Nebulized heparin and salbutamol versus salbutamol alone in acute exacerbation of chronic obstructive pulmonary disease requiring mechanical ventilation: a double blind randomised controlled trial

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Shared in data collection and statistical analysis and made valuable contributions in writing and revising the manuscript.

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Responsible for the conception and design of the study, analysis of the data, writing and revising the manuscript.

The type of manuscript: original article.

Presentation: This work hasn’t been presented in any meetings and hasn’t been published elsewhere.

Short running title: Heparin–salbutamol-Pulmonary Disease

Implication statement: The research team validated the efficacy and safety of nebulised heparin (25000 IU/6h/day) and salbutamol (5mg/6h/day) for a maximum of 14 days to increase ventilator-free days (VFDs) among mechanically ventilated AECOPD patients.

Quick Look

Current knowledge:
COPD and its acute exacerbation create a hypercoagulable state. The use of anticoagulation in AECOPD abolishes the pathophysiology of the process of bronchial inflammation. Nebulised heparin was found to be effective in reducing the days of mechanical ventilation in critically ill patients and in patients with smoke inhalational injury.
What this paper contributes to our knowledge:
Coadministration of nebulised heparin (25000 IU/6h/day) and salbutamol (5mg/6h/day) for a maximum of 14 days decreased the inflammatory process and increased the ventilator-free days (VFDs) among mechanically ventilated AECOPD patients. Heparin nebulisation was safe and wasn’t associated with any bleeding hazards.

This work was done at: internal medicine intensive care unit of Ain-Shams university hospitals, Cairo, Egypt.

Trial registration: ClinicalTrials.gov Identifier: NCT03333395- https://clinicaltrials.gov/ct2/home

Declarations
List of abbreviations
AECOPD: Acute exacerbation chronic obstructive pulmonary disease; APTT: Activated partial thromboplastin time; BMI: Body mass index; BPM: Breath per minute; ČK: cytokines; cm H₂O: Centimetre water; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein;ED: endotoxins; FEV1/FVC: Ratio between forced expiratory volume in first second and forced vital capacity; FEV1: Forced expiratory volume in the first second; FVC: Forced vital capacity; FIO2: Fraction of inspired oxygen; Hb: Haemoglobin; HIT: Heparin induced thrombocytopenia; I: E ratio: Inspiratory to expiratory ratio; ICU: Intensive care unit; IU: International units; LTs: Leukotrienes; MV: Mechanical ventilation; NA: neutrophil aggregation; NPPV: Non-invasive positive pressure ventilation; NS: Normal saline; PaCO₂ :Partial pressure of CO₂ in arterial blood; PaO₂/FiO₂: Ratio between partial pressure of oxygen in arterial blood and the fraction of inspired oxygen; PaO₂: Partial pressure of O₂ in arterial blood; PEEP: Positive end expiratory pressure; pH: Decimal logarithm of the reciprocal of the hydrogen ion activity; PLA2: Phospholipase A2; PLT: Platelet count; PS: Pressure support; RMANOVA: repeated measures ANOVA (analysis of variance); SABA: Short-acting β₂-agonists; SC: Subcutaneous; SD: Standard deviation; SIMV: Synchronized intermittent mandatory ventilation; SNOSE: Sequential numbered opaque and sealed envelope; SpO₂: Oxygen saturation in arterial blood; TNFα: tissue necrosis factor α; TV: Tidal volume; VILI: Ventilator-induced lung injury; VFDs: ventilator-free days.

Ethics approval and consent to participate
Ethical approval from Ain Shams University hospitals research committee was obtained (FMASU R 26/ 2017). Written informed consent was taken from all the patients, their parents or their guardians before any study procedure was conducted.

Availability of data and materials
The data that supported the findings of this study were available from Ain Shams university hospitals and they weren’t publicly available. Data were however available for the authors upon reasonable request after permission of Ain Shams university.

Conflicts of interest: The authors had disclosed no conflicts of interest.

