

## Original Article



# The effect of endotracheal administration of N-acetyl cysteine and heparin on the level of secretion and partial thromboplastin time in acute respiratory distress syndrome patients under mechanical ventilation: A randomized clinical trial study

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## Abstract

**Background and aims:** Acute respiratory distress syndrome (ARDS) treatment is supportive, and there is no currently approved treatment for it. This study, therefore, aimed to investigate the effect of endotracheal administration of N-acetyl cysteine (NAC) and heparin on the level of secretion and partial thromboplastin time (PTT) in ARDS patients under mechanical ventilation.

**Methods:** In this clinical trial study, 70 patients aged over 18 years (30 women and 40 men) admitted to the intensive care unit were randomly selected following the allocation rule and then divided into two groups (intervention and control). In addition to the routine and available treatments in the ward given to the patients in both groups, the control group also received 10 mL of normal saline every six hours through the endotracheal route, while the intervention group received 500 units of heparin plus 200 mg of NAC dissolved in 10 mL of normal saline every six hours through the same administration route.

**Results:** The mean and standard deviation levels of PTT in the control and intervention groups were  $30.3743 \pm 7.78008$  and  $32.2286 \pm 8.31047$ , respectively, with no significant difference ( $P > 0.05$ ); the volume of secretion on days 1-3 was not significantly different between the two groups, but the difference was statistically significant from day 4 onwards ( $P < 0.05$ ).

**Conclusion:** Taking the combination of NAC and heparin through the endotracheal route was effective in reducing pulmonary secretion, and may have been considered a considerable positive step in providing patients suffering from acute respiratory failure and under mechanical ventilation with supportive care. However, it is recommended that further clinical studies be conducted before arriving at any definitive conclusion.

**Keywords:** Acute respiratory failure, N-acetyl cysteine, Heparin, Mechanical ventilation

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## Introduction

Acute respiratory distress syndrome (ARDS) is a rapidly progressive disease that initially manifests with shortness of breath, tachypnea, and hypoxemia, and then rapidly progresses to respiratory failure (1). In 1994, a national conference of specialists from Europe and the United States published a series of diagnostic criteria for the disease. The main symptoms of ARDS are bilateral pulmonary infiltration, severe hypoxemia, predisposing conditions, and lack of left heart failure evidence (according to clinical conditions or based on obstructive pulmonary arterial pressure of 18 mm or less). These criteria indicate known conditions called acute pulmonary damage (2,3). ARDS treatment is supportive, including mechanical ventilation, stress ulcer prophylaxis, venous thromboembolism, and nutritional support (4).

N-acetyl cysteine (NAC) is traditionally used as a mucolytic agent and has antimicrobial and vasodilation effects (5). It is also applied to prevent kidney damage

during contrast-sensitive imaging, eradicate *Helicobacter pylori*, and prevent deafness associated with the use of gentamicin in dialysis patients; moreover, it is consumed as a dietary supplement (6,7).

NAC is a mucolytic drug that reduces the viscosity of the phlegm through the de-polymerization of mucopolysaccharides and is employed as an inhaler as an adjunct to respiratory ailments that are associated with increased sputum in the catheter chip and cystic fibrosis (8). Campus et al investigated the effects of NAC on preventing acute renal failure and septic lupus erythematosus in mice exposed to mechanical ventilation. In this study, after the administration of 4.3 g/L of water to rats, NAC reduced the incidence of pulmonary edema and acute renal failure, while it improved sepsis in mice by reducing oxidative stress (9). Likewise, Miller et al evaluated the effect of heparin and NAC on the treatment of patients with lung damage due to smoke inhalation with 30 participants under mechanical ventilation and

found that the rate of pulmonary damage to ARDS progressively decreased after the administration of the studied drugs (10).

Heparin is mainly used to prevent and treat intraventricular thromboembolism and pulmonary embolism, prevent mural thrombosis after myocardial infarction, and treat myocardial infarction patients with unstable angina (11). Heparin also reduces interleukin 6 (IL-6), tumor necrosis factor (TNF), and other malignant mediators in the lung (12,13). Zhao et al observed that heparin is capable of suppressing the lethal response and acute lung injury associated with sepsis, supporting the notion that heparin may be a potential therapeutic agent for conditions associated with septic shock (14). Overall, the findings of the studies highlight the effect of heparin on the repair of damaged lung tissues.

