Original article

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Combination of subcutaneous and inhaled heparin: A study on lung oxygenation and ventilation in patients with severe COVID-19 on mechanical ventilation

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Abstract

***Objective*: To analyze lung oxygenation and ventilation effects with combined subcutaneous and inhaled heparin for severe coronavirus disease 2019 (COVID-19) on mechanical ventilation.**

***Design*: A pilot observational retrospective cohort study using secondary data from medical records in August 2020-April 2021.**

***Setting*: Patients with severe COVID-19 on mechanical ventilation in the primary Intensive Care Unit (ICU).**

***Patients and participants*: Consecutive sampling was used to recruit 20 participants with severe COVID-19 on mechanical ventilation according to inclusion and exclusion criteria. Patients were divided into two groups: one received subcutaneous systemic heparin (HS) 5,000 IU every 12 hours. The other (combined heparin [HC]) received subcutaneous heparin 5,000 IU every 12 hours and inhaled heparin 25,000 IU every 6 hours.**

***Measurements and main results*: Blood gas analyses conducted on days 0 to 5 measured lung oxygenation and ventilation, analyzed using analysis of variance (ANOVA) same-subject design, and one-way ANOVA evaluated differences on observation days. Improvements in lung oxygenation and ventilation were observed in both groups. The HS group showed at least one pair of observation days with different results, while the HC group had no differences on any day, meaning lung oxygenation improved with only subcutaneous heparin. Lung ventilation in HS and HC groups showed at least one pair of different days, meaning lung ventilation improved in both groups.**

***Conclusion*: Subcutaneous heparin is sufficient for improving lung ventilation and oxygenation in severe COVID-19 mechanical ventilation.**

Key words: Heparin, lung ventilation and oxygenation, severe COVID-19, mechanical ventilation.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), began in 2019. A large proportion of its mortality rate is caused by massive pulmonary emboli or thrombosis in the lung vasculature. (1) Patients with severe SARS-CoV-2 infection experience acute respiratory distress syndrome (ARDS), multi-organ failure, high levels of inflammatory cytokines (cytokine storm), higher levels of plasma markers of coagulation such as D-dimer, increased prothrombin time, and a lower platelet count. (2) Coagulopathy is a common complication in patients

with severe COVID-19. The higher the patient's coagulation marker level, the higher the patient's mortality risk. (3)

The point of entry for the SARS-CoV-2 virus is the nasal cavity via airborne transmission. (4) In most cases, the disease is restricted to the upper respiratory system. The ability of the virus to penetrate the lower respiratory system depends on many factors, including comorbidities and immune status. In cases where patients have severe COVID-19 with ARDS and require mechanical ventilation, systemic anticoagulation therapy is recommended to prevent hypercoagulation. (5) Due to the airborne route of transmission, inhaled drugs should help prevent and/or minimize the disease's severity.

Inhalational therapy is a common humidification strategy for patients with mechanical ventilation. The possibility that inhalational therapy will be successful at reaching the alveoli depends on the type of humidification device used, aerosol particles produced, the quantity of drugs administered, and the flow rate. Studies have shown that for patients on mechanical ventilation, inhaled heparin reduced the length of hospital stay and improved the Murray Lung Injury Score (MLIS). (5) It also increased the number of ventilator-free days. Moreover, inhaled heparin is well tolerated, even when used with other anticoagulants. (6)

The improvement of respiratory failure is generally evaluated using the oxygenation parameter arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) ratio in accordance with the Berlin criteria (7) for ARDS. PaO2 is influenced by the oxyhemoglobin dissociation curve and pH, and the alveolar-arterial gradient (A-a gradient) component already includes a parameter that reflects changes in PaO2 according to the level of alveolar ventilation. Therefore, measurement of the A-a gradient in hypoxemic ARDS, as for ARDS with COVID-19, may help evaluate the improvement or worsening of a patient's condition or their response to an administered therapy.

In this study, we hypothesized that administering systemic heparin subcutaneous and inhaled heparin to patients who had contracted COVID-19 with severe ARDS and were on mechanical ventilation would create more improvement in lung ventilation and oxygenation than treating with subcutaneous heparin alone.