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Total number of Figures: 5

Total number of Tables: 2

Declaration:

All authors had read, revised and approved the final manuscript, and all authors believe that the requirements for authorship have been met and the manuscript represents honest work.

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Nebulized heparin and salbutamol versus salbutamol alone in acute exacerbation of chronic obstructive pulmonary disease requiring mechanical ventilation: a double blind randomised controlled trial

Running title: Heparin–salbutamol-Pulmonary Disease
Abstract

Background: Nebulised heparin was effectively used for management of many pulmonary diseases. However, its effect on mechanically ventilated patients with acute exacerbation chronic obstructive pulmonary disease (AECOPD) has never been studied. This study aimed to assess the efficacy of nebulised heparin and salbutamol to increase ventilator-free days; the number of days the patient is off mechanical ventilation alive, among mechanically ventilated AECOPD patients and nebulised heparin effect on respiratory and coagulation functions.

Methods: In this double-blind controlled study, sixty adults mechanically ventilated patients with AECOPD were randomly allocated into two equal groups; HS and S. In Hgroup, the patients received nebulised heparin (25000 IU) and salbutamol (5 mg) every 6 h while patients in Sgroup received nebulised salbutamol (5 mg) alone. The treatment was continued while patients remained ventilated for a maximum of 14 days. The primary outcome was duration of ventilator-free days (VFDs) at day 14 from randomisation. The PaCO₂, PaO₂/FiO₂ ratio, the number of nebulisation cessions withheld and any other complications were also recorded (secondary outcomes).

Results: Patients in HS group had a significant more VFDs ((4.7 (3.3) compared with those in S group (2.4 (2.6), (P=0.007)). Both groups were comparable as regards all other variables.

Conclusions: Co-administration of nebulised heparin and salbutamol, compared with salbutamol alone, significantly increased ventilator-free days among the mechanically ventilated AECOPD patients without increasing the bleeding hazards.

Keywords: Asthma, Chronic Obstructive Pulmonary Disease Overlap Syndrome, Artificial Respiration, Heparin, Albuterol, C-Reactive Protein.
Introduction

Chronic obstructive pulmonary disease (COPD) was the fourth leading cause of mortality in the world \[1\]. Its prevalence in Egypt is almost 10% \[2\]. COPD is a progressive disease and is associated with acute exacerbation (AECOPD) periods\[1\]. Despite the widespread use of non-invasive positive pressure ventilation (NIPPV) in the management of AECOPD, it isn’t suitable for all patients and may be associated with a 60% risk of intubation\[1,3,4\]. The main pathophysiologic causes of AECOPD are peribronchial inflammation and broncho-constriction, accordingly short-acting β₂ agonists (e.g. Salbutamol), antibiotics and corticosteroids are considered cornerstones in the management \[1,5\].

Beside its anticoagulant effect, heparin decreases the adherence of bacteria and viruses to the bronchial surface and possesses an anti-inflammatory effect \[6,7\]. Recently nebulised heparin has been added for management of many pulmonary situations; exacerbation of bronchial asthma, smoke inhalational injury and critically ill mechanically ventilated patients \[8,9,10\], however, its effect on mechanically ventilated AECOPD patients is unknown and hasn’t been studied yet. In theory, adding nebulized heparin to ventilated AECOPD treatment may shorten the duration of the mechanically ventilation.

This study aimed to assess the efficacy of nebulised heparin and Salbutamol (albuterol) to increase ventilator-free days among mechanically ventilated AECOPD patients (primary outcome) and its effect on respiratory, coagulation functions and C-reactive protein (CRP) (secondary outcomes).
**Materials and Methods**

This double-blind randomised controlled study was approved by ethics committee of the faculty of medicine, Ain Shams University, Cairo, Egypt (FMASU R 26/ 2017) and registered at ClinicalTrials.gov (NCT03333395). This study was conducted between the 1st of February to the 30th of September 2017 at internal medicine intensive care unit of Ain-Shams university hospitals.

