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Research Article

Magnesium Sulfate Extended Infusion as an Adjunctive Treatment for Complicated Covid-19 Infected Critically Ill Patients

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Abstract: *Coronaviridae* family from which coronavirus descends is the recent major health concern that threats the humanity worldwide. The novel flu-like coronavirus disease COVID-19 is responsible for infecting 2,257,789 individual as of 18th of April. COVID-19 health consequences include acute respiratory distress syndrome ARDS, pneumonia, hypoxic lung, sepsis multi-organ failure, respiratory arrest and eventually causing death. Interestingly, pneumonia caused by novel coronavirus was associated with coagulopathy disorder, elevated D-dimer, fibrin degradation product, disseminated intravascular coagulation DIC all are part of the hyper coagulability status of COVID-19 patients. the most commonly drugs used now to treat COVID19 symptoms is causing serious cardiac adverse reaction such as QTc prolongation caused by the combination of HCQ and Azithromycin which is the most commonly used regimen for the treatment of COVID19, here comes the role of magnesium sulfate (MgSO4) which is an inorganic salt commonly known as Epsom salt as an adjunctive therapy as extended release infusion to the patients suffering from previous serious conditions and their complications that the patients may develop in late stage of the disease. Magnesium sulfate is a cheap, safe and readily available medication can be a drug of choice in supportive treatment of COVID-19 especially critically ill patients with promising crucial beneficial medical effects.

Keywords: COVID-19, Cytokine storm , Radical storm ,Oxidative stress, Erythropoiesis, Hyper-viscosity, Magnesium sulfate, Extended infusion, hyper-coagulable status, Hypertension, QT Prolongation.

INTRODUCTION

The pandemic disease classified according to the world health organization (WHO) the coronavirus infectious disease known commonly as COVID19 caused by the severe acute respiratory syndrome coronavirus 2 {SARS-CoV-2}, is a very serious disease spreading in the globe and it had made such a massive health and economical destruction to nation and individuals as it is considered a huge challenge to the world since the world wars(Wang C *et al*. 2020). Since health complication the disease can cause vary among the infected patients from mild to the critically ill status caused to the patients whom might develop serious and fatal condition because of the disease (Singhal, 2020). The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, haemoptysis, diarrhoea, dyspnoea, rhinorrhoea, sneezing, sore throat and lymphopenia (Yi,Philip, *et al*.,2020). Some patients suffer from vomiting. A subgroup of patients infected with COVID19 and whom severely ill might develop cytokine storm syndrome which is a systemic hyperinflammatory state reaction that is associated with increased levels of inflammatory cytokines, it is now known that the novel coronavirus COVID19 is considered to cause a cytokine storm syndromes and immunosuppression condition to the infected patients in late stage of the disease, and knowing that COVID19 cause also oxidative stress conditions to some critically ill patients caused by the viral infection and heme dissociation, and increased clinical deterioration of the patients. After attacking the beta-hemoglobin chain leading to the detachment of iron from the porphyrin and causing hemolysis, blood hyper viscosity state and erythropoiesis to the patient that may lead to high blood pressure. In addition to that they might be suffering from free heme accumulation and radical storm because the novel virus attacks the heme group. Free heme accumulates in blood leading to monocyte increased scavenging effect and more release

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of oxygen reactive species ROS that creates further tissue damage and end up with severe oxidative stress status. The virus has higher mortality rate in elderly and especially with comorbid illness.

Magnesium, known as the forgotten electrolyte, is the second most abundant cation intracellularly and extremely important for physiological functions. Elemental magnesium is found in high concentrations in bones, heart, muscles and throughout network of nerves, also find it working away inside every cell of the body. Magnesium keeps heart rhythms steady, maintains muscle functions, metabolizes glucose, ensures nerves fire properly, creates cellular energy and helps to synthesize the basic building blocks of life – DNA, RNA and proteins.it has an important role in immunity enhancement. It is responsible for macrophage activation and lymphocyte proliferation. It acts as an antacid to reduce heartburn or an antibiotic to fight infection. It is used in the treatment of seizures in women with eclampsia, torsade de pointes, severe asthma exacerbations, constipation, and barium poisoning. Magnesium deficiency is proved to cause glutathione depletion which worsens the oxidative stress condition and anti-oxidant defense system is disturbed this is an evidence for relation between magnesium and oxidative stress. Magnesium deficiency is common in hospitalized patients especially ICU admitted, also can occur as a consequence of gastrointestinal symptoms that appear on some COVID-19 patients. In this review article we will discuss the potential advantages of magnesium sulfate in controlling complications of COVID-19.

