. This charge improves its tendency to bind to RNA with the negative charge of viruses and promotes the cross-linking of the viral RNA protein. Moreover, as methylene blue is Zn⁺² ionophore, which inhibits the elongation of RNA-dependent RNA polymerases that are not observed in the human body, it is suggested to potentially inhibit SARS-CoV-2 (15).

Methylene blue is a tricyclic phenothiazine that has been approved for use in the treatment of methemoglobinemia (14). Methemoglobin (Fe⁺³) is actually the oxidized form of hemoglobin (Fe⁺²). Methemoglobin is unable to carry oxygen, and its excessive amounts can lead to cellular ischemia and shock. Methylene blue is able to protect against hypoxic/ischemic damages (16). However, the use of methylene blue is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency due to the increased risk of hemolytic anemia. Moreover, its concomitant use with serotonin reuptake inhibitors is also contraindicated (17).

In contrast, methylene blue acts as an effective inhibitor of guanylyl cyclase and prevents vascular smooth muscle relaxation by blocking the release of *guanosine* 3',5'-monophosphate (cGMP) without a direct effect on the NO production while the use of NO inhibitors is limited due to their non-specificity in blocking different NOS isoforms. Therefore, nitric oxide synthase inhibitors

are not currently used clinically because they have the risk of extensive tissue necrosis and higher mortality rates. Consequently, this drug should receive due attention considering its benefits (18).

According to reports from previous clinical studies, the intravenous administration of methylene blue at doses greater than 2-3 mg/kg has been associated with success and safety against septic shock (19). In the current pandemic, Bojadzic et al also stated that the entry of a SARS-CoV-2 spike-bearing pseudo-virus into ACE2-expressing cells with similar IC₅₀ (3.5 μ M) is inhibited by methylene blue. Therefore, its anti-viral activity against SARS-CoV-2 through proton pump inhibitor inhibitory activity is facilitated by blocking its binding to the ACE2-expressing cells. The availability as well as the cost-effectiveness of this drug as an inhaled or oral medication has made it beneficial in treating and preventing the COVID-19 (20).

It is of great significance to start the treatment early as it is impossible to reverse the tissue damage that has already occurred. Therefore, it is recommended that the methylene blue oral therapy with a normal dose of 200 mg daily be given at the first sign of COVID-19 to prevent an over-inflammatory response.

Although some other clinical trials have been conducted, the researchers are not allowed to report them due to their incompleteness. However, it seems that methylene blue is of interest to many other researchers. In the near future, by summarizing the results of further studies, we can more accurately identify the best course of treatment for this disease and recognize the optimal dose of this drug and the appropriate duration of its administration.

Silymarin

Silymarin potentially modulates virus-specific and non-specific T cell proliferation and exerts anti-inflammatory effects by suppressing the production of interferon gamma (IFN- γ), IL-10, TNF- α , IL-6, and IL-4. Therefore, it can have strong anti-inflammatory activity in patients with asthma and chronic obstructive pulmonary disease (COPD). In addition to its anti-inflammatory activity, it can act as a liver protector and have anti-oxidant and anti-coagulant properties (21, 22).

In an animal study on CLP mice, silymarin indicated a better protection against the inflammatory cytokine IL-1 β than acalabrutinib (as a standard anti-inflammatory drug) (23). The induction of TNF- α is suppressed, and its serum concentration along with the IFN- γ , IL1 β , and other pro-inflammatory cytokines is reduced by silymarin. Moreover, the P38 activities and the mitogen-activated protein kinase (MAPKs) ERK1/2, which may contribute to immunosuppression, are repressed by silymarin. The mentioned point can manage the organ failure that is caused by cytokine storm in acute COVID-19 (24,25).

It should be noted that baricitinib is used to treat rheumatoid arthritis, has a very similar anti-inflammatory

activity to that of silymarin, and is currently recommended as a treatment for COVID-19 (26).

For example, in a registered clinical trial with the trial code of NCT04394208, the oral administration of silymarin (240 mg daily for three days) was considered to assess clinical outcomes, the length of hospital stay, the mortality rate, and other outcomes in patients with COVID-19. So far, no report of the results of this clinical trial has been published.