In ARDS patients, due to high levels of oxidation and cellular degradation, the administration of antioxidants can slow down the process of degradation and improve the symptoms of patients (15). Given the importance of the issue and the lack of definitive treatment for the disease, the purpose of this study was to investigate the effect of the combination of the endotracheal administration of NAC and heparin on the level of secretion and partial thromboplastin time (PTT) in ARDS patients under mechanical ventilation.

## Materials and Methods

### Design of study and data collection

In this double-blind clinical trial study, 70 patients aged over 18 years (30 women and 40 men) admitted to the intensive care unit were randomly selected following the allocation rule and then divided into two groups (intervention and control) (Figure 1). To conduct this trial, the patient's secretions were collected by a suction device every six hours for seven days and recorded on a checklist. In addition, the patients' PTT levels were recorded concerning their preclinical tests.

### Sample size and sampling

The sample size was calculated at 35 for each group according to the following equation:

$$N = \frac{(s_1^2 + s_2^2)(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2}{(\mu_1 - \mu_2)^2}$$

The inclusion criteria included ARDS (diagnostic criteria for ARDS including acute onset, severe hypoxemia, bilateral pulmonary infiltration, absence of left atrial hypertension, age over 18 years, mechanical ventilation conditions, and admission to intensive care units). Patients were selected if they were referred to the ICU and were eligible for the study. Then, they were divided into

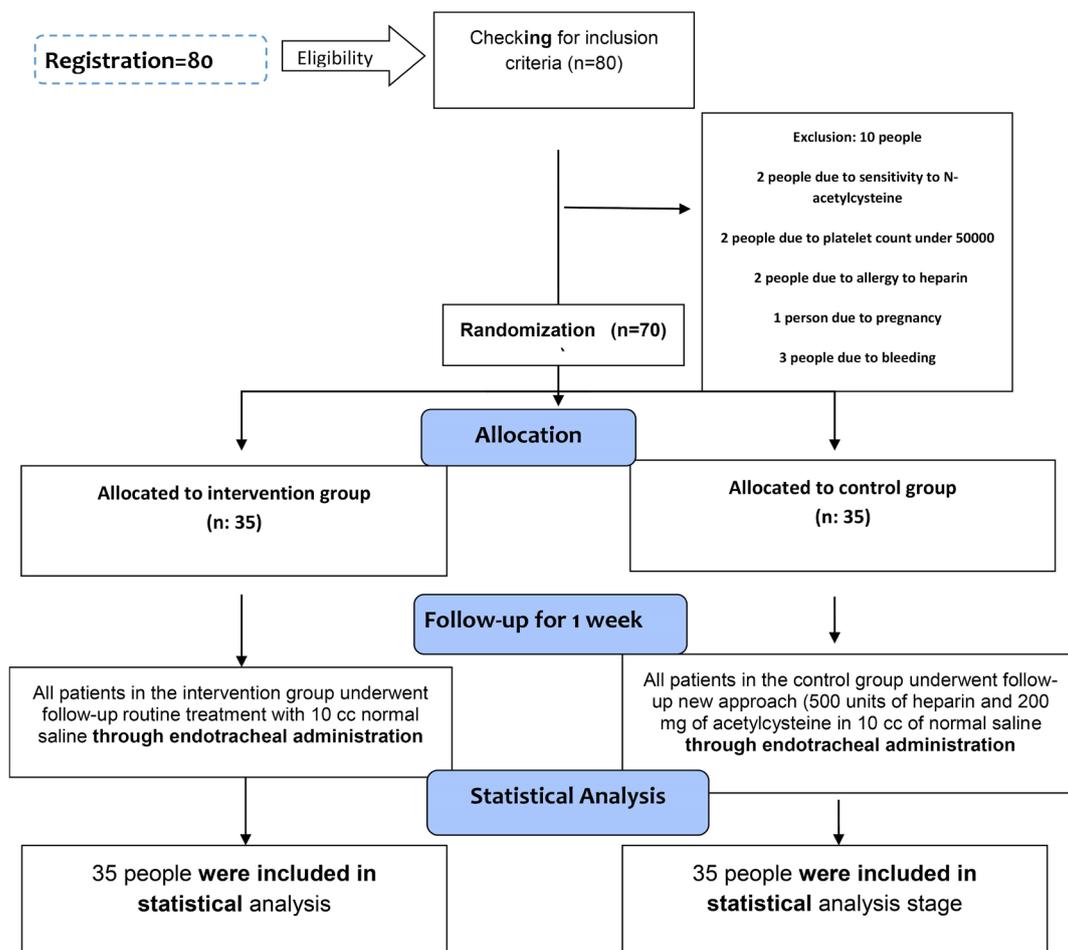


Figure 1. Consort Flowchart of the study.