Sixty adult COPD patients with primary respiratory failure not responding to NIPPV were included in this study. Randomization method was done according to computer generated table of random numbers. Allocation concealment was done by drawing a sequential numbered, opaque and sealed envelope (SNOSE) to randomize the patients into two groups: HS group or S group (30 patients in each group). Randomization day was considered as day 0. Written informed consent was taken from all the patients, their parents or their guardians before any study procedure was conducted. Patients, aged 18 – 70 years, had a BMI ≤ 40 kg.m\(^{-2}\) with stage II to IV according to Global Initiative for Chronic Obstructive Lung Disease spirometric classification. The research team excluded patients who were already mechanically ventilated for more than 24 h, expected to be extubated within 48 h, pregnant, or had history of ischemic heart disease, pulmonary bleeding (within the previous three months), bleeding diathesis, allergy to heparin, or history of heparin induced thrombocytopenia (HIT).

According to our ICU policy and guidelines, on patient admission, an arterial cannula (in the radial artery of the non-dominant hand) and a central line were inserted and daily blood samples for lab were withdrawn. Patients received standard medications, including analgeo-sedative, fluid management, antibiotic according to sputum culture, steroids and thrombo-prophylaxis (enoxaparin 40 IU SC once/day).
All patients received nebulisation of a 5ml solution; 2.5 ml (5mg) of nebulised salbutamol solution (preservative-free Ventolin, GlaxoSmithKline Inc.) added to 2.5 ml normal saline (NS). This was followed by either nebulisation of heparin (25000IU, heparin sodium; Nile Company for Pharmaceuticals and Chemical Industries–A.R.E.) in HS group or 5 ml of NS in S group. The medication for the second nebulisation was prepared by the pharmacist of the ICU and then handed to the nurse in charge who was blinded to the nature of the medication to be nebulised and didn't share in any further part of the study. All data were recorded by ICU residents who followed-up the patients and unaware of the nature of the second nebulization medication and were not involved in any other part of the study.

The nebulisation session lasted for at least 10 min (for each medication). This regimen was repeated every 6 h and continued while patients remained ventilated for a maximum of 14 days.

The nebulisation medication was added to a nebulisation chamber (Ameco Technology; particle size: 0.5–10 um, nebulisation rate: > 0.3 ml/min) connected to the inspiratory limb of the breathing circuit 15 cm from the Y of the circuit. The heat and moisture exchanger were removed during nebulization. All patients were mechanically ventilated using the Synchronized Intermittent Mechanical Ventilation (SIMV) mode with or without pressure support (PS), with a targeted tidal volume (TV): 6–8 ml/kg, rate: 12–14 breath per minute (bpm), inspiratory: expiratory ratio (I:E ratio): 1:3, positive end expiratory pressure (PEEP): 5–10 cmH2O, fraction of inspired oxygen (FiO2) (40%–60%) and upper pressure levels were maintained at or below 35 cm H2O to target arterial oxygen saturation (SpO2) of 88%–92%. Pressure support ventilation was used to wean the patient.
The weaning process was started by optimizing the respiratory mechanical and biochemical parameters; i) treatment of the cause of exacerbation, ii) spontaneous respiratory volume (Vt)>0.005 L/kg of body weight, iii) maximal spontaneous inspiratory effort (PImax)≤25 cm H2O, iv) heart rate <140/min, v) body temperature <37.5°C, vi) hemoglobin >100 g/L, vii) partial arterial oxygen pressure (PaO2)>60 mm Hg with inspired oxygen fraction (FiO2)≤0.4, extrinsic positive end-expiratory pressure (PEEP)<5 cm H2O, viii) no need for vasoactive and/or inotropic support, PaO2/FiO2 ratio >200, and RR/Vt ratio <100. Patients who fulfilled those criteria were given two hours spontaneous breathing trial (SBT) using PSV with an initial positive pressure of 15 cm H2O. Patients who withstood the SBT were extubated, while those who included spontaneous respiratory rate >25/min, SatO2<90%, FiO2≤0.4, heart rate >140/min (or more than 20% change from the initial heart rate), PaO2≤60 mm Hg, pH≤7.30, and restlessness were tagged as failure of weaning and mechanical ventilation with SIMV was continued.

