SYSTEMATIC REVIEW

Role of Nebulized Heparin in Clinical Outcome of COVID-19 Patients with Respiratory Symptoms: A Systematic Review

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Abstract

Coronavirus disease-2019 (COVID-19) is an extremely contagious illness caused by the SARS-CoV-2 virus and has been declared a pandemic by the World Health Organization (WHO). There are currently no particular treatments, however, nebulized heparin has been offered as a viable therapy. The purpose of this systematic review is to assess the efficacy of nebulized heparin in COVID-19 patients with respiratory symptoms.

Methods: Relevant studies were identified through a systematic search of the PubMed, Medline, Embase, Cochrane Library and Web of Science, and Scopus databases. The search terms included "nebulized heparin," "COVID-19," and "SARS-CoV-2." Studies that evaluated the use of nebulized heparin in COVID-19 patients with respiratory symptoms were included. The rest of the studies along with those that were not published in English were excluded. The systematic review was registered under PROSPERO-CRD42023413927.

Observations: Five studies have been included in this systematic review. Case reports, case series, observational studies, and randomized controlled trial (RCT) comprised the studies. The patient sample sizes ranged from 2 to 98. The studies assessed the efficacy of nebulized heparin in COVID-19 patients with variable disease severity. The evaluated outcomes included mortality, hospital stay duration, oxygen requirements, and laboratory parameters.

Conclusion: Based on the clinical studies included in this systematic review, nebulized heparin may be useful in the management of COVID-19. Oxygen saturation was greater, inflammatory indicators were lower, and hospital stays were shorter in these patients. However, the studies had limitations, including inconsistent sample sizes, varying dosages of nebulized heparin, and no control groups. Nebulized heparin in patients with COVID-19 needs to be studied further to determine its safety and effectiveness.

Keywords: Acute respiratory distress syndrome, Coronavirus disease-2019, Nebulized heparin, Pandemic, Randomized study, Randomized controlled trial, Respiratory failure, SARS, SARS-CoV-2, Unfractionated heparin.

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Highlights

- This review integrates five clinical studies evaluating the efficacy of nebulized heparin in the treatment of coronavirus disease-2019 (COVID-19) pneumonia.
- In patients who received nebulized heparin, oxygen saturation was greater, inflammatory markers were lower, and hospital stays were short with no significant adverse effects.
- However, the studies had flaws, including inconsistent sample sizes, varying dosages of nebulized heparin, and no control groups.

Introduction

Background

Patients having COVID-19-related acute respiratory distress syndrome (ARDS) are known to have high levels of coagulation parameters, including D-dimer, prothrombin time, and reduced platelet count.[1,2] This leads to widespread endothelial dysfunction as well as microvascular and macrovascular pulmonary arterial thrombosis, which in turn leads to an increase in dead space and impairment of oxygenation even in the absence of reduced pulmonary compliance. Some of the specific pulmonary findings in severe disease include pulmonary fibrin deposits in the alveolar spaces as has been seen in postmortem studies and lung biopsies performed on COVID-19 patients with ARDS.[3–5] Additionally, extensive pulmonary microvascular thrombi were observed in the arteries, small arteries, and arterioles of these patients. The unique properties of unfractionated heparin include antiviral, anti-inflammatory, and anticoagulation which are relevant in SARS-CoV-2 infection.[6,7] Nebulized unfractionated heparin (UFH) has been shown to have numerous positive effects in clinical studies. Nebulized UFH has an anticoagulant effect and the added advantage of being delivered locally to the lungs, targeting pulmonary fibrin deposition and inflammation. This type of administration is superior to intravenous administration because

