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Original Research Article

Magnesium Sulfate Extended Infusion as an Adjunctive Treatment for COVID-19 Infected for Anaesthesia

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Abstract: ***Introduction:*** The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) creates a global pandemic and affects more than 200 countries/regions. As of July 30, 2020, the cumulative number of confirmed cases of COVID-19 in the world exceeded 16 million. SARS-CoV-2-infected patients are more likely to be admitted to the hospital and enter the intensive care unit, with high mortality. The most common symptoms of COVID-19 patients are fever and cough**.** ***Objective:*** To assess the magnesium sulfate extended infusion as an adjunctive treatment for covid-19 infected for anaesthesia. ***Materials and Methods:*** The prospective study was undertaken Department of Anesthesiology, Medical College for women and Hospital, Uttara, Dhaka, Bangladesh from July to December 2021. Of the 157 anesthesiologists who responded to this survey, 57 (36.0%) reported using magnesium sulfate in anesthesia. All patients received standard therapy for asthma, while the treatment group received an intravenous magnesium sulfate bolus of 50-75 mg/kg (0.2-0.3 mmol/kg) followed by 40 mg/kg/h (0.16 mmol/kg/h) for 4 h. Patients were monitored for cardiorespiratory complications. The treatment group underwent four blood draws to assess pharmacokinetic parameters. ***Results:*** Of the 157 anesthesiologists who responded to this survey, 57 (36.0%) reported using magnesium sulfate in anesthesia. The highest participants 50 years above 48(30.5%), 31-40 years 28(17.8%) and 0-10 years 04(2.5%). The frequency of use of adjuvant drugs in anesthesia is described. The number and percentage of clinical effects (n/%) for the use of magnesium sulfate in anesthesia were (in descending order, more than one response per participant allowed): postoperative analgesia (41/71.9%), reduction of anesthetic consumption (59/68.4%), prevention and treatment of preeclampsia and seizures in eclampsia (36/63.1%), prevention and treatment of arrhythmias (29/50.8%), reduction of the dose of neuromuscular blockers (28/49.1%), prevention of postoperative chronic pain (27/47.36%), bronchodilation (25/43.85%), prevention of hyperalgesia post remifentanil use (26/45.61%). All anesthesiologists reported using the intravenous route (57/100.00%) to administer magnesium sulfate. Other routes were used less frequently: muscular (3/5.2%), nerve plexus (1/1.7%), spinal (1/1.7%), regional intravenous anesthesia (2/3.5%), wound infiltration (2/3.5%), inhalation (1/1.7%), and oral (1/1.7%). It should be noted that some adverse events were reported as severe, i.e., respiratory depression (4), hypotension (4), residual curarisation (4), hypermagnesemia (2) and bradycardia (1). Prevention and treatment of shivering (9/15.7%), facilitation of tracheal intubation without the use of neuromuscular blocker agent (8/14.0%), reduction of nausea and vomiting (7/12.2%). 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. ***Conclusion:*** Magnesium sulfate is a cheap, safe and readily available medication can be a drug of choice in supportive treatment of COVID-19 especially

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critically ill patients with promising crucial beneficial medical effects.

Keywords: COVID-19, Erythropoiesis, Magnesium sulfate, extended infusion, hyper-coagulable status.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) creates a global pandemic and affects more than 200 countries/regions. As of July 30, 2020, the cumulative number of confirmed cases of COVID-19 in the world exceeded 16 million [1]. SARS-CoV-2-infected patients are more likely to be admitted to the hospital and enter the intensive care unit [2], with high mortality. The most common symptoms of COVID-19 patients are fever and cough [3, 4]. Many patients especially in intensive care unit have organ function damage including acute respiratory distress syndrome (ARDS), cardiac injury, acute kidney injury, and liver dysfunction [5, 6]. 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. 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 finds 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. Electrolytes such as *sodium, potassium, calcium, and magnesium* are essential basic elements to maintain cell normal physiological condition function [7]. Magnesium is the main cation in human cells, mainly concentrated in the mitochondria. Its content is the fourth most abundant after sodium, potassium and calcium in human body. There are no vaccines or approved drugs available to eradicate the virus for the prevention and treatment of COVID-19 until now. 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. All efforts at drug design and clinical trials of already approved drugs are creditable and worthy. Magnesium, an essential substance for basic biochemical reaction, participates in a cluster of normal physiological function and metabolism, such as the transport of potassium ion or calcium ion [8, 9], energy metabolism, protein and nucleic acid synthesis [10]. After long-term research, excellent effects of magnesium have been demonstrated in the prevention and treatment of various diseases. In this review, we provide the evidences and novel insights into the role of magnesium supplementation in COVID-19 supportive treatment. Therefore, magnesium homeostasis regulates reproductive system, cardiovascular system, digestive system, neurological system and respiratory system, etc, maintaining normal human health.