Given the medicinal safety of silymarin and the regulatory role of its various cytokines, as well as the antiviral effects of its derivatives such as silibinin and *Silybum marianum*, it could be a suitable option for controlling SARS-CoV-2-induced infection. However, due to the limited laboratory, animal, and human studies on the clinical effectiveness of this drug, it is required to conduct various clinical studies to confirm its effectiveness and determine the dose and duration of the treatment based on the severity and various manifestations of the disease.

Hyperbaric oxygen therapy (HBOT)

According to the guidelines of the National Institutes of Health (NIH), standard oxygen therapy (such as face mask, invasive ventilation, non-invasive ventilation, nasal cannula, and extracorporeal membrane oxygenation) is recommended for patients with severe COVID-19 disease and an acute hypoxemic respiratory failure (27).

The main goal of all oxygen therapy methods is to increase the level of oxygen saturation (SpO_2) to 92%-96%. The administration of HBOT is another method of oxygen delivery, in which patients breathe 100% pure oxygen at a high pressure. By intensifying oxygen pressure in the alveoli, HBOT can have a positive effect on the lung function; improve respiration, increase hemoglobin amount, and supply oxygen to patients' tissues. In fact, HBOT provides the tissue perfusion exchange capacity due to the increased rate and duration of oxygen diffusion. The mentioned point distinguishes HBOT from other oxygen therapy methods (28,29).

As the patients breathe in a hyperbaric chamber, they are likely to have fewer complications than the case of using the mechanical ventilation. Therefore, HBOT can be one of the safest interventions to compensate for the lack of oxygen. However, some reports have suggested that the use of HBOT with a pressure greater than 2.0 ATA may be associated with some complications such as middle and lung barotrauma, oxygen poisoning, earache, and claustrophobia (30,31). However, if the standard of oxygen pressure is observed, complications cannot threaten the patient.

In general, studies conducted in the recent pandemic have indicated the effect of HBOT on improving lung clearance, increasing arterial blood gases, and improving hypoxia (29-31) as the increase of oxygen in plasma due to HBO_2 can interfere with the development of interstitial fibrosis in the lungs, decrease the risk of multiple organ

failure because of the total abated COVID-19 viral load, mobilize stem cells, postpone the onset of severe interstitial pneumonia, and block the inflammatory cascade.

In addition, in a clinical trial, the mortality rate of patients treated with HBOT as compared with the control group was 10% to 22%, respectively (32); however, no mortality was reported in the other clinical trials.

Despite the effectiveness of this method for oxygenation in patients with COVID-19, one of its main shortcomings is its unavailability in all medical centers as it requires a large space, and several HBOT devices are needed in medical centers. The mentioned points limit its use in the current epidemic, in which many patients need oxygen. Therefore, by conducting more clinical trials with larger sample sizes, its effective results can be confirmed with more confidence, and medical centers can be encouraged to create such spaces for providing this particular treatment.

Naltrexone

As mentioned earlier, SARS-CoV-2 infection causes lung tissue damage, respiratory failure, and multiple organ failure in patients by producing and propagating severe pro-inflammatory cytokine storms. ERK1/2 phosphorylation status is positively correlated with virus load, and the inhibition of ERK1/2 suppresses the viral replication and infection. Thus, molecular components that are able to interfere with the binding of SARS-CoV-2 spike protein to ACE2, inhibit hyper-inflammatory cytokine storms, or block ERK1/2 phosphorylation have a significant potential to inhibit viral entry and infectivity (33).

Spike, as the main structural protein of the coronavirus, binds to host cell receptors and acts as a mediator between virus invasion and host. Spike is actually broken down into S1 and S2 by host cell proteases such as TMPRSS2. The main function of S1 is to bind to the surface receptor of the host cell. ACE2 and the subunit S2 mediate cell-virus fusion and cell-cell membrane. Thus, the structural integrity of the spike and the activation of this breakdown play a key role in the invasion and pathogenicity of the virus (34).

Therapeutic strategies to prevent the coronavirus entry into host cells by targeting spike proteins or ACE2 receptors on the host surface are valuable for developing anti-viral drugs. According to the results provided by previous research studies, the receptor-binding domain (RBD) sequence of SARS-CoV-2 interacts with the ACE2 receptor from the host, and this RBD-ACE2 complex plays a key role in the virus invasion and severity (34). In this regard, the low-dose of naltrexone appears to interact with ACE2. Naltrexone is a non-peptide opioid antagonist drug that can suppress the release of pro-inflammatory cytokines of high fat/lipopolysaccharides from both macrophage cells and adipose tissue macrophages. In addition to its anti-inflammatory properties, it has the ERK1/2 inhibitor and has the potential to disrupt the binding of ACE2 to the RBD. As the low-dose administration of this drug has

the required ability to prevent the progression of several diseases without significant complications, it has attracted researchers' attention in the current epidemic (35,36).