intervention and control groups based on the allocation rule. Patients who were pregnant, and/or had heparin and NAC, platelet count under 50000, and active bleeding were excluded from the study.

### Procedure

After the approval of the research project at the Research and Technology Deputy of Shahrekord University of Medical Sciences, the solutions were prepared in labeled bottles without specifying their contents. One bottle contained 5000 units of heparin and 200 mg of NAC in 10 mL of normal saline, and the other contained only 10 cc of normal saline. The intervention group received 5000 units of heparin plus 200 mg of NAC every six hours via endotracheal administration plus routine care, but the control group received 10 mL of normal saline every six hours via endotracheal administration plus routine treatment. The protocol was applied for seven days in both groups. After recording data in SPSS (version 17), independent *t* tests and multivariate analysis were used to conduct data analysis (consort chart).

### Results

The participants of the intervention and control groups included 19 (54%) men and 17 (46%) women, as well as 20 (57%) men and 15 (43%) women, respectively. Additionally, the average age of participants in the control and intervention groups was  $56.02 \pm 12.35$  and  $54.91 \pm 15.06$  years, respectively, with no statistically significant difference between the two groups (Table 1).

The two groups were not significantly different in terms of gender and age. The results showed that SOFA criteria in both groups were not significantly different ( $P > 0.05$ , Table 2).

The results indicated that the mean ( $\pm$ SD) PTT levels in the intervention and control groups were  $32.2286 \pm 8.31047$  and  $30.3743 \pm 7.78008$ , respectively, with no statistically significant difference between the two groups ( $P > 0.05$ , Table 3).

As a result, the endotracheal administration of heparin and NAC did not affect the level of PTT in patients.

Based on our results, the level of the volume of discharge on days 1-3 was not significantly different between the two groups ( $P > 0.05$ ), but there was a statistically significant difference from day 4 onwards ( $P < 0.05$ , Table 4).

### Discussion

Our results demonstrated that the endotracheal administration of heparin and NAC to ARDS patients under mechanical ventilation in the ICU did not affect their PTT level. Heparin is an anticoagulant drug and is monitored using a PTT test (17). In addition, it exerts healing effects on pulmonary tissues (18). Miller et al studied the effect of heparin and NAC on the treatment of patients with lung damage due to smoke inhalation; to this end, they selected 30 patients who were under mechanical ventilation. After the administration of the drugs, the results showed that the rate of pulmonary damage due to ARDS represented a progressive decrease (10). Similarly, Dixon et al investigated the effect of neoplastic heparin on acute lung injury. They enrolled 16 patients under mechanical ventilation with acute lung injury to examine the effects and side effects of different heparin doses. Their findings revealed that the use of non-proliferated heparin in these patients was possible. Endotracheal administration did not lead to any serious complications and caused a change in the patients' PTT level only at high doses (18).

In the study by Miller et al, heparin and NAC reduced the tissue damage; in the other study by Dixon et al, heparin cause a change in the patients' PTT only at high doses. Although in our study PTT level was not significantly different between the two groups, the increasing trend was evident in the intervention; however, a definitive conclusion requires further study.

The results indicated that the volume of discharge in the intervention increased from day 4 onwards, which was statistically significant compared with the control group.

NAC is a mucolytic drug that reduces the viscosity of the phlegm through the de-polymerization of mucopolysaccharides and is used as an inhaler as an adjunct to respiratory ailments that are associated with increased sputum in the catheter chip and cystic fibrosis

Table 1. Demographic characterization of participants

Variable		Intervention	Control	P value
Gender	Men	19 (54%)	20 (57%)	0.816
	Women	17 (46%)	15 (43%)	
Age (Mean $\pm$ SD)		54.91 $\pm$ 15.06	56.02 $\pm$ 12.35	0.157

Note. SD: Standard deviation.

