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Original article

Evaluation Effects of Nebulized Hypertonic Saline and Nebulized Corticosteroids in Patients with Acute Respiratory Distress Syndrome

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Abstract

Background: Acute respiratory distress syndrome (ARDS) is a common clinical syndrome of acute respiratory failure as a result of diffuse lung inflammation and oedema manifested by hypoxemia and stiffness in the lungs. **This study aimed to** assess the efficacy of each of nebulized hypertonic saline and nebulized budesonide in improving respiratory mechanics, hypoxic index (PaO_2/ FiO_2), LIS (Murray score), mortality, duration of intensive care unit, and mechanical ventilation days in acute respiratory distress syndrome patients. **Methods:** This randomized, double-blind, placebo-controlled study was conducted on 90 patients with ARDS. Patients were randomly assigned into 3 equal groups: group I: received standard ICU ARDS care and nebulized hypertonic saline 3% (5ml) /12hr, Group II: received standard ICU ARDS care and nebulized corticosteroids/12hr and Group III: received standard ICU ARDS care and normal saline 0.9% (5ml) nebulizer /12hr as a placebo. **Results**: Regarding the outcome, ICU stay and MV duration were significantly shorter in group II compared to group I and III ($P<0.05$) and was significantly shorter in group I compared to group III ($P<0.05$). The mortality rate was insignificantly different among the studied groups. **Conclusion:** Nebulized corticosteroids improve the outcomes and shorten the ICU stay duration and mechanical ventilation days in patients with ARDS compared to nebulized normal and hypertonic saline. In addition, nebulized budesonide improved oxygenation (PaO_2/ FiO_2), peak inspiratory pressure, and plateau airway pressures.

Keywords: Nebulized; Hypertonic Saline; Corticosteroids; Acute Respiratory Distress Syndrome.

Introduction

Acute respiratory distress syndrome (ARDS) is a common clinical syndrome of acute respiratory failure as a result of diffuse lung inflammation and oedema manifested by hypoxemia and stiffness in the lungs. ARDS represents a significant proportion of patients with a prolonged hospital stay, especially ICU care, with a longer duration of mechanical ventilation (1). ARDS can be precipitated by a variety of causes. The main pathological features are extensive damage to the barriers of lung epithelial and endothelial cells diffuse damage to lung capillaries, enhanced permeability, and the neutrophil influx into the lung tissue, resulting in multiple injuries to organ function leading to respiratory failure and high mortality (2).

Despite progress in elucidating the mechanisms of lung dysfunction during ARDS, the standard of care for managing ARDS patients is supportive care with mechanical ventilation. Unfortunately, mechanical ventilation generates physical forces that can exacerbate lung injury and lead to further lung damage (3). To date, no specific pharmacotherapy has proven effective against ARDS (4). Since inflammation is thought to contribute to the pathogenesis of ARDS, it is rational to explore modulating therapies for this inflammation, provided the adverse effect of such treatment is not excessive (5).

Hypertonic saline (HTS), at a cellular level, decreases alveolar macrophage activation, PMN recruitment, priming and activation, as well as cell surface adhesion molecule expression. Clinically, inhaled HTS is used to treat inflammation in cystic fibrosis (CF) and neonatal bronchiolitis. HTS inhalation has been proposed as a therapy to increase hydration of airway surface liquid in patients with CF. Such results could suggest that nebulized HTS attenuates ARDS by suppressing epithelial inflammation, supporting further research to its use as a novel strategy to treat ARDS (6).

Besides, the role of corticosteroids in ARDS therapy is still controversial. It has been hypothesized that their potent anti-inflammatory effects have benefits in ARDS. However, corticosteroids is still not considered as standard of care in patients with ARDS, and the heterogeneity in responses among patients with ARDS is a possible reason for the uncertain response to this treatment (7).

The purpose of the study was to assess the efficacy of each of nebulized hypertonic saline and nebulized budesonide in improving respiratory mechanics, hypoxic index (PaO_2/ FiO^2), LIS (Murray score), mortality, duration of intensive care unit, and mechanical ventilation days in acute respiratory distress syndrome patients.

Patients and methods

This randomized, double-blind, placebo-controlled study was conducted on 90 patients with ARDS and was carried out in Department of Critical Care Medicine – Benha University Hospitals, during the period from July 2023 to December 2024.

An informed written consent was obtained from the patients. Every patient received an explanation of the purpose of the study and had a secret code number. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University.

Inclusion criteria were adult patients of both sexes aged 18- 60 years old who should fulfill the criteria of ARDS according to Berlin's definition as the following (8): [Lung injury of acute, within 1 week of an apparent clinical insult and with progression of respiratory symptoms, bilateral opacities on chest imaging not explained by other lung pathology, respiratory failure not explained by heart failure or volume overload and decreased PaO_2/FiO^2 ratio: (Mild ARDS: ratio is 201 – 300, Moderate ARDS: 101 – 200 and Severe ARDS: ≤ 100)].

Exclusion criteria were patients age younger than 18 years or older than 60 years, with chronic obstructive pulmonary disease, restrictive respiratory insufficiency, pneumonia, increased intracranial pressure, bronchopleural fistula, heart failure, hypernatremic patients, liver cell failure, end-stage chronic renal failure on hemodialysis, acute myocardial infarction, neuromuscular disease, and evidence of fluid overload confirmed by echocardiogram conducted on patients suspected to have left side disorder.

