

Role of nebulized heparin inhalation on mechanically ventilated critically ill patients

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Introduction Mechanical ventilation is one of the most important tools in the treatment of respiratory failure in critically ill patients, but it may cause lung injury and inflammatory response in the whole body.

Aim of work The aim of our study was to justify the effect of nebulized heparin on morbidity, oxygenation parameters, lung mechanics, and mortality in mechanically ventilated critically ill patients who are assumed to require mechanical ventilation for more than 48 h for different indications.

Patients and methods This study was conducted on 50 ICU patients who were in need of mechanical ventilation for more than 48 h. They were grouped randomly into two groups. One of the two groups was given nebulized heparin sodium until weaning or for a maximum of 14 days. Patients with coagulopathy or scheduled for any invasive intervention that may lead to bleeding were excluded. In addition, patients who were weaned or who died before day 4 of admission were also excluded. Both groups were followed up for a maximum of 28 days. The study medication was reduced or withheld if any significant bleeding occurred. The endpoint results were primary oxygenation parameters [mainly arterial oxygen partial pressure (PaO₂)/inspired oxygen fraction (FIO₂)] and ventilator-free days. All other data were recorded and analyzed to find out the adverse positive effect of heparin nebulization.

Results Data analysis revealed that the following data showed no statistically significant difference within groups over time or between the two groups: PaCO₂, pH, PaO₂, HCO₃, SO₂, PaO₂/FIO₂, FIO₂×mean airway pressure/PaO₂, peak inspiratory pressure, mean airway pressure, tumor necrosis factor α , systolic blood pressure, diastolic blood pressure, hemoglobin, hematocrit value, white blood cells count, platelet count, prothrombin concentration, international normalized ratio, presence of bloody sputum, ICU-free days at day 28, ventilator-free days at day 28, acute renal failure-free days at day 28, vasopressor-free days at day 28, and mortality and sputum culture results at day 4. However, the following data showed a statistically significant difference in

the heparin-treated group: plateau pressure showed a statistically significant decrease between days 1 and 4 in the heparin-treated group ($P=0.003$) and a statistically significant difference when we compared the percentage change between the two groups ($P=0.015$). Compliance rate showed a statistically significant increase between days 1 and 4 in the heparin-treated group ($P=0.019$) but when we compared the percentage change between the two groups the difference was not statistically significant ($P=0.256$). Activated partial thromboplastin time showed a statistically significant increase between days 1 and 4 in the heparin-treated group ($P=0.001$), but when we compared the percentage change between the two groups the difference was not statistically significant ($P=0.153$). No cases of heparin-induced thrombocytopenia was noted in the heparin-treated group, nor was there major bleeding or need for blood transfusion related to the tested medication in this group.

Conclusion We recommend nebulized heparin as a safe drug that has a favorable effect in patients receiving mechanical ventilation especially with reduced compliance as in cases of acute respiratory distress syndrome.

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Introduction

Mechanical ventilation is an important tool in the management of respiratory failure in the critically ill patient. It is required for the management of respiratory failure resulting from various clinical conditions such as acute respiratory distress syndrome (ARDS), pneumonia, sepsis, chronic obstructive pulmonary disease, and asthma. Although mechanical ventilation can be a lifesaving intervention, it is known to carry several side effects and risks [1].

Mechanical ventilation can increase the level of inflammatory mediators within the lungs, and treatment with the antagonists of these mediators may reduce it [2]. A number of potential targets

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have been identified in preclinical studies. Increased levels of several inflammatory mediators [including tumor necrosis factor (TNF) α , interleukin-6, and interleukin-10] were found in ex-vivo and in-vivo rat models subjected to injurious mechanical ventilation [3].

TNF has been consistently implicated in the pathogenesis of acute lung injury (ALI)/ventilator-induced lung injury, both clinically and in experimental models [4]. In addition, lower TNF- α levels in both the serum and bronchoalveolar lavage fluid from patients at risk for ARDS exhibited a good negative predictive value for ARDS development [5].

Heparin and related molecules can bind electrostatically to the positively charged nuclear localization sequence of NF- $\kappa\beta$ and prevent it from translocation to the nucleus. Blocking of this transcriptional factor can potentially reduce inflammatory gene activation and regulate the gene expression and production of proinflammatory cytokines, chemokines, and adhesion molecules [6].