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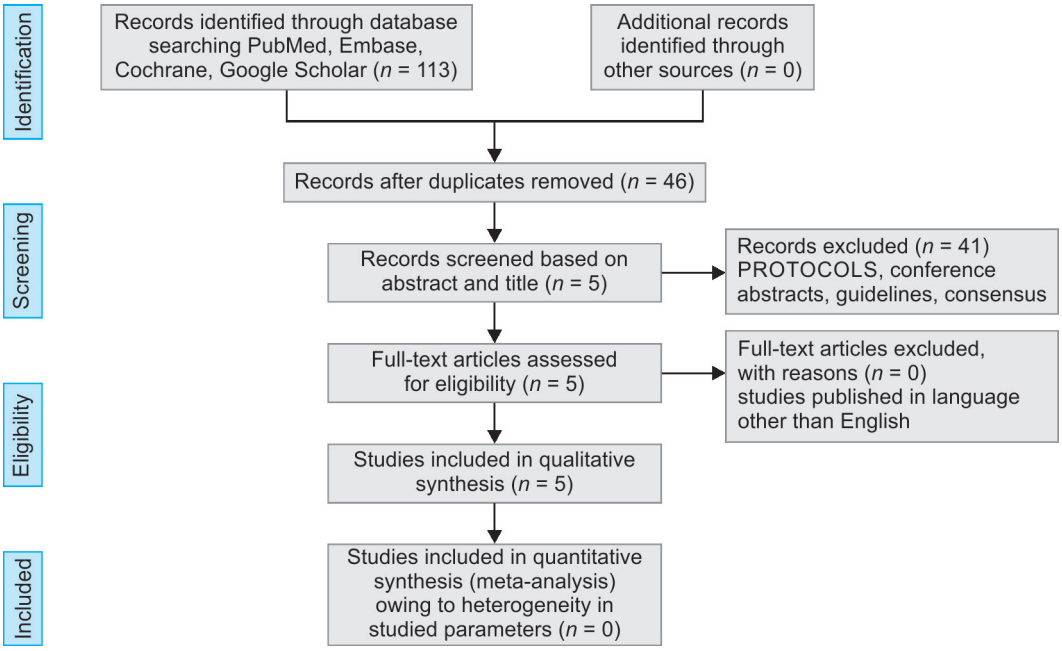

Fig. 1: PRISMA 2009 flow diagram

it allows for higher dosages, boosts local efficacy, lowers the risk of bleeding throughout the body, and is more effective overall.[8–10] Importantly, previous research has shown that after nebulization, the levels of UFH in systemic circulation are not significant. This shows that it can be utilized along with systemic, therapeutic, or prophylactic anticoagulation without any concern for added impact on systemic anticoagulation.[11,12]

Review Question: Can nebulized heparin therapy help improve the clinical outcome among COVID-19 patients with respiratory symptoms?

Objective: Our primary objective was to address our research question and find whether nebulized heparin has a role in improving outcomes in patients suffering from COVID-19 with respiratory symptoms. The primary objective was to assess patient improvement based on parameters, such as improved oxygenation, levels of inflammatory markers, shorter periods of mechanical ventilation, and a reduced length of hospitalization. The secondary objectives were to note any side effects with nebulization like bleeding and or derangement of coagulation parameters.

Methods

Search Strategy

A systematic search was made in the databases of PubMed, MEDLINE, EMBASE, Cochrane Library, Web of Science, and Scopus utilizing the keywords – "Heparin", "COVID-19", "COVID pneumonia" and "COVID ARDS", last search was completed on April 15, 2023. The systematic review was registered under PROSPERO-CRD42023413927. We thoroughly reviewed the abstracts and titles of studies to find information about the effectiveness and safety of nebulized heparin for patients with COVID-19 infections. However, we excluded studies involving pediatric patients, animal studies, and studies not published in the English language. Additional relevant publications were also identified from cross-references. We included adult patients, of any sex, ethnicity, having COVID-19 infection and presented with respiratory symptoms. The data collected in each study comprised the patient population, details of the intervention given (such as nebulized heparin dosage, frequency, timing, and duration), duration of ICU stay, mortality rates, length of mechanical ventilation, duration of ICU-free days, and safety endpoints (such as bleeding and coagulation parameters).

Study Selection

The titles and abstracts of the studies were screened for relevance by two reviewers, BG and NG. The eligibility of the full-text articles was then assessed based on the inclusion and exclusion criteria. Any disagreements were resolved through discussion with a third reviewer, PA.

