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Case Report

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Could nebulized heparin be the magic treatment for COVID-19 Pneumonia and ARDS?

Abstract

Background: The global spread of the novel strain of coronavirus referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in the continuous rise in the hospitalization of people suffering from COVID-19 in various parts of the world. The predominant symptoms experienced by patients diagnosed with SARS-CoV-2 infection include pneumonia and acute respiratory distress syndrome (ARDS). These symptoms have contributed to the high mortality rate of COVID-19 patients across the globe. Recent studies have indicated that nebulized unfractionated heparin (UFH) can be employed in the treatment of pneumonia and acute respiratory distress syndrome (ARDS) in hospitalized patients who have been diagnosed with SARS-CoV-2 infection.

Case description: The case study for this investigation was a 37-year-old Saudi woman who had muscular dystrophy, bronchial asthma, and diabetes mellitus. This hospitalized patient who was a wheelchair bound was admitted to the intensive care unit (ICU) due to the onset of severe COVID-19 related pneumonia and ARDS. The patient was intubated and placed on high mechanical ventilation support with protective lung strategy (low tidal volume and high PEEP level), prone positioning, administering inhaled nitric oxide therapy, and the intravenous infusion methylprednisolone together with antiviral agents and empiric antibiotics for seven days. Despite the administration of this maximal therapy, she continued to have refractory hypoxemia and severe ARDS. As a result, a high dose of UFH was administered to the patient through nebulization. After administering nine different doses of nebulized UFH, the patient's oxygenation and inflammatory markers have remarkably improved, then she had a very smooth course and successfully weaned off mechanical ventilation.

Conclusion: This treatment strategy resulted in a significant improvement in the P/F ratio, a remarkable reduction in the bilateral lung infiltrates and inflammatory markers and eventually weaning of mechanical ventilation in the COVID-19 patient. This case suggests that nebulized UFH has a strong scientific and biological basis to test its use as a therapy for COVID-19 pneumonia and ARDS as it may offer huge clinical benefit across the time course of the disease as well may prevent progression of infection If administered early at the onset of symptoms, and may finally prevent the needs for mechanical ventilation.

Learning points: Randomized controlled trials should be carried out to investigate the clinical impacts of nebulized UFH in both prevention and treatment of COVID-19 pneumonia/AERDS.

Keywords: COVID-19, SARS-CoV-2, pneumonia, unfractionated heparin, nebulization, ARDS.

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Introduction

The incidence and global spread of the novel strain of coronavirus referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in the continuous rise in the hospitalization of people suffering from COVID-19 in various parts of the world. The predominant symptoms experienced by patients diagnosed with SARS-CoV-2 infection include pneumonia and acute respiratory distress syndrome (ARDS).[1] The onset of ARDS leads to the production of inflammatory cytokines, which damage the lungs and impairs breathing in about 23% of COVID-19 patients who are critically ill.[2] A recent publication has revealed that the mortality rate of patients diagnosed with COVID-19 who experience pneumonia and ARDS exceeds 66%.[3-5] This high mortality rate has been associated with the rise in the plasma markers, such as D-dimers, prolonged prothrombin activity and reduce the total platelet count in individuals suffering from COVID-19.[6-10] Moreover, the production of cytokines that causes the damage of major organs increases the severity of SARS-CoV-2 infection among patients that have been admitted to COVID-19 wards. In this focused case review, we present the rationale for the use of nebulized UFH for

COVID- 19 pneumonia and ARDS in hospitalized patients and calling for an urgent, global investigation of its therapeutic effect for this condition.

Case description

A 37-year-old Saudi woman who was suffering from muscular dystrophy, bronchial asthma, and diabetes mellitus served as a case study for this investigation after signing an off able drug consent. This hospitalized patient was bound to a wheelchair due to her inability to move and was placed on B2 agonist and steroid inhalers to alleviate the symptoms of bronchial asthma. Two years ago, the patient was admitted to the intensive care unit (ICU) due to the onset of severe community-acquired pneumonia caused by a bacterial infection. As a result, she had a stormy course and subjected to tracheostomy,

high mechanical ventilation support and very difficult weaning of mechanical ventilator. Fortunately, the patient fully recovered after a month and discharged home. On February 2021, she was rushed to the emergency department for treatment after experiencing pyrexia, dry cough, loss of taste and smell, body pain, and dyspnea for 4 days. It was later discovered that she had been in contact with patients diagnosed with COVID-19.[11] The result of the nasopharyngeal swab specimen obtained from the patient confirmed that she was infected with SARS nCoV-2 RNA.

