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Effect of Nebulized Heparin on Mechanically Ventilated Patients

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ABSTRACT

Background: Nebulized heparin can shorten the duration of mechanical ventilation in people with acute respiratory distress syndrome (ARDS). The current study examines whether nebulization with heparin provides similar benefits compared to normal saline. **Method:** A six-month randomized controlled trial was conducted in a tertiary care hospital. The study included patients who were intubated during their stay in the intensive care unit (ICU) and required mechanical ventilation for more than 48 hours. Both groups of patients had a PaO2/FiO2 ratio of less than 300. Enrolled patients were randomly assigned to two groups using a lottery method: Group A received nebulized heparin, while Group B received nebulized normal saline. The researchers measured the PaO2/FiO2 ratio in both groups at baseline, day 3 and day 7. They also recorded the number of days without ventilator support and mortality during the first 28 days for both groups. **Results:** A total of 108 subjects between the ages of 18 and 60 years, regardless of gender, admitted to the intensive care unit (ICU) and requiring mechanical ventilation were included in the study. The results of our study showed that in group A the mean PaO2/FiO2 ratio was 222.7 ± 65.51 standard deviation (SD), while in group B on the third day it was 200.6 ± 60.8 SD (p = 0, 07). On day 7, the mean PaO2/FiO2 ratio was 227.4-218.3 SD in group B and 218.3-49.1 SD in group A (p=0.41). In terms of ventilator-free days, the mean duration (composite) was 16.9 x 9.1 standard deviations in group A and 12.6 x 7.9 standard deviations in group B for the 28-day period (p=0.01) . **Conclusions:** No significant differences in the mean PaO2/FiO2 ratio between the two groups on day 3 and day 7 were observed. However, looking at both survivors and non-survivors, as well as survivors alone, patients who received aerosolized heparin had significantly more ventilation-free days compared to those who received placebo. No significant differences were found between the two groups in terms of mortality over the 28-day period.

Keywords: Mechanical ventilation, Nebulized heparin, Ventilator-associated lung injury

INTRODUCTION

The duration of mechanical ventilation (MV) in the intensive care unit (ICU) varies by patient, ranging from a single day to several weeks or months [1]. Shorter ventilation durations have been associated with a lower risk of infection and shorter hospital stays [2]. Prolonged ventilation can lead to lung inflammation and damage due to fibrin deposition in the lung microcirculation and alveolar sacs, compromising ventilation and perfusion [3]. Heparin, commonly used as an anticoagulant in thrombotic disorders, has shown the potential to reduce pulmonary edema, leukocyte activation, and fibrin deposition. Nebulized heparin, which can reach the lower airways and exert local anticoagulant effects, has been studied as a treatment option, particularly in acute respiratory distress syndrome (ARDS) [4]. Heparin also has anti-inflammatory and immunomodulatory properties, and when aerosolized directly into the lungs, it can help reduce inflammation, prevent fibrin deposition, and promote fibrinolysis. These effects can potentially improve lung function and reduce the need for ventilation [6]. A proposed mechanism of action of aerosolized heparin in ARDS is its ability to prevent fibrin accumulation, which can impair gas exchange and cause lung damage [7]. By inhibiting fibrin production, improving oxygenation, and reducing the need for mechanical ventilation, nebulized heparin can prevent fibrin formation in the lungs [7]. Clinical studies have demonstrated the beneficial effects of nebulized heparin in ARDS, including shorter ventilation times and improved oxygen delivery [8].

The anti-inflammatory, anticoagulant, and immunomodulatory properties of aerosolized heparin have made it a potential treatment option for acute respiratory distress syndrome (ARDS). Nebulized heparin is believed to work by inhibiting fibrin deposition and reducing inflammatory cytokines in the lungs. Clinical studies have shown that nebulized heparin can improve lung function and reduce the time on mechanical ventilation in ARDS patients. Prolonged mechanical ventilation can result in acute lung injury characterized by severe inflammation and acute hypoxemic respiratory failure. The lungs are susceptible to damage from mechanical ventilation, including ventilator-associated lung damage and ventilator-associated pneumonia. ARDS, a critical disease syndrome, evolves through a complex molecular and clinical cascade. In-hospital mortality rates for acute lung injury/ARDS range from 34 to 55 percent, with multiple organ failure being the leading cause of death. There are currently no effective treatments or specific preventive measures for acute lung injury. Therefore, researchers are actively searching for potential therapies or technologies to treat this debilitating condition. However, treatments such as prostaglandins, prone positioning, and steroids have not yet demonstrated a reduction in mortality rates from ARDS.