Randomization: was performed according to computer-generated random number tables, and allocation to treatment group was done using the sealed opaque envelope technique. According to randomization, patients were then randomly assigned into three groups I, II & III as the following: **Group I:** received standard ICU ARDS care and nebulized hypertonic saline 3% (5ml) /12hr, **Group II:** received standard ICU ARDS care and nebulized corticosteroids/12hr and **Group III:** received standard ICU ARDS care and normal saline 0.9% (5ml) nebulizer /12hr as a placebo.

Group I patients (nebulized hypertonic saline group) received hypertonic 3% saline nebulizer for the first three days. Inhaled hypertonic saline 3% was supplied in a dose of 5 ml twice daily at a fixed time that was administered with a jet nebulizer and the fill volume was connected to a compressor with an adequate air flow. Group II patients (nebulized corticosteroids group was receive budesonide nebulizer for the first three days. 1 mg enveloped ampoule in aluminum foil (2 ml suspension available as Pulmicort Respules®) every 12 hours at a fixed time was used in a

pressurized nebulizer, the ampoule was gently shaked and then was squeezed into the nebulizer. Group III received normal saline 0.9% (5ml) nebulizer /12hr for three days as a placebo.

All studied cases were subjected to the following: Detailed history taking, including [Personal history: age, gender, occupation, marital status, present history: complaint, history of present illness onset, duration, progression of symptoms related to ARDS, details of any precipitating factors, presenting complaint related to respiratory distress, past history: chronic medical conditions, previous episodes, and any known drug or environmental allergies, family history of asthma, COPD, ARDS, or any other relevant conditions such as cardiovascular diseases, autoimmune disorders and smoking history]. **Full clinical examination: General examination including [**vital signs (blood pressure, temperature, heart rate and oxygen saturation using pulse oximetry), chest, cardiac, lower limbs and upper limbs, assessment of any alertness or altered mental status, signs of malnutrition or cachexia and signs of accessory muscles using, nasal flaring, tripod position] **and local examination; [**by inspection, palpation, percussion, and auscultation]. **Laboratory investigations [**complete blood count, random blood glucose, C-reactive protein, kidney and liver function tests, urine analysis, arterial blood gas (ABG) analysis, coagulation profile, electrolyte panel, blood cultures, sputum cultures and urine cultures]. **Chest X-ray**: to assess lung pathology, extent of consolidation, or presence of effusions. **Computed tomography (CT)** of the chest.

All patients with ARDS were eligible to receive the standard ICU care for ARDS patients as the following: standard monitoring of vital data by continuous ECG, pulse oximeter monitoring, non-invasive blood pressure monitoring (every hour or earlier), and frequent assessment of respiratory parameters. Arterial blood gases were sampled at least once every day (or more if clinically indicated). Chest X-ray was conducted at least once every day. Patients were ventilated with non-invasive ventilation (or invasive ventilation in case of its contraindication or failure) according to the following criteria: [Resistant hypoxemia to FiO_2 >0.6 with PaO_2 <60mmHg, hypercapnia $PaCO_2$ >50mmHg or with PH <7.2, severe tachypnea with RR >40, disturbed conscious level and hemodynamic disturbance related to respiratory failure (dysrhythmias, hypotension ±30% of basal blood pressure level)]. The patients' ventilator management was done according to lung-protective strategy. The assessment of tolerance of weaning for mechanically ventilated patients was conducted daily, utilizing spontaneous breathing trials if feasible.

The following measurements were obtained:

Arterial blood gas (ABG) before and after each intervention using (GEM

premiere 3500 machine). The main gasometrical variables pH, PO_2, hypoxic index, and PCO_2 were measured in all groups daily and when there is change in patient condition or change in mode or data of mechanical ventilator. Hypoxic index = PO_2 known from ABG/ FiO_2 as applied on the ventilator. Lung mechanics that were estimated every 24 hour and included the following: [Peak inspiratory pressure (PIP (cmH_2O), plateau pressure (Pplt (cmH_2O)), positive end expiratory pressure [PEEP (cmH_2O)] required, airway resistance (cmH_2O/L/S): = (PIP-Pplt / inspiratory flow rate), Static compliance (Cst (ml/cmH2O) = (Exhaled tidal volume)/ (Plateau pressure - PEEP)]. APACHE II score (9) was evaluated. SOFA score that was measured daily from day 1 to day 3 (10). X-ray was done daily and was examined for the presence of lung infiltrates congestion, consolidation, etc. Na and CL daily measurement. Murray score was calculated daily (lung injury score) in the morning. Daily urinary output and cumulative fluid balance at the end of 3rd day.

Nebulized hypertonic saline method:

Nebulized 3% HS (NEBU-dose hypertonic), and the comparator is 0.9% NA (NEBU-dose isotonic). Both are produced by Manufacturing, SL and are used in standard hospital practice. The treatment was delivered through nebulization using oxygen with 5 L of oxygen flow, or through a compressed air-driven jet nebulizer (PARI Boy Junior) every 12 hours for three times a day, until discharge. Supportive care was similar for both groups. Standard therapy includes suctioning secretions and water–electrolyte balance maintenance. All activities were recorded in the medical records.