Physical, laboratory, and radiological examination

The physical examination of the patient showed that the woman has mild signs of respiratory distress. She had a body temperature of 37.6°C, blood pressure of 112/65 mmHg, pulse rate of 70 bpm, and respiratory rate of 15 bpm. She had oxygen saturation level of 94% on high flow nasal cannula. On the other hand, the laboratory investigations on admissions revealed that the patient had a lymphocyte count of 0.321×103/µL and white blood cell count of 2.50×103/µL. The laboratory test results also showed that the woman had a normal neutrophil count and coagulation profile. The patient had a BUN unit of 1.6 mmol/L, procalcitonin concentration of 0.05 ng/mL, creatinine level of 13 µmol/L, LDH of 338 µL, magnesium ion concentration of 0.73 mmol/L D-dimer concentration of 0.05 mg/L, sodium ion concentration of 135 mmol/L, and ferritin concentration of 310 ng/mL. Furthermore, the result of the venous blood gas analysis indicated the occurrence of metabolic acidosis that is characterized by a pH of 7.28, pCO_2 of 63, pO_2 76, PFR of 76, and HCO_3 of 25. The result of the chest radiograph showed the presence of bilateral lung infiltrates suggesting ARDS (Figure 1).

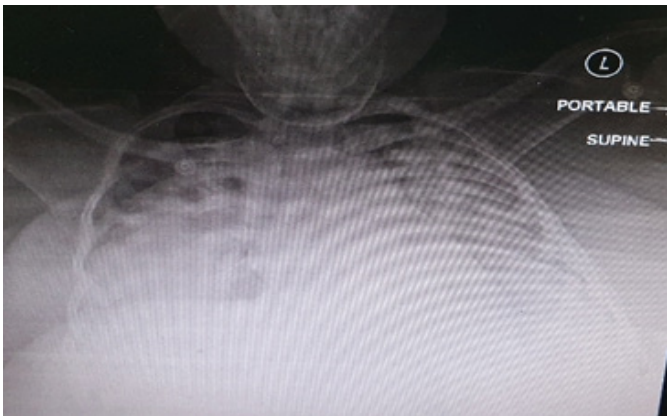

Figure 1 Chest x-ray on admission showing bilateral basal consolidation with evolving ARDS.

The hospital's course of action and management procedure

The patient was transferred and admitted to the COVID-19 ward. They administered prophylactic enoxaparin, along with intravenous steroid and empiric antibiotics. On the first day of admission in the COVID-19 ward, the patient was stable without symptoms of dry cough and fever. However, she developed tachypnea and acute hypoxic respiratory failure on the second day of admission. As a result of the onset of severe ARDS, the patient was transferred to the hospital's ICU, where she was intubated and placed on prolonged mechanical ventilation support. The patient was managed by the protocols of the ARDS Network that include protective lung strategy by maintaining a low tidal volume and high PEEP level of 16 on the ventilator, the prone positioning of the patient, and the intravenous infusion of, with methylprednisolone (1mg g/kg per day), antiviral agents Favipiravir and empiric antibiotics such as azithromycin and ceftriaxone for seven days. Due to the onset of refractory hypoxemia, inhaled nitric oxide therapy has been commenced therapy. The concentration of nitric oxide administered to the patient was 20 ppm. Although the aforementioned protocols were employed to ensure the effective management of the medical condition, the patient continued to experience refractory hypoxemia and severe ARDS with a P/F ratio that was less than 100 mm/Hg for 2 days.