Data Extraction

Data were collected from each study by utilizing a standardized form and inputting it into a Microsoft Excel spreadsheet (Microsoft Inc., USA), information such as the year and country of publication, study design, patient demographics, and patient outcomes was extracted. This included data on study and patient characteristics, intervention details, and outcome measures. However, statistical analysis for publication bias using a funnel plot and Egger's test was not conducted. The review follows the PRISMA guidelines for systematic review and meta-analysis and the Patient, Intervention Comparison, Outcome, (PICOS) Study Design was used to identify potential studies for inclusion (Tables 1 and 2).

Studies

For each intervention, reviews were given the highest priority, followed by randomized controlled trials (RCTs), observational studies, and lastly, case series and case reports were considered if no better evidence was available.

Risk of bias assessment: This was not done due to heterogeneity in the published data and limited RCTs.

Table 1: PICOS framework

Population	Adult patients with COVID-19 pulmonary disease
Interventions	Nebulized heparin
Controls	Normal saline
Outcomes	Primary objectives: • Improvement of oxygenation • Inflammatory markers • Patient outcome • Mortality benefit • Length of stay • Duration of mechanical ventilation days
Study design	Randomized controlled trials Observational studies Case series

Table 2: The PRISMA guidelines for this systematic review

1. Identification
   - Database searching: PubMed, EMBASE, Cochrane Library, and Web of Science
   - Date of search: Till April 15th 2023
   - Keywords used: Nebulized heparin, COVID-19, SARS-CoV-2, and coronavirus
   - Language restriction: English
2. Screening
   - Titles and abstracts screened for relevance
   - Full-text articles assessed for eligibility
   - Any discrepancies resolved through discussion with a third reviewer
3. Eligibility
   - Inclusion criteria: Studies that assessed the role of nebulized heparin in COVID-19 patients
   - Exclusion criteria: Studies that did not report on nebulized heparin or COVID-19 patients
4. Included studies
   - Total number of studies included: 5
   - Study design: 1 randomized controlled trial, 4 observational studies
5. Data extraction
   - Data extracted using a standardized form
   - Extracted data included study characteristics, patient characteristics, intervention details, and outcome measures
6. Data synthesis
   - Data synthesized narratively due to heterogeneity of studies

Data synthesis: The data were synthesized narratively, given the heterogeneity of the studies in terms of interventions, populations, and outcome measures.

Review Results

After applying the inclusion criteria, five studies were identified that met the eligibility requirements for this systematic review.[13–18] Out of these, the majority were retrospective and observational, while only one study was a prospective, RCT. Demographic characteristics were similar in almost all the studies with the majority of patients being males and more than 50 years of age. The patient sample sizes ranged from 2 to 98, involving a total of 246 COVID-19 patients (Table 3).

COVID-19 Patient Subsets

There was heterogeneity in COVID-19 patient symptomatology. While van Haren[13] and DeNucci Gilberto[15] took COVID-19 hospitalized patients, Gupta B et al.[16] and Douen et al.[17] incorporated mild-to-moderate category of COVID-19 patients, and Erelel M et al.[14] studied COVID-19 patients with respiratory distress in their study (Table 4).

Dosage of Nebulized Heparin

There was heterogeneity in dosage, frequency, time to commencement, and duration of nebulized heparin therapy too in various studies. van Haren[13] studied three different groups of dosage and frequency of nebulized UFH (5000 IU q8h, 10000 IU q4h, or 25000 IU q6h), Gupta B et al.[16] used 10000 IU 6 hourly, Erelel M et al.[14] 4000 IU 12h, DeNucci Gilberto,[15] and Douen A et al.[17] used 25000 IU q6h in their studies (Table 3).

28-day Mortality

According to van Haren et al.'s study,[13] 29.6% (29 out of 98 patients) of the overall cohort died while in the hospital. Meanwhile, In Gupta B et al.'s[16] research, the mortality rate was 16.6%. However, the use of nebulized heparin did not affect mortality, which was instead linked to the severity of COVID-19 and the comorbidities of the patients. In DeNucci Gilberto et al.'s[15] observational study, nebulized UFH resulted in lower mortality rates (15.8% or 6 out of 38 patients) than standard care (27% or 10 out of 37 patients), but the difference was not statistically significant. Douen A et al.[17] found that the use of nebulized heparin provided a mortality benefit. (Table 4).