Nebulized corticosteroids:

Nebulized budesonide was prepared as 1 mg ampoule enveloped in aluminum foil (2 ml suspension available as Pulmicort Respules®) to be used in a pressurized nebulizer (not used in ultrasonic nebulizers) the ampoule was gently shaked and then squeezed into the nebulizer. Nebulization was performed using specific ventilator nebulizer (Aeroneb Pro-Aeroneb professional nebulizer system Aerogen (Ireland) Ltd., Galway, Ireland, SN: AP-1107867) with an oxygen flow of 8 L/min. Nebulization of either budesonide (2 ml, 1 mg concentration) in the group was connected after the Y-connection into the endotracheal tube every 12 h at a fixed time for three successive days. Before each nebulization, recruitment maneuver is done by increasing peak airway so as to get a plateau pressure of 30 cmH2O for 30 s. The nebulization lasted 15 min. for each session and was performed twice daily (at 9 a.m. and 9 p.m.). The anesthetist who was doing nebulization was blinded about the nature of nebulized drug. Furthermore, nebulization was stopped if hemodynamic instability occurred (HR or MAP >or <20% of the prenebulization recorded).

Outcomes:

Primary outcome included a 50% reduction in lung injury score (Murray score) from its original value (D 50%). The score was calculated every 24 hours (6). Secondary outcomes were estimating days on mechanical ventilator, length of stay in ICU, complications and mortality rate.

Approval Code: MS 31-5-2023

Sample size

Patients were randomized by the Closed Envelope Method. The sample size was calculated using G power sample size calculator version 3.1.9. The calculated minimal sample size is 90 patients; these patients were divided to three groups.

Statistical analysis:

Statistical analysis was done by SPSS v28 (IBM©, Armonk, NY, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analyzed by ANOVA (F) test with post hoc test (Tukey). Repeated measurements within the same group were compared by repeated measures ANOVA (F) test. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test. A two tailed P value < 0.05 was considered statistically significant.

Results

In this study, 117 patients were assessed for eligibility, 18 patients did not meet the criteria and 9 patients refused to participate in the study. The remaining 90 patients were randomly allocated into three groups (30 patients in each). All allocated patients were followed-up and analyzed statistically. **Figure 1**

There was an insignificant difference among the studied groups regarding the baseline characteristics (age, sex, weight, height and BMI), risk factors (smoking, HTN, DM), causes of ARDS and APACHE II score. **Table 1**

In groups I, II and III, pH, PCO_2 and HCO_3 were insignificantly different between the 3 readings at 1^{st}, 2^{nd} and 3^{rd} day and each other. There was an insignificant difference among the studied groups regrading pH, PCO_2 and HCO_3 at the 3 readings at 1^{st}, 2^{nd}, and 3^{rd} day. In group I, II, PO_2 was significantly increased at the 3^{rd} day compared to the 1^{st} & 2^{nd} day ($P<0.05$). In group III, PO_2 was insignificantly different among the different days. PO_2 at the 1st day was insignificantly different among the studied groups. At the 2nd day, PO_2 was significantly higher in group II compared to group I and group III ($P=0.046$, <0.001). PO_2 at the 3^{rd} day was significantly higher in group II compared to group I and group III was significantly higher in group I compared to group III ($P<0.001$), In group I, III, FIO_2 was insignificantly different between different readings, while in group while

in group II, FIO_2 was significantly decreased in 2nd day and 3rd day compared to 1st day, FIO_2 at the 1st day was insignificantly different among the studied groups. Meanwhile at the 2nd day, FIO2 was significantly lower in group II compared to group I and group III (P<0.009, <0.002), with no significant difference between group I and group III. At the 3rd day, FIO_2 was significantly lower in group II compared to group I and group III (P<0.003, <0.001), and was insignificantly different between group I and III, PO_2/FiO_2 at the 2nd day was significantly higher in group II compared to group I and group III and was significantly higher in group I compared to group III. PO_2/FiO_2 on the 3rd day was significantly higher in group II compared to group I and group III and was significantly higher in group I compared to group III, **Table 2**

In group I, III PIP was significantly decreased at the 2nd and 3rd day compared to the 1st day (P<0.05), while, in group II PIP significantly decreased at the 3rd day compared to 2nd day. PIP at the 1st, 2nd and 3rd day was significantly lower in group II compared to group I and group III (P<0.05) and was significantly lower in group I compared to group III (P<0.05). In group II, Pplt was significantly decreased at the 2nd and 3rd day compared to the 1st day (P=0.032, <0.001), and was significantly decreased at the 3rd compared to the 2nd day. In group I, and III. Pplt significantly decreased at the 3rd day compared to the 1st day. Pplt at the 1st, 2nd and 3rd day was significantly lower in group II compared to group I and group III (P<0.05) and was significantly lower in group I compared to group III (P<0.05). In group I, III, PEEP was insignificantly different among the three readings. In group II, PEEP significantly decreased at the 2nd day compared to the 3rd day, with no significant difference between the 1st and 3rd day and between the 2nd and 3rd day. PEEP on the 1st day was insignificantly different among the studied groups. PEEP on the 2nd day was significantly lower in group II compared to group I and group III and was significantly lower in group I compared to group III. PEEP on the 3rd day was significantly lower in group II compared to group I and group III, with no significant difference between group I and group III. **Table 3**

In group I, II and III, SOFA score at the 2nd day and 3rd day was significantly decreased compared to the 1st day (P<0.05), and at the 3rd day was significantly decreased compared to the 2nd day (P<0.05), SOFA score at the 1st day was significantly lower in group I and group II compared to group III (P<0.001, <0.001). At the 2nd day, SOFA score was significantly lower in group II compared to group I and group III (P<0.001, <0.001) and was significantly lower in group I compared to group III (P<0.001). At the 3rd day, SOFA score was significantly lower in group II compared to group I and group III (P<0.001, <0.001). Na, CL levels were insignificantly different between the 3 readings and each other's. Serum

electrolytes (Na, CL,) at the 1st, 2nd and the 3rd day were insignificantly different among the studied groups. **Table 4**