Unfractionated heparin inhibits lipopolysaccharide-induced activation of endothelial cells through inhibition of p38MAPK and NF- $\kappa\beta$ [7]. Heparin has been shown to bind to the surface of neutrophils and can inhibit their degranulation [8]. Further, heparin is able to inhibit neutrophil activation in response to thrombin-stimulated platelet products, in addition to inhibiting thrombin-induced platelets [9].

Aim of the work

The aim of our study was to justify the effect of nebulized heparin on the morbidity, oxygenation parameters, lung mechanics, and mortality of mechanically ventilated critically ill patients assumed to require mechanical ventilation for more than 48 h for different indications.

Patients and methods

This study was conducted in the respiratory ICU of New Kasr-Al-Aini Teaching Hospital and in the ICU of Beni-Suif University Hospital from October 2012 to January 2014. The study protocol was approved by local ethical committee and informed consent was taken .

Patients who had undergone mechanical ventilation for any indication and were assumed to require mechanical ventilation for more than 48 h were included in this study.

Exclusion criteria

Patients with the following criteria were excluded from our study.

- (1) Patients who received mechanical ventilation for more than 24 h before enrollment.
- (2) Patients who required mechanical ventilation for more than 48 h in a previous admission to the ICU during the current hospital admission.
- (3) Patients who received any of the following at the time of screening: renal replacement therapy, therapeutic doses of heparin or low-molecular-weight heparin, warfarin, protamine, high-frequency ventilation, or extracorporeal membrane oxygenation.
- (4) History of pulmonary hemorrhage in the previous 3 months.
- (5) History of uncontrolled bleeding or a significant bleeding disorder during current admission.
- (6) History of intracranial hemorrhage in the past 12 months (a clipped subarachnoid aneurysm is acceptable).
- (7) Patients with epidural catheter in place or likely to be placed within the next 48 h.
- (8) Patients with central nervous system affection that may impair weaning from mechanical ventilation.
- (9) Patients who were candidates for surgery during the next 12 h.
- (10) Patients who had been weaned or had died during the first 4 days.

Study design

This study was conducted on 50 ICU patients who were in need of mechanical ventilation for more than 48 h; they were selected and grouped randomly as follows.

- (1) Group I: These patients were given nebulized heparin sodium until weaning or for a maximum of 14 days.
- (2) Group II: These patients were considered as the comparative group.

Both groups were followed up for 28 days. Laboratory tests were followed up for the first 14 days only. The endpoint results were primary oxygenation parameters [mainly arterial oxygen partial pressure (PaO₂)/inspired oxygen fraction (FIO₂)] and ventilator-free days. All other data were recorded and analyzed (on days 1 and 4) to find out the adverse/positive effect of heparin nebulization.

Heparin sodium at a dose of 25 000 U/5 ml was given by nebulization to group I in the inspiratory limb of the ventilator before the Y-piece every 4 h (150 000 U/day). No dose adjustment was made for heparin administration for deep venous thrombosis prophylaxis, and nebulized heparin was given for a maximum of 14 days from randomization.

Weaning criteria

Spontaneous breathing trial was followed as the primary method of weaning, with other methods (e.g. gradual reduction of synchronized intermittent mandatory ventilation or pressure support titration) adopted as per the clinical condition. The decision to wean was taken on the basis of the following criteria.

- (1) Resolution or stabilization of the underlying disease process.
- (2) No evidence of residual pharmacologic neuromuscular blockage (if it was used).
- (3) Presence of spontaneous respiratory efforts.
- (4) Hemodynamic stability (no recent increase in pressor or inotrope requirements).
- (5) Ventilator parameters such as:
 - (a) FIO₂ less than or equal to 0.5.
 - (b) Positive end-expiratory pressure (PEEP) less than or equal to 10 cmH₂O.
 - (c) Minute ventilation less than 15 l/min.
- (6) pH 7.35–7.50.

Criteria for a failed spontaneous breathing trial [10]

Inadequate gas exchange.

- (1) Unstable ventilatory/respiratory pattern.
- (2) Hemodynamic instability.
- (3) Change in mental status.
- (4) Signs of increased effort in breathing.
- (5) Onset of worsening discomfort±dysphoresis.

If any of these criteria were met, spontaneous breathing trial was terminated and the patient was placed back on previous ventilator settings for at least 24 h.