Materials and methods

This was a pilot observational retrospective cohort study conducted from August 2020 to April 2021 using secondary data from medical records. This study used secondary data under ethical clearance issued by the local ethical committee.

Consecutive sampling was used to recruit 20 patients being treated for COVID-19 with severe ARDS and who were on mechanical ventilation. We divided the patients into two groups: The first group received only systemic heparin subcutaneously (HS) at a dose of 5,000 IU every 12 hours, while the second group (heparin combination [HC]) received a systemic heparin dose of 5,000 IU every 12 hours, along with inhaled heparin at a dose of 25,000 IU every 6 hours.

Patients' ages ranged from 18 to 86 years. We excluded patients who had been on mechanical ventilation for less than 5 days, were expected to be extubated within 5 days, were pregnant, had bleeding diathesis, or had received anticoagulant therapy before being diagnosed with severe COVID-19. Patients were also excluded if their medical record indicated that heparin therapy had been discontinued due to prolonged activated partial thromboplastin time (aPTT) greater than twice the reference value, increased D-dimer, the presence of bloody sputum or blood stain, or the occurrence of spontaneous bleeding.

All patients received standard medication, (8) including invasive mechanical ventilation, analgesic, sedative, fluid management, antibiotic, steroid, and thromboprophylaxis. Upon a patient's admission to the intensive care unit (ICU), an arterial cannula and a central line were inserted, and blood samples were taken at the same time every morning. Inhalation therapy was administered using a jet nebulizer Aerogen Pro (Aerogen, Galway, Ireland) connected to the ventilator. We evaluated blood gas analysis results on days 0 to 5. The independent variable was heparin dose, and the dependent variables were improvement in lung oxygenation assessed through the PaO2/FiO2 ratio, and lung ventilation assessed through the A-a gradient.

The outcomes to be measured were an improvement or worsening of lung oxygenation and ventilation, which were assessed by analysis of variance (ANOVA) on SPSS v. 27 for Windows® using the same-subject design. To evaluate differences on each observation day, we used one-way ANOVA. The data were presented as mean±standard deviation (SD), number, and frequency. The level of significance was set to a p-value of <0.05.

Results

A total of 20 patients completed the study, with 10 of them assigned to the HS group and 10 to the HC group (**Figure 1**). Patient characteristics (gender, age, and comorbidities) were homogeneous (**Table**

1).

In the HS group, lung oxygenation assessment using the PaO2/FiO2 ratio showed at least one pair of observation days with different results, while the HC group showed no significant differences in this ratio on any of the days (**Table 2**). This means that lung oxygenation improved when only subcutaneous heparin was administered.

The A-a gradients in the HS and HC groups showed at least one pair of different days, which indicates that lung ventilation, as measured with alveolar-arterial oxygen difference (AaDO2), improved with the use of intravenous heparin and also in combination with inhaled heparin (**Table 2**). It is interesting that using the combined heparin improved lung ventilation but not lung oxygenation, while oxygenation and ventilation were both improved with subcutaneous heparin administration alone.

Discussion

The benefit of heparin for preventing and minimizing hypercoagulation in patients with severe COVID-19 has been well documented. (9) Heparin binds vascular endothelium, preventing hypercoagulation in COVID-19. (10) It is proposed that inhaled heparin reduces the formation of hyaline membranes and micro thrombosis in the lungs; prevents hyperinflammation, increasing the release of nitric oxide (NO); prevents the formation of deoxyribonucleic acid (DNA) neutrophil extracellular traps (NETs), which can interfere with gas exchange in the lungs; and has a mucolytic effect. (2)

In this pilot study, we showed that the use of a combination of subcutaneous and inhaled heparin improved ventilation in patients with COVID-19, and the use of only subcutaneous heparin improved both ventilation and oxygenation in patients. We used the timeline because before March 2021 patients with COVID-19 only used prophylactic or therapeutic heparin systemic, while after March 2021 inhaled heparin started to be used for severe COVID-19 on mechanical ventilation.