Murray score at the 1st day was insignificantly different among the studied groups. At the 2nd day, Murray score was insignificantly different between group I and group II and group I and group III, while Murray score was significantly higher in group III compared to group II, at 3rd day, Murray score was significantly lower in group II compared to group I and group III (P<0.05). In group I and III, Murray score was insignificantly different among the three readings. In group II, Murray score was insignificantly different between 1st day and 3rd day compared to 2nd day while was significantly lower in 3rd day compared 1st day. **Table 4**

Regarding the outcome, ICU stay and MV duration were significantly shorter in group II compared to group I and III (P<0.05) and was significantly shorter in group I compared to group III (P<0.05). The mortality rate was insignificantly different among the studied groups. **Table 5**

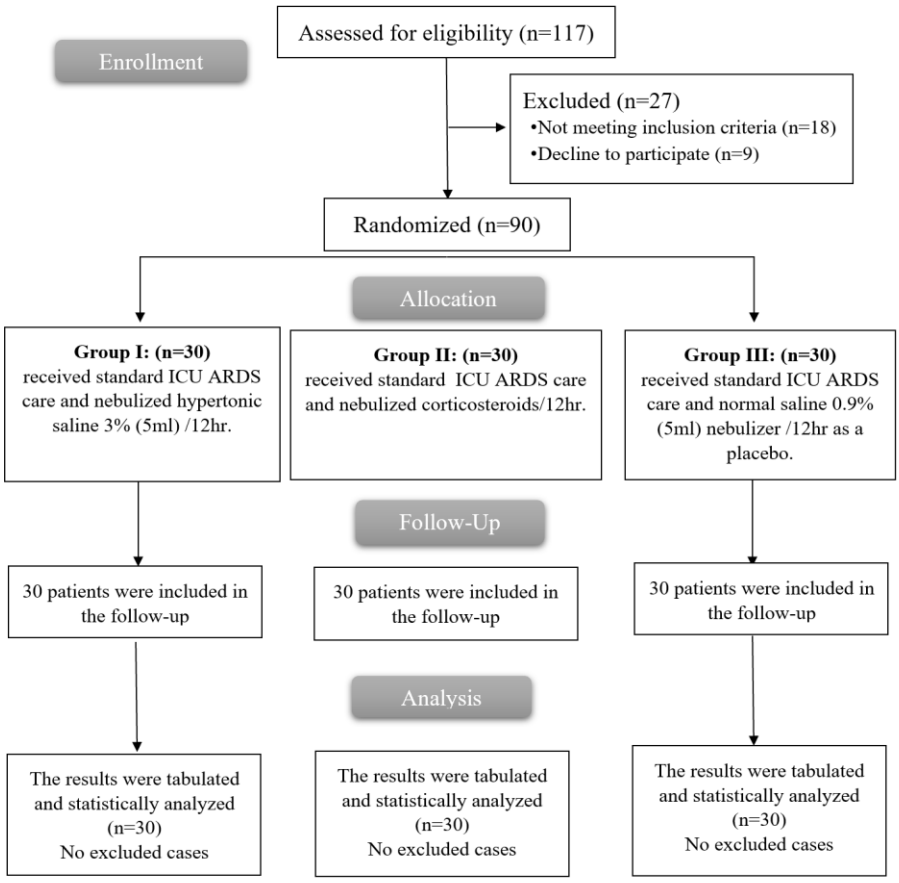

Figure 1: CONSORT flowchart of the enrolled patients

Table 1: Baseline characteristics, risk factors, causes of ARDS and APACHE II score of the studied groups

		Group I (n=30)	Group II (n=30)	Group III (n=30)	P value
Age (years)	**Mean± SD**	38.7 ± 11.54	37.5 ± 12.97	41.2 ± 10.99	0.472
	Range	20 - 55	20 - 60	21 - 60	
Sex	**Male**	13 (43.33%)	15 (50%)	16 (53.33%)	0.732
	Female	17 (56.67%)	15 (50%)	14 (46.67%)	
Weight (Kg)	**Mean± SD**	75.9 ± 9.55	78 ± 10.45	76.9 ± 11.4	0.726
	Range	61 - 94	60 - 94	60 - 95	
Height (m)	**Mean± SD**	1.67 ± 0.04	1.65 ± 0.04	1.66 ± 0.04	0.131
	Range	1.59 - 1.73	1.59 - 1.72	1.59 - 1.72	
BMI (Kg/m^2)	**Mean± SD**	27.3 ± 3.74	28.8 ± 4.04	28.1 ± 5.11	0.406
	Range	21.38- 33.15	21.26- 35.82	20.76- 36.72	
		Risk factors			
Smoking		13 (43.33%)	11 (36.67%)	15 (50%)	0.581
HTN		13 (43.33%)	19 (63.33%)	16 (53.33%)	0.299
DM		14 (46.67%)	10 (33.33%)	13 (43.33%)	0.551
		Causes of ARDS			
Multiple trauma		10 (33.33%)	9 (30%)	11 (36.67%)	0.964
Sepsis		6 (20%)	7 (23.33%)	8 (26.67%)	
Aspiration		4 (13.33%)	4 (13.33%)	5 (16.67%)	
Pancreatitis		6 (20%)	5 (16.67%)	3 (10%)	
Multiple transfusion		4 (13.33%)	5 (16.67%)	3 (10%)	
APACHE II score	**Mean± SD**	21.6 ± 8.51	21.8 ± 8.09	22.3 ± 7.7	0.932
	Range	7-33	7-34	9-34	