The duration of ventilator-free days (VFDs) (the primary outcome) was evaluated at day 14. The number of patients successfully weaned from mechanical ventilation (MV), changes in PaCO2 level (during MV), the average daily ratio of PaO2/FiO2 (during MV), the CRP quantitative titre (measured daily), activated partial thromboplastin time (APTT), and any complications were recorded (secondary outcomes). The PaO2/FiO2 and PaCO2 were measured each day at 7 AM. No changes in the ventilator settings or the patient’s position were permitted for the 10 min before this measurement. In case of suction or lavage of blood-tinged sputum, the next nebulisation cession will be withheld. In case of occurrence of HIT, increased APTT more than double the normal, evident pulmonary bleeding, or death the patient was dropped out.
In order to facilitate blinding, the study medications were prepared by a pharmacist and given by the nurse in charge; both of them were not involved in any other part of the study.

The PaCO₂, the PaO₂/FiO₂ and the CRP titre were daily assessed and they were presented every other day to avoid redundancy of data.

**Statistical Analysis**

Based on a similar pervious study [14], 26 patients were required in each group, assuming the power=0.80 and 5% alpha error (2-tailed)[15]. To compensate dropout cases, 30 patients in each group were recruited. Coded data were tabulated and statistically analysed using the Statistical Package for Social Sciences version 22.0 (IBM Corp., Chicago, USA, 2013). Data were presented as means ± (standard deviation [SD]), numbers, frequencies and percentages. Data were analysed using the independent t-test, RMANOVA, chi-square test, or the log-rank test as appropriate. The level of significance was set to P value < 0.05.
Results

A total of 55 patients completed the study; 28 in the HS group and 27 in the S group (Fig 1). Patients’ characteristics, associated co-morbidities, basal respiratory variables, known risk factors of worsening COPD and laboratory results were comparable (Table 1).

The patients in the HS group had a significantly longer VFDs; higher number of days the patients were off mechanical ventilation alive; (4.7(3.3) vs. 2.4(2.6) P= 0.007; Table 2). The survival analysis scale showed that the percentage of the successfully weaned patients was higher in the HS group (P=0.009; Fig 2). The other respiratory variables; the PaCO2 levels (P value=0.075; Fig 3), PaO2/FiO2 (P value=0.069; Fig 3) and the rate of decrease in the CRP level (P value= 0.185; Fig 4) were comparable in both groups.

Generally, the study medications were well tolerated by the patients in both groups. The number of withheld cessions of nebulisation/patient in the HS group were comparable to that of the S group (5.8(2.2) vs. 4.8(1.4), P= 0.064; Table 2). Similarly, blood product usage didn’t show any significant difference between the groups, with only nine patients requiring blood transfusion in the HS group and seven in the S group. None of the patients in both groups had suspected HIT (a decrease in platelet count). The maximum increase in the APTT from the baseline level over the study period was higher in the HS group despite not reaching statistical significance (39.5(2.5) vs. 39.1(1), P= 0.407; Table 2).
Discussion

MV, either “invasive” or “noninvasive”, is not a therapy but is a form of life support until the cause of underlying acute respiratory failure is reversed with medical therapy. This study demonstrated that HS group was associated with higher VFDs as compared to S group. This effect may be due to improvement of oxygenation, ventilation (Fig.3), and/or inflammation (Fig.4) that, despite not reaching statistical significance showed an improvement trend over the 14 days in the HS group.

Many studies confirmed the anti-inflammatory and immune-modulatory effects of heparin\textsuperscript{[16, 17]} (Fig 5). A variety of clinical trials studying patients with inflammatory processes e.g. inflammatory bowel disease and cardiopulmonary bypass confirmed this\textsuperscript{[18, 19]}. It was even found to reduce the histological and clinical evidence of pulmonary microvascular thrombosis in patients with acute pulmonary inflammation following cardiac surgery \textsuperscript{[20]}. Moreover, inhalational heparin has an anti-asthmatic property confirmed by different clinical models of bronchial asthma \textsuperscript{[8, 21]} and inpatients with smoke inhalational injury \textsuperscript{[8, 9, 21, 22]}. Heparin nebulisation also improved oxygenation and increased the ventilator-free days in critically ill mechanically ventilated patients and was found to be comparable to nebulized corticosteroid (budesonide) in decreasing the risk of ventilator-induced lung injury (VILI)\textsuperscript{[14, 23]} which highlighted its anti-inflammatory effect. Subcutaneous low-molecular-weight heparin improved the pulmonary functions and decreased the days of mechanical ventilation among the AECOPD ventilated patients. \textsuperscript{[24, 25]}