The ability of the inhaled drug to reach the pulmonary alveoli, where the SARS-CoV-2 virus binds to the pulmonary alveolar pneumocyte cells, depends on the type of nebulizer, the size of aerosol generated, the quantity of inhaled drug reaching the lower respiratory tract, and the gas flow rate. Bendstrup (11) found that the produced aerosol particles were smaller when using a sidestream jet nebulizer for heparin inhalation, and higher flow rates and the assumption of greater water loss during nebulization were not proven. The dose reaching the lower respiratory tract was higher when inhalation was administered using a jet nebulizer than when an ultrasonic nebulizer was used. An advanced drug delivery system, the formulation of inhaled drugs, the particle size of the formulation, and whether the polymer or drug carried are also involved in delivering inhaled heparin to the pulmonary alveoli. In this study, we used Aerogen Pro (Aerogen, Galway, Ireland), a jet nebulizer with vibrating mesh technology connected to the ventilator, with a flow rate of >0.2 ml/minute. The particles generated from this type of nebulizer are smaller with higher gas flow rates. The dosage of heparin inhalation was also high (>60,000 IU/day), but the heparin preparation widely available here is liquid sodium heparin, with a molecular weight of 1039.9 g/mol. (12) Deposition upon pulmonary administration is largely controlled by the particle or droplet size of the drug formulation. Bai et al. (13) showed that heparin in a dry powder inhaler (DPI) preparation was more efficacious for pulmonary delivery than a solution formulation. The study used a DPI formulation of low molecular weight heparin (LMWH) with lactose as the carrier. The solid drug particle with elongated lactose crystals provided a more efficient deposition of the drug than liquid droplets, with a 1.5-fold increase in relative bioavailability (41.6%) compared to the liquid formulation (32.5%). Benstrup et al. (11) showed that with the dosage of 400,000 IU, heparin delivered by sidestream jet nebulizer at a flow rate of 10 l/min corresponded to 32,000 IU heparin administered to the lower respiratory tract (LRT). This study determined that inhaled heparin at a dose of ≤32,000 IU also safely reached the LRT.

The duration of inhalation of heparin also had a role in drug particle deposition in the pulmonary system. In Benstrup's study, (11) the dose of 100,000 IU was given over 15 minutes, while the dose of 400,000 IU was given over 60 minutes. In this study, the duration of inhalation was the same for both groups, but the frequency was different.

Patients with severe COVID-19 who require mechanical ventilation can suffer from both pulmonary and systemic inflammation, leading to multi-organ dysfunction in those at high risk. In this case, systemic heparin should provide more benefits to prevent or minimize the incidence of inflammation as compared to the combination of subcutaneous and inhaled heparin. In the early stage of SARS-CoV-2 infection, which involves the upper respiratory tract, the use of inhaled heparin as soon as possible may be beneficial, although further studies with larger sample sizes are necessary to support this.

The limitations of this study were its small sample size, the use of secondary data, and the lack of an only inhaled heparin group. These may limit data variation and lead to an inability to control for confounding variables.

Conclusion

The observed groups showed significant differences in the improvement of pulmonary ventilation, but the improvement was more significant in patients receiving subcutaneous heparin only. The oxygenation function showed more significant improvement in the subcutaneous heparin group than in the combined heparin group. Finally, subcutaneous heparin therapy was sufficient to improve lung ventilation and oxygenation in patients with severe COVID-19 who were on mechanical ventilation.

Acknowledgments

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Table 1. Participant demographic and clinical characteristics

	HS Group	HC Group	p-value
Age (years)	60.8±10.4	58.1±18.6	0.692
Gender			0.063
- Male	8	3	
- Female	2	7	
Comorbidities			
- Ischemic stroke	4	1	0.280
- Pulmonary tuberculosis	1	1	0.999
- Diabetes mellitus	2	3	0.739
- Chronic hypertension	1	4	0.280
- Septic AKI	1	0	0.739
- Pneumonia	3	1	0.481
- Diabetic ulcer	1	0	0.739
- COPD	1	1	0.739
- Hyperkalemia	1	0	0.999
- Anemia	1	0	0.739
- CHF	0	0	0.739
- CAD	0	1	0.739
- Liver cirrhosis	0	1	0.739
- Atrial septal defect II	0	1	0.739
- Lung edema	0	1	0.739
- Dementia, Alzheimer	0	1	0.739