BMI: body mass index, HTN: hypertension, DM: diabetes mellitus, APACHE: acute physiology and chronic health evaluation

Table 2: Arterial blood gas of the studied groups

	Group I (n=30)	Group II (n=30)	Group III (n=30)	P value
		pH		
1st day	7.38 ± 0.1	7.36 ± 0.10	7.39 ± 0.09	0.302
	7.2 - 7.56	7.2 - 7.54	7.23 - 7.56	
2nd day	7.39 ± 0.08	7.37 ± 0.08	7.39 ± 0.07	0.769
	7.24-7.54	7.24 - 7.55	7.23 - 7.52	
3rd day	7.37 ± 0.1	7.41 ± 0.07	7.396 ± 0.08	0.470
	7.22-7.55	7.25 - 7.55	7.23 - 7.54	
P value within group	$P^{\#}$= 0.857	$P^{\#}$= 0.382	$P^{\#}$=0.935	
	$P^{\#\#}$= 0.461	$P^{\#\#}$= 0.184	$P^{\#\#}$=0.875	
	$P^{\#\#\#}$= 0.354	$P^{\#\#\#}$= 0.608	$P^{\#\#\#}$= 0.799	
		PCO_2 (mmHg)		
1st day	39.37 ± 6.73	41.39±6.98	38.69 ± 6.14	0.252
	23-52	26.9-54	27.1-58	
2nd day	39.19 ± 6.27	40.26 ±5.97	39.64 ± 5.95	0.791
	29-50	24 - 49.5	24-55	
3rd day	39.65 ± 7.55	39.52 ± 5.7	40.17 ± 6.16	0.920
	27.5-55	25-49.3	23-58	
P value within group	$P^{\#}$=0.915	$P^{\#}$=0.507	$P^{\#}$=0.547	
	$P^{\#\#}$=0.877	$P^{\#\#}$=0.264	$P^{\#\#}$=0.357	
	$P^{\#\#\#}$= 0.795	$P^{\#\#\#}$= 0.624	$P^{\#\#\#}$= 0.738	
		HCO_3 (mEq/L)		
1st day	23.54 ± 3.61	22.34 ± 3.52	24.02±3.87	0.195
	14.8-29	15.6-32	17-31	

2nd day	24.45 ± 3.95 16-30	22.66 ±2.96 18-30	24.2±3.69 16-29.2	0.114	
3rd day	23.71 ± 5.12 14.2-32.6	23.69 ± 3.04 16-31	24.64 ± 2.72 18.8-29.3	0.541	
P value within group	P#=0.357 P##=0.887 P###= 0.531	P#=0.710 P##=0.118 P###= 0.187	P#=0.854 P##=0.475 P###= 0.601		
		PO_2 (mmHg)			
1st day	76.2 ± 14 55-106	80.57 ± 12.42 60-106	74.03 ± 10.28 56-95	0.118	---
2nd day	79.33 ±14.14 58-109	86.67 ± 13.93 59-114	73.7 ± 9.83 55-96	**0.001***	**P1= 0.046*** P2=0.079 **P3<0.001***
3rd day	89.8 ± 24.6 55-163	95.23 ± 20.49 55-146	73.9 ± 13.8 55-100	**<0.003***	**P1= .356*** **P2=0.003*** **P3<0.001***
P value within group	P#=0.392 **P##=0.011*** **P###=0.048***	P#=0.079 **P##=0.001*** **P###=0.063**	P#=0.898 P##=0.966 P###=0.949		
		FIO_2 (%)			
1st day	84.37 ± 11.11 63-100	83.267±10.85 62-100	87.433±10.26 70-100	0.302	---
2nd day	79.267±14.39 52-100	68.533±16.41 50-100	83.933±13.08 60-100	**<0.004***	**P1<0.009*** P2=0.193 **P3<0.002***
3rd day	79.933±15.51 55-100	66.867±17.61 42-100	85.4±13.2 62-100	**<0.003***	**P1<0.003*** P2=0.147 **P3<0.001***
P value within group	P#=0.130 P##=0.208 P###=0.864	**P#<0.001*** **P##<0.001*** P###=0.706	P#=0.254 P##=0.508 P###=0.667		
		PO_2/FiO_2			
1st day	92.7 ± 25.4 64-156.92	98.512±20.75 63.16-163.08	85.68±14.76 58.59-120.27	0.062	
2nd day	104.7 ± 32.12 62-171.15	135.273±41.69 59-219.23	90.386±20.48 55-126.39	**0.001***	**P1=0.003*** P2=**0.043*** **P3<0.002***
3rd day	119 ± 43.82 55-208.97	154.893±52.84 55-261.9	90.341±28.41 55-161.29	**<0.001***	**P1<0.005*** **P2=0.003*** **P3<0.001***
P value within group	P#=0.113 **P##=0.006*** P###=0.154	**P#<0.001*** **P##<0.001*** P###=0.116	P#=0.312 P##=0.429 P###=0.994		

PCO2: partial pressure of carbon dioxide, HCO3: Bicarbonate, FIO2: fraction of inspired oxygen, PO2: partial pressure of oxygen, P#: p value between 1st & 2nd day, P##: p value between 1st & 3rd day, P###: p value between 2nd &3rd day, P1: p value between group 1&2, P2: p value between group 1&3, P3: p value between 2&3,

