Does nebulized heparin have value in acute respiratory distress syndrome patients in the setting of polytrauma?

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Background Several studies have been conducted with anticoagulants in the setting of experimental lung injury in animals and acute respiratory distress syndrome (ARDS) in humans. However, the clinical evidence for pulmonary anticoagulant therapy is still limited.

Aim We aimed to assess the value of the use of nebulized heparin in ARDS patients in the setting of polytrauma.

Patients and methods Eighty patients admitted with polytrauma and diagnosed to have ARDS and mechanically ventilated were enrolled. Patients were divided randomly into two groups, and each group included 40 patients: group 1 received nebulized heparin at a dose 5000 IU every 4 h, and group 2 served as control. All clinical and laboratory data were recorded. Patients were followed up during their whole ICU stay. All data were statistically analyzed.

Results The mean age of the studied patients was 34.35±14.6 and 34.87±14.86 years in group 1 and group 2, respectively. After 1 week, patients in group 1 had significant improvement in their PO_2/FiO_2 and lung injury severity score compared with patients in group 2 (231.1±42.7 and 1.82±0.66 vs. 203.6±45.9 and 2.35±0.35, $P<0.001$, respectively). Group 1 spent less days on mechanical ventilation and their length of ICU stay was lower compared with group 2 (9.6±13.5 and 12.7±4.3 days vs. 13.5±3.1 and 17.7±3.7 days, respectively, $P<0.001$). Other outcome parameters such as development of multiple organ dysfunction syndrome, the need to use vasoactive agents, and mortality did not differ between both groups (12, 62.5, and 20% vs. 15, 57.5, and 22.5%, $P=0.5$, 0.41, and 0.61, respectively).

Conclusion Nebulized heparin may be beneficial and safe but has no survival benefit in ARDS patients in the setting of polytrauma.

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Keywords: acute respiratory distress syndrome, lung injury score, nebulized heparin, PO_2/FiO_2

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Introduction

Pulmonary coagulopathy is one of the main characteristic features of acute respiratory distress syndrome (ARDS) [1–4], pneumonia [1,5,6], and inhalation injury [7]. Moreover, potential alteration in pulmonary coagulation balance was demonstrated in mechanically ventilated patients. Evidence points to the fact that the extent of pulmonary coagulopathy correlates with the severity of acute lung injury (ALI) and predicts poor outcome in ALI [1,8–10].

The inhalation route for drug administration has been used for many years, mainly in the airway diseases. This approach has been also discussed in ARDS, where direct application of drugs through an inhalational route could represent a valid alternative approach to systemic administration [11].

In 2008, Dixon *et al*. [12] have examined the effects of nebulized heparin in ARDS. Although their results indicate that this type of therapy did not cause significant changes in blood gases or lung mechanics, a trend for an increasing systemic anticoagulant effect with higher doses was impressive.

Several studies have been conducted with anticoagulants in the setting of experimental lung injury in animals and ARDS in humans. However, the clinical evidence for pulmonary anticoagulant therapy is still limited. A major limitation in the majority of the studies of anticoagulants in ARDS patients is that the patient population studied is not homogeneous, as there are differences in the primary insult and/or patient factors. This study aimed to assess the value of the use of nebulized heparin in ARDS complicating polytrauma patients.

Patients and methods

This study was a prospective study conducted on 80 polytrauma patients admitted to critical care department of Cairo University and El Galaa Military Hospital and diagnosed to have ARDS and mechanically ventilated within 24 h of their admission from December 2014 to December 2015.

A polytrauma patient is defined as a patient who has two or more severe injuries in at least two areas of the body [13]. ARDS was defined according to Berlin

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criteria by timing (within 1 week of clinical insult or onset of respiratory symptoms), radiographic changes (bilateral opacities not fully explained by effusions, consolidation, or atelectasis), origin of edema (not fully explained by cardiac failure or fluid overload), and severity based on the PaO_2/FiO_2 ratio on 5 cm of continuous positive airway pressure [14]. Following enrollment, patients were randomly divided into two groups, and each group included 40 patients: group 1 received 5000 IU heparin mixed with 3 ml of normal saline nebulized every 4 h in addition to all other standard management methods of ARDS and group 2 served as the control.

All patients underwent full clinical examination and laboratory investigation including complete blood picture, coagulation profile, kidney and liver functions, creatine phosphokinase, blood gases, and lactate level. Chest radiography was done daily for all patients during their mechanical ventilation (MV) period. Acute physiology and chronic health evaluation II and lung injury severity scores (LISS) were calculated upon admission. The LISS was reassessed 1 week after admission for all patients. Patients were followed up during their ICU stay and compared regarding their laboratory results and different outcome parameters including mortality. Any patients with any of the following were excluded: died within 24 h of admission, age less than 18 years, pregnant females, thrombocytopenia defined as less than 50 000 platelets/mm^3, and coagulopathy defined as international normalized ratio greater than 1.5. Informed consent was taken from patients' first-degree relatives.

