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Original Article

Role of Nebulized Heparin in Patients with Acute Respiratory Distress Syndrome on Mechanical Ventilation

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Abstract:

Background: *Acute respiratory distress syndrome (ARDS) is a grave condition, where pulmonary coagulopathy; an important contributor to hypoxia, which ultimately cause multiorgan dysfunction and leads to death. Heparin is an anticoagulant, that has the potential to modify that coagulopathy. So, in addition of current guideline, nebulized heparin may be beneficial for treating patients with ARDS on mechanical ventilation.*

Methods: *This is a randomized controlled trial. A total of 74 sample sizes had been estimated by using statistical formulas. In this study, patients were diagnosed as ARDS according to Berlin definition by the ICU physicians. Study patients were allocated systemically in two groups. The randomized procedure involved first assigning the initial ARDS patient by a coin flip, subsequent patients were then assigned alternately to the intervention or control group on their order of diagnosis (odd-even sequence). One group received nebulized heparin in addition to protocolized treatment for ARDS and another group received only protocolized treatment for ARDS. Patients received the intervention, got nebulized heparin 5000u mixed with 2 ml normal saline/BD for a week along with protocolized treatment for ARDS and patients of control group or standard of care group, got only protocolized treatment but no heparin nebulization.*

Result: *The mean tidal volume was significantly different on the third day and fifth day ($p < 0.05$), no significant difference regarding the mean respiratory index (PaO_2/FiO_2) on the first day, while it increased significantly in the intervention group on the third, fifth and seventh day ($p < 0.05$). There was no significant difference of platelet count and APTT in two groups ($p > 0.05$).*

Conclusion: *The administration of heparin nebulization can enhance oxygenation, evidenced by improving PaO_2/FiO_2 in ARDS patients on mechanical ventilation.*

Keywords: *Acute respiratory distress syndrome (ARDS), acute lung injury (ALI), Heparin, Nebulized Heparin.*

Introduction:

Acute Respiratory Distress Syndrome (ARDS) is a rapidly developing, secondary inflammatory lung injury caused by various pulmonary and non-pulmonary insults, such as pneumonia, sepsis, and trauma.[1] ARDS affects about 10% of ICU patients and is associated with high mortality, especially among those requiring mechanical ventilation.[2] Diagnosis relies on the Berlin criteria, which use the PaO_2/FiO_2 ratio to classify severity.[3] Despite advances in supportive care, including lung-protective ventilation strategies, mortality remains significant. Pulmonary coagulopathy and fibrin deposition play key roles in ARDS pathogenesis, contribute to lung injury and impaired gas exchange. Heparin acts by inhibiting fibrin formation, neutralizing cytotoxic extracellular histones, and suppressing neutrophil activation and inflammatory cytokine release, thereby reducing both thrombosis and inflammation in the lungs.[4] These combined anticoagulant and anti-inflammatory actions of heparin form the biological rationale for its use in ARDS management, with evidence suggesting it may improve oxygenation and clinical outcomes. [5-6] However, definitive recommendations for nebulized heparin in ARDS are lacking, warranting further investigation.

Methodology:

This was a prospective quasi-experimental unblinded randomized controlled trial conducted in the Non-COVID ICU at Dhaka Medical College Hospital (DMCH) from October 2022 to March 2024. Purposive sampling was used,

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and total 62 patients were enrolled. Ethical approval was obtained from the Ethical Review Committee (ERC) of DMCH before commencing the study. The primary outcome measured was the respiratory index (PaO_2/FiO_2).

Participant Selection: Patients included were adults with ARDS requiring mechanical ventilation, diagnosed by ICU physicians using the Berlin definition. Legal guardians provided informed written consent. Exclusion criteria included heparin sensitivity, current anticoagulation, bleeding disorders, recent intracranial hemorrhage, pregnancy, immunocompromised status, malignancy, COPD, or hepatic encephalopathy with portal hypertension.

Data Collection and Intervention: Patients were allocated to intervention or control groups by coin flip and alternate assignment based on diagnosis time. The randomized procedure involved first assigning the initial ARDS patient by a coin flip, subsequent patients were then assigned alternately to the intervention or control group (odd-even sequence). The intervention group received nebulized heparin (5000 units in 2 ml saline twice daily for 7 days) plus standard ARDS management. The control group received standard ARDS management only, including nebulized budesonide and salbutamol. All patients were managed with pressure assist-controlled ventilation, targeting plateau pressures of 30–35 cm H_2O.

Study Timeline and Evaluation: Data were collected on days 1, 3, 5, and 7 for each patient. Recorded variables included respiratory index (PaO2/FiO2), expiratory tidal volume, platelet count, and APTT. Patients were monitored for clinical bleeding, thrombocytopenia, or prolonged APTT, with discontinuation criteria for adverse events.

Statistical Analysis: Data were entered into SPSS version 23.0. Quantitative data were expressed as mean ± SD, and categorical data as frequency and percentage. Mann-Whitney U, chi-square, and paired t-tests were used for statistical analysis, with significance set at $p<0.05$.