Patients were considered suitable for extubation if they were hemodynamically stable with an oxygen saturation of at least 95% while ventilated on pressure support less than or equal to 10 cmH₂O, PEEP less than or equal to 5 cmH₂O, and FIO₂ less than or equal to 50% and after passing the weaning parameters with intact cough reflex and need for endotracheal suction arising only at intervals greater than 4 h.

The following data were collected and subjected to statistical analysis.

- (1) Results of clinical examination on admission, including Glasgow Coma Scale and Acute Physiology and Chronic Health Evaluation II scores on admission in both groups.
- (2) Daily arterial blood gases.
- (3) Results of other investigations on admission (as clinically indicated):
 - (a) Liver and kidney functions (on day 1 and when indicated).
 - (b) Complete blood count (on days 1 and 4 and when indicated).
 - (c) Plain chest radiography.
- (4) Daily record of data for the patients still on ventilation for a maximum of 14 days from randomization.
 - (a) Ratio of PaO₂ to FIO₂.
 - (b) Oxygenation index (FIO₂×mean airway pressure/PaO₂).
 - (c) Daily ventilation parameters: PEEP, FIO₂, plateau pressure, mean airway pressure, and peak airway pressure.
- (5) Lung compliance on days 1 and 4.
- (6) Coagulation profile [prothrombin time, platelet count, international normalized ratio (INR), and activated partial thromboplastin time (aPTT)] on days 1 and 4 for both groups.
- (7) Nonbronchoscopic lavage using 10 ml of sterile saline for culture (on day 4 for both groups) and TNF level (on days 1 and 4 for group I and day 4 only for group II).
- (8) Adverse events such as blood-stained sputum or frank blood in sputum, red cell transfusions, and any significant bleeding after randomization.
- (9) Ventilator-free days on day 28 (nonsurvivors were assumed to have zero free days.)
- (10) Days free of vasopressor and acute renal failure during the first 28 days.
- (11) ICU-free days during the first 28 days.
- (12) Mortality on day 28.

Results

Data analysis revealed that the following data were not statistically significantly different within groups over time or when the percentage change between the two groups was compared: PaCO₂, pH, PaO₂, HCO₃, SO₂, PaO₂/FIO₂, FIO₂×mean airway pressure/PaO₂, peak inspiratory pressure, mean airway pressure, TNF α, systolic blood pressure, diastolic blood pressure, hemoglobin, hematocrit value, white blood cells count, platelet count, prothrombin concentration, INR, presence of bloody sputum, ICU-free days on day 28, ventilator-free days on day 28, acute renal

Table 1 Data collected on admission and day 4 only

Parameter	Group I (N=25) (mean±SD)	Group II (N=25) (mean±SD)	Significance (P value)
Age (years)	56.24±14.1	56.68±12.8	0.868
Glasgow Coma Scale	12±2.5	11±2.7	0.379
APACHE II score	15±5	15±5	0.592
TNF at day 4 (pg/ml)	27.42±9.8	25.07±7.73	0.453

APACHE II, Acute Physiology and Chronic Health Evaluation II; TNF, tumor necrosis factor.

Table 2 Hemoglobin and hematocrit

Parameter	Hemoglobin (mean±SD) (g/dl)			Hematocrit (mean±SD) (%)		
	Group I	Group II	P value (d1G1/d1G2)	Group I	Group II	P value (d1G1/d1G2)
Day 1	11.1±3.23	10.6±2.21	0.826	32.8±8.48	31.2±6.49	0.749
Day 4	10.6±2.48	9.6±1.8		31.5±7.69	28.26±5.31	
P value (d1/d4)	0.486	0.065		0.420	0.064	

No statistical significant difference was found in hemoglobin and hematocrit between the two groups, nor on follow-up within each group.

Table 3 Total leukocytic count and platelet count

Parameter	Total leukocytic count (mean±SD) ($\times 10^3/\text{cm}^3$)			Platelet count (mean±SD) ($\times 10^3/\text{mm}$)		
	Group I	Group II	P value (d1G1/d1G2)	Group I	Group II	P value (d1G1/d1G2)
Day 1	15.79±7.76	12.4±4.59	0.11	212±86.55	213.24±97.94	0.857
Day 4	16.78±6.74	11.81±4.36		202.8±101.1	183.64±78.33	
P value (d1/d4)	0.670	0.594		0.145	0.689	

No statistically significant difference was found in TLC and PLT count between the two groups, nor on follow-up within each group.

