LETTER TO THE EDITOR

Nebulized Heparin to Reduce COVID-19-induced Acute Lung Injury: A Prospective Observational Study

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Abstract

Background: High mortality due to COVID-19 disease has been a serious concern, a few of the causes being disseminated intravascular coagulation (DIC) and venous thromboembolism. Considering this, some experts have used heparin. However, its role still needs to be validated.

Materials and methods: This study predicts the role of nebulized heparin in decreasing the severity of lung injury caused by COVID-19. Thirty patients admitted with COVID-19 acute respiratory distress syndrome (ARDS) in the intensive care unit (ICU) of All India Institute of Medical Sciences, Rishikesh, were included in this study, which was conducted over a period of 3 months. Patients were nebulized with 2 mL of heparin 5,000 units/mL IV formulation diluted with 3 mL of 0.9% sodium chloride, every 6 hours for a total duration of 7 days. Improvement in oxygenation (ratio of partial pressure of oxygen in blood and fraction of inspired oxygen delivered, pO_2/FiO_2 ratio) was calculated as the primary outcome. Other parameters like effect on inflammatory markers (neutrophil-lymphocyte ratio, total leukocyte count, interleukin (IL-6), and D-dimer values), time to liberate from mechanical ventilation, and hospital stay were calculated as secondary outcomes.

Results: In our study population, the mean age was 54.5 years and the majority of patients were males (79.0%). All patients received prone ventilation and none of them required tracheostomy. However, 5 patients (16.6%) succumbed to illness. After nebulization with unfractionated heparin, no statistically significant difference was seen in the neutrophil-lymphocyte ratio (mean = 6.87, $p = 0.318$) and interleukin (IL-6) levels (mean = 62.85, $p = 0.6$) over 7 days. Similarly, the D-dimer level also had no statistically significant change (mean = 1853.73 $p = 0.570$). However, there was a statistically significant improvement in oxygenation (pO_2/FiO_2 ratio) over 7 days (mean = 184.96, $p = 0.00$). Similarly, there was a significant improvement in PaO_2 (84.17 ± 33.82) and SO_2 (92.30 ± 3.49). Although, no significant changes were seen in the partial pressure of carbon dioxide on nebulized heparin administration.

Conclusion: Administration of nebulized heparin in COVID-19 pneumonia with mild ARDS may improve oxygenation and result in the improvement of inflammatory markers with variable sensitivity and specificity.

Keywords: Acute respiratory distress syndrome, COVID-19, Nebulized heparin.

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High mortality due to COVID-19 disease has been a serious concern, a few of the causes being Disseminated Intravascular Coagulation (DIC) and venous thromboembolism. Considering this, some experts have used heparin. However, its role still needs to be validated.

This study predicts the role of nebulized heparin in decreasing the severity of COVID-19-induced lung injury. After institutional ethical clearance [via letter no AIIMS/IEC/21/, dated January 9, 2020, and Clinical Trials Registration Number CTRI/2020/12/029613 (Registered on: 07/12/2020)], under a prospective, observational cohort design, this pilot study involved the collection, classification, and analysis of 30 adult patients admitted to the intensive care unit (ICU) of a tertiary care institute in between July and September 2020, diagnosed with acute COVID pneumonia, and required oxygen therapy.

Patients with heparin allergy, deranged coagulation studies, and pregnancy were excluded.

Patients were nebulized with 2 mL of Heparin 5,000 units/mL IV formulation diluted with 3 mL of 0.9% sodium chloride, every 6 hours for a total of 7 days. Improvement in oxygenation parameters like partial pressure of oxygen (pO_2), the fraction of inspired oxygen (FiO_2), (pO_2/FiO_2 ratio or PFO) ratio were calculated as the primary outcomes. Other parameters like effect on inflammatory markers (neutrophil-lymphocyte ratio (NLR), total leukocyte count (TLC), interleukin-6 (IL-6) and D-dimer values), time to liberate from mechanical ventilation and hospital stay were calculated as secondary outcomes.

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In our study population, the Wilcoxon rank test was performed for parameters including pO_2, FiO_2, PFO, total leukocyte count (TLC), neutrophil-lymphocyte ratio (NLR), interleukin-6 (IL6), and D-dimer and there was a significant difference in partial pressure of oxygen on day 2, day 7 and PFO on day 2 and 7 as compared to baseline with a large effect size and significant p value ($p < 0.001$) (Table 1). However, five patients (16.6%) succumbed to illness due to disease pathology and comorbidities and death was unrelated to heparin therapy (Table 2). The study drug was well tolerated, and no adverse events were noted in any patient.