An interview was held with the relatives of the patient to discuss alternative treatment solutions to enhance oxygenation and reduce the inflammation of the lungs.[11] The family members were asked to select either of these two treatment solutions: the provision of venovenous extracorporeal membrane oxygenation (ECMO) support or the trial of an off-label use of high dose of unfractionated heparin (UFH) through nebulization. At the end of the interview, the patient's family appended their signature in an informed consent form to commence the administration of a high dose of UFH through nebulization. A dose of 25,000 units/mL was administered to the patient at 6 hours interval. On the second day, the physicians noticed a marvelous improvement in the P/F ratio after the administration of nebulized UFH. The P/F ratio of the patient increased from 80 to 280 mmHg on the second day to 390 mm/Hg on the seventh day. The physicians also noticed that there was a remarkable reduction in the bilateral lung infiltrates and inflammatory markers, which was evident in the patient's chest radiograph (Figure 2).

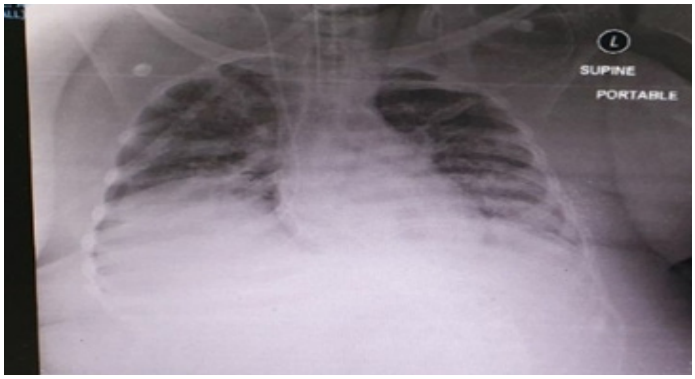

Figure 2 Chest x-ray on Day 3 after starting heroine nebulization showing marked improvement.

After administering nine different doses of nebulized UFH, the concentration inflammatory markers and blood gases returned to normal (Table 1), and lung mechanics also improved (Table 2). As a result, the patient was extubated and moved to a regular ward in the hospital. The patient course this time was very smooth compared with the previous admission and the patient went home after a total of 15 days in the hospital. Interestingly the patient did not develop any secondary bacterial infections or MDR organisms during her stay in the hospital and antibiotics was stopped after completing 7 days without needs for escalation.

Discussion

The occurrence of severe cases of SARS-CoV-2 infection is often associated with other health complications such as the destruction of alveolar walls, coagulopathy, hyper inflammation, microvascular thrombosis, and enhanced synthesis of neutrophil extracellular traps

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(NETS), which promotes the death of epithelial cells that make up lung tissues. SARS-CoV-2 penetrates human cells by combining with an angiotensin-converting enzyme-2 (ACE-2). The genes responsible for the synthesis of ACE-2 are mostly found in the epithelial cells that make up lung tissues.[11,13] The transcription and translation of these genes lead to the production of ACE-2, which prevents the breakdown of angiotensin II in the cell. The continuous synthesis of angiotensin II triggers various cell signaling mechanisms that lead to the initiation of the coagulation pathway. The onset of the blood clotting cascade results in enhanced expression of tissue factors, severe vasoconstriction, destruction of endothelial cells, and damage to the lungs.

Table 1 inflammatory markers before, during and after heparin nebulization

Laboratory Results	**Reference Range**	ICU D1	ICU D2	ICU D3	ICU D4	ICU D5	ICU D6	ICU D7	ICU D8	ICU D9	ICU D10	ICU D11 EXT D1	ICU D12 EXT D2	ICU D13 EXT D3
		48 h pre-NH	**24 h pre-NH**	**D1 NH**	**D2 NH**	**D3 NH**	**D4 NH**	**D5 NH**	**D6 NH**	**D7 NH**	**D8 NH**	**D9 NH**	**D10 NH**	**24 h post-NH**
WBC (×10³µ/l)	4-11	3.6	4.3	8	11	13	8	8.4	6.8	10.8	8.3	11.3	10.8	14.4
CRP (mg/l)	0-7	-	75.7	-	168	39	13.5	-	-	2.1	2.5	-	-	2.1
Procalcitonin (ng/ml)	<0.05	-	0.03	-	-	0.02	0.07	-	-	-	0.11	0.01	0.01	0.02
LDH (µ/l)	85-227	-	433	-	-	422	269	223	-	195	160	189	143	162
Ferritin (ng/ml)	2-4	-	-	-	-	-	-	-	-	-	-	-	77	22
D-dimer(mg/l)	0-0.55	0.64	0.55	0.89	0.55	0.70	0.32	0.31	-	0.21	-	-	-	0.19
Lymphocytes (×10³/µl)	1-5	0.31	0.34	0.37	0.61	0.86	0.96	1.0	1.52	1.54	1.62	1.50	1.69	1.59

*Abbreviation: h, hours; NH, nebulized heparin; D, Day; EXT, extubation; WBC, White Blood Cell; CRP, C-Reactive Proteins; LDH, lactate dehydrogenase.