Table 4 INR

Parameter	INR (mean±SD)		
Group day	Group I	Group II	P value (d1G1/d1G2)
Day 1	1.26±0.23	1.24±0.25	0.527
Day 4	1.3±0.2	1.34±0.42	
P value (d1/d4 within group)	0.338	0.056	

No statistically significant difference was found in PC and INR between the two groups, nor on follow-up within each group.

INR, international normalized ratio; PC, platelet count.

Table 5 aPTT

Parameter	aPTT (mean±SD) (s)		
Group day	Group I	Group II	P value (d1G1/d1G2)
Day 1	30.23±4.39	34.22±5.86	0.015*
Day 4	32.13±4.58	34.83±6.11	
P value (d1/d4 within group)	0.001*	0.212	

*There was a statistical significant difference in aPTT on day 1 between the two groups, and on follow-up there was a statistically significant increase in aPTT in group I and decrease in group II.

aPTT, activated partial thromboplastin time.

failure-free days on day 28, vasopressor-free days on day 28, and mortality and sputum culture results on day 4.

However, the following data showed a statistically significant change in the heparin-treated group.

Table 6 PaO₂ and SpO₂

Parameter	PaO ₂ (mean±SD) (mmHg)			SpO ₂ (mean±SD) (%)		
	Group I	Group II	P value (d1G1/d1G2)	Group I	Group II	P value (d1G1/d1G2)
Group day						
Day 1	99.42±48.9	101.85±39.66	0.634	93.73±7.69	94.736±6.29	0.691
Day 4	98.348±35.7	116.67±38.6		95.34±5.11	97.4±2.62	
P value (d1/d4)	0.710	0.174		0.368	0.154	

No statistically significant difference was found in PaO₂ and SpO₂ between the two groups, nor on follow-up within each group.

Table 7 PaCO₂ and FIO₂

Parameter	PaCO ₂ (mean±SD) (mmHg)			FIO ₂ (mean±SD)		
	Group I	Group II	P value (d1G1/d1G2)	Group I	Group II	P value (d1G1/d1G2)
Group day						
Day 1	43.46±18.76	42.42±21.098	0.362	0.458±0.07	0.52±0.08	0.171
Day 4	38.94±13.09	36.684±11.81		0.484±0.09	0.5±0.09	
P value (d1/d4)	0.113	0.134		0.206	0.102	

No statistically significant difference was found in PaCO₂ and FIO₂ between the two groups, nor on follow-up within each group.

Table 8 PEEP

Parameter	PEEP (mean±SD) (cmH ₂ O)		
	Group I	Group II	P value (d1G1/d1G2)
Group day			
Day 1	3.9±2.29	4.4±1.47	0.124
Day 4	4.3±1.97	3.8±2.03	
P value (d1/d4 within group)	0.157	0.102	

No statistically significant difference was found in PEEP and CVP between the two groups, nor on follow-up within each group. CVP, central venous pressure; PEEP, positive end-expiratory pressure.

Table 9 PaO₂/FIO₂ ratio

Parameter	PaO ₂ /FIO ₂ ratio (mean±SD)		
	Group I	Group II	P value (d1G1/d1G2)
Group day			
Day 1	230±140.8	204.6±92.4	0.749
Day 4	206.6±68.5	240.4±87.2	
P value (d1/d4 within group)	0.753	0.098	

No statistically significant difference was found in PaO₂/FIO₂ ratio between the two groups, nor on follow-up within each group.

Table 10 Peak airway pressure and mean airway pressure

Parameter	Peak airway pressure (mean±SD) (cmH ₂ O)			Mean airway pressure (mean±SD) (cmH ₂ O)		
	Group I	Group II	P value (d1G1/d1G2)	Group I	Group II	P value (d1G1/d1G2)
Group day						
Day 1	29.92±6.06	24.72±6.66	0.002*	10.72±2.09	10.15±3.75	0.04*
Day 4	29.4±5.4	24.2±5.75		11.12±2.07	9.8±2.94	
P value (d1/d4)	0.404	0.660		0.246	0.863	

*There was a statistically significant difference in all parameters on day 1 between the two groups, and on follow-up there was no statistically significant change.

Table 11 Plateau pressure and compliance

Parameter	Plateau pressure (mean±SD) (cmH ₂ O)			Compliance (mean±SD) (ml/cmH ₂ O)		
	Group I	Group II	P value (d1G1/d1G2)	Group I	Group II	P value (d1G1/d1G2)
Group day						
Day 1	22.2±5.57	18.32±4.78	0.005*	31.89±12.62	30.856±13.76	0.727
Day 4	20.32±5.25	17.92±3.51		33.83±13.65	31.98±13.15	
P value (d1/d4)	0.003*	0.959		0.019*	0.092	

*There was a statistically significant difference in plateau pressure on day 1 between the two groups, and on follow-up there was a statistically significant decrease in plateau pressure and increase in compliance rate in group I.

