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RESEARCH ARTICLE

Effect of Bronchoscopy on the Outcome of Patients with Severe Sepsis, Acute Respiratory Distress Syndrome and Complicated by Ventilator Associated Pneumonia from Prolonged Ventilation

Mohamed Gaber Ibrahium Mostafa Allam[1,2]

[1]*Department of Anesthesia, ICU and Pain Management, Faculty of Medicine, Ain Shams University, Cairo, Egypt*
[2]*Consultant Intensivist, King Abd el Aziz Specialist Hospital, Taif, KSA*

Abstract:

Introduction:

65% of patients in Intensive Care Units (ICU) with severe sepsis and/or severe traumatic lung contusion are complicated with pneumonia and respiratory failure, which need long-term ventilation. Sepsis is a common finding in such patients; it is either a cause of ventilator associated pneumonia (VAP) or a complication of VAP. VAP is one of the most common complications of prolonged ventilation. Both diagnostic and therapeutic bronchoscopies could be used to improve the outcome in those patients by controlling septic reactions and improve lung mechanics through the clearing of the small airways from purulent discharge.

Aims of Work:

To evaluate the effect of the use of bronchoscopy in patients with Acute respiratory distress syndrome (ARDS), severe sepsis and complicated by VAP as regards, improve the general condition of those patients, improve lung mechanics, control all signs of both VAP and sepsis, accelerate weaning from the ventilator, shorten the duration of ICU stays and its effect on mortality rate in those patients.

Materials and Methods:

200 patients were selected after 4 days of ventilation because of ARDS due to either severe traumatic lung contusion or a severe lung infection. Those who still showed unresolved ARDS (diagnosed by hypoxic index less than 200, bilateral parenchymatous lung infiltration on the chest X ray, ABG showed PH > 7.30), Severe sepsis diagnosed by >12 SOFA score (Sequential Organ Failure Assessment) and developed VAP diagnosed by >6 CPIS score (clinical pulmonary infection score) were included in two groups of 100 patients in each. Only patients of group B did three bronchoscopies and BAL was sent for culture, while patients of group A continued on the traditional way of management and sputum was sent for culture. Improvement of ARDS & VAP, weaning from ventilation, duration of ICU stay, improvement of one/all parameters of both SOFA & CPIS scores, morbidity, and mortality were recorded and compared within 14 days.

Results:

Patients of group B showed significant improvement in APACHII score (acute physiological assessment and chronic health evaluation score), GCS (Glasgow coma scale), parameters of both SOFA score and CPIS score, hemodynamics parameters, LDH (lactate dehydrogenase), and C-Reactive protein levels. A significantly higher number of patients were weaned from the ventilator and discharged from ICU. There was no significant difference between the two groups regarding the mortality rate.

Conclusion:

The use of bronchoscopy can improve general conditions, control all signs of severe sepsis, VAP, improve lung mechanics, improve ARDS, accelerate weaning from the ventilator, and shorten the ICU stay but has no effect on mortality rate in those patients with severe sepsis with ARDS and complicated by VAP from prolonged ventilation.

Clinical Trial Registration Number: My study is already registered in the clinical trial, and all the information is present in this study. The clinical trial number is NCT04553367, and is registered by my name.

Keywords: Bronchoscopy, Sepsis, ARDS, Patients, LDH, ventilation.