MATERIALS AND METHODS

The prospective study was undertaken Department of Anesthesiology, Medical College for women and Hospital, Uttara, Dhaka, Bangladesh from July to December 2021. Of the 157 anesthesiologists who responded to this survey, 57 (36.0%) reported using magnesium sulfate in anesthesia. All patients received standard therapy for asthma, while the treatment group received an intravenous magnesium sulfate bolus of 50-75 mg/kg (0.2-0.3 mmol/kg) followed by 40 mg/kg/h (0.16 mmol/kg/h) for 4h. Patients were monitored for cardiorespiratory complications. The treatment group underwent four blood draws to assess pharmacokinetic parameters. Electronic questionnaire used in this research, composed few questions that addressed the following aspects: duration of practice of anesthesiology, use of magnesium sulfate and other anesthesia adjuvants, indications, complications and doses of magnesium sulfate in anesthesia.

RESULTS

Table 1: Age duration of anesthesia practice (n=157)

Time of practice of anesthesia	*n*	%
0-10 yrs	04	2.5
11–20 yrs	10	6.3
21–30 yrs	21	13.3
31–40 yrs	28	17.8
41–50 yrs	45	28.6
50 years or more	48	30.5

Of the 157 anesthesiologists who responded to this survey, 57 (36.0%) reported using magnesium sulfate in anesthesia. The highest participants 50 years above 48(30.5%), 31-40 years 28(17.8%) and 0-10 years 04(2.5%). The length of time of anesthesia practice among the respondents is shown in Table 1. The number and percentage of clinical effects (n/%) for the use of magnesium sulfate in anesthesia were (in descending order, more than one response per participant allowed): postoperative analgesia (41/71.9%), reduction of anesthetic consumption (59/68.4%), prevention and treatment of preeclampsia and seizures in eclampsia (36/63.1%), prevention and treatment of arrhythmias (29/50.8%), reduction of the dose of neuromuscular blockers (28/49.1%), prevention of postoperative chronic pain (27/47.36%), bronchodilation (25/43.85%), prevention of hyperalgesia post remifentanil use (26/45.61%).

Table-2: Frequency of adverse events during use of magnesium sulfate witnessed at least once by the anesthesiologist (N=57)

Adverse events	***n***	**%**
Systemic arterial hypotension	18	31.5
Residual neuromuscular blockade	15	26.3
Hypermagnesemia	3	5.2
Intravenous injection pain	3	5.2
Respiratory depression	3	5.2
Heat sensation	2	3.5
Bradycardia	2	3.5
Facial/cervical flushing	1	1.7
Tachycardia	1	1.7
Intense sedation	2	3.5
Cardiac arrhythmia	1	1.7
Prolonged emergence from anesthesia	1	1.7
Myocardial depression	1	1.7
None	4	7.0

Table-2 shows the frequency of adverse events during use of magnesium sulfate witnessed at least once by the anesthesiologist. The most commonly reported were hypotension, residual neuromuscular blockade, hypermagnesemia, intravenous injection pain, and respiratory depression. All anesthesiologists reported using the intravenous route (57/100.00%) to administer magnesium sulfate. Other routes were used less frequently: muscular (3/5.2%), nerve plexus (1/1.7%), spinal (1/1.7%), regional intravenous anesthesia (2/3.5%), wound infiltration (2/3.5%), inhalation (1/1.7%), and oral (1/1.7%).

Table-3: Anesthesiologists using magnesium sulfate anesthesia (n = 57)

	N	**%**
Mild	44	77.1
Moderate	11	19.2
Severe	2	3.5

Of the adverse events reported, 77.1% of the cases were considered of mild gravity (Table-3). It should be noted that some adverse events were reported as severe, i.e., respiratory depression (4), hypotension (4), residual curarisation (4), hypermagnesemia (2) and bradycardia (1). Prevention and treatment of shivering (9/15.7%), facilitation of tracheal intubation without the use of neuromuscular blocker agent (8/14.0%), reduction of nausea and vomiting (7/12.2%), prevention and treatment of laryngospasm (6/10.5%), control of fasciculation and myalgia after succinylcholine (5/8.7%), prevention of myoclonus after intravenous injection of etomidate (4/7.01%), treatment of tetanus (4/7.01%), adjuvant in spinal anesthesia (3/5.2%), decrease in platelet aggregation (2/3.5%), attenuation of the sympathetic response to tracheal intubation (1/1.7%) and extension of duration of motor block on subdural anesthesia (1/1.7%).