Table 3: Lung mechanics of the studied groups

	Group I (n=30)	Group II (n=30)	Group III (n=30)	P value	
		PIP (cmH_2O)			
1st day	32.1±3.36 24-37	30.467±3.67 25-37	34.767±2.11 29-37	**<0.001***	**P1= 0.050*** **P2=0.005*** **P3<0.001***
2nd day	29.9±3.53 24-36	28.033±2.97 23-33	32.933±3.89 26-38	**<0.001***	**P1= 0.030*** **P2=0.002*** **P3<0.001***
3rd day	29.067±3.04 24-35	26.167±3.67 22-33	31.5±3.43 25-37	**<0.001***	**P1= 0.017*** **P2=0.016*** **P3<0.001***
P value within group	**$P^{\#}$=0.016*** **$P^{\#\#}$=0.001*** $P^{\#\#\#}$=0.331	**$P^{\#}$=0.007*** **$P^{\#\#}$<0.001*** **$P^{\#\#\#}$=0.034***	**$P^{\#}$=0.027*** **$P^{\#\#}$<0.001*** $P^{\#\#\#}$= 0.136		
		Pplt (cmH_2O)			
1st day	25.1±3.44 20-31	23.5±2.19 21-29	27.167±2.78 20-31	**<0.001***	**P1= 0.035*** **P2=0.013*** **P3<0.001***
2nd day	24.5±2.58 20-30	21.867±2.34 18-26	26.7±2.67 20-30	**<0.001***	**P1<0.001*** **P2=0.001*** **P3<0.001***
3rd day	23.5±2.71 19-28	19.833±2.53 17-26	25.567±2.94 20-30	**<0.001***	**P1<0.001*** **P2=0.005*** **P3<0.001***
P value within group	$P^{\#}$= 0.448 **$P^{\#\#}$= 0.050*** $P^{\#\#\#}$= 0.149	**$P^{\#}$= 0.007 *** **$P^{\#\#}$<0.001*** **$P^{\#\#\#}$= 0.002 ***	$P^{\#}$= 0.510 **$P^{\#\#}$= 0.035*** $P^{\#\#\#}$= 0.124		
		PEEP (cmH_2O)			
1st day	10.433± 2.5 7-15	10.5±2.93 7-15	10.933±2.5 7-15	0.712	---
2nd day	10.633± 2.87 5-15	8.667±2.23 5-12	12.2±2.72 7-16	**<0.001***	**P1= 0.004*** **P2=0.034*** **P3<0.001***
3rd day	10.966± 2.6 8-15	9.2±3.1 5-15	11.433±4.33 5-16	**0.030***	**P1= 0.001*** P2=0.791 **P3=0.038***
P value within group	$P^{\#}$=0.775 $P^{\#\#}$=0.426 $P^{\#\#\#}$=0.643	**$P^{\#}$=0.009*** $P^{\#\#}$=0.101 $P^{\#\#\#}$=0.448	$P^{\#}$=0.066 $P^{\#\#}$=0.586 $P^{\#\#\#}$=0.415		
		Airway resistance (cmH_2O/L/S)			
1st day	14±9.58 2-32	13.933±7.66 4-32	15.2±6.4 4-32	0.788	----
2nd day	10.8±8.15 2-32	12.333±6.54 2-30	12.467±8.35 -6-32	0.650	----
3rd day	11.133±7.25 2-24	12.667±7.54 4-30	11.867±8.34 -4-28	0.744	----
P value within group	$P^{\#}$=0.169 $P^{\#\#}$=0.197 $P^{\#\#\#}$=0.868	$P^{\#}$=0.388 $P^{\#\#}$=0.521 $P^{\#\#\#}$=0.856	$P^{\#}$=0.160 $P^{\#\#}$=0.088 $P^{\#\#\#}$= 0.782		
		Static compliance (Cst (ml/cmH_2O)			
1st day	30.1 ± 9.83 16.67-57.14	33.7 ± 11.94 20-66.67	27.1 ± 9.82 17.39-57.14	0.057	----
2nd day	32.3 ± 12.92 16-80	32.8 ± 9.74 21.05-50	29.7 ± 8.79 18.18-57.14	0.471	----
3rd day	35.2 ± 12.04 21.05-80	45.9 ± 32.98 25-200	33.7 ± 15.56 16.67-66.67	0.075	----
P value within group	$P^{\#}$=0.455 $P^{\#\#}$=0.074 $P^{\#\#\#}$=0.367	$P^{\#}$=0.760 $P^{\#\#}$=0.063 **$P^{\#\#\#}$=0.043***	$P^{\#}$=0.285 **$P^{\#\#}$=0.053*** $P^{\#\#\#}$=0.220		

PIP: peak inspiratory pressure, Pplt: plateau pressure, PEEP: positive end expiratory pressure.