Naltrexone can be more effective in preventing the infection of the host cell by binding to the central cavity composed of SARS-CoV-2 RBD and the ACE2 receptor (34). Moreover, this drug has been recognized as a modulator of immunity and an antagonist for the TLR4 (Toll-like receptor 4) receptor and opioids (37). It has several mechanisms of action, and it has been reported that it can stimulate the release of β -endorphins by acting on an opioid receptor. Furthermore, it can significantly reduce the serum pro-inflammatory cytokines IL-1, IL-2, IL-12, and IL-18 (38). Importantly, the lower cost, the lower complications, no reported interaction with other drugs, and its availability can make this drug as an adjunctive drug with an immunomodulatory role that can be recommended to be administered in combination with other anti-viral drugs in patients with COVID-19.

Vitamin K

Given the importance of vitamin K-dependent proteins in the coagulation as well as the elastic fiber metabolism, vitamin K can play a role in the pathogenesis of COVID-19 and can mediate between lung damage and thrombosis. Therefore, paying attention to the level of this vitamin is one of the key points in reducing the mortality rate and preventing the progression of this disease (39).

Recent studies have revealed that during SARS-CoV-2, vitamin K levels decrease, which may be due to the deficiency of this vitamin before the onset of the disease or its rapid consumption during the infection. The decrease of vitamin K is manifested by an increase in dephosphorylated-uncarboxylated matrix Gla-protein (dp-ucMGP) levels as vitamin K reserves are depleted for the carboxylation of MGP, which leads to higher levels of dp-ucMGP. In addition, the rate of elastic fiber breakdown increases following SARS-CoV-2 infection, and the rate of its degradation has a significant correlation with dp-ucMGP levels (39,40).

In fact, due to the increased proteolytic activity in these patients' lungs, the degradation of elastic fiber is accelerated, which increases the vulnerability of elastic fiber to calcium, up-regulates MGP synthesis, and leads to reduced extrahepatic vitamin K reserves. The rate of elastic fiber degradation is associated with poor outcomes in some lung diseases such as COPD, bronchiectasis and cystic fibrosis, or even COVID-19-induced pneumonia (39,41).

In addition, the status of hepatic pro-coagulant vitamin K, measured by protein induced by vitamin K absence or antagonist-II (PIVKA-II), is severely affected although dp-ucMGP increases in COVID-19 (39). Based on the micronutrient triage theory, approximately 50% of S protein synthesis takes place in the endothelial cells, and the liver proteins are preferentially activated over

extrahepatic proteins, which indicates that uncarboxylated S protein fraction also increases (42). The mentioned point can result in an increase in the risk of thrombosis. A further burden is imposed on vitamin K reserves due to the consumption of clotting factors during thrombosis as the demand for activating recently-synthesized coagulation factors to compensate for the used ones increases (43). By prioritizing carboxylation of pro-coagulant factors, a gradual decrease in the active endothelial protein S gradually shifts the balance toward coagulation.

In addition, it seems that increasing the use of pulmonary vitamin K during SARS-CoV-2 pneumonia can disrupt the therapeutic balance between the vitamin K antagonists dose and vitamin K intake levels. Moreover, vitamin K is a useful supplement for vitamin D as there is evidence that it can act as an anti-inflammatory agent by suppressing NF- κ B signal transduction. It may also have a protective effect against oxidative stress by blocking the production of active oxygen species (44,45).

Therefore, considering the consequences of vitamin K deficiency in lung diseases, it seems that more studies can be performed to evaluate the effect of the vitamin K administration on the progression of COVID-19 disease and prevention of some possible complications of this disease.

Thiamine

Evidence suggests that patients with severe COVID-19 experience a variety of neurological symptoms such as altered mental status, musculoskeletal symptoms, and acute cerebrovascular disease (46). Some studies have reported the astrocytic activation and damage as the first attack on the central nervous system of patients with moderate to severe COVID-19 disease. The astrocytic activation and damage are evidenced by higher plasma concentrations of glial fibrillary acidic protein and higher concentrations of plasma neurofilament light (47).