DISCUSSION

The clinical stages of COVID-19 symptoms and features are varied among the infected patients (Singhal, 2020). And it is ranging from asymptomatic state to acute respiratory distress syndrome (ARDS) and multiorgan dysfunction and progressing pneumonia that leads to respiratory failure and death in subgroup of patients (Liu *et al*. 2015). This progression of the novel coronavirus 2019 disease in infected patients is associated with extreme rise in inflammatory cytokines level caused by what is called as Cytokine release syndrome (CRS) or "Cytokine storm" (Mehta *et al*. 2020). Cytokine storm is a hyperinflammatory syndrome characterized by a fatal increase of cytokine level in blood that can be developed in association with a severe viral infection including COVID19(Liu *et al*. 2015). This notably increase cytokine levels such as IL-6, IL-10, and TNF-α and activation of T lymphocytes, macrophages, and endothelial cells are now associated with severe and late stage of the COVID19 disease(Pedersen and Ho, 2020) since it is known that deficiency of magnesium leads to inflammation state and since it is observed following in vivo magnesium treatment that Magnesium sulfate ($MgSO_4$) has shown to have the ability to suppress the proinflammatory cytokines expression(Sugimoto *et al*. 2012). This has been also observed in the neonate of pregnant women as magnesium has the ability to cross the placenta and decrease the cytokine level for both maternal and fetus (Liu *et al*. 2015). The anti-inflammatory and immunomodulatory effect of MgSO4 come from its ability to reduces monocyte-mediated IL-6 and TNF-α production, reversibly regulates cytokine production via transcriptional regulation and decreasing cytokine level by reducing NF-κB activation and increasing IκBα levels which is a critical regulator of the transcription factor NFκB, which induces expression of a wide range of genes involved in immunlogical and inflammatory responses(Sugimoto *et al*. 2012). And thus, we can conclude that Magnesium sulfate ($MgSO_4$) can attenuates excessive inflammation caused by the novel corona virus 2019 in the infected patients by its ability to decreases Inflammatory Cytokine production (Sugimoto *et al*. 2012).

The novel coronavirus 2019 has shown the ability to attacks the Beta-1 Chain of Hemoglobin in late stage of the disease and captures the heme porphyrin to inhibit human heme metabolism so this lead to the dissociation of the iron and this happens as the viral protein of COVID19 infects hemoglobin by the immune hemolysis of the erythrocyte(Wenzhong and Hualan. 2020). This attack will cause less hemoglobin that can carry oxygen and carbon dioxide thus the lung cells will have extremely intense poisoning and inflammatory due to the inability to exchange carbon dioxide and oxygen frequently and that's explain the respiratory complication that occur to the infected patients (Wenzhong and Hualan. 2020). This attack explains also the increase in the iron ferritin level in COVID19 patients which many hospitals are using now to monitor the progression of the disease in the infected patients (Zhou *et al*. 2020). The hemolysis resulting from this attack will lead to hyperproduction of red blood cells or what is known as dysfunctional erythropoiesis which characterized by increased nonfunctional red blood cells to functional red blood cells ratio (Moreau *et al*. 2012). Also, will elevate blood viscosity as a result of the red blood cell shape deformity caused by the attack of COVID19 to the hemoglobin (Wenzhong and Hualan. 2020), (Perez & Estes, 2020). Disseminated intravascular coagulation (DIC) which is a systemic syndrome characterized by enhanced activation of coagulation with some intravascular fibrin formation and deposition maybe occur to the infected patients as well, however this condition maybe caused not only due to hemoglobin attack but also may be caused by the oxidative stress condition the coronavirus can cause to patients in some point of the disease(Salvemini & Cuzzocrea, 2002).Since higher hemoglobin causes higher morbidity the role of Magnesium sulfate ($MgSO_4$) in the hyper-viscosity state and DIC will be based on the antiplatelet activity of Magnesium sulfate in human platelets (Sheu *et al*. 2002). This activity is explained by the ability of MgSO4 to induce membrane fluidity changes with

resulting interference of fibrinogen binding to the GPIIb/IIIa complex and then followed by inhibition of phosphoinositide breakdown and thromboxane A2 formation, and might also trigger the formation of cyclic AM, ultimately leading to inhibition of both intracellular Ca2+ mobilization and phosphorylation which consider rate limiting steps in platelet aggregations(Sheu *et al*. 2002). And thus, suggesting that Magnesium sulfate ($MgSO_4$) can attenuates hyper-viscosity and intravascular coagulation complications caused by the novel corona virus 2019 in the infected patients (Sheu *et al*. 2002).