Deposition of fibrin in the alveolar sacs and pulmonary microcirculation during prolonged mechanical ventilation can result in lung damage, impairing alveolar ventilation and perfusion, and initiating or exacerbating pneumonia. In this study, the focus was on patients on mechanical ventilation for more than 24 hours to investigate the potential anti-inflammatory benefits of heparin. Therefore, the study compared the effects of nebulized heparin to those of normal saline (placebo) in patients on mechanical ventilation in the intensive care unit.

MATERIALS AND METHODS

Study Design and Setting

The study is based on a randomized controlled trial (RCT) design and was conducted in the intensive care unit of Shaheed Zulfiqar Ali Bhutto Medical University Teaching Hospital-PIMS, a tertiary care hospital in Pakistan. The study was conducted over a period of 7 months.

Sample Technique and Sample Size

Study participants were randomly assigned to either the control or treatment arm using a lottery method, which helped eliminate bias in the sampling process. When conducting a randomized controlled trial, random sampling offers several advantages [11]. The sample size was determined using the WHO sample size calculator using a 95% confidence level (CI), 80% power, and a population standard deviation of 8.5 with a 5% margin of error. Based on these statistical assumptions, each study group was assigned a sample size of 54 cases. A total of 108 patients were included in the study. The expected mean duration of ventilation days was 18 days in the heparin nebulization group, while it was approximately 22.6 days in the placebo (saline nebulization) group.

Protocols for the Sample Collection

Patients who met the following criteria were considered eligible for the study: those admitted to the Intensive Care Unit (ICU) requiring mechanical ventilation (MV) with a PaO2/FiO2 ratio less than 300, or those who during were intubated during their stay in the ICU and remained in MV for more than 48 hours. Patients who did not meet these predefined protocols received usual care in the intensive care unit. The predefined protocols specified that patients who were already on ventilation prior to

hospital admission, were admitted to ventilation for less than 24 hours and had a history of recent intracranial haemorrhage, were receiving thrombolytic therapy, had hypersensitivity to heparin, had a pulmonary haemorrhage had an epidural catheter in place or was scheduled to be placed, had significant thrombocytopenia or a bleeding tendency, or had an existing neuromuscular condition requiring prolonged ventilation would receive usual care rather than participate in the study.

Throughout the study, patients were monitored according to pre-designed protocols. In the absence of the principal investigator, a co-member of the research study examined and observed the results of each patient. Adverse events were classified as mild to severe. In the event of an unusual reaction, the staff on duty responded promptly and coped with such adverse events.

Data Collection Procedure

Data collection began upon receipt of ethical approval. Written informed consent, which was also given orally, was obtained from each patient's caregiver or legal guardian. Only after obtaining informed consent were patients enrolled in the study and randomly assigned to one of two groups: Group A received nebulized heparin, while Group B received nebulized normal saline using the lottery method for random allocation. Upon admission, demographic information including gender, age and other relevant information was recorded. Basic clinical data such as the reason for admission (medical or surgical), the preliminary diagnosis and information on comorbid conditions were also documented. Data on clinical and radiological examinations, treatment plans, sputum characteristics, adverse drug reactions, cell transfusions, and the use of inotropic support in the form of vasopressors were routinely recorded throughout the period that patients were on a ventilator in the ICU. The presence of renal insufficiency was defined based on renal function according to the KDIGO classification.

Antimicrobials during Heparin were administered as per our Departmental Protocol

To prevent ventilator-associated pneumonia (VAP) within the first 96 hours after mechanical ventilation or hospital-acquired pneumonia (HAP) occurring between 48 and 96 hours after hospital admission, two antibiotic regimens were followed: cefoperazone + sulbactam 2, 0 g administered every 12 hours for 7-10 days, together with moxifloxacin 400 mg once daily for the same period. Alternatively, ciprofloxacin 400 mg every 8 hours could be given for 7 to 10 days. For VAP that occurred after 96 hours of mechanical ventilation support or HAP that occurred after 96 hours of hospitalization, antibiotic therapy consisted of piperacillin + tazobactam 4.5 g every 6 hours for 7-10 days, taken together with moxifloxacin 400 mg once daily same Duration. Alternatively, ciprofloxacin 400 mg every 8 hours could be given for 7 to 10 days.