Table 12 Comparison between days 1 and 4 regarding TNF α in group I using the Wilcoxon signed-rank test

TNF in lavage (mean \pm SD) (pg/ml)		
Day 1	Day 4	Significance (<i>P</i> value)
28.6 \pm 9.7	27.42 \pm 9.8	0.051

No statistically significant change occurred in TNF 'in bronchial lavage' in group I.
TNF, tumor necrosis factor.

Table 13 Comparison between the two groups regarding endpoint parameters using the Mann-Whitney *U*-test

Parameter	Group I (mean \pm SD)	Group II (mean \pm SD)	Significance (<i>P</i> value)
ICU-free days at day 28	6 \pm 9	4 \pm 8	0.433
ICU-free days at day 28 without nonsurvivors	9 \pm 10	6 \pm 9	0.354
Ventilator-free days at day 28	10 \pm 11	7 \pm 10	0.266
Ventilator-free days at day 28 without nonsurvivors	14 \pm 11	10 \pm 10	0.287
Acute renal failure-free days at day 28	23 \pm 10	23 \pm 10	0.978
Acute renal failure-free days at day 28 without nonsurvivors	28 \pm 1.5	28 \pm 0	0.317
Vasopressor-free days at day 28	21 \pm 11	22 \pm 11	0.773
Vasopressor-free days at day 28 without nonsurvivors	27 \pm 2	27 \pm 3.6	0.951
TNF in lavage day 4 (pg/ml)	27.42 \pm 9.8	25.07 \pm 7.73	0.453

No statistically significant difference was found in any of the parameters in the two groups.
TNF, tumor necrosis factor.

Table 14 Comparison between the two groups regarding patient weaning success using the Pearson's χ^2 -test

	Groups [<i>n</i> (%)]				Significance (<i>P</i> value)
	Group I		Group II		
Patients	Weaned	Not weaned	Weaned	Not weaned	
All patients	10 (40)	15 (60)	7 (28)	18 (72)	0.370
Patient after omitting nonsurvivors	9 (47)	8 (53)	7 (41)	10 (59)	0.492

- (1) Plateau pressure showed a statistically significant decrease between days 1 and 4 in the heparin-treated group ($P=0.003$) and the difference was significant when we compared the percentage change between groups ($P=0.015$).
- (2) Compliance rate showed a statistically significant increase only between days 1 and 4 in the heparin-treated group ($P=0.019$), but when we compared the percentage change between groups the difference was not statistically significant ($P=0.256$).
- (3) aPTT showed a statistically significant increase between days 1 and 4 in the heparin-treated group ($P=0.001$) but when we compared the percentage change in each group with each other this change was not statistically significant ($P=0.153$).

No cases of heparin-induced thrombocytopenia were noted in the heparin-treated group, nor was there major bleeding or need for blood transfusion related to the tested medication in this group.

Discussion

The current study was designed to assess the effects of nebulized heparin on the mechanically ventilated patient with respect to its safety and effects on morbidity and mortality (Tables 1,8 and 14).

A similar study conducted by Dixon *et al.* [11] was taken as a guide, with some modifications in the selection criteria (Dixon's study was performed on ALI patients, but our study was conducted on any patient expected to be mechanically ventilated for more than 48 h) and methodology.

The mean age of the studied patients was 56.24 \pm 14.1 years in group I versus 56.68 \pm 12.8 years in group II with a predominance of male sex in both groups (76 and 64% in groups I and II, respectively) without a statistically significant difference between the two groups ($P=0.355$). chronic obstructive pulmonary disease-associated respiratory failure was the predominant reason for mechanical ventilation in group I (36%), whereas pneumonia was the predominant reason in group II (28%). Radiographic

Table 15 Comparison between the two groups regarding percentage change from days 1 to 4 [(d1 value-d4 value)/d1 value×100] using the Mann–Whitney U-test