In contrast to our study a retrospective review designed by Kashefi et al. concluded that alternating treatments of heparin and N-acetylcysteine/albuterol nebulisation every 4 h on adult inhalation injury patients didn’t reduce mortality or duration of mechanical ventilation and. This finding may be explained by the low dose of (5000 IU/ per dose) \textsuperscript{[26]}. 
In a trial studying the effects of different doses of nebulised heparin on the coagulation activation, nebulised heparin was found to increase APTT in a dose dependent manner, however at a dose of 100000 IU/day this increase was modest and wasn't associated with any adverse events[27].

Also, Shute et al, proved that neulised heparin in 75,000 or 150,000 IU/day for 21 days in moderate to very severe COPD patients significantly increased FVC following 7 days of treatment[28]. These results might be explained by an earlier study on the intrapulmonary administered heparin that proved that it was absorbed rapidly by the alveolar membrane and released gradually into the blood and the study done by Bendstrup et.al, that concluded that nebulised heparin was cleared slowly form the lungs, and that 39% of it was still present in the lungs 24 h after nebulisation[29, 30]. Based on those results, the research team decided to adjust treatment protocol to add enoxaparin SC as a prophylaxis against thromboembolic complications and to withhold heparin nebulisation if increased APTT more than double the normal or in case of serious bleeding and neither of them occurred. Our results correlated well with all the studies done on the nebulised heparin, whether it resulted in ventilation improvement or not confirming the absence of any bleeding hazards in response to its usage.[8, 10, 14, 23-25, 27, 28]

Heparin nebulisation on the other hand, didn't prove its effectiveness in reversing histamine induced bronchospasm suggesting mediating its effects by mechanisms not involving smooth muscles[8,16]. And this mandated the adding of bronchodilators to the management. In this context, short acting β 2 agonists alone or in combination are recommended[5].
The dose of 5.0 mg of nebulised salbutamol was based on the review study on the management of COPD exacerbations by Rodriguez-Roisin. He found that inspiratory capacity increased significantly at 30 and 90 min after the administration of 5.0 mg of nebulised salbutamol to acute-on-chronic air trapping and lung hyperinflation patients [5].

Dixon et al. showed that the pulmonary lavage markers of coagulation activation didn’t decrease in the heparin group [14]. However, he contradicted this in a letter to the editor later when he studied higher doses (up to 400000IU/day) and was allowed to do further coagulation markers [31].

In this study, the team chose the CRP as a biomarker of inflammation. The CRP isn’t only an easy and important marker in COPD but is also an early marker of exacerbation [32]. Its increase indicates bacterial infection in AECOPD and the need for the use of antibiotics in the treatment [32-35]. Its serial measurements were beneficial in assessing the efficacy of treatment [34, 36]. Despite the absence of a statistical significance between the two groups in the CRP level, the research team observed a decreasing trend of CRP levels more in the heparin treated patients (Fig 4). This could be explained by the effect of heparin in decreasing adherence of bacteria to bronchial mucosa [6].