Patient Response to Treatment

If there is no improvement in the patient's condition after the first 48 hours of treatment, as indicated by the following factors: a) an increase in total leukocyte count (TLC), b) a deterioration in chest x-ray (CXR), c) persistent fever above 39 °C, d) a decrease in the PaO2/FiO2 (PF) ratio, the treatment approach is changed. In such cases, patients are switched from initial empiric therapy to the following regimen: meropenem 2 g administered every 8 hours for 7 to 10 days, co-administered with moxifloxacin 400 mg once daily for the same period. Alternatively, ciprofloxacin 400 mg every 8 hours for 7 to 10 days can be given. The treatment strategy is based on the patient's outcome, with a follow-up visit to assess the effectiveness of the modified therapy. If a patient dies during his hospital stay, no further data collection is required. If, on the other hand, the patient is discharged, this provides valuable information about the number of ventilation-free days.

Ethical Approval

The current study received PIMS Ethics Review Board (ERB) ethical approval with reference number F.1-1/2015/ERB/SZABMU. After ethical approval, the data collection process was initiated, and participants gave verbal consent.

Statistical Analysis

The collected data were analysed with the statistical software SPSS version 20. Different statistical techniques have been used for different types of data. The mean standard deviation (SD) was calculated for quantitative variables such as age and length of stay in the intensive care unit. Frequency and percentage were calculated for qualitative variables such as gender and pulmonary function. To compare the length of stay in the ICU between the heparin and control groups, an independent sample t-test was performed. Likewise, an independent t-test was used to compare pulmonary function tests between the two groups. A significance level of p 0.05 was considered statistically significant. In addition, the data were stratified by gender and age, and the chi-square test was applied to assess any associations within each stratum.

RESULTS

Demographic Characteristics

A total of 108 patients between the ages of 18 and 60 were included in the study, the majority of whom were male. In the control group (Group A), 59.3% (n=32/54) were men and 40.7% (n=22/54) were women. In the treatment group (Group B), 57.4% (n=31/54) were men and 42.6% (n=23/54) were women. The mean age was 38.2 years (8.9 SD) for patients in group A and 39.1 years (9.5 SD) for patients in group B. Regarding the age distribution, 74.1% (n = 40/ 54) of patients in group A between 18 and 40 years old. and 25.9% (n=14/54) were between 41 and 60 years old. In group B, 57.4% (n=31/54) of the patients were between 18 and 40 years old and 42.6% (n=23/54) were between 46 and 70 years of age. The PaO2/FiO2 ratio was measured in both groups at baseline, day 3 and day 7. Ventilation-free days and mortality were recorded during the first 28 days for both patient groups.

Table 1. Demographics and baseline characteristics.

Variables	Treatment Group N (%)	Control Group N (%)	Total (%)
Gender			
Male	32 (29.6)	31 (28.7)	63 (58.3)
Female	22 (20.3)	23 (21.2)	45 (41.7)
Age (years)			
18-40	40 (37)	31 (28.7)	71 (65.7)
41-60	14 (12.9)	23 (21.2)	37 (41.6)
Respiratory Failure			
Type I Respiratory Failure	20 (18.5)	21 (19.4)	41 (37.9)
Type II Respiratory Failure	8 (7.4)	9 (8.3)	17 (15.7)
Co-morbidities			
Septic Shock	19 (17.5)	18 (16.6)	37 (34.2)
Status Epilepticus	7 (6.4)	6 (5.5)	13 (12)

Baseline Patient Characteristics

In group A, 37.0% (n=20/54) of the patients were diagnosed with type I respiratory failure, 14.8% (n=8/54) with type II respiratory failure, and 35.2% (n=8/54) with type II respiratory failure =19/54) a septic shock and 13.0% (n=7/54) with status epilepticus. In Group B, the percentages were 38.9% (n=21/54), 16.7% (n=9/54), 33.3% (n=18/54), and 11.1% (n= 6/54) (Table 4). Mean PaO2/FiO2 was 161.9 ± 63.1 SD in group A patients and 161.6 ± 63.2 SD in group B patients at baseline (p=0.968).