Table 2. SOFA criteria in two groups of participants

Variable		Intervention (Mean $\pm$ SD)	Control (Mean $\pm$ SD)	P value
SOFA criteria	Cr	1.43 $\pm$ 1.36	1.33 $\pm$ 1.24	0.746
	PLT	183800 $\pm$ 64361.02218	191685.7143 $\pm$ 66116.55102	0.615
	Bilirubin	1.1249 $\pm$ 0.50005	0.9914 $\pm$ 0.44682	0.243
	PaO <sub>2</sub> /FiO <sub>2</sub>	297.8571 $\pm$ 88.57770	289.4286 $\pm$ 79.32409	0.676
	GCS	9.9657 $\pm$ 2.12242	10.5486 $\pm$ 2.85959	0.336
	MAP	6.1114 $\pm$ 1.62078	5.8371 $\pm$ 1.59283	0.478

Note. SOFA: Sequential organ failure assessment; Cr: Creatinine; PLT: Partial thromboplastin time; GCS: Glasgow coma scale; MAP: Mean arterial pressure; SD: Standard deviation.

**Table 3.** Mean (standard deviation) partial thromboplastin time in intervention and control groups

Variable	Intervention	Control	P-value
PTT	32.2286±8.31047	30.3743±7.78008	0.339

Note. PTT: Partial thromboplastin time.

**Table 4.** Mean (standard deviation) volume of discharge in intervention and control groups

Lung secretion	Intervention	Control	P-value	
Days	Day 1	9.06172±21.4338	7.84784 ± 22.9167	0.477
	Day 2	9.84845±23.0882	8.12564±23.0882	0.607
	Day 3	8.12564±23.0882	7.76936±23.7097	0.07
	Day 4	9.27297±23.4375	7.76936±23.7097	0.04
	Day 5	10.31672±22.8017	14.12785±27.1154	0.05
	Day 6	12.44399±22.5893	13.22549±27.7885	0.01
	Day 7	13.22549±27.7885	9.26222±20.8036	0.01

(8). In an animal study, Zhao et al observed that heparin effectively reduced mortality, improved pathological changes in the lung, suppressed myeloperoxidase, and reduced IL-6, TNF, and other mediators in the lung (14), which is consistent with the finding of the current study.

The findings of a study by Liu et al on the protective effects of NAC on pulmonary injury caused by fat embolism with 36 mice revealed that NAC (150 mg/kg) reduced the pathological and biochemical changes in the lung tissue induced by a fat embolism (19), which is clinically helpful in experimental settings.

Likewise, Amini et al found that the perioperative administration of NAC, vitamin C, and selenium was not effective in preventing acute kidney injury and associated morbidity and mortality after off-pump coronary artery bypass graft. Although the structure of these studies was different from that of our project (20), the results contradict those of our findings. However, Campus et al, focusing on the effects of NAC in preventing acute renal failure and sepsis in mice under mechanical ventilation, reported that after the administration of 4.3 g/L of water to rats, NAC reduced the incidence of pulmonary edema and acute renal failure, while improving sepsis in mice by reducing oxidative stress (9). Elevated secretion due to the combination of NAC and heparin through endotracheal administration in our study is in line with the findings of the above-cited studies, approving the healing effect of NAC and heparin on the lung tissue.

## Conclusion

Although the combination of the endotracheal administration of NAC and heparin was not effective on the level of PTT, the effectiveness of NAC and heparin in increasing pulmonary secretion via endotracheal administration was a highly positive step in the supportive care of the patients with acute respiratory failure under mechanical ventilation, as it can be easily applied by the anesthetic team; however, the confirmation of this result requires further studies in the clinical field.

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## Authors' contribution

FY contributed to data collection/drafting manuscript and supervision of the study. SS contributed to administrative/technical/material support and performed critical revisions for important intellectual content. AH participated in administrative/technical / material support and supervision of the study. Finally, FY contributed to the study design, data analysis, and supervision of the study.

## Conflict of interests

None.

## Ethical approval

The protocol of the study was approved by the Ethics Committee of Shahrekord University of Medical Sciences (ethics code: IR.SKUMS.REC.1396.182 issued on 26 November 2017) and the Iranian Registry of Clinical Trials code (identifier: IRCT20190205042631N1).

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