This study had several limitations. First, this study was carried out at a single center. However, the research team believed that the study provided valuable clinical information for assessing ICU outcomes of using nebulised heparin and salbutamol in AECOPD patients, as the study population was disease specific. Second, the results of this study were evaluated at day 14 and not at day 28 because 28 days would be a relatively long duration considering that most of AECOPD would be extubated before this duration, to omit mortality cases from assessment and for fear of missing data collection including spirometry results and the patients’ mortality data and a potential unmet need of
healthcare resources. We assumed a timeframe of 14 days would be enough. Our results showed that nearly 20% of patient remained ventilated after the 14 days’ timeframe (Fig. 2) which makes the 14 days’ timeframe (and not the VFDs) was a limitation in our study and the research team recommends increasing the timeframe of VFDs evaluation in any future study considering mechanically ventilated AECOPD. Third, a larger sample size is required to achieve significant differences in the side effects. Fourth, time to hospital discharge, which is an important outcome because of its economic implications, wasn’t examined. It should be considered in further randomised clinical trials.

Nevertheless, this study also had some strength. First, all the patients were subjected to prolonged mechanical ventilation along with its hazards of lung damage. Second, the randomised and double-blind design decreased the possibility of bias. Third, the use of VFDs as an outcome provided an added value because of its statistical power to detect a treatment effect than the binary outcome measure of mortality [37]. Survivors of respiratory failure from COPD tend to return to baseline lung function very slowly (i.e., weeks to months). However, the risk for re-hospitalization and re-intubation for patients with COPD is increased markedly after an episode of respiratory failure requiring mechanical ventilation. COPD patients continue to experience significantly increased rates of severe exacerbations and use of healthcare resources, indicating a potential unmet need in this group of patients [38]. The need for new pharmaceutical therapies and protocols of treatments with the aim to reduce severe exacerbations is evident and may in the future be of benefit for this high-risk population.

Possible roles of heparin and salbutamol nebulisation in targeting the pathophysiology of AECOPD were presented in Fig 5.
In conclusion, Co-administration of nebulised heparin and salbutamol, compared with salbutamol alone, significantly increased ventilator-free days among the mechanically ventilated AECOPD patients without increasing the bleeding hazards.
References


Table 1. Demographic and Clinical Characteristics of the Study Participants

<table>
<thead>
<tr>
<th></th>
<th>HS Group (n=28)</th>
<th>S Group (n=27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; years</td>
<td>45.8 (5.5)</td>
<td>45.2 (5.7)</td>
<td>0.673</td>
</tr>
<tr>
<td>BMI; kg.m⁻²</td>
<td>27.9 (2.0)</td>
<td>27.5 (2.2)</td>
<td>0.556</td>
</tr>
<tr>
<td>Gender; male/female</td>
<td>23/5</td>
<td>21/6</td>
<td>0.686</td>
</tr>
<tr>
<td>Current smoking</td>
<td>23</td>
<td>25</td>
<td>0.422</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>6</td>
<td>7</td>
<td>0.695</td>
</tr>
<tr>
<td><strong>Associated co-morbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>16</td>
<td>20</td>
<td>0.187</td>
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<tr>
<td>Previous Stroke</td>
<td>9</td>
<td>7</td>
<td>0.612</td>
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<tr>
<td>Hypertension</td>
<td>25</td>
<td>23</td>
<td>0.705</td>
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<tr>
<td>Chronic liver disease</td>
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<td>6</td>
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<tr>
<td>Renal impairment</td>
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<td>5</td>
<td>0.469</td>
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<tr>
<td><strong>Etiology of exacerbation</strong></td>
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<td>H. influenza</td>
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<tr>
<td>Streptococcus pneumoniae</td>
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<td>5</td>
<td></td>
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<tr>
<td>Common cold (viral)</td>
<td>3</td>
<td>4</td>
<td>0.901</td>
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<tr>
<td>Exposure to dust</td>
<td>4</td>
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<tr>
<td>Unidentifiable cause</td>
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<td>2</td>
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<tr>
<td><strong>Base line values</strong></td>
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<tr>
<td>Hb; g/dL</td>
<td>12.7 (1.0)</td>
<td>12.8 (0.8)</td>
<td>0.668</td>
</tr>
<tr>
<td>PLT; 10³/uL</td>
<td>260.1 (48.1)</td>
<td>273.7 (35.0)</td>
<td>0.235</td>
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<td>APTT; sec</td>
<td>38.6 (1.6)</td>
<td>39.0 (1.3)</td>
<td>0.421</td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td>40.4 (2.3)</td>
<td>39.2 (2.6)</td>
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</tr>
<tr>
<td>FEV1/FVC; %</td>
<td>61.7 (2.4)</td>
<td>61.7 (2.7)</td>
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<td>SO₂; %</td>
<td>88.0 (2.4)</td>
<td>87.2 (2.2)</td>
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</tr>
<tr>
<td>PaO₂; mmHg</td>
<td>72.7 (2.6)</td>
<td>71.8 (2.5)</td>
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<tr>
<td>pH</td>
<td>7.3(0.12)</td>
<td>7.3(0.14)</td>
<td>0.274</td>
</tr>
</tbody>
</table>