Outcomes

In group A, the mean PaO2/FiO2 value of the patients was 222.7 65.51 SD, while in group B it was 200.6 60.8 SD on day 3 (p=0.074, Table 8). On day 7, the mean PaO2/FiO2 was 227.4, 218.3 SD in group B and 218.3, 49.1 SD in group A (p=0.417). No significant difference in PaO2/FiO2 was observed between the two groups on day 3 and day 7. Mean PaO2/FiO2 at baseline, day 3 and day 7, and ventilator-free days are presented in Table 2. The combined ventilation-free days (both survivors and non-survivors) were significantly higher in heparin-nebulized patients (Group A) than in the placebo group (Group B). In group A, mean ventilator-free days were 16.9 x 9.1 SD, while in group B they were 12.6 x 7.9 SD over a 28-day period (p = 0.11).

Table 2. Mean PaO2/FiO2 at baseline, day 3 and day 7, and ventilator-free days in both groups.

Group		Mean PaO2/FiO2	SD	P-value
Baseline	Group-A	161.9	63.1	0.96
	Group-B	161.6	63.2	
Day 3	Group-A	222.7	65.5	0.07
	Group-B	200.6	60.8	
Day 7	Group-A	227.4	66.1	0.41
	Group-B	218.3	49.1	
Ventilator Free Days				
Composite	Group-A	16.9	9.1	0.01
	Group-B	12.6	7.9	
Survivors Only	Group-A	21.2	3.4	0.00
	Group-B	16.6	3.9	

Among the survivors, after assigning 0 ventilator-free days to those who expired during the study period, the mean ventilator-free days were 21.2 ± 3.4 SD in Group A and 16.6 ± 3.9 SD in Group B over a period of 28 days (p=0.001). There was no significant difference observed in terms of mortality between the two groups. In Group A, 20.4% (n=11/54) of patients died, while in Group B, 24.1% (n=13/54) of patients died within the 28-day period (p=0.643). Figure 1 illustrates the time intervals and the PaO2/FiO2 values in both groups.

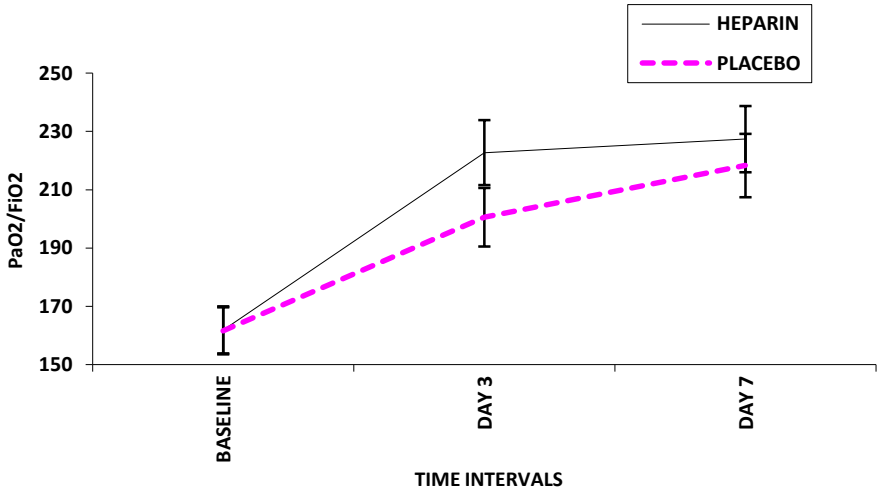

Figure 1. PaO2/FiO2 at different time intervals in both group

Stratification for Effect Modifiers

Mortality data was analyzed with stratification based on age and gender. In the age group of 18-40 years, mortality occurred in 17.5% (n=7/40) of patients in Group A, while it was observed in 22.6% (n=7/31) of patients in Group B (p=0.594). Among patients aged 41-60 years, mortality was observed in 28.6% (n=4/14) of Group A patients and in 26.1% (n=6/23) of Group B patients (p=0.869). In the male population, mortality was recorded in 21.9% (n=7/32) of Group A patients and 25.8% (n=8/31) of Group B patients (p=0.714). Among females, mortality was observed in 18.2% (n=4/22) of Group A patients and 26.7% (n=5/23) of Group B patients (p=0.766). The ventilator-free days (composite) data was also stratified by age and gender, as shown in Table 3.