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1. INTRODUCTION

Healthcare-associated pneumonia represents up to 27% of all ICU infections, and those types of pneumonia could also be a complication of severe lung contusion due to chest trauma. Of that pneumonia, 90% occur in mechanically ventilated patients, costing approximately 10,962.5 United States dollars/year [1, 2]. Severe sepsis could be a cause of ventilator-associated pneumonia (VAP) or may be one of its major systemic complications [1 - 3]. 65% of patients with sepsis are associated with pneumonia, especially VAP. Both conditions are frequently found in most of the ventilated ICU patients. Mortality rate for VAP with sepsis is 18%–30% [2 - 4]. Some evidence was raised by many researchers that diagnostic bronchoscopy may improve VAP related outcomes and thus improve or even stop the cascade of septic reaction, although this is also disputed in the literature [2 - 5]. But still source control through the removal of mucus plugs from the endotracheal tube and small airway could improve outcomes and put this maneuver as one of the respectable lines of management of VAP with sepsis [6, 7]. On the basis of previous reports, our hospital established the use of the aggressive bronchoscopic toilet for VAP patients with severe sepsis as a standard line of management. We have developed an informal, clinician-driven protocol involving bronchoscopic diagnosis with broncho-alveolar lavage (BAL), and serial therapeutic bronchoscopies for patients believed to be at high risk. The number of serial bronchoscopies is based on the appearance of the airway and the volume of purulent secretions in the previous evaluation. Patients, who were believed by the treatment team to be at high risk for a respiratory decline from VAP and showed an aggressive septic reaction, especially those who had thick secretions or difficulty clearing their airways, were generally treated in this manner. Based upon our experience with this practice, we conducted this study to monitor the effect of this maneuver in lowering mortality in those with VAP and severe sepsis, improve clinical resolution of VAP in septic patients, accelerate weaning from the ventilator, control the cascade of sepsis and shorten the duration of ICU stay.

2. MATERIALS AND METHODS

This prospective cohort study was conducted on 200 patients admitted to our intensive care unit in King Abdul-Aziz Specialized Hospital, Taif, KSA, between July 2020 and December 2021 in the surgical ICU. King Abdul-Aziz Specialized Hospital research and Ethical committee approved the project and written consent from all patients was taken from the first-degree relatives of the patients.

Inclusion criteria: Adult patients aged >18-<65 years, those who were intubated and ventilated due to ARDS with a severe lung infection and/or traumatic lung contusion, those who had hypoxic index less than 200 [PO_2/FIO_2 less than 200], and had bilateral parenchymatous lung infiltration on their chest X ray, those who showed PH > 7.30 on their ABG, and those who had respiratory rate >25 min. All those patients were ventilated for 4 days with CMV with respiratory rate 12/min, PEEP 5 cm/ H_2O, FIO_2 adjusted to maintain their arterial oxygen saturation above 90%, and sedated with both fentanyl and midazolam intravenous infusion to adjust their sedation level to achieve Richmond Agitation-Sedation Scale (RASS) -2 to -3 as illustrated in Table **1** [8]. All patients received broad spectrum antibiotics in the form of meropenem 1 gm slowly intravenous every 8 hours in this period (four days). Feeding started on the second day of ventilation to all patients through a feeding pump at a rate of 70 ml insure plus (Abbot company) with 1.47 kilo-calorie/ml to supply patients with approximately 2500 kilo-calorie in 24 hours calculated by approximately 35 kilo-calorie/kg. The 5 points of bundle for VAP prevention were strictly applied to all patients: Elevation of the head of the bed 30º to 45º, daily evaluation for possible extubation, the use of endotracheal tubes with subglottic secretion drainage, oral care with oral antiseptics, initiation of safe enteral nutrition within 24-48 hours from ICU admission and ventilation.

200 patients included in our study from those who completed ventilation for 4 days and showed no improvement and still had unresolved ARDS diagnosed in our study (PO_2/FIO_2 less than 200, bilateral parenchymatous lung infiltration on the chest X ray, ABG showed PH > 7.30), had severe sepsis which diagnosed in our study by >12 on SOFA score [1, 9], developed VAP as a complication from mechanical ventilation which diagnosed in our study by > 6 on CPIS score [10], were randomly allocated in two groups, 100 patients in each. The randomization sequence was created using Excel 2007 (Microsoft, Redmond, WA, USA) with a 1:1 allocation using random block sizes of 2 and 4 by an independent doctor. In this way, sequence generation and type of randomization can be expressed at the same time.

All patients selected underwent a percutaneous tracheostomy on the same day of selection.