Length of Stay in Hospital/Time to Discharge

DeNucci Gilberto et al.[15] patients who received nebulized UFH had a comparable time to discharge as those in the standard care group. van Haren et al.[13] reported that survivors had a mean time to hospital discharge of 12.3 ± 9.4 days. Gupta B et al.,[16] found that patients who were given nebulized heparin had a hospital stay duration of 19.43 ± 10.146 days (Table 4).

Mean PaO_2 or PaO_2/FiO_2

van Haren[13] et al. reported improved oxygenation using WHO, MOCS score, and decreased FIO_2 over time in patients receiving high doses of nebulized heparin (25 000 IU q8h). Gupta B et al.[16] reported significant improvement in oxygenation (pO_2/FIO_2 ratio) over 7 days (mean = 184.96, $p = 0.00$). Also, PaO_2 (84.17 ± 33.82) and SO_2 (92.30 ± 3.49) showed significant improvement. In a study conducted by Erelel M et al.[14] it was observed that 75.8% of the patients in the Device Group who initially required complete oxygen support were able to breathe in "room air" without support on day 10 as compared with day 1. According to DeNucci Gilberto et al.[15] the use of UFH resulted in lower mechanical ventilation rates in the mITT population (OR: 0.31; $p = 0.08$) (Table 4).

Coagulation and Hematological Factors Studied

van Haren et al.[13] reported an increase in activated partial thromboplastin time (APTT) from 34 to 38 sec (insignificant). DeNucci Gilberto et al.[15] found that there were no significant differences in APTT between the two treatment groups. Gupta

Table 3: Demographic and intervention characteristics of the studies

Authors	*Type of study*	*N (total no. of patients)*	*Total no. of patients who received nebulized heparin*	*Type of study*	*Age-group*	*Male: female ratio*	*Heparin dose and frequency*	*Outcome parameters assessed*
van Haren et al.,[13] 2021	Multicenter case series (3)	98	98	Prospective observational case series	66 ± 17 years	52%:48%	Nebulized UFH (5000 IU q8h, 10000 IU q4h, or 25000 IU q6h	APTT, SpO_2/FIO_2
Gupta B et al.,[16] 2023	Single center	30	30	Prospective observational study	Mean age 54.5	79%:21%	10000 U 6 hourly	pO_2/FIO_2 ratio, LOS, mortality benefit
Mustafa et al.,[14] 2021	Single center	80	40	Randomized controlled trial	60.02 ± 10.04	57%:43	4000 IU 12 h	Improvement in SpO_2, PaO_2
DeNucci Gilberto et al.,[15] 2023	Two centers	75	38	Randomized control study	51.95 ± 12.39	63%:27	25000 IU 6 h	Mortality, Length of hospital stay
Douen A et al.,[17] 2021	Single center	3	3	Case reports	60.6	67%:27%	25000 IU 6 h	Mortality benefit

and team (16) reported that IL6 levels at day 7 were 59.09 ± 110.45 compared with baseline levels of 62.85 ± 101.52 after treatment. According to Erelel M et al.[14] the control group showed significantly higher levels of C-reactive protein (CRP), while the Device Group had significantly higher levels of ferritin, leukocyte count, and neutrophil/lymphocyte ratio (all <0.01). However, there was no difference in D-dimer levels between the two groups (Table 4).

Adverse Outcomes

van Haren et al.[13] reported that 16 patients (out of 98) had minor bleeding including epistaxis ($n = 8$), mouth bleeding ($n = 2$) and blood-tinged sputum ($n = 5$), and unspecified bleeding ($n = 1$). DeNucci Gilberto[15] and Gupta B et al.[16] reported no adverse outcomes with the usage of nebulized heparin (Table 4).