When considering the age group of 18-40 years, the mean ventilator-free days were 17.2 ± 8.7 SD in Group A, whereas in Group B, it was 13.5 ± 8.1 SD during the 28-day period (p=0.010). Among individuals aged 41-60 years, the mean ventilator-free days were 15.9 ± 10.5 SD in Group A, while in Group B, it was 11.3 ± 7.7 SD (p=0.021). Analyzing by gender, in males, the mean ventilator-free days were 16.8 ± 9.4 SD in Group A, whereas in Group B, it was 12.1 ± 7.9 SD (p=0.011). Among females, the mean ventilator-free days were 16.9 ± 8.9 SD in Group A, and in Group B, it was 13.4 ± 8.2 SD (p=0.023) over the 28-day period. Ventilator-free days (considering only survivors) were also stratified by age and gender. In the age group of 18-40 years, the mean ventilator-free days were 20.9 ± 3.7 SD in Group A and 17.5 ± 3.8 SD in Group B (p=0.002, Table 13). Among individuals aged 41-60 years, the mean ventilator-free days were 22.3 ± 1.4 SD in Group A and 15.4 ± 3.9 SD in Group B (p=0.001). Analyzing by gender, in males, the mean ventilator-free days were 21.6 ± 2.9 SD in Group A and 16.2 ± 3.6 SD in Group B (p=0.001). Among females, the mean ventilator-free days were 20.7 ± 3.8 SD in Group A and 17.1 ± 4.4 SD in Group B (p=0.023), as depicted in Table 4.

Table 3. Mortality in both groups (stratification as per age and gender).

Variables		Mortality	Group		Total	P-Value (X2)
			Heparin	Placebo		
Age Groups	18-40 Years	Present	7 (17.5%)	7 (22.6%)	14 (19.7%)	0.594
		Absent	33 (82.5%)	24 (77.4%)	57 (80.3%)	
	41-60 Years	Present	4 28.6%	6 26.1%	10 27.0%	0.869
		Absent	10 71.4%	17 73.9%	27 73.0%	
Gender	Males	Present	7 21.9%	8 25.8%	15 23.8%	0.714
		Absent	25 78.1%	23 74.2%	48 76.2%	
	Females	Present	4 18.2%	5 21.7%	9 20.0%	0.766
		Absent	18 81.8%	18 78.3%	36 80.0%	

Table 4. Mean ventilator-free days (survivors) in both groups.

Variables		Group	Mean (Days)	SD	P-Value*
Age Groups	18-40 Years	Heparin	20.9	3.7	0.002
		Placebo	17.5	3.8	
	41-60 Years	Heparin	22.3	1.4	0.001
		Placebo	15.4	3.9	
Gender	Males	Heparin	21.6	2.9	0.001
		Placebo	16.2	3.6	
	Females	Heparin	20.7	3.8	0.023
		Placebo	17.1	4.4	

*t-test statistics

DISCUSSION

Heparin, a powerful natural anticoagulant produced by various cells in the body including mast cells, basophils and endothelial cells, is widely used in clinical settings for its anticoagulant properties. Previous clinical studies have shown that nebulized heparin can shorten the duration of mechanical ventilation in patients with acute respiratory distress syndrome (ARDS). In our present study, we aimed to compare nebulized heparin with normal saline in patients undergoing mechanical ventilation. Our results are consistent with previous reports in the literature. Dixon et al. conducted a study to evaluate the efficacy of nebulized heparin in patients expected to require mechanical ventilation for a prolonged period (>48 hours) [12]. They observed a significantly higher number of ventilation-free days in the survivors on day 28 after administration of aerosolized heparin. McIntire et al. studied the efficacy and safety of nebulized heparin in ventilated adults within 48 hours of confirmed inhalation injury [13]. Tuinman et al. conducted a systematic review of clinical and preclinical studies to evaluate the efficacy and safety of nebulized anticoagulants [6]. The results of our study are consistent with these previous investigations.