Table 2 Respiratory parameter and lung mechanics before, during and after heparin nebulization

Respiratory Parameter and Lung Mechanics	ICU D1	ICU D2	ICU D3	ICU D4	ICU D5	ICU D6	ICU D7	ICU D8	ICU D9	ICU D10	ICU D11	ICU D12	ICU D13
	48 h pre-NH	**24 h pre-NH**	**D1 NH**	**D2 NH**	**D3 NH**	**D4 NH**	**D5 NH**	**D6 NH**	**D7 NH**	**D8 NH**	**D9 NH**	**D10 NH**	**24 h post-NH**
Ventilator Mode	PCV	PCV	PCV	PCV	PCV	PCV	PCV	SIMV	SIMV	PS	EXT D1	EXT D2	EXT D3
PEEP	14	14	14	16	16	15	15	13	11	9	-	-	-
FIO_2	100	80	70	50	50	50	40	30	30	30	21	21	21
PH	7.28	7.36	4.16	7.46	7.47	7.46	7.42	7.52	7.43	7.42	7.52	7.39	7.39
PCO_2 mmHg	63	43	39	39	37	44	49	36	46	40	42	41	42
Hco3 mmol/l	25	23	25	28	25	30	31	29	29	29	32	24	25
PO_2 mmHg	76	70	100	100	187	144	104	119	98	110	109	101	119
Spo_2 %	88	93	97	97	99	99.6	99.3	98.2	96	98.5	96.7	97	97.2
pO_2(a)/ FIO2CmmHg	70	76	143	280	375	359	347	397	327	368	362	-	-
Compliance	34	33	40	40	35	29	35	51	46	36	-	-	-
Plateau Pressure	32	32	31	32	31	31	25	18	19	21	-	-	-

*Abbreviation: h, hours; D, Day; NH, nebulized heparin; EXT, extubation; PEEP, peak inspiratory airway pressure.

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A critical review of the previous case series has indicated that there is an important relationship between the occurrence of severe cases of coagulopathy in COVID-19 patients and the unfavorable outcomes of clinical treatment.[14] For instance, the results of a study carried out by Tang et al.[10] provided compelling proof of high concentrations of D-dimers and degradation products of fibrin in hospitalized individuals who died due to the COVID-19 infection. The authors further documented that a longer partial thromboplastin time and the prothrombin time were recorded in hospitalized people who died from COVID-19 infection, compared to the survivors who were hospitalized. Similarly, in another study, Klok et al.[15] investigated the composite outcome of administering pharmacological thromboprophylaxis to patients diagnosed with COVID-19 infection. The results of the study confirmed that COVID-19 patients who experienced severe symptoms of coagulopathy suffered from ischemic stroke, symptomatic pulmonary embolism (PE), myocardial infarction, and deep-vein thrombosis. The cases of systemic arterial embolism were observed in 49% of the hospitalized patients, while pulmonary embolism was documented in 87% of the patients.[15] Furthermore, another recent study carried out by Helms et al.[8] showed that COVID-19 patients who experience severe symptoms of ARDS suffered from various thrombotic complications compared to COVID-19 patients who were not diagnosed with ARDS. These studies prove that there is an important relationship between the severity of coagulopathy in COVID-19 patients and the unfavorable outcomes of clinical treatment.

UFH is a type of glycosaminoglycan molecule that is synthesized by various cells in living organisms.[16] The specific roles of this biological molecule are often linked to the activities carried out in the basement membrane, respiratory surfaces, endothelial cells, and extracellular matrices. Heparin is mainly synthesized by mast cells and preserved as granules in humans. This glycosaminoglycan molecule constitutes 30% of the dry biomass of the granules found in mast cells.[17] The selection and application of nebulized UFH to alleviate pneumonia and ARDS in patients infected with SARS-CoV-2 virus are based on the results derived from various research investigations.