Discussion

Nebulized medicines have been used in primary pulmonary disorders, such as asthma, chronic obstructive pulmonary disease (COPD), severe bronchopulmonary infections, colonized tracheobronchial tree as prophylaxis, or treatment of infection in cystic fibrosis patients for more than 20 years. These medicines include bronchodilators, antibiotics, mucolytics, and many other medicines. Because of its mucolytic properties, UFH has been successfully used in the treatment of cystic fibrosis patients without posing any safety concerns.[18,19] Specifically, inhaled nebulized UFH has been used safely in patients who are already receiving systemic anticoagulation treatment. In acute lung injury and many other respiratory diseases, inhaled therapies have a time-tested and established role.[20] This is because the lungs have a large surface area, highly vascular parenchyma, and a large absorption capacity. This has resultant effects on COPD, asthma, and other bronchopulmonary diseases. Nebulized heparin has been successfully used in other modalities like burn injury.[21] The bioavailability of heparin in the lungs and airways is significantly enhanced by nebulization without any local and systemic bleeding.[22] When nebulized UFH was used in other respiratory settings, there were no reported local side effects such as bleeding in the lung. In a study involving healthy volunteers, researchers investigated the effect of inhaled heparin on lung function and coagulation by administering a dose of 32000 IU of UFH to the lower respiratory tract. The study concluded that there was no impact on pulmonary function.[23] It was possible to demonstrate a dose-dependent anticoagulant effect on both the circulating blood (anti-factor Xa, APTT) and the endothelial cells as a release of tissue factor pathway inhibitor.[24] This effect was observed in the blood. When the receptor binding domain of the SARS-CoV-2 Spike S1 protein binds to UFH, it causes a change in shape that stops the virus from infecting human bronchial epithelial cells. The antiviral effect of UFH is significant and concentration-dependent, and threptic concentration is achieved by inhalation mode. Inhaled UFH reduces COVID-associated lung injury by reducing the deposition of fibrin, hyaline membrane formation, and prevention of microvascular thrombosis, due to its anticoagulation and anti-inflammatory properties. Nebulized heparin has been shown to improvise inflammation, oxygenation and pulmonary fibrin deposition in animal studies as well.[5,25] Studies on humans are small, but they suggest that nebulized UFH reduces pulmonary fibrin deposition, slows down the advancement of acute lung injury, and accelerates the recovery process. In early-stage trials of patients suffering from acute lung injury and similar conditions, nebulized UFH improved lung injury, increased the duration of time without ventilator support, and reduced pulmonary dead space.[26]

This review integrates five clinical studies evaluating the efficacy of nebulized heparin in the treatment of COVID-19 pneumonia.

In a study conducted by DeNucci Gilberto et al.[15] the primary endpoint was the length of hospital stay (LOS) improvement. The study found that there was no significant difference in LOS between the group receiving heparin and the control group.

Table 4: Comparison of various parameters included in studies

	Preoperative parameters tested	*Patients condition*	*Time to commencement of UFH treatment*	*Duration of treatment*	*Patient outcome*	*Adverse outcomes*	*Limitations*
van Haren et al.[13] 2021	APTT baseline	COVID-19 hospitalized patients, modified ordinal clinical scale 3–5	–	6 ± 3.2 days	The oxygen saturation/FiO_2 ratio and the FiO_2 improved after the commencement of inhaled UFH (change in slope, $p < 0.001$).	16 patients had minor bleeding including epistaxis ($n = 8$), mouth bleeding ($n = 2$) and blood-tinged sputum ($n = 5$), and unspecified bleeding ($n = 1$). All these patients except three were on concomitant therapeutic doses of UFH ($n = 3$) or LMWH ($n = 10$) at the time of these events	This was a retrospective case series without a control group The treatment was given in a range of doses, methods and duration, and severity of COVID-19 disease was not uniform and varied from patients admitted for COVID-19 without oxygen requirement to mechanically ventilated patients. Also, the observation that patients who received inhaled nebulized UFH showed worsening oxygenation before starting this treatment suggests a selection bias
Gupta B et al.[16] 2023	TLC, NL ratio, IL6, D-dimer, PaO_2/FIO_2	COVID-19 mild-to-moderate category patients	On admission	7 days	Time to separate from mechanical ventilation in days (m ± SD) 12.87 ± 10.54 Duration of hospital stay in days (m ± SD) 19.43 ± 10.146	Five patients (16.6%) succumbed to illness	Absence of a control group, sample size too small to draw conclusions regarding efficacy or potential infrequent deleterious effects
Mustafa et al.[16] 2021	SpO_2, ferritin, CRP, leukcocyte, NL ratio	COVID-19 severe category patients	On admission	10 days	Nebulized heparin group required less supply of oxygen, no intubations whereas three patients had to be intubated in control group. Respiratory symptoms on day 1, were better in device group	None reported	The device and control groups were nonrandomized due to severe pandemic conditions. Changes in the biochemical parameters after the 10-day trial meant that CRP, ferritin, D-dimer, and lymphocyte counts were not considered as this was too short period to quantitatively account for parametric changes