Ventilatory settings

All patients received MV through commercially available ventilators (Puritan-Bennett 840 or Dräger Evita IV) with volume-controlled mode. Tidal volume was set to be 6–8 ml/kg. Predicted body weight in kg was calculated from the following formula: 2.3×(height in inches−60)+45.5 for women or +50 for men [15]. The respiratory rate was adjusted to deliver the expected minute ventilation requirement (generally, 7–9 l/min). FiO_2 and positive end-expiratory pressure were adjusted to maintain an arterial oxygen saturation of 88–92%. Ventilator adjustments were made to keep the plateau pressure (measured during an inspiratory hold of 0.5 s) less than 30 cmH_2O, and to keep accepted blood gas parameters with permissive hypercapnia. All patients were lightly sedated to minimize ventilator–patient dyssynchrony. All patients included in the study were screened daily to assess feasibility of weaning from MV.

Statistical analysis

Data were statistically described in terms of mean±SD, median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student's t test for independent samples. For comparing categorical data, χ^2 test was performed. Exact test was used instead when the expected frequency is less than 5. All statistical calculations were done using computer program statistical package for the social science (SPSS, version 20; SPSS Inc., Chicago, Illinois, USA).

Results

The mean age of the studied patients was 34.35±2.32 and 34.87±14.86 in group 1 and group 2, respectively. Of them, 55 (68.8%) were male. General characteristics of the studied patients are illustrated in Table 1.

Surprisingly, we did find that platelet count was lower in group 1 compared with group 2, yet this finding was statistically insignificant. Other admission parameters of hemostatic profile were comparable between the two groups. However, the follow-up platelet count was significantly lower in group 1 compared with group 2 (Table 2).

After 1 week, patients in group 1 had significant improvement in their PO_2/FiO_2 and LISS compared with patients in group 2 (231.1±42.7 and 1.82±0.66 vs. 203.6±45.9, and 2.35±0.35, $P<0.001$, respectively) (Fig. 1).

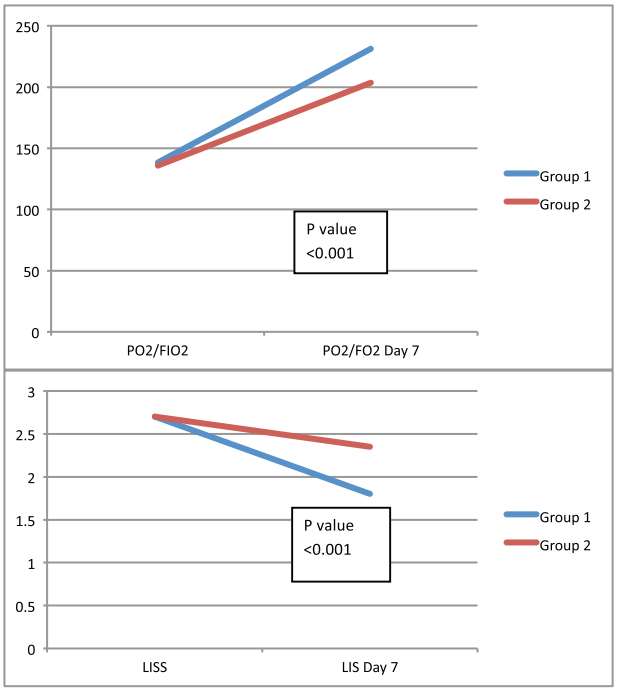
Significant difference was found in the heparin-treated patients compared with the control group regarding the duration they spent on MV, as well as their length of ICU stay (9.6±13.5 and 12.7±4.3 days vs. 13.5±3.1 and 17.7±3.7 days, respectively,

Table 1 General characteristics of the studied patients

	Group 1	Group 2	*P* value
Age (years)	34.3±14.6	34.8±14.8	0.87
Sex (male)	27 (67.5)	28 (70.0)	0.50
APACHE II	19.5±5.2	20.7±5.4	0.31
GCS	12.6±2.0	12.4±2.76	0.61
Lactate (mmol/l)	3.3±1.7	3.1±1.7	0.58
Hb (g/dl)	11.6±1.9	13.1±0.9	0.34
Albumin (g/dl)	3.1±0.2	3.0±0.2	0.48
PO_2/FiO_2	138.3±42.4	135.68±41.4	0.77
LISS	2.7±0.4	2.7±0.4	0.83

Data are presented as mean±SD or *n* (%). APACHE II, acute physiology and chronic health evaluation; FiO_2, fraction of inspired oxygen; GCS, Glasgow coma scale; Hb, hemoglobin; LISS, lung injury severity score; M, males; PaO_2, arterial partial oxygen pressure.

Figure 1



Comparison between two groups regarding their changes of PO_2/FiO_2 and LISS. PaO_2, arterial partial oxygen pressure; FiO_2, fraction of inspired oxygen; LISS, lung injury severity score.