Data were presented as frequency or mean (SD) as appropriate.
### Table 1: continue

<table>
<thead>
<tr>
<th>Risk factors of worsening COPD</th>
<th>HS Group</th>
<th>S Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of COPD (years mean SD)</td>
<td>18.7 (1.5)</td>
<td>18.1 (1.6)</td>
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<tr>
<td>COPD related hospitalization in 5</td>
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<tr>
<td>Exacerbations in previous year</td>
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<td>14</td>
<td>0.694</td>
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<tr>
<td>Antibiotic therapy</td>
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<td>Inhaled steroid therapy</td>
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<td>23</td>
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<tr>
<td>Theophylline therapy</td>
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<td>10</td>
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<tr>
<td>Mucous hypersecretion</td>
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<td>22</td>
<td>0.561</td>
</tr>
</tbody>
</table>

APTT: Activated partial thromboplastin time; BMI: basal mass index; FEV1: Forced expiratory volume in first second % of predicted; FEV1/FVC: Ratio between forced expiratory volume in first second and forced vital capacity; Hb: Haemoglobin; PaCO₂: Partial pressure of CO₂ in arterial blood; PaO₂: Partial pressure of O₂ in arterial blood; pH: Decimal logarithm of the reciprocal of the hydrogen ion activity; PLT: Platelet count; SO₂: Arterial oxygen saturation. All spirometry values were taken when the patient first presented in the emergency room (ER).
Table 2. Outcome, Tolerability and Safety

<table>
<thead>
<tr>
<th></th>
<th>HS Group(n=28)</th>
<th>S Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator free-days (VFDs)</td>
<td>4.7 (3.3)</td>
<td>2.4 (2.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Number of Doses of nebulisation withheld</td>
<td>5.8 (2.2)</td>
<td>4.8 (1.4)</td>
<td>0.064</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>9</td>
<td>7</td>
<td>0.612</td>
</tr>
<tr>
<td>APTT Max (sec)</td>
<td>39.5 (2.5)</td>
<td>39.1 (1.0)</td>
<td>0.407</td>
</tr>
<tr>
<td>APTT elevation (sec)</td>
<td>0.9 (1.8)</td>
<td>0.2 (0.9)</td>
<td>0.053</td>
</tr>
<tr>
<td>APTT Max ≥ 40.0 sec</td>
<td>13</td>
<td>9</td>
<td>0.322</td>
</tr>
<tr>
<td>Double APTT</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>HIT</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>3</td>
<td>0.669</td>
</tr>
</tbody>
</table>

Data were presented as frequency or mean and (SD) as appropriate. APTT: Activated partial thromboplastin time; HIT: Heparin induced thrombocytopenia; VFDs: Ventilator free-days.
Figure 1: Flowchart of patients.
**Figure 2:** Survival curve showing the percentage of ventilated patients in HS group was lower than S group during the 14 days of assessment (P=0.009).
Figure3: Respiratory functions. The overall PaCO2 levels (P value=0.075) and PaO2/FiO2 ratios (P value=0.069) were comparable in both groups.
Figure 4: Rate of decrease of C-reactive protein (CRP) levels in both groups was comparable and was presented by a Line graph with error bars. RMANOVA test was used; Group effect, (P value=0.185).
Figure 5: Possible roles of heparin and salbutamol nebulisation in targeting the pathophysiology of AECOPD.