DeNucci Gilberto et al.[15] 2023	APTT(baseline and peak), heparin-induced thrombocytopenia	COVID-19 hospitalized patients with WHO modified ordinal clinical scale (MOCS) score 3–5	Minimum of 1 h to a maximum of 27 h following hospital admission, with a median time of 4 h	There was a significant treatment benefit among patients receiving nebulized UFH on top of standard of care vs patients treated with standard of care only as assessed by the WHO MOCS. Nebulized UFH treatment arm showed numerically lower rates of intubation. There were no significant differences in APTT between the two treatment groups Subjects receiving nebulized UFH had a similar number of oxygen-free survival days compared with the standard of care group	No cases recorded of pulmonary bleeding, heparin-induced thrombocytopenia, or anaphylaxis during or immediately after administration of nebulized UFH, or any other adverse events Mortality was numerically lower in nebulized UFH on top of standard of care (6 out of 38 patients; 15.8%) vs standard of care (10 out of 37 patients; 27.0%), but this difference was not statistically significant (OR: 0.51, $p = 0.2349$)	Subgroup analysis is not done due to the small sample size. Other limitations included the heterogeneity of the clinical status of patients on admission to the hospital, the change in vaccination status through the progress of the trial and the open label status of the treatment arms
Douen A et al.[17] 2021	Chest X-ray	COVID-19 moderate category with pneumonia	On admission	Improved ventilator support, increased number of ventilator-free days, decreased atelectasis, improved CO_2 elimination, and reduced mortality	None reported	Since this is a case report observation cannot be generalized, also there is risk of publication bias

APTT, activated partial thromboplastin time; LMWH, low-molecular-weight heparin

However, subjects who received nebulized UFH had a similar time to discharge as the standard of care group. It is important to note that various factors, such as age, co-morbidities, and rate of recovery from COVID-19 can affect this outcome. In the rest of the studies, it varied from 12.3 ± 9.4 days as reported by van Haren et al.[13] to 19.43 ± 10.146 days (Gupta B et al).[16]

Comparison of Mortality Outcome

van Haren et al.[13] reported slightly high mortality in the overall cohort (29.6%). Though these patients were significantly sicker compared with survivors, had a significantly lower S/F ratio and higher FIO_2 (0.76 ± 0.25 vs 0.49 ± 0.31, $p < .001$) since the initiation of inhaled UFH. Gupta B[16] noted the mortality rate as 16.6% owing to disease pathology and comorbidities. DeNucci Gilberto et al.[15] found that mortality was numerically lower for nebulized UFH (6 out of 38 patients; 15.8%) vs standard of care (SOC) (10 out of 37 patients; 27.0%), but not statistically significant.