Table-4: Magnesium sulfate intravenous doses most commonly used in the induction of general anesthesia and sedation (n = 57)

	Doses	**n**	**%**
Induction of general	<30 mg.kg−1	9	15.7
anesthesia	30–40 mg.kg−1	21	36.8
	40–50 mg.kg−1	7	12.2
	50–60 mg.kg−1	2	3.5
	No use for induction ofgeneral anesthesia	18	31.5
Sedation	<30 mg.kg−1	11	19.2
	30–40 mg.kg−1	5	8.7
	40–50 mg.kg−1	2	3.5
	50–60 mg.kg−1	1	1.7
	No use for sedation	38	66.6

Table-4 shows the dosages of intravenous magnesium sulfate commonly used for induction of general anesthesia and sedation.

DISCUSSION

The clinical stages of COVID-19 symptoms and features are varied among the infected patients [11]. And it is ranging from asymptomatic state to acute respiratory distress syndrome (ARDS) and multiorgan dysfunction and pneumonia that to respiratory failure and death in subgroup of patients [12]. In our study survey responses were received from 157 (9.57%) participants. The length of time of anesthesia practice among the respondents is shown in Table 1. 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) [13]. 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 [12]. 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 [14], 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 (MgSO4) has shown to have the ability to suppress the proinflammatory cytokines expression [15]. 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 [12]. 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 [15]. And thus, we can conclude that Magnesium sulfate (MgSO4) can attenuates excessive inflammation caused by the novel corona virus 2019 in the infected patients by its ability to decreases Inflammatory Cytokine production [15]. Of the 157 anesthesiologists who responded to this survey, 55 (35.0%) reported using magnesium sulfate in anesthesia. The number and percentage of clinical effects (n/%) for the use of magnesium sulfate in anesthesia were (in descending order, more than one response per participant allowed): postoperative analgesia (41/71.9%), reduction of anesthetic consumption (59/68.4%), prevention and treatment of preeclampsia and seizures in eclampsia (36/63.1%), prevention and treatment of arrhythmias (29/50.8%), reduction of the dose of neuromuscular blockers (28/49.1%), prevention of postoperative chronic pain (27/47.36%), bronchodilation (25/43.85%), prevention of hyperalgesia post remifentanil use (26/45.61%). 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 [16]. 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 thats explain the respiratory complication that occur to the infected patients [16]. 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 [17]. 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 [18,19]. 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 [20]. Since higher hemoglobin causes higher morbidity the role of Magnesium sulfate (MgSO4) in the hyper- viscosity state and DIC will be based on the antiplatelet activity of Magnesium sulfate in human platelets [21]. 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 [21]. And thus, suggesting that Magnesium sulfate (MgSO4) can attenuates hyper- viscosity and intravascular coagulation complications caused by the novel corona virus 2019 in the infected patients [21]. Table 3 shows the frequency of adverse events during use of magnesium sulfate witnessed at least once by the anesthesiologist. The most commonly reported were hypotension, residual neuromuscular blockade, hypermagnesemia, intravenous injection pain, and respiratory depression. All anesthesiologists reported using the intravenous route (57/100.00%) to administer magnesium sulfate. Other routes were used less frequently: muscular (3/5.2%), nerve plexus (1/1.7%), spinal (1/1.7%), regional intravenous anesthesia (2/3.5%), wound infiltration (2/3.5%), inhalation

(1/1.7%), and oral (1/1.7%). The role of Magnesium sulfate (MgSO4) 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 [22]. And thus, suggesting that MgSO4 can have antioxidant effect in patients infected with COVID19 showing symptoms of oxidative stress in late stage [23]. Of the adverse events reported, 77.1% of the cases were considered of mild gravity (see Table 4). It should be noted that some adverse events were reported as severe, i.e., respiratory depression (4), hypotension (4), residual curarisation (4), hypermagnesemia (2) and bradycardia (1). Prevention and treatment of shivering (9/15.7%), facilitation of tracheal intubation without the use of neuromuscular blocker agent (8/14.0%), reduction of nausea and vomiting (7/12.2%), prevention and treatment of laryngospasm (6/10.5%), control of fasciculation and myalgia after succinylcholine (5/8.7%), prevention of myoclonus after intravenous injection of etomidate (4/7.01%), treatment of tetanus (4/7.01%), adjuvant in spinal anesthesia (3/5.2%), decrease in platelet aggregation (2/3.5%), attenuation of the sympathetic response to tracheal intubation (1/1.7%) and extension of duration of motor block on subdural anesthesia (1/1.7%). Knowing that there is a direct relationship between blood pressure and blood viscosity [24, 25]. 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 [26]. 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 [26]. 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 [27]. 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) [26]. Table 5 shows the dosages of intravenous magnesium sulfate commonly used for induction of general anesthesia and sedation. 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 [28]. 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) [29]. TdP is a distinct form of ventricular tachycardia occurring in patients with marked QT prolongation [30]. 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 [29]. 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 [31]. 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 [31].

CONCLUSION

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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