Parameter	Group I % change		Group II % change		Significance (<i>P</i> value)
	Mean	SD	Mean	SD	
Compliance (ml/cmH ₂ O)	-6.39	13.79	-5.33	12.4	0.256
PEEP (cmH ₂ O)	0	0	13.04	34.44	0.122
FIO ₂	-7.2	23.32	2.8	8.15	0.093
Systolic blood pressure (mmHg)	-8.89	37.21	-3.01	30.1	0.083
Diastolic blood pressure (mmHg)	-5	28.16	-18.05	101.28	0.114
Mean blood pressure (mmHg)	-10.03	30.01	-7.99	52.3	0.027*
PaO ₂ /FIO ₂	-13.73	59.19	-34.12	66.54	0.299
FIO ₂ ×mean airway pressure/PaO ₂ (cmH ₂ O/mmHg)	-31.45	100.6	10.41	37.6	0.190
pH	-0.11	1.4	-0.31	1.38	0.961
PaCO ₂ (mmHg)	0.85	48.17	5.3	26.18	0.587
PaO ₂ (mmHg)	-15.47	54.26	-29.62	65.34	0.554
HCO ₃ (mmol/l)	-3.79	29.57	0.48	20.68	0.705
SpO ₂ (%)	-2.36	11.25	-3.33	8.545	0.704
Hb (g/dl)	-0.74	20.12	3.93	11.27	0.603
PLT (×10 ³ /mm)	9.7	20.82	-2.08	28.35	0.409
aPTT (s)	-6.56	7.98	-2.63	11.45	0.153
Peak inspiratory pressure (cmH ₂ O)	0.81	10.51	0.79	9.28	0.688
Mean airway pressure (cmH ₂ O)	-5.16	15.95	1.27	10.91	0.305
Plateau pressure (cmH ₂ O)	7.07	13.72	0.22	11.59	0.015*

*The percentage change in the two groups was statistically significantly different in the following parameters: mean blood pressure, serum potassium, and plateau pressure.

aPTT, activated partial thromboplastin time; Hb, hemoglobin; PEEP, positive end-expiratory pressure; PLT, platelet.

Table 16 Comparison between the two groups regarding mortality at day 28 using Pearson Chi-Square Test

Group I		Survivors		Group II		Survivors		Significance (<i>P</i> value)
No.	%	No.	%	No.	%	No.	%	
8	32%	17	68%	8	32%	17	68%	

No statistical significant difference was found in survival of the two groups.

findings revealed similar results (hyperinflation was 36% in group I and pneumonia was 40% in group II).

The tested groups were compared at baseline with regard to age ($P=0.868$), Glasgow Coma Scale ($P=0.379$), Acute Physiology and Chronic Health Evaluation II score ($P=0.592$), hemoglobin ($P=0.826$), platelet count ($P=0.857$), PaO₂/FIO₂ ($P=0.749$), PEEP applied ($P=0.124$), compliance ($P=0.727$), and FIO₂ applied ($P=0.171$) and there were no statistically significant differences. On the other hand, the following data showed statistically significant differences: partial thromboplastin time ($P=0.015$), urea ($P=0.046$), creatinine ($P=0.032$), serum potassium ($P=0.002$), peak inspiratory pressure ($P=0.002$), mean airway pressure ($P=0.04$), plateau pressure ($P=0.005$), systolic blood pressure ($P=0.039$), and diastolic blood pressure ($P=0.047$). Hence, direct comparisons between the two groups at day 4 were avoided whenever possible.

Each group's data were compared between days 1 and 4 and the following was detected.

There was no statistically significant difference in either group in terms of arterial blood gas parameters (pH, PaCO₂, PaO₂, HCO₃, and SpO₂) (Tables 6 and 7). This matched the results of Li *et al.* [12], who found that there was no statistical difference in pH, PaO₂, and PaCO₂ at the beginning versus the end of 5 h of mechanical ventilation in sheep given nebulized heparin. Our result also matched that of Dixon *et al.* [11], who found that there was no significant difference between groups in the partial pressure of arterial carbon dioxide over the course of the study period (days when the patients remained on mechanical ventilation to a maximum of 14 days from randomization).