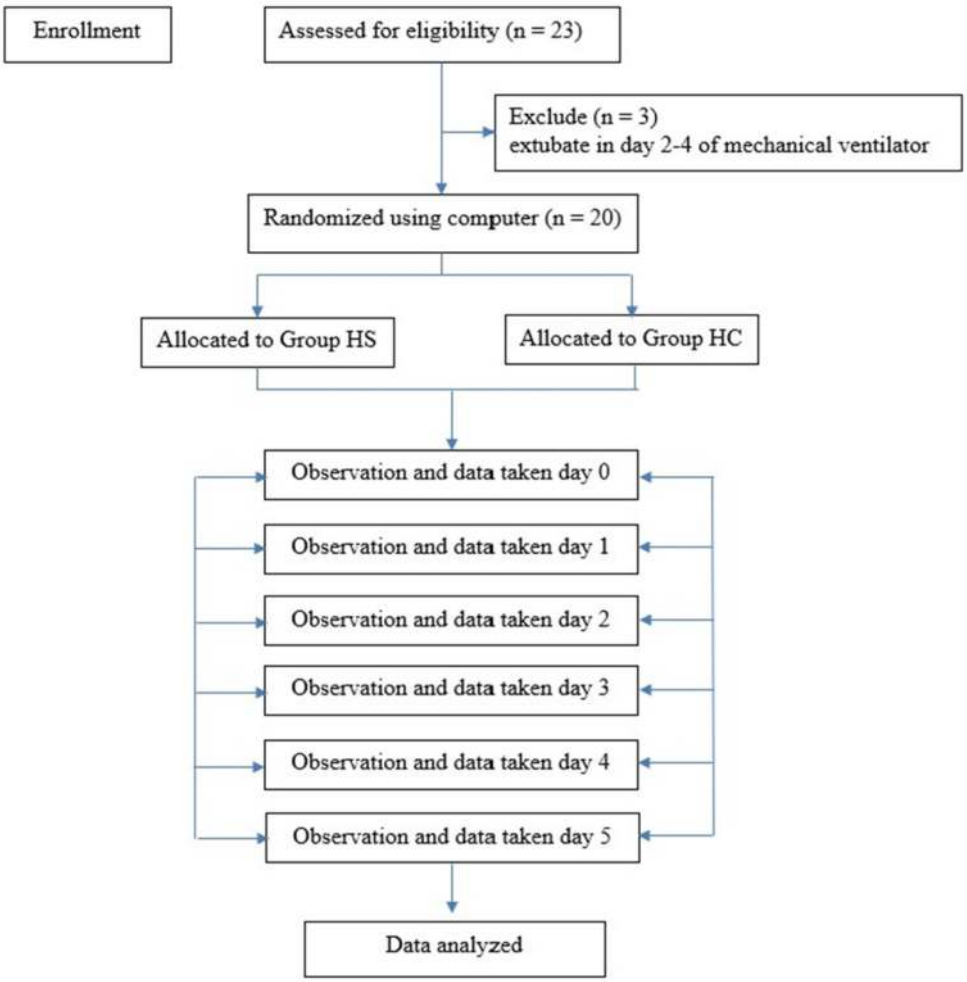
Legend: HS=subcutaneous heparin; HC=combined heparin; AKI=acute kidney injury; COPD=chronic obstructive pulmonary disease; CHF=congestive heart failure; CAD=coronary artery disease.

Table 2. Comparison of lung oxygenation and ventilation levels at each observation

	Group	Observation day						p-value
		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	
Lung oxygenation PaO2/FiO2	HS	82.9±23.0	105.7±19.6	122.0±19.0	154.2±28.3	180.7±41.0	176.5±35.5	0.001
	HC	84.6±38.6	102±32.2	167.9±132.2	165.2±74.2	143.4±47.5	147.9±59.7	0.067
Lung ventilation A-a gradient	HS	505.1±140.7	524.6±60.4	460.9±45.7	420.5±45.1	369.9±59.4	349.1±85.9	0.002
	HC	566.7±53.6	519.8±78.6	461.8±151.3	423.3±123.1	411.7±113.1	456.5±105.2	0.004

Legend: PaO2=arterial partial pressure of oxygen; FiO2=fraction of inspired oxygen; HS=subcutaneous heparin; HC=combined heparin; A-a gradient=alveolar-arterial gradient.

Figure 1. Data collection procedure



Legend: HS=subcutaneous heparin; HC=combined heparin.

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