Severe sepsis was documented in our study by > 12 on Sequential Organ Failure Assessment (SOFA) score illustrated in Table **2**. While VAP was documented in our study by >6 on CPIS score illustrated in Table **3**. Patients of group A continued on the conventional way of management mentioned previously. Bronchoscopies were done three times for patients of group B only. These bronchoscopies were done on the first, sixth and eleventh day of the studied periods. Bronchoscopies were done with the following precautions: The treating team used a flexible bronchoscopy (Olympus BF-160) adult size for this maneuver, all patients were kept sedated by both midazolam and fentanyl infusion to get sedation score (RASS-2/-3), FIO_2 was increased to 100% during the procedure, xylocaine spray 10% was used (Astra Zeneca company), two puffs were applied in each nostril before the rubber tube of the bronchoscope was introduced into the nose of those patients. Patient's head was kept elevated at 40 degrees during the procedure. The ventilator was adjusted on CMV (controlled mechanical ventilation mode) with same previous parameters mentioned before. During the procedure, four syringes of 10 ml of normal saline (NS) were injected through the bronchoscopy into the airways for washing, followed by suction of that saline in order to keep the airways clean and dry. The fluid sucked after injection of the first 10 ml NS (BAL) was sent for qualitative culture. Monitoring of patients during the procedure was done by using SPO_2, non-invasive blood pressure measurement, and electro cardiac gram.

* Address correspondence to this author at the Department of Anesthesia, ICU and Pain Management, Faculty of Medicine, Ain Shams University , Cairo, Egypt; E-mail: mgaberallam@yahoo.com

Table 1. Shows Richmond agitation-sedation scale [9].

Score Term Description
+4 Overtly Combative and Violent to Staff
+3 Very agitated and removes tube(s) or catheter(s)
+2 Agitated and fights ventilator
+1 Anxious but no aggressive movements
0 Alert and calm
−1 Drowsy but has sustained awakening (eye contact to voice >10 s)
−2 Light sedation and awakens with eye contact to voice (<10 s)
−3 Moderate sedation with eye opening to voice (but no eye contact)
−4 Deep sedation with no response to voice, but movement or eye opening to physical stimulation
−5 Unarousable with no response to voice or physical stimulation

Table 2. Shows SOFA score [1, 10].

SOFA Score	1	2	3	4
Respiration: PaO_2/FIO_2 (mm Hg)	<400	<300	<220	<100
Coagulation profile: Platelets count in $10^3/mm^3$	<150	<100	<50	≤20
Liver: Bilirubin (mg/dL)	1.2-1.9	2.0-5.9	6.0-11.9	≥12.0
Cardiovascular: Hypotension	MAP <70	Dopamine ≤5 or dobutamine (any)	Dopamine >5 or norepinephrine ≤0.1	Dopamine >15 or norepinephrine >0.1
CNS:Glasgow Coma Score indicator for septic encephalopathy	13-14	10-12	6-9	<6
Renal: Creatinine (mg/dL) or urine output (UOP) (mL/d)	1.2-1.9	2.0-3.4	3.5-4.9 or UOP<500	≥5.0 or UOP <200

Abbreviations: MAP: mean arterial blood pressure, PaO_2: partial pressure of oxygen in arterial blood.

Table 3. Shows CPIS score [11].

CPIS	0	1	2
Tracheal secretion	Rare	Abundant	Abundant & purulent
Chest X-ray infiltrate	No infiltrate	Diffuse	Localized
Temperature ºC	≥ 36.5 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39 or ≤ 36
Leucocytic count per mm^3	≥ 4000and ≤ 11000	< 4000 or > 11000	< 4000 or > 11000 +band form ≥ 500
Hypoxic index PaO_2/FIO_2 mmHg	>240 or ARDS	--	≤ 240 and no evidence of ARDS
Microbiology	Negative	--	Positive

Note: Exclusion criteria: post-cardiac arrest, patients with systemic diseases such as diabetes and hypertension.

Table 4. Demographic data of the studied patients' groups.