Another relevant study by Ghiasi et al. 60 seriously ill adult patients who had to be mechanically ventilated for a period of more than 48 hours were involved [14]. One group received nebulized heparin (10,000 U every 6 hours) for 5 days, while the corresponding control group received nebulized budesonide. Although their results indicated a higher number of ventilator-free days in survivors with heparin administration, the difference was not statistically significant. In our study, we observed a significant difference in ventilation-free days with heparin administration. This disparity can be attributed to the use of normal saline as a placebo in our study, whereas Ghiasi et al. used nebulized budesonide in the control group [14]. There was no statistically significant difference in the mean daily PaO2/FiO2 ratio between the two groups (187 11.6 vs. 171 11.6, P=0.35). Our study provided similar results, with no significant difference in daily PaO2/FiO2 ratio between the groups on days 3 and 7 [15]. It should be noted that longer hospital stays due to infections can lead to increased treatment costs [16–21].

In a study by Glas et al. The pooled analysis performed evaluated the effects of nebulized anticoagulants on ventilated intensive care patients [22]. The primary endpoint was the number of ventilation-free days at day 28, and data from five studies involving 286 patients were included. The results showed that patients treated with nebulized heparin had a higher number of ventilator-free days compared to the control group. Remarkably, no significant clinical bleeding was observed in our study. Reducing length of hospital stay and overall cost of therapy are important factors, as Khan et al. point out. [16, 19]. In other recent studies, even higher doses of up to 70,000 IU have been used without causing bleeding problems. However, our study has several limitations that should be recognized. First, the sample size was small, which may limit the generalizability of the results to a larger population. The follow-up period was relatively short, which may have limited the ability to observe any long-term effects of nebulized heparin. Additionally, the study lacked double-blindness, meaning patients, clinicians, and researchers knew who was receiving nebulized heparin and who was not. Although our study provides valuable insight into the potential benefits of

nebulized heparin for patients on mechanical ventilation, it is important to consider its limitations when interpreting the results and evaluating their practical implications.

CONCLUSIONS

On day 3 and day 7, no significant difference in mean PaO2/FiO2 was observed between the two groups. However, when considering both survivors and non-survivors, as well as only survivors, patients who received aerosolized heparin had significantly higher off-ventilator days compared to those who received placebo. There was no significant difference in mortality between the two groups over 28 days.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

All the authors equally contributed to this manuscript.