Results:

This prospective randomized controlled trial was conducted in the ICU of the Department of Anesthesia, Pain, Palliative and Intensive Care at Dhaka Medical College. Total 62 patients were ultimately enrolled according to inclusion and exclusion criteria. During the study, two patients from the intervention group died on day two, and two from the control group died on day one and two, all due to septic shock with ARDS and multiple organ dysfunction; one additional intervention group patient was transferred to another hospital on day two, and no patients were extubated before seven days. Thus, final analysis included 28 patients in the intervention group and 29 in the control group, with the main objective being to evaluate whether nebulized heparin improves oxygenation in ARDS patients.

Table I: Distribution of patients by age (N=62) on day 1

Age (in years)	Intervention group (n=31) Frequency (%)	Control group (n=31) Frequency (%)	p-value
≤20	5 (71.4)	2 (28.6)	
21-30	8 (61.5)	5 (38.5)	
31-40	6 (54.5)	5(45.5)	0.349^{ns}
41-50	6 (50)	6 (50)	
51-60	6(31.6)	13 (68.4)	
Mean ± SD	37.09 ± 14.79	43.58 ± 14.41	0.079^{ns}

ns = not significant

Table I shows that most participants in the intervention group (8, 61.5%) were aged 21–30 years, while most in the control group (13, 68.4%) were aged 51–60 years; however, the difference in age distribution and mean age (37.09 ± 14.79 vs 43.58 ± 14.41 years) between the groups was not statistically significant ($p > 0.05$).

Seventeen out of 32 patients (53.1%) in the Intervention group were male, and 16 (53.3%) were male in Control group. The statistical difference is not significant ($p >0.05$). Male Female ratio in intervention group was M:F = 1.15:1 and in control group was M:F = 1:1.07.

Table II: Distribution of patients by cause for ARDS between two groups (N=62 on day one)

Causes of ARDS	Intervention Group (n=31) Frequency (%)	Control Group (n=31) Frequency (%)	p-value
Pneumonia	10 (32.3)	12 (38.7)	0.596^{ns}
Aspiration	6 (19.4)	5 (16.1)	0.740^{ns}
Sepsis	5 (16.1)	6 (19.4)	0.740^{ns}
TRALI	4 (12.9)	3 (9.7)	0.688^{ns}
Acute pancreatitis	4 (12.9)	3 (9.7)	0.688^{ns}
Near drowning	2 (6.5)	2 (6.5)	$>0.99^{ns}$

ns = not significant

Table II shows that majority of the participants in both groups had pneumonia (32.3% vs 38.7%), followed by aspiration (19.4% vs 16.1%), sepsis (16.1% vs 19.4), TRALI and acute pancreatitis (12.9% vs 9.7%).

Table-III: Distribution of patients by mean Respiratory Index (PaO_2/FiO_2) in Two Groups (excluding 4 deaths and one drop out between day one and two: n=57)

Days	Intervention Group (n=28) Mean ± SD	Control Group (n=29) Mean ± SD	p-value
Day 1	147.50 ± 13.65	151.46 ± 13.27	$^{b}0.077^{ns}$
Day 3	157.03 ± 19.14	147.79 ± 13.19	$^{b}0.001^{s}$
Day 5	184.96 ± 24.10	144.77 ± 13.11	$<^{b}0.001^{s}$
Day 7	191.03 ± 30.67	140.99 ± 13.29	$<^{b}0.001^{s}$

ns = not significant; s = significant

Table-III shows that, there was no significant difference regarding the mean respiratory index (PaO_2/FiO_2) on the first day, while it increased significantly in the intervention group on the third, fifth and seventh day.

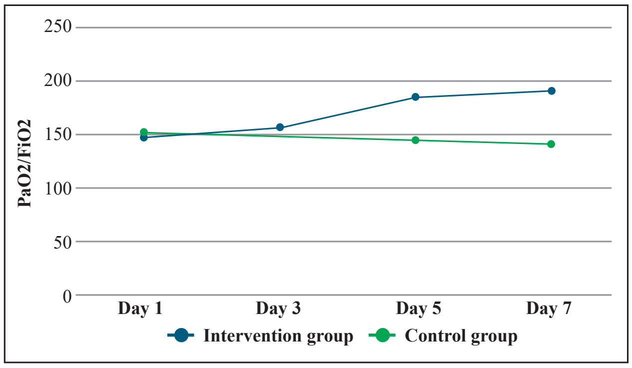

Figure-1: Changes in mean respiratory index over the 7 days of the study

Table-IV: Distribution of patients by Respiratory Index (PaO_2/FiO_2) in Day 1 and Day 7 within group (n=57)

Group	Days		p-value
	Day 1	Day 7	
Intervention Group (n=28)	147.50 ± 13.65	191.03 ± 30.67	<0.001[s]
Control Group (n=29)	151.46 ± 13.27	140.99 ± 13.29	<0.001[s]

s = significant

Table-IV shows that, mean respiratory index significantly increased in intervention group from day 1 to day 7 and mean respiratory index significantly decreased in control group from day 1 to day 7 ($p < 0.05$). Table-V shows that, there was no significant difference of platelet count in two groups. Table-VI shows that, there was no significant difference of APTT in two groups ($p > 0.05$).