-	Group A		Group B		*P value*
Age Group	**(n=100)**	**%**	**(n=100)**	**%**	
18-22years	35	35.0	32	32.0	0.905 N.S.
23-35	27	27.0	28	28.0	
36-45	28	28.0	27	27.0	
46-50	10	10.0	13	13.0	
Sex	**(n=100)**	**%**	**(n=100)**	**%**	***P value***
Male	75	75.0	80	80.0	0.553 N.S.
Female	15	15.0	20	20.0	
Causes of Ventilation in our Study	**(n=100)**	**%**	**(n=100)**	**%**	***P value***
COPD with bronchitis	28	28.0	30	30.0	0.233 N.S.
Aspiration pneumonia.	12	12.0	9	9.0	0.125 N.S.

(Table 4) contd.....

-	Group A		Group B		*P value*
Age Group	**(n=100)**	**%**	**(n=100)**	**%**	
Severe lung contusion.	43	43.0	45	45.0	0.422 N.S.
Bronchiectasis	17	17.0	16	16.0	0.725 N.S.

Abbreviation: N.S. non-significant.

The duration of the study was selected to be 2 weeks and the evaluation of all patients in both groups was done in three periods, at the end of the first 5 days, at the end of the second 5 days, and at the end of the last 4 days.

All patients in both groups were followed by APACHII score (acute physiological assessment and chronic health evaluation), GCS, parameters of both SOFA score and CPIS score, hemodynamic parameters (the use of inotropes and the stability of mean arterial blood pressure during the studied period) and laboratory parameters by measuring both LDH level and C-Reactive protein level.

APACHII score, GCS, core temperature (one parameter in CPIS score), and hemodynamic stability were used as indicators for general condition improvement. While controlling all parameters of both SOFA score and CPIS score used as indicators for sepsis control. Both compliance measurements and responses to recruitment maneuvers were used as an indicator for lung mechanics improvement. Recruitment maneuver is considered a clinical test of lung compliance and starts to increase the peak inspiratory pressure to 40 cm/H_2O for 40 seconds and observe the saturation (SpO2) if improved to more than 95% considered responders in our study) [12]. Both hypoxic index and parenchymatous lung infiltrate in the chest X-ray were used as indicators of ARDS improvement.

Both LDH and C-reactive protein were used as a laboratory indicator to decrease lung tissue destruction and recovery of lung tissue from both VAP and sepsis. Results of both enzymes were collected and compared among all patients in both groups in the studied period. The number of patients weaned from the ventilators in both groups was recorded and compared. Extubated patients stayed in the ICU for 24 hours for observation and were then discharged from the ICU. The number of discharged patients were recorded and compared.

Three microbiological results were collected from all patients during the studied period, at the end of the first five days, at the end of the second five days and the last one collected at the end of the studied period to confirm the bacteriological cure. Microbiological results were collected from patients of group A through qualitative sputum. While microbiological results were collected from patients of group B through BAL.

If one/all measured indicators showed no improvement in any patient in both groups during the studied period, this considered morbidity documented and compared between the two groups. A number of patients who failed to be weaned from the ventilator during the studied period, considering morbidity, were also documented and compared between the two groups. A number of patients discharged from the ICU within the studied period were recorded and compared between the two groups.

2.1. Statistical Analysis of the Data

Data were fed to the computer using IBM SPSS software package version 21.0.

Qualitative data were described using numbers and percentages. Comparison between different groups regarding categorical variables was tested using the Chi-square test.

2.2. Chi-square Test

It tests the association between qualitative nominal variables, and it is performed mainly on frequencies. It determines whether the observed frequencies differ significantly from the expected frequencies.

2.3. Sample Size

The sample size was calculated based on a previous study and by using Med Calc statistical software, assuming the area under ROC to be 0.80, an alpha of 0.05, and power of study 90.0%. A typical advice is to reject the null hypothesis H0 if the corresponding p-value is smaller than 0.05. A minimum sample size required for this study was 200 patients, 100 patients in each group. The number of expired patients from the two groups was collected and compared, then the new number of patients was recalculated after the expired patients were subtracted from the total sample size giving us a new sample size. It was 3 times in the study: at the end of the first 5 days, at the end of the second 5 days, at the end of the last four days. The significant P value is marked as (*) beside the significant number in our study.