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REFERENCES

1. Karlsson V, Bergbom I, Forsberg A: The lived experiences of adult intensive care patients who were conscious during mechanical ventilation: a phenomenological-hermeneutic study. Intensive and critical care nursing 2012, 28:6-15.
2. Čiginskienė A, Dambrauskienė A, Rello J, Adukauskienė D: Ventilator-associated pneumonia due to drug-resistant Acinetobacter baumannii: risk factors and mortality relation with resistance profiles, and independent predictors of in-hospital mortality. Medicina 2019, 55:49.
3. Jorens P, Van Marck E, Snoeckx A, Parizel P: Nonthrombotic pulmonary embolism. European Respiratory Journal 2009, 34:452-474.
4. C Sebag S, A Bastarache J, B Ware L: Therapeutic modulation of coagulation and fibrinolysis in acute lung injury and the acute respiratory distress syndrome. Current pharmaceutical biotechnology 2011, 12:1481-1496.
5. Cesaretti M, Luppi E, Maccari F, Volpi N: Isolation and characterization of a heparin with high anticoagulant activity from the clam Tapes phylippinarum: evidence for the presence of a high content of antithrombin III binding site. Glycobiology 2004, 14:1275-1284.
6. Tuinman PR, Dixon B, Levi M, Juffermans NP, Schultz MJ: Nebulized anticoagulants for acute lung injury-a systematic review of preclinical and clinical investigations. Critical care 2012, 16:1-10.
7. Bastarache JA, Blackwell TS: Development of animal models for the acute respiratory distress syndrome. Disease models & mechanisms 2009, 2:218-223.
8. Juschten J, Tuinman PR, Juffermans NP, Dixon B, Levi M, Schultz MJ: Nebulized anticoagulants in lung injury in critically ill patients—an updated systematic review of preclinical and clinical studies. Annals of translational medicine 2017, 5.
9. Zhou M-T, Chen C-S, Chen B-C, Zhang Q-Y, Andersson R: Acute lung injury and ARDS in acute pancreatitis: mechanisms and potential intervention. World journal of gastroenterology: WJG 2010, 16:2094.
10. Olapour A, Rashidi M, Foroush FJ, Akhoondzadeh R, Hosseini N: Effect of Nebulized Heparin on Weaning off Intubated Patients with Acute Respiratory Distress Syndrome (ARDS) Admitted to Intensive Care Unit (ICU): A Randomized Clinical Trial. Anesthesiology and Pain Medicine 2021, 11.
11. Khan FU, Fang Y: Effectiveness of pharmacist-led brief educational intervention for adherence to the antibiotics for lower respiratory tract infections (EATSA) in Post-conflict rural areas of Pakistan: study protocol for a randomized controlled trial. Antibiotics 2021, 10:1147.
12. Dixon B, Smith RJ, Campbell DJ, Moran JL, Doig GS, Rechnitzer T, MacIsaac CM, Simpson N, van Haren FM, Ghosh AN: Nebulised heparin for patients with or at risk of acute respiratory distress syndrome: a multicentre, randomised, double-blind, placebo-controlled phase 3 trial. The Lancet Respiratory Medicine 2021, 9:360-372.

13. McIntire AM, Harris SA, Whitten JA, Fritschle-Hilliard AC, Foster DR, Sood R, Walroth TA: Outcomes following the use of nebulized heparin for inhalation injury (HIHI Study). Journal of burn care & research 2017, 38:45-52.
14. Ghiasi F, Sadeghian M, Emami M, Kiaie BA, Mousavi S: A pilot study of nebulized heparin for prevention of ventilator induced lung injury: comparative effects with an inhaled corticosteroid. Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine 2017, 21:634.
15. Chen W, Janz DR, Shaver CM, Bernard GR, Bastarache JA, Ware LB: Clinical characteristics and outcomes are similar in ARDS diagnosed by oxygen saturation/Fio2 ratio compared with Pao2/Fio2 ratio. Chest 2015, 148:1477-1483.
16. Khan FU, Fang Y, Khan Z, Khan FU, Malik ZI, Ahmed N, Khan AH, Rehman Au: Occurrence, associated risk factors, and treatment of surgical site infections in Pakistan. European Journal of Inflammation 2020, 18:2058739220960547.
17. Khan FU, Khan Z, Ahmed N, Rehman AU: A general overview of incidence, associated risk factors, and treatment outcomes of surgical site infections. Indian Journal of Surgery 2020, 82:449-459.
18. Khan FU, Khan Z, Fang Y: Need of Guidelines and Antimicrobial Stewardship in Pakistan for Perioperative Surgical Practices to Prevent Surgical Site Infections. Journal of the College of Physicians and Surgeons Pakistan 2020, 30:882-884.
19. Khan Z, Ahmed N, Rehman AU, Khan FU, Saqlain M, Martins MAP, Rahman H: Audit of pre-operative antibiotic prophylaxis usage in elective surgical procedures in two teaching hospitals, Islamabad, Pakistan: An observational cross-sectional study. PloS one 2020, 15:e0231188.
20. Khan Z, Ahmed N, Zafar S, Khan FU, Saqlain M, Kamran S, Rahman H: Audit of antibiotic prophylaxis and adherence of surgeons to standard guidelines in common abdominal surgical procedures. Eastern Mediterranean Health Journal 2020, 26.
21. Khan FU, Khan Z, Rehman Au, Rabbi F, Ahmed N, Fang Y: Perception of surgical teams towards surgical site infections in tertiary care hospital Islamabad, Pakistan. Indian Journal of Surgery 2020, 82:394-401.
22. Glas G, Neto AS, Horn J, Schultz M: Nebulized heparin for patients under mechanical ventilation: a conventional data meta-analysis. Critical Care 2015, 19.