Firstly, different randomized and non-randomized control trials have been carried out on hospitalized individuals diagnosed with severe lung injury and other similar medical conditions. The results of these trials provided compelling evidence that the application of nebulized UFH decreased the initiation of the blood clotting cascade, microvascular thrombosis, as well as pulmonary dead space, and enhanced the impact of clinical treatments in hospitalized individuals. Furthermore, the use of a high dose of nebulized UFH improved mechanical ventilation and oxygenation in hospitalized people infected with SARS-CoV-2 virus. Secondly, scientific research has revealed that UFH has significant mucolytic and anti-viral effects against SARS-CoV-2 virus. This biological molecule also alleviates the symptoms triggered by the occurrence of coagulation and inflammation of the lungs.[16,17] In view of this, many researchers have explored the mechanism of action of UFH against SARS-CoV virus and the prevention of the penetration of the virus into the cells of mammals.[18-22] The results of these research investigations revealed that the application of a high dose of nebulized UFH prevents the onset of lung infections caused by SARS-CoV-2 virus. Most importantly, a high dosage of nebulized UFH prevents the attachment of SARS-CoV-2 to ACE-2 and the occurrence of COVID-19 infection in mammalian cells.

Over the years, researchers have discovered various pieces of evidence, which prove that nebulized UFH has significant anti-viral impacts that enhance the effectiveness of the host's defense mechanisms. The first proof is based on the preexisting knowledge that mast cells are localized along the blood vessels in the human body, particularly along capillaries and venules[23] The second evidence is rooted in the fact that organs like lung tissues and the alimentary canal have a high amount of mast cells compared to other parts of the human body.[24] The third proof is based on the knowledge that heparin is a macromolecule that is conserved in a wide array of species, including those without a blood-clotting pathway. Therefore, Nader et al.[25] inferred that the production of heparin in various species is quintessential to carrying out different biological functions that are not related to the initiation of the blood clotting process. This suggestion was validated in a study conducted by Porzionato et al.[23] which indicated that many pathogenic bacteria and viruses rely on the interactions between proteoglycan molecules like heparin sulfate to penetrate and adhere to tissue surfaces in different hosts.

Past research studies have also indicated that UFH prevented the penetration of viral pathogens like the herpes simplex virus (HSV), SARS-associated coronavirus, and the human immunodeficiency virus (HIV) into the cells of mammals.[18- 22,26,27] In addition, a recent research investigation carried out by Mycroft-West et al.[28] revealed that the attachment of unfractionated heparin to the receptor-binding domain of the SARS-CoV-2 Spike S1 protein triggers a change in the conformation of the macromolecule that inhibits the attachment of the viral pathogen to ACE-2. Subsequent investigations by researchers have further proven that the effects of the attachment of heparin to the receptor-binding domain of the SARS-CoV-2 Spike S1 protein vary with the molecular weight of the molecule.[29] In view of this, it can be inferred that heparins with a high molecular weight will exhibit a significant magnitude of attachment compared to similar molecules with a low molecular weight.

Heparin molecules have anti-inflammatory properties, which enables them to inhibit the production of chemicals associated with the inflammation of tissues.[30-34] For instance, during the onset of SARS-CoV-2 infection, heparin prevents the synthesis of cytokines and adhesion substances that mediate the attachment of inflammatory cells to tissues. Heparin also enhances oxygenation on mechanical ventilation and increases the production of nitric oxide.[35-38] A study carried out by Camprubi-Rimblas et al.[39] demonstrated that heparin molecules decrease the synthesis of pro-inflammatory cytokines in damaged macrophages that are localized in the alveoli of the human pulmonary system. The authors further documented that the biological molecule inhibits the NF-kB pathway that is associated with the production of pro-inflammatory mediators in the cells of the alveoli. Similarly, a research investigation conducted by Chimenti et al.[40] indicated that the nebulization of heparin reduces the synthesis of NF-kB effectors, pro-inflammatory cytokines, and TGF-β effectors in lung cells. The main mechanisms of action through which heparin alleviates the symptoms triggered by the onset of SARS-CoV-2 infection include the inhibition of the activity of heparinase and the decline in the production of adhesion substances in the cells of the alveoli.