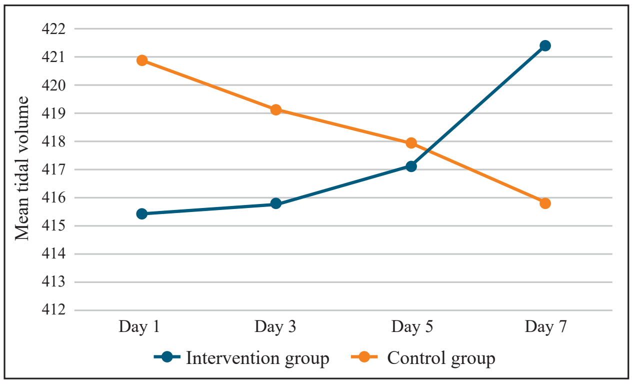

Figure-2: Changes in mean tidal volume (Exhaled tidal volume) over the 7 days of the study

Fig 2 shows that, mean exhaled tidal volume significantly increased from day 1 to day 7 in the intervention group and mean tidal volume significantly decreased from day 1 to day 7 in the control group ($p < 0.05$).

Table-V: Distribution of Patients by Platelet Count (n=57)

Days	Intervention group (n=28) Mean ± SD	Control group (n=29) Mean ± SD	p-value
Day 1	157405.35 ± 7866.48	157495.62 ± 11661.68	0.968[ns]
Day 3	151851.42 ± 12095.11	151767.79 ± 10575.00	0.981[ns]
Day 5	145862.50 ± 14666.62	149585.62 ± 14290.07	0.140[ns]
Day 7	143918.82±17480.25	147452.34±16769.53	0.062[ns]

ns = not significant

Table-VI: Distribution of patients by APTT (n=57)

Days	Intervention group (n=28) Mean ± SD	Control group (n=29) Mean ± SD	p-value
Day 1	28.00 ± 2.02	29.48 ± 3.98	0.227[ns]
Day 3	28.67 ± 2.14	29.87 ± 3.84	0.438[ns]
Day 5	29.28 ± 2.35	30.39 ± 3.74	0.354[ns]
Day 7	30.05 ± 2.41	30.89 ± 3.76	0.701[ns]

ns = not significant

Discussion :

This prospective randomized controlled trial at Dhaka Medical College ICU evaluated the effect of nebulized heparin in ARDS patients, enrolling 62 participants after applying strict inclusion and exclusion criteria; five were excluded due to early death. Baseline characteristics, including age and sex, showed no significant differences between groups, which is consistent with findings from Olapour et al and Ghiasi et al, both of which also reported balanced demographics between intervention and control groups.[7-8] Pneumonia was the leading cause of ARDS in both groups, in line with Dixon et al, who found pneumonia as a predominant risk factor in ARDS cohorts.[6]

The intervention group demonstrated significant improvements in mean tidal volume and respiratory index (PaO_2/FiO_2) from day 1 to day 7, while the control group declined, closely mirroring results several studies, who all reported enhanced oxygenation and pulmonary mechanics with nebulized heparin.[7-9]

No patient died between 3rd day and 7th day of the study period in the present study. These improvements did not translate to statistically significant differences in mortality or extubation before seven days, which is consistent with the CHARLI multicenter trial where nebulized heparin did not improve the primary endpoint of physical function at day 60 but did show secondary benefits such as less progression of lung injury, faster recovery, and more survivors at home.[6]

Platelet count and APTT showed no significant differences between groups and no bleeding complications occurred, supporting the safety profile of nebulized heparin as seen in Ghiasi et al, Mohammad et al, Hakim et al, and a recent meta-analysis by Zhang et al, which all found no increased risk of bleeding with nebulized heparin at standard doses.[5,7-8.10] However, Saleh & Omar observed a significant drop in platelet count with higher heparin doses in polytrauma patients, a finding not replicated in the current or other ARDS-focused studies.[11]

Other multicenter and experimental studies have shown that nebulized heparin reduces pulmonary dead spaces, through inhibition of local fibrin formation, microvascular thrombosis and hyalin membrane formation , contributing to better oxygenation and potentially shorter ventilation duration, though the impact on long-term survival and ICU stay remains uncertain and may depend on patient population, dose, and study design.[12-14] Overall, this study supports the evidence that nebulized heparin improves oxygenation and lung mechanics in ARDS patients without increasing bleeding risk (in the short term), but larger and more homogeneous multicenter trials are needed to clarify its effect on mortality and long-term outcomes. To improve the credibility of our study duration needed to be longer than seven days to assess duration of mechanical ventilation, risk of bleeding and mortality (specially first 28 day mortality).

Limitations: Sample size was smaller than estimated.

Conclusion:

Heparin nebulization likely improves oxygenation in ARDS patients on mechanical ventilation in early days of ICU stay.

Conflict of interest: None

Funding: Self funded

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