Regarding other oxygenation parameters, in this study it showed no significant difference in either group (P

value for $\text{PaO}_2/\text{FIO}_2$ and $\text{FIO}_2 \times \text{mean airway pressure}/\text{PaO}_2$ (Table 9). This was in accordance with the results of Dixon *et al.* [13], who found that nebulized heparin did not cause significant changes in the ratio of PaO_2 to FIO_2 . In addition, Dixon *et al.* [11] found that the average daily $\text{PaO}_2/\text{FiO}_2$ ratio while ventilated was similar in the nebulized heparin and nebulized placebo groups (194.2 ± 62.8 vs. 187 ± 38.6 mmHg, $P=0.6$). However, they found that, although not statistically significant, the $\text{PaO}_2/\text{FiO}_2$ ratios were higher from day 3 in the heparin group, which did not match our findings ($\text{PaO}_2/\text{FIO}_2$ was 230 ± 140.8 on day 1 vs. 206.6 ± 68.5 on day 4 in group I and 204.6 ± 92.4 vs. 240.4 ± 87.2 in group II) (Table 9).

In contrast, Murakami *et al.* [14] found that the $\text{PaO}_2/\text{FiO}_2$ ratio dropped markedly in saline-treated sheep with induced ARDS. However, in the heparin-nebulized group, the drop was significantly attenuated after 12 h. The pulmonary shunt fraction increased in the saline-treated group, reaching 50–60% at 24 h, but was significantly lower in the heparin-nebulized group.

In the current study, there were no statistically significant changes in either group regarding peak inspiratory pressure and mean airway pressure (Table 10).

When we assessed plateau pressure and compliance, we found a statistically significant decrease in plateau pressure and increase in compliance in group I (the heparin-treated group). This statistically significant change was not found in group II (Table 11). In contrast, Dixon *et al.* [13] found that there was no statistically significant change in lung compliance for the dosage, nor in the interaction between dosage and time.

TNF was tested before and after treatment with nebulized heparin in group I but no statistically significant difference was noted (Table 12). The same result was seen when we compared the two groups on day 4 (Table 13). This was similar to the findings of Hofstra *et al.* [15], who stated that bronchoalveolar levels of TNF and histopathology of the lungs were not affected by nebulization with anticoagulants.

This finding also matched that of Dixon *et al.* [11], who noted that levels of TNF in pulmonary lavage fluid were similar in the two groups at baseline and on each day that samples were taken following enrollment in the groups (with nebulized heparin and placebo).

Regarding systolic blood pressure, we noted an increase in mean value from days 1 to 4 in group I only (106 ± 22 mmHg on day 1 and 112 ± 31 mmHg on day 4 in group I vs. 118 ± 25 mmHg on day 1 and 118 ± 24 mmHg on day 4 in group II), but these changes were not statistically significant ($P=0.156$ and 0.833 , respectively).

Diastolic blood pressure showed an increase in mean value from days 1 to 4 in both groups (68 ± 14 mmHg on day 1 and 70 ± 18 mmHg on day 4 in group I vs. 74 ± 17 mmHg on day 1 and 75 ± 14 mmHg on day 4 in group II), but this increase was not statistically significant ($P=0.127$ and 0.932 , respectively).

However, when the mean arterial blood pressure was analyzed we noticed an increase in mean blood pressure in group I only (79 ± 15 mmHg on day 1 and 84 ± 22 mmHg on day 4), which was statistically significant ($P=0.022$), whereas group II did not show that increase (89 ± 19 mmHg on day 1 and 89 ± 16 mmHg on day 4) ($P=0.888$) (Table 15).

This contradicted the results of Murakami *et al.* [16], who noted that the mean arterial pressure decreased and was not attenuated by intravenous heparin administration in sheep with induced ALI.

Comparison of hemoglobin, hematocrit value, white blood cells, platelet count, and INR showed no statistically significant difference between days 1 and 4 in the two groups (Tables 2–4). There was no need for blood transfusion related to the drug tested.

Yip *et al.* [17] tested the effect of nebulized heparin at a dose of 30 000 U/day on burn patients with inhalation lung injury; they noted that platelet count and prothrombin time followed a similar trend in both groups (nebulized heparin with *N*-acetyl cystine or salbutamol group and control group). In addition, there were no statistical differences in the mean platelet counts of the treatment and the control group over the 7 days.

Regarding aPTT there were no statistically significant differences in group II. However, in group I, we noted a statistically significant increase in aPTT (Table 5) but this increase did not reach the therapeutic level. This matched the results of Dixon *et al.* [13], who monitored the anticoagulation effect of nebulized heparin at doses of 50 000, 100 000, 200 000, and 400 000 U/day and found no serious adverse events for any dose.