$P<0.001$). However, other outcome parameters such as occurrence of significant bleeding episodes necessitating blood transfusion, development of multiple organ dysfunction syndrome, the need to use vasoactive agents, and mortality did not differ between both groups (Table 3).

Discussion

There is growing evidence pointing to the potential value of nebulized anticoagulant in attenuating pulmonary coagulopathy and inflammation in preclinical studies of lung injury. In addition, the data from human trials suggested that nebulized heparin for ARDS may be beneficial and safe, but sufficient data are still limited. This study confirmed the value of nebulized heparin in ARDS patients in the setting of polytrauma, as our results indicate significant improvement of PO_2/FiO_2 and LISS in the heparin-treated group compared with the other group. Moreover, they spent less days on MV compared with the other group. Similarly, Dixon *et al.* [16] reported that heparin-treated patients had higher PO_2/FiO_2 from day 3 compared with the non-heparin-treated group. In addition, they mentioned that heparin administration was associated with a higher number of ventilator-free days among survivors at day 28 (22.6±4.0 vs. 18.0 ±7.1, P=0.02). They also added that NO was used

Table 2 Comparison between the two groups regarding their hemostatic profile

	Group 1	Group 2	*P* value
PT (s)	12.2±3.2	11.9±3.6	0.69
INR	1.17±3.4	1.09±4.1	0.74
Baseline APTT (s)	38.5±3.9	38.4±3.7	0.90
Baseline PLT ($\times10^3$/mm^3)	218.1±7.6	235.7±42.9	0.08
Follow-up APTT (s)	38.9±4.0	38.5±3.8	0.61
Follow-up PLT ($\times10^3$/mm^3)	217.6±42.1	241.8±47.4	0.018

APTT, activated partial thromboplastin time; INR, international normalized ratio; PLT, platelet count; PT, prothrombin time.

Table 3 Comparison between the two groups regarding different outcome parameters

	Group 1	Group 2	*P* value
MV duration	9.6±13.5	13.5±3.1	<0.001
LOS	12.7±4.3	17.7±3.7	<0.001
Significant bleeding [*n* (%)]	4 (10)	2 (5)	0.33
MODS [*n* (%)]	5 (12.5)	6 (15)	0.5
Need to VA agents [*n* (%)]	25 (62.5)	23 (57.5)	0.41
Mortality [*n* (%)]	8 (20)	9 (22.5)	0.61

LOS, length of ICU stay; MODS, multiple organ dysfunction syndrome; MV, mechanical ventilation; VA, vasoactive.

less frequently in the heparin group (0 vs. 19%, P=0.05).

On the contrary, Holt *et al.* [17] and Kashefi *et al.* [18] failed to demonstrate a clinical benefit of combined nebulization of heparin, *N*-acetylcysteine, and albuterol in a cohort of adult inhalation injury patients; rather, they mentioned that this combination may increase the development of pneumonia in their cohort. The different population of their study and our study may explain this contradictory result. In 2016, an individual patient data meta-analysis [19] provides no convincing evidence for the benefit of heparin nebulization in intubated and ventilated ICU patients. However, three out of five studies included in this meta-analysis were carried out on patients with inhalational injury. Thus, this result should not be generalized on different types of patients.

Our study also showed that during the ICU stay the platelet count was found to be significantly lower in the heparin-treated group compared with the control group, raising the possibility of systemic absorption of nebulized heparin even in a small dose that we used. Despite this finding, occurrence of significant bleeding necessitating blood transfusion did not differ in both groups. In addition, activated partial thromboplastin time showed no significant difference in both groups. This confirmed the previous report of Yip *et al.* [20], who mentioned that nebulized heparin did not potentiate the risk of

bleeding in burns patients with ALI. In line with these results, Dixon *et al.* [16] found no significant difference between heparin and placebo groups regarding activated partial thromboplastin time, and the number of patients who needed blood transfusion.This study failed to prove any survival benefit from the use of nebulized heparin. In addition, the need to use vasoactive agents or development of multiple organ dysfunction syndrome did not differ between both groups. Previous reports demonstrating the effects of nebulized heparin on the duration of MV and other outcome parameters such as mortality in patients with ALI have been conflicting. Unlike our result, Miller *et al.* [21] mentioned that there was a statistically significant survival benefit in their treated group that was most pronounced in patients with acute physiology and chronic health evaluation III scores greater than 35. In two other studies no beneficial effects of heparin nebulizations were seen [17,18].

Conclusion

The use of nebulized heparin may be beneficial and safe in ARDS patients in the setting of polytrauma. However, its survival benefit is still questionable.

Study limitations

In addition to the relatively small sample size, we used a low dose of nebulized heparin seeking for more patient safety. Therefore, we did not assess the use of higher doses of nebulized heparin regarding their safety and efficacy. In addition, despite the fact that our heparin-treated patients had lower platelet count compared with the control group, we did not confirm or exclude the occurrence of heparin-induced thrombocytopenia in these patients.

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Nil

Conflicts of interest

There are no conflicts of interest.

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