Table 4: SOFA score, serum electrolytes and Murray score of the studied groups

	Group I (n=30)	Group II (n=30)	Group III(n=30)	P value	Post hoc
1st day	10.60 ± 1.28 9 - 13	10.53 ± 1.36 8 - 12	12.67 ± 0.99 11 - 14	**<0.001***	P1= 0.838 **P2<0.001*** **P3<0.001***
2nd day	8.63 ± 1.25 7 - 10	7.0 ± 0.91 5 - 8	9.97 ± 1.4 8 - 12	**<0.001***	**P1<0.001*** **P2<0.001*** **P3<0.001***
3rd day	6.8 ± 1.1 5 - 8	5.33 ± 1.12 4 - 7	7.2 ± 1.13 6 - 9	**<0.001***	**P1<0.001*** P2=0.170 **P3<0.001***
P value within group	**P#<0.001*** **P##<0.001*** **P###< 0.001***	**P#<0.001*** **P##<0.001*** **P###< 0.001***	**P#<0.001*** **P##<0.001*** **P###< 0.001***		
		Serum electrolytes			
		Na + (mEq/L)			
1st day	139.1 ± 2.45 135 - 143	139.37 ± 2.57 136 - 143	140.43 ± 2.94 136 - 145		0.128
2nd day	139.43 ± 3.46 135 - 145	140.33 ± 2.17 136 - 143	139.5 ± 3.64 132 - 145		0.472
3rd day	139.47 ± 2.36 135 - 143	140.07 ± 2.57 136 - 143	139.9 ± 3.39 134 - 145		0.695
P value within group	P#=0.669 P##=0.558 P###=0.965	P#=0.121 P##=0.296 P###=0.666	P#=0.297 P##=0.518 P###= 0.661		
		CL + (mEq/L)			
1st day	102.3 ± 3.15 96 - 108	101.36 ± 2.59 96 - 108	102.3 ± 3.21 97 - 109		0.646
2nd day	101.23 ± 3.49 96 - 106	100.93 ± 3.63 96 - 106	99.5 ± 2.89 96 - 106		0.107
3rd day	100.23 ± 2.86 96 - 106	100.93 ± 3.48 96 - 106	101.07 ± 3.35 96 - 106		0.093
P value within group	P#=0.178 P##=0.078 P###=0.230	P#=0.231 P##=0.387 P###=1.00	P#=0.234 P##=0.475 P###=0.874		
		Murray score			
1st day	2.558±0.52 2-3.5	2.433±0.56 2-3.75	2.642±0.58 1.5-3.5	0.348	---
2nd day	2.55±0.59 1.5-3.75	2.225±0.78 1.25-4	2.692±0.58 1.5-4	**0.019***	P1=0.073 P2=0.308 **P3<0.001***
3rd day	2.483±0.77 1.5-4	1.992±0.85 1-4	2.808±0.59 2.25-4	**<0.039***	**P1<0.030*** **P2=** 0.071 **P3<0.001***
P value within group	P#=0.954 **P##=**0.661 P###=0.708	P#=0.242 **P##=0.021*** P###=0.273	P#=0.741 **P##=**0.274 P###=0.442		

P#: p value between 1st & 2nd day, P##: p value between 1st & 3rd day, P###: p value between 2nd &3rd day, *: statistically significant as p value <0.05, P1: p value between group 1&2, P2: p value between group 1&3, P3: p value between group 2&3.

Table 5: Outcome of the studied groups

	Group I (n=30)	Group II (n=30)	Group III (n=30)	P value	Post hoc
ICU stay (days)	16.233±2.01 13-20	11.933±1.01 10-13	24.467±5.05 17-34	**<0.001***	**P1<0.001*** **P2< 0.001*** **P3<0.001***
MV duration (days)	12.133±2.16 9-16	9.067±1.66 7-13	14.933±2.78 10-19	**<0.001***	**P1<0.001*** **P2<0.001*** **P3<0.001***
Mortality	8(26.67%)	5(16.67%)	8(26.67%)	0.571	---

ICU: intensive care unit, MV: mechanical ventilation, *: statistically significant as p value <0.05, P1: p value between group 1&2, P2: p value between group 1&3, P3: p value between group 2&3.

Discussion

In our study, there was an insignificant difference among the studied groups regarding the baseline characteristics (age, sex, weight, height and BMI). There was an insignificant difference among the studied groups regarding the risk factors including smoking, HTN, DM. The causes of ARDS including multiple traumas, sepsis, aspiration, pancreatitis, and multiple transfusion were insignificantly different among the studied groups.

In accordance with us, Sobhy et al. (6) showed that age, sex, and BMI were insignificantly different between groups receiving hypertonic or normal saline.

According to our study, there was an insignificant difference among the studied groups regarding APACHE II score. In group I, II and III, SOFA score at the 2nd day and 3rd day was significantly decreased compared to the 1st day (P<0.05), and at the 3rd day was significantly decreased compared to the 2nd day (P<0.05). SOFA score at the 1st day was significantly lower in group I and group II compared to group III (P<0.001, <0.001), with no significant difference between group I and group II. At the 2nd day, SOFA score was significantly lower in group II compared to group I and group III (P<0.001, <0.001) and was significantly lower in group I compared to group III (P<0.001). At the 3rd day, SOFA score was significantly lower in group II compared to group I and group III (P<0.001, <0.001), with no significant difference between group I and group III.

In parallel with our findings, Hashemian et al (11) demonstrated that there were no significant differences regarding APACHE II score between the budesonide and control groups.

In the current study, there was an insignificant difference among the studied groups regrading pH, PCO2 and HCO3 at the 3 readings at 1st, 2nd, and 3rd day. In group I and II, PO2 was significantly increased at the 3rd day compared to the 1st & 2nd day (P<0.05), with no significant difference between 1st & 2nd day. In group III PO2 was insignificantly different among the different days. PO2 at the 1st day was insignificantly different among the

studied groups. At the 2nd day, PO2 was significantly higher in group II compared to group I and group III (P=0.046, <0.001), with no significant difference between group I and group III. PO2 at the 3rd day was significantly higher in group II compared to group I and PO2 was significantly higher in group I compared to group III (P<0.001). In group I, III, FIO2 was insignificantly different between different readings, while in group II, FIO2 was significantly decreased in 2nd day and 3rd day compared to 1st day. PO2/FiO2 at the 2nd day was significantly higher in group II compared to group I and group III and was significantly higher in group I compared to group III. PO2/FiO2 on the 3rd day was significantly higher in group II compared to group I and group III and was significantly higher in group I compared to group III.