Improvement in Clinical Parameters – Oxygenation Status, Hemodynamics

van Haren et al.[13] observed improved oxygenation using the WHO MOCS score and decreased requirement of FIO_2 over time in patients receiving high doses (25 000 IU q8h) in both intubated and non-intubated patients. It is important to note that the improvements observed could have happened on their own, without any external factors. Also, since there was no control group, we need to be careful when interpreting these findings. However, the fact that the study included a diverse range of doses, duration, and COVID-19 severity levels suggests that inhaled nebulized UFH is a safe option for COVID-19 treatment. Gupta B et al.[16] also noted significant improvement in oxygenation (pO_2/FIO_2 ratio) over 7 days (mean = 184.96, $p = 0.00$). Similarly, the improvement in PaO_2 (84.17 ± 33.82) and SO_2 (92.30 ± 3.49) was significant as well. But this study was limited to the use of nebulized heparin in the i COVID pneumonia initial phase with mild-to-moderate ARDS. The absence of a control group and its small size was also a drawback. Erelel M et al.[14] conducted a trial and classified patients with severe disease course as the "Device Group." Out of 33 patients in the Device Group who initially required complete oxygen support, 25 (75.8%) were able to breathe in "room air" without oxygen support by day 10 of the study. The reduction in oxygen requirement to correct hypoxemia in the Device Group was statistically significant compared with that of the control group ($p < 0.01$), hence the improvement was more homogenous and predictable. DeNucci Gilberto et al.[15] reported that mechanical ventilation rates were lower with UFH in the mITT population (OR 0.31; $p = 0.08$).

Coagulation Effects/Derangements

None of the studies reported derangement of coagulation parameters such as APTT and D-dimer. According to a study by van Haren et al.[13] patients who were not receiving therapeutic heparin infusion experienced a slight increase in their APTT when using nebulized UFH However, the increase, from 34 to 38 seconds was not clinically significant, as the peak value still fell within the normal APTT range. Meanwhile, patients who were receiving therapeutic heparin infusion experienced a nonsignificant increase in peak APTT when using inhaled nebulized UFH, although the sample size was limited to only three patients. Six patients missed a total of 25 doses of inhaled nebulized UFH due to epistaxis. Because of the presence of blood in the sputum of four patients, a total of 13 doses could not be administered. Epistaxis, blood-tinged sputum, and bleeding in the gastrointestinal tract, respectively, caused the inhaled nebulized UFH treatment to be discontinued in three patients (Table 4).

Heparin is available in a variety of delivery systems, including liquid dosage form, which can be injected, or inhaled via a nebulizer or a soft-mist inhaler, both of which are commercially available.

For maximum drug accumulation at the site of action and to provide an "enclosed system" to reduce contamination of environmental from saliva dispersion into the air, soft-mist inhaler technology was favored.[22] As a result, healthcare workers and patients in a clinical setting faced a much lower risk of exposure to environmental contamination. The disposable nature of the soft-mist inhaler used in this study makes it ideal for use during a pandemic. Its mechanism makes it possible to fine-tune the dosage with each use. In this way, doctors would be able to tailor a treatment plan to the evolving needs of each patient. Erelel M et al.[14] studied that following the application of nebulization, 57.08% of the droplets were concentrated over 3–5 stages of the impactor, with a cut-off diameter of 4.76–1.74 m. Fine particle fraction (FPF) was calculated to be 44.4%, mass median aerodynamic diameter (MMAD) was 5.37 m, and geometric standard deviation (GSD) was 1.63 m. A MMAD within a range of 1–5 m has been reported to aid in drug retention in the lower respiratory region. These findings suggest that the majority of the LMWH inhalation solution formed droplets that could get deposited in the bronchus and bronchiole region of the lung.

The majority of the studies found nebulized heparin safe which is consistence with published literature. In one study, several patients developed minor bleeding in the form of epistaxis and blood-stained sputum and two patients had major bleeding. These patients were also on therapeutic anticoagulation at the same time.

Limitations

Meta-analysis of outcome parameters was not done as there was heterogeneity in COVID-19 patients, also the outcome parameters were not uniform in various studies, nebulized heparin was also used in different dosages/formulations in various devices and variable duration of time. Limitations of individual studies are summarized in Table 4.

Conclusion

Based on the clinical studies included in this systematic review, nebulized heparin may be useful in the management of COVID-19. Oxygen saturation was greater, inflammatory indicators were lower, and hospital stays were shorter in patients who received nebulized heparin, according to the published research. However, the studies had flaws, including inconsistent sample sizes, varying dosages of nebulized heparin, and no control groups. Nebulized heparin in patients with COVID-19 needs to be studied further to determine its safety and effectiveness and more research into the effects and side effects of nebulized heparin in individuals with COVID-19 is required.

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