Bloody sputum incidence was 28% in group I versus 36% in group II. Analysis revealed that there was no

statistical significance for this difference ($P=0.544$). No frank bleeding or marked bleeding tendency was noted in either group. This was similar to the findings of Dixon *et al.* [13], who have not recorded any serious adverse event in their patients except for one patient in the 400 000 U/day group who developed blood-stained respiratory secretions after the seventh dose. In addition, Ahmed *et al.* [18] failed to demonstrate any anticoagulant effect of inhaled heparin on bleeding tendency in his trial on patients with bronchial asthma. This was confirmed by Dixon *et al.* [11].

No cases of heparin-induced thrombocytopenia was reported in any of our patients, matching the results of Yip *et al.* [17].

The mean number of ICU-free days was 6 ± 9 days in group I versus 4 ± 8 days in group II. Group I showed more number of ICU-free days but this was not statistically significant ($P=0.433$) even after omitting nonsurvivors ($P=0.354$) (Table 13). Our results were similar to those of Dixon *et al.* [11], who found that the duration of ICU stay was 9.4 ± 7.4 in the heparin-treated group versus 14.0 ± 13.1 days in the control group ($P=0.2$). In addition, Yip *et al.* [16] showed that the median length of ICU stay was 6 days in the heparin-treated group compared with 7 days in the control group.

The mean number of ventilator-free days was 10 ± 11 days in group I versus 7 ± 10 days in group II. Group I showed more ventilator-free days but this was not statistically significant ($P=0.266$) even after omitting nonsurvivors ($P=0.287$) (Table 13). When we compared the percentage of weaning in each group (40% in group I vs. 28% in group II), it was higher in group I but this was not statistically significant ($P=0.37$) even after omitting nonsurvivors ($P=0.492$). This result was similar to that of Yip *et al.* [17], who showed that the median duration of intubation was 5 days in both groups.

In contrast, Dixon *et al.* [11] found that nebulized heparin was associated with improved number of ventilator-free days among survivors at day 28 (22.6 ± 4.0) in the heparin-treated group versus 18.0 ± 7.1 in the control group ($P=0.02$).

Mean acute renal failure-free days was 23 ± 10 days in both groups, and this was not statistically significant ($P=0.978$) even after omitting nonsurvivors ($P=0.317$) (Table 13). This result was similar to that of Dixon *et al.* [11], who found that the average number of renal failure-free days among survivors at day 28 (28 days in

both groups) showed no statistically significant difference between the two groups ($P=0.09$).

Mean vasopressor-free days was 21 ± 11 days in group I versus 22 ± 11 days in group II, and this was not statistically significant ($P=0.773$) even after omitting nonsurvivors ($P=0.951$) (Table 13). Our results were similar to those of Dixon *et al.* [11], who found that the number of vasopressor-free days among survivors at day 28 was $24.7(\pm 3.2)$ in the heparin-treated group versus 22.0 ± 7.0 days in the control group ($P=0.12$).

The number of deaths in both groups was eight persons (32%) (no statistically significant difference; $P=1$) (Table 16). This was similar to the finding of Dixon *et al.* [11], who found that mortality at day 28 was similar in the two groups ($P=0.7$).

Limitations in the current study

- (1) The sample size for the groups is small.
- (2) The incidence of bleeding and other complications reported in the study depended mostly on the documentation of nurses and other physicians.
- (3) The indications for mechanical ventilation were relatively broad at enrollment.

Conclusion

From the current study, we conclude the following.

- (1) Heparin at a dose of 100 000 to 150 000 U/day is a safe drug when used through nebulization and does not affect coagulation markedly.
- (2) Nebulized heparin improved the compliance rate and significantly reduced the plateau pressure in our tested patients.
- (3) Nebulized heparin did not affect oxygenation, mortality, vasopressor-free days, incidence of acute renal failure, prothrombin concentration, hemoglobin concentration, and platelet count in the tested group.
- (4) The number of ventilator-free days was higher in the heparin-treated group but did not reach a statistically significant value.

Recommendations

Nebulized heparin is a safe drug that has a favorable effect in patients receiving mechanical ventilation, especially with reduced compliance as in ARDS.

Repetition of this study on a larger scale would verify its results as there are no available studies on a larger number of patients.

- (1) Nebulized heparin should be tested on specific indications of mechanical ventilation to detect the effect of heparin on individual disease.

A similar study should be conducted over a longer follow-up period as it may show a statistically significant difference regarding ventilator-free days and mortality.

Acknowledgements

Conflicts of interest

None declared.

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