In agreement with our findings, Mohamed and Meguid (12) found no significant difference between the budesonide and saline (placebo) groups regarding PH (P = 0.214) and PaCO2 (P = 0.651). However, PaO2/FiO2 was significantly higher in budesonide group compared to saline (placebo) group.

According to our findings, in group I and III, peak inspiratory pressure (PIP) was significantly decreased at the 2nd and 3rd day compared to the 1st day (P<0.05), with no significant difference between the 2nd and the 3rd day while, in group II, PIP significantly decreased at the 3rd day compared to 2nd day. PIP at the 1st, 2nd and 3rd day was significantly lower in group II compared to group I and group III (P<0.05) and was significantly lower in group I compared to group III (P<0.05).

In line with our results, Zaytoun et al (13) reported that no significant difference was found between the HTS and control groups at different periods of the study as regard PIP.

Regarding to the present study, in group II, plateau pressure (Pplt) was significantly decreased at the 2nd and 3rd day compared to the 1st day (P=0.032, <0.001), and was significantly decreased at the 3rd compared to the 2nd day. In group I, and III, Pplt significantly decreased at the 3rd day compared to the 1st day, with no significant difference between the 1st and 2nd day and between the 2nd and 3rd day. Pplt at the 1st, 2nd and 3rd day was significantly lower in group II compared to group I and group III (P<0.05) and was significantly lower in group I compared to group III (P<0.05).

In agreement with our findings, Mohamed and Meguid (12) found that Pplt was significantly lower in budesonide group compared to saline (placebo) group (P<0.032). In contrast with our results, Zaytoun et al (13) reported that no significant difference was found between the HTS and control groups at different periods of the study as regard plateau pressure.

In the present study, in group I and III, PEEP was insignificantly different among the three readings. In group II, PEEP significantly decreased at the 2nd

day compared to the 3rd day, with no significant difference between the 1st and 3rd day and between the 2nd and 3rd day. PEEP on the 1st day was insignificantly different among the studied groups. PEEP on the 2nd day was significantly lower in group II compared to group I and group III and was significantly lower in group I compared to group III. PEEP at the 3rd day was significantly lower in group II compared to group I and group III, with no significant difference between group I and group III.

In agreement with our findings, Mohamed and Meguid (12) found no significant difference between the budesonide and saline (placebo) groups regarding PEEP (P = 0.783).

According to our results, in group I, II and III, the airway resistance was insignificantly different between the three readings and each other's. The airway resistance at the 1st, 2nd and the 3rd day was insignificantly different among the three groups. In group I, II and III, the static compliance was insignificantly different between the three readings and each other's. The static compliance at the 1st, 2nd and the 3rd day was insignificantly different among the studied groups.

In line with our results, Zaytoun et al (13) reported that no significant difference was found between the HTS and control groups at different periods of the study as regard the static compliance and airway resistance.

As regard to the current study, in group I, II and III, Na, CL levels were insignificantly different between the 3 readings and each other's. Serum electrolytes (Na, CL,) at the 1st, 2nd and the 3rd day were insignificantly different among the studied groups.

In line with our results, Zaytoun et al (13) reported that there were no significant changes after hypertonic saline nebulizer in the study group during study period regarding serum Na and serum Cl- .

In the present study, Murray score at the 1st day was insignificantly different among the studied groups. At the 2nd day, Murray score was insignificantly different between groups I, II and groups I, III, while Murray score was significantly higher in group III compared to group II. At 3rd day, Murray score was significantly lower in group II compared to group I and group III ($P<0.05$) and was insignificantly different between group I and III. In group I and III, Murray score was insignificantly different among the three readings. In group II, Murray score was insignificantly different between 1st day and 3rd day compared to 2nd day while was significantly lower in 3rd day compared 1st day.

In agreement with our findings, Mohamed and Meguid (12) found no significant difference between the budesonide and saline (placebo) groups regarding Murray score at the 1st day.

In disagreement with us, Sobhy et al. (6) showed that the Murray score from day 1 till day 8 was significantly different between groups receiving hypertonic or normal saline ($p<0.001$). Days that showed a reduction in Murray score (LIS score) by >50% of its initial value (i.e. day zero) are termed as D50%.

Regarding the current study, the outcome, ICU stay, and mechanical ventilation (MV) duration were significantly shorter in group II compared to group I and III ($P<0.05$) and was significantly shorter in group I compared to group III ($P<0.05$). The mortality rate was insignificantly different among the studied groups.

Sakulchit and Goldman (14) investigated the effects of nebulized HTS in the treatment of hospitalized infants with viral bronchiolitis on the respiratory epithelium and the mucociliary transport. The study demonstrated that the duration of hospital stay in cases treated with 3% HTS group showed a 25% reduction, compared to a 0.9% reduction with the NS group.

Conclusion

Our study revealed that nebulized corticosteroids improve the outcomes and shorten the ICU stay duration and mechanical ventilation days in patients with ARDS compared to nebulized normal and hypertonic saline. In addition, nebulized budesonide improved oxygenation (PO2 and FiO2), peak inspiratory pressure, and plateau airway pressures.

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