The hemoglobin is also a significant source of superoxide generation in red blood cells and since there is an electron transfer in the interaction between the heme iron and oxygen in oxygenated Hb and when Hb oxygenates, knowing that the virus attack both oxygenated and unoxygenated Hb the heme iron normally remains in the Fe(II) ferrous state but any alterations in this exchange like in Hb auto-oxidizes this result in the formation of methemoglobin which is the ferric Fe(III) state and superoxide thus hyperoxidative stress state in patients will occur(fibach & Rachmilewitz, 2008). The role of Magnesium sulfate ($MgSO_4$) in this critical situation comes from the ability of MgSO4 to interact with alkyl radicals, this interaction could afford protection against oxidative damage of the plasma membrane (Abad C *et al*. 2014). And thus, suggesting that MgSO4 can have antioxidant effect in patients infected with COVID19 showing symptoms of oxidative stress in late stage (Abad C *et al*. 2014).

Knowing that there is a direct relationship between blood pressure and blood viscosity (Letcher *et al*. 1981), (Fowkes FG *et al*. 1993). Thus the high blood viscosity caused by the COVID19 patients Is suggested to lead to high blood pressure in the infected patients at late stage of the disease and since that many major medical organizations worldwide consistently recommend Magnesium sulfate(MgSO4) as the agent of choice and in the first line for treatment of eclampsia and as prophylaxis of eclampsia in patients with severe pre-eclampsia(Lu & Nightingale, 2002). Preeclampsia is a condition that can develop during pregnancy characterized by high blood pressure; however, preeclampsia can progress to eclampsia, which is defined as the development of seizures in the women (Lu & Nightingale, 2002). And since pre-eclampsia and eclampsia are risk factor for HELLP syndrome in pregnant women that may lead to disseminated intravascular coagulation (DIC) which can make emergency surgery a serious challenge (Garg R *et al*. 2009). From here we can say that MgSO4 will be good choice in hypertensive patients infected with COVID19 disease showing such serious complication as it has shown effectiveness as hypertensive and anti-hyperviscosity in patient with HTN and DIC (Lu & Nightingale, 2002).

The world now is frantically trying to find the key treatments for the COVID19 infectious disease, recently the use of Chloroquine and Hydroxychloroquine in combination with antibiotics drugs such as Azithromycin is considered the number one option on table globally, especially after the study done in France on March 17th/2020 (Gautret *et al*, 2020). But the adverse reactions resulting from the use of this drug regimen have been seriously fatal as it led to the prolongation of the QTc interval and increases the risk of Torsade de pointes (TdP) (Juurlink,2020). TdP is a distinct form of ventricular tachycardia occurring in patients with marked QT prolongation (Tzivoni *et al*. 1988). Noting that Azithromycin itself does not usually cause clinically significant prolongation of the QTc interval but the combination with either chloroquine or HCQ increases the risk of TdP resulting in fatal condition thus monitoring of the QTc interval at baseline and daily for the entire duration of treatment is a must to all patients receiving this drug regimen and this is considered one of the drawbacks(Juurlink,2020). It is approved that Magnesium giving as IV Magnesium sulfate is very effective for suppression of the short-term recurrences of Torsade de pointes (TdP) and is the agent of choice and the first line drug for the immediate treatment of the TdP associated with both the congenital and the acquired forms of QTc prolongation as in the case of QTc prolongation caused by the HCQ/Azithromycin combination(Khan, 2020). Magnesium is also considered a very safe option as the therapy with magnesium sulfates can be immediately initiated as soon as the diagnosis of QTc prolongation or TdP is made with only flushing sensation reported as side effect during the use of magnesium sulfate intravenous injection therapy for the complications (Khan, 2020).

CONCLUSION

In late December 2019, our fight against corona has started and yet there is neither officially approved anti-coronavirus 19 nor effective vaccines, supportive measures and symptomatic treatment is the main approach. Magnesium sulfate has antioxidant, anti-inflammatory and immunomodulatory effect so it can effectively treat and prevent the 'cytokine storm' status and the hyper-oxidative stress state the COVID19 which make it is a cheap therapeutic option, safe and easily administered and widely available. We believe using magnesium sulfate extended infusion, to reduce mortality and morbidity of COVID-19 and it is cost-effective. Further well-designed clinical studies need to be conducted to enable a definitive decision to be reached regarding the best magnesium sulfate regimen.

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