3. RESULTS

Table **4** represents the demographic data of patients in both groups and shows no significant difference between the two groups regarding age, sex, and causes of ventilation included in our study.

Table **5** compares the mortality rates in both groups all over the studied duration and shows non-significant differences between the two groups in all studied durations as (5, 5 and 4 patients) died at the end of 5,10,14 days consecutively from group A while (4, 5and 4 patients) died from group B at the same time of the study.

Table **6** compares APACH II scores of patients in both groups all over the studied duration and shows significant improvement in that score in patients of group B in all studied duration as (35,54 and 65 patients) score <15 at the end of 5, 10, and 14 days consecutively, while (9, 24 and 26 patients) in group A achieved the same score at the same time of the study.

Table 5. Mortality recorded in both groups during the studied period.

Mortality Reported	Group A (n=100)		Group B (n=100)		*P value*
End of 1ST 5 Days	**NO**	**%**	**NO**	**%**	**0.985 N.S.**
	5	5.0	4	4.0	
End of 2nd 5 Days	5	5.0	5	5.0	1.0 N.S.
End of 3rd 4 Days	4	4.0	4	4.0	1.0 N.S.
Total mortality	14	14.0	13	13.0	0.93 N.S.

Abbreviation: N.S. non-significant.

Table 6. APACHII scores for all patients in the studied period.

APACHII	Group A		Group B		*P value*
End of the 1st 5 Days	**(n=95 Patients)**	**%**	**(n=96 Patients)**	**%**	
>25	38	40.0	15	15.6	
25-21	31	32.6	20	20.8	0.001*
20-15	17	17.9	26	27.1	
<15	9	9.5	35	36.5	
End of the 2nd 5 Days	**(n=90 Patients)**	%	**(n=91 Patients)**		
>25	25	27.8	15	27.5	
25-21	21	23.3	20	23.1	0.0125*
20-15	20	22.2	20	22.0	
<15	24	26.7	36	27.5	
End of the 3rd 4 Days	**(n=86 Patients)**	**%**	**(n=87 Patients)**		
>25	19	22.1	5	5.7	
25-21	20	23.3	7	8.0	0.0001*
20-15	21	24.4	10	11.5	
<15	26	30.2	65	74.7	

* Represent Significant P value.

Table **7** compares the GCS scores of patients in both groups all over the studied duration and shows significant improvement in that score in patients of group B in all studied durations as (36, 64 and 75 patients) had a score >12 at the end of 5, 10, and 14 days consecutively, while (10, 35 and 51 patients) in group A achieved the same score at the same time of the study.

Table **8** compares MAP of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied durations as (34, 60 and 74 patients) had MAP >95 mmHg at the end of 5,10,14 days consecutively, while (11, 25 and 50 patients) in group A achieved the same MAP at the same time of the study.

Table **9** compares the bilirubin levels of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied duration as (40, 67 and 72 patients) had bilirubin <1.9 mg/dL at the end of 5, 10 and 14 days consecutively, while (19, 34 and 48 patients) in group A achieved same bilirubin level at the same time of the study.

Table 7. The GCS of all patients in the studied period.

Conscious Level by GCS	Group A		Group B		*P value*
End of the 1st 5 Days	**(n=95 Patients)**	**%**	**(n=96 Patients)**	**%**	0.0001*
<6	40	42.1	15	15.6	
6-9	30	31.6	20	20.8	
10-12	15	15.8	25	26.0	
>12	10	10.5	36	37.5	
End of the 2nd 5 Days	**(n=90 Patients)**	**%**	**(n=91 Patients)**		0.003*
<6	15	16.7	6	6.6	
6-9	18	20.0	9	9.9	
10-12	22	24.4	12	13.2	
>12	35	38.9	64	70.3	

(Table 7) contd.....

Conscious Level by GCS	Group A		Group B		*P value*
End of