The biological molecule also prevents the entry and attachment of inflammatory cells into the tissues of the lungs.[41] In addition, Mulloy[41] demonstrated the pharmacological effects of heparin in the prevention of endothelial injuries caused by SARS-CoV-2 infection. The level of effectiveness of UFH was discovered and validated by carrying out pre-clinical trials using suitable animal models. For instance, a pre-

clinical study conducted by Lever et al.[42] proved that UFH has a higher anti-inflammatory effect compared to low molecular weight heparin molecules. In view of this, the authors suggested that UFH exhibits pharmacological properties that may be useful in the alleviation of hyper inflammation in hospitalized individuals who are diagnosed with SARS-CoV-2 infection. Similarly, Zhang et al.[43] emphasized that the various anti-viral and anti-inflammatory properties of heparin may be quintessential in the treatment of hyper inflammation in people who are diagnosed with SARS-CoV-2 infection.

The anticoagulant effects of heparin have made the molecule a suitable treatment solution for the alleviation of symptoms associated with systemic fibrin deposition.[44] Some research studies have proven that heparin prevents the initiation of the coagulation pathway through several mechanisms of action. These mechanisms include acting as a catalyst to enhance the activity of antithrombin, decreasing the expression of tissue factors during the onset of a viral infection, enhancing the initiation of the pathway that inhibits the expression of tissue factors, and promoting the synthesis of heparin sulfate through the production of plasminogen activators by endothelial cells.[34,45] This mechanism of action enables the nebulized heparin molecules to decrease inflammation and limit the onset of fibrin disposition in the lungs.

Other studies have also documented the anti-inflammatory effects of nebulized UFH.[30-33] These research publications documented that the mode of action of UFH does not involve entry into the systemic circulation of the human body. In addition, the application of nebulized UFH did not cause major side effects when used to enhance the functions of the lungs. For instance, a study carried out by Camprubi-Rimblas et al.[34] indicated that the use of nebulized UFH for the treatment of acute respiratory distress syndrome decreases the risks of systemic bleeding in hospitalized patients. In this regard, researchers have recommended the application of nebulized UFH as a systemic therapeutic agent for ARDS and for the prophylactic treatment of coagulopathy.

Most importantly, the clinical proof of the efficacy of nebulized UFH in the treatment of SARS-CoV-2 infection shows that the administration of this therapeutic agent contributes significantly to positive clinical outcomes compared to other treatment solutions.[10]

For instance, the results of a non-randomized control trial carried out by Tang et al.[46] provided compelling evidence of the efficacy of nebulized UFH in the treatment of SARS-CoV-2 infection. The authors reported that the administration of heparin to hospitalized patients who exhibited symptoms caused by high levels of D-dimers and sepsis-induced coagulopathy increased the survival rate of these individuals compared to other treatment solutions (Figure 4).

The result of another observational research carried out to investigate the effects of the application of nebulized UFH on the survival rate of hospitalized individuals diagnosed with SARS-CoV-2 infection showed that the therapeutic solution reduced the mortality rate of these patients significantly.[47] In contrast, this effect was not observed in patients who did not receive systemic anticoagulation treatment.[47] Based on the outcome of this investigation, Paranjpe et al.[47] inferred that the administration of UFH had better clinical impacts in hospitalized individuals suffering from COVID-19.

On the whole, the outcome of different studies on the therapeutic properties of nebulized UFH shows that the treatment solution provides clinical benefits over the time course of SARS-CoV-2 infection.[11,46-48] The several modes of action of nebulized UFH also make this therapeutic agent a suitable choice for the prophylactic treatment of COVID-19. In addition, nebulized UFH can be administered during the onset of the SARS-CoV-2 infection to reduce the progression of the disease. The antiviral, anti-inflammatory, and anti-coagulation effects of nebulized UFH make it a preferable option for the alleviation of pneumonia and ARDS that characterize the progression of SARS-CoV-2 infection.