Given that the vitamin B1 (thiamine) deficiency causes abnormalities in the expression of key proteins of astrocytes and disrupts the integration of neurons, it can be stated that the pathophysiology of the thiamine deficiency is related to astrocytes. In addition, thiamine deficiency may be associated with increased levels of cytokines and increased oxidative stress and inflammation (48). Therefore, it appears that thiamine decrease can play a significant role in the development of cytokine storms in these patients and is exacerbated by sepsis, furosemide, and hemodialysis.

As a dietary supplement, this vitamin has anti-oxidant properties, inhibits the production of cytokines, modulates the pro-inflammatory response of Th17, increases the anti-inflammatory activity, and reduces the symptoms of the virus-induced neurological inflammation (49).

Therefore, this vitamin is prescribed as a treatment for other viral infections and is effective in controlling and improving inflammatory symptoms (50). Regarding

COVID-19, Vatsalya et al introduced thiamine as a therapeutic agent to reduce the neurological symptoms caused by COVID-19. They presented the thiamine dose of 79-474 mg/d in reducing the pro-inflammatory response of Th17 cells and stated that there were no complications in the administration of the thiamine dose of 200 mg (51).

A 1500 mg maximum oral dose of thiamine was administered to healthy subjects in a pharmacokinetic study. The results of the study indicated rapid absorption. Furthermore, no to mild adverse effects were reported following the 4000 mg thiamine administration in children (52).

Therefore, higher doses of thiamine for treating cytokine storm COVID-19 can be considered a safe treatment as it is soluble in water and is excreted via urine in case of its excessive amount. Consequently, the administration of this vitamin can be further investigated in COVID-19 therapeutic studies due to its high safety and its strong association with the suppression of cytokine activity and inflammation.

Conclusion

In summary, reviewing the evidence from other studies suggests that NAC (intravenous, oral, or inhalation administration) may have potential therapeutic benefits in suppressing cytokine storms, reducing inflammation and tissue damage, protecting T cells, replenishing intracellular glutathione, and eliminating extracellular scavenging ROS radicals due to its cost-effectiveness and lack of toxicity risk. In addition, oral methylene blue (200 mg) at the onset of the first signs of COVID-19 can act as an effective inhibitor of guanylyl cyclase and prevent excessive inflammatory response. Moreover, silymarin as a safe herbal medicine, with a regulatory role of cytokines, can be a good option to control infection caused by this virus. However, further studies are required to identify the effective dose and the duration of treatment based on the severity of the disease and its manifestations.

Hyperbaric oxygen therapy is also a method of high-pressure oxygenation that can have a positive effect on lung function, improve respiration, increase hemoglobin capacity, and oxygenate the tissues of these patients by increasing the oxygen pressure in the alveoli. However, the unavailability of the required device in all medical centers and the lack of a special chamber due to the limited hospital space can be the disadvantages of this method.

Naltrexone, as one of the non-peptide opioid antagonist drugs, can interact with ACE2 even at low-doses and disrupt the binding of ACE2 to the RBD. It has anti-inflammatory and suppressive properties of pro-inflammatory cytokines. Therefore, due to the ability of the low-dose of this drug to prevent the progression of this disease, naltrexone in combination with other anti-viral drugs can be recommended as an adjunct drug with an immunomodulatory role in patients with COVID-19.

Moreover, the administration of vitamin K antagonists

through the prevention of thrombosis has potentially beneficial effects on the course of the disease such that it can act as an anti-inflammatory agent by suppressing NF- κ B signal transduction and also has a protective effect against oxidative stress by blocking the production of active oxygen species. However, further studies are required to evaluate the effectiveness of the vitamin K antagonist administration as compared to other classes of anti-coagulants in the progression of the disease and the occurrence of some possible complications.

Finally, thiamine can inhibit the production of cytokines, modulate the pro-inflammatory response of Th17, increase anti-inflammatory activity, and reduce the symptoms of virus-induced neurological inflammation. In addition, its administration at higher doses (due to its solubility in water) can be considered a safe treatment to suppress cytokine storms.

Thus, in general, it is evident that NAC and other antidotes examined in this review can significantly reduce the length of hospital stay, the need for mechanical ventilation, and the mortality rate of patients with COVID-19.

Authors' contribution

SHZ and AMM were the principal investigators of the study. MF and GHD were included in preparing the concept and design. SHZ and AMM revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.ARI.MUI.REC.1401.042). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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