Table 1: Comparative hematological and oxygenation parameters

	m ± *SD*		*Median*					
Comparative parameters	*Before*	*After*	*Before*	*After*	*Effect size*	*Z-score*	*p-value*	*r*
Total leukocyte count at day 7 vs baseline	10673.97 ± 6126.48	9586.33 ± 847.15	9050	9000	Small effect size	0.595	0.552	0.1086
Total neutrophil at day 7 vs baseline	63.63 ± 22.10	68.90 ± 17.22	67.00	72.35	Small effect size	0.422	0.673	0.0770
Lymphocyte count day 7 vs baseline	25.62 ± 21.51	20.36 ± 14.29	36	29	Small effect size	0.586	0.56	
NLR at day 7 vs baseline	5.84 ± 7.88	6.87 ± 6.75	3.49	3.60	Small effect size	0.998	0.318	0.1822
IL6 at day 7 vs baseline	59.09 ± 110.45	62.85 ± 101.52	20.35	24.00	Small effect size	0.524	0.600	0.095
D-dimer at day 7 vs baseline	1299.27 ± 2699.16	1853.73 ± 3091.14	100	275.00	Small effect size	0.568	0.570	0.1037
Partial pressure of oxygen (PaO_2) at day 2 vs baseline	56.21 ± 21.88	81.59 ± 19.66	63.3	128	Strong effect size and significant *p*-value	3.14	0.000	0.573
PFO at day 2 vs baseline	94.39 ± 72.68	148.95 ± 84.63	63.3	128.08	Strong effect size and significant *p*-value	3.14	0.000	0.573
Partial pressure of oxygen (PaO_2) at day 7 vs baseline	56.21 ± 21.88	84.17 ± 33.82	53		Strong effect size and significant *p*-value	3.63	0.000	0.66
PFO at day 7	94.39 ± 72.68	142.23 ± 81.21	vs 63.3		Strong effect size, and significant *p*-value	3.55	0.000	0.647

r values above 0.1 can be described as small, values above 0.3 can be described as moderate, and values above 0.5 can be described as strong

Table 2: Demographic and other parameters

Age in years (median, minimum, maximum)	56.50, 20.00, 76.00
Male *n* (%)	25 (83.3%)
Female *n* (%)	5 (16.7%)
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
Number of patients treated with prone positioning (*n*, %)	30 (100%)
Number of patients who required tracheostomy	0
Number of patients died (*n*, %)	5 (16.6)

Heparin, when administered through a nebulized route, targets fibrin deposition in the lungs and allows higher doses leading to better efficacy locally. Also, it does not enter systemic circulation, hence can be used along with systemic anticoagulation without increasing the risk of bleeding.[1] This study demonstrated that the nebulized heparin in the initial phase of COVID pneumonia with mild to moderate ARDS could be helpful in improving oxygenation. Other inflammatory markers also showed improvement in response with nebulized heparin, although the values were insignificant. Various studies have authenticated the immune-modulatory and anti-inflammatory action of heparin.[2] Multiple animal models of acute lung injury have also revealed that nebulized heparin played a vital role in reducing microvascular thrombosis and hyaline membrane formation.[3] At the molecular level, heparin inhibits the function, expression and/or synthesis of adhesion molecules, cytokines, angiogenic factors and complement. However, in our study, nebulized heparin has shown a high neutrophil-lymphocyte ratio (NLR) ratio, (MD = 3.60, *N* = 30) high interleukin-6 (IL-6), (MD = 24.00, *N* = 30), and high D-dimer (MD = 275.00, *N* = 30) at day 7, though with a small effect size. Ideally, more time frame is required to follow the trend as these inflammatory markers take time to resolve our findings are in line with those from the published literature and clinical experience, which show that inhaled nebulized unfractionated heparin (UFH) is very safe for patients with a wide variety of respiratory diseases.[4,5]

Administration of nebulized heparin in COVID-19 pneumonia with mild ARDS may significantly improve oxygenation and PFO, however, no substantial improvement in inflammatory markers is seen. Limitations of this study included the absence of a control group, a small number of patients enrolled and the patients had mild to moderate ARDS. Our study was consequently too small to draw conclusions regarding efficacy or potential infrequent deleterious effects.

More robust studies are needed to assess clinically relevant outcomes like mortality and duration of mechanical ventilation and its effect on moderate-severe ARDS patients with COVID-19 disease.

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