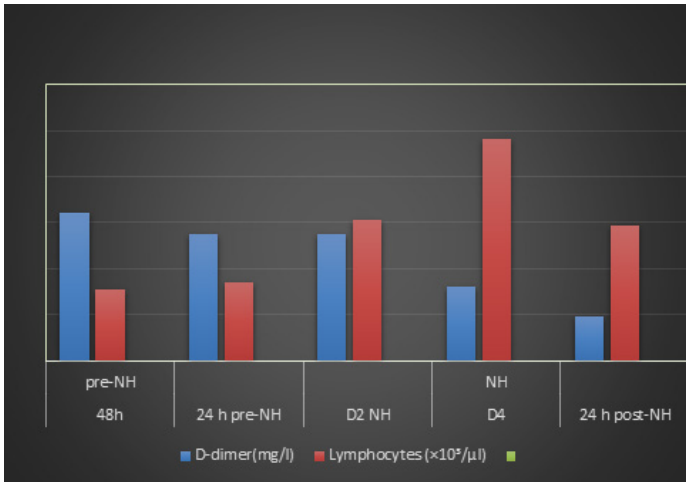

Figure 3 LDH and Lymphocytes count in relation to UFH nebulization.

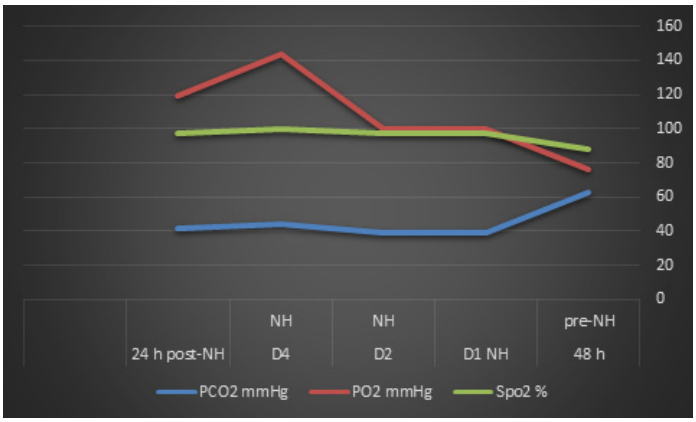

Figure 4 Pco2, Po2 and Spo2% in relation to UFH Nenulization.

Many research studies have demonstrated that nebulized UFH reduced the inflammation of the lungs, and enhanced the recovery rate of COVID-19 patients.[30-33] Although the wide availability and cost-effectiveness of this drug make it a potential treatment solution for the alleviation of COVID-19 symptoms in hospitalized individuals, large-scale clinical studies must be conducted to evaluate the impacts of nebulized UFH on the mortality rate of people diagnosed with SARS-CoV-2 infection. In order to ascertain the generalizability of the outcome of large-scale research studies, the investigations should be connected by a global health network.

Conclusion

This article review may provide convincing clue of the efficacy of nebulized UFH in the treatment of pneumonia and ARDS that are experienced by hospitalized patients who have been diagnosed with SARS-CoV-2 infection. This intervention in our case resulted in a

significant improvement in the P/F ratio, a remarkable reduction in the bilateral lung infiltrates and inflammatory markers, and significant improvement in the mechanism of ventilation in the COVID-19 patients. It is well known that high doses nebulized UFH has antiviral, anti-inflammatory, anti-coagulant, and mucolytic properties that improve the recovery and survival rates of hospitalized individuals admitted to COVID-19 wards.

Moreover, the multiple mechanisms of action of nebulized UFH make this therapeutic solution a preferable choice for the prophylactic treatment of COVID-19 and the inhibition of the progression of the disease in hospitalized individuals. Other benefits such as the wide availability, high safety and cost-effectiveness of the drug make it a suitable treatment solution for the alleviation of COVID-19 symptoms in hospitalized individuals.

Based on the beneficial effects of nebulized UFH in the treatment of COVID-19 disease, a call has been issued out to concerned stakeholders to conduct large scale studies to investigate the clinical impacts of this therapeutic solution in the alleviation of COVID-19 related pneumonia and ARDS in hospitalized patients across the globe.

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Conflicts of interest

There are no conflicts of interest regarding the publication of this paper.

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Informed consent

Not applicable.

Author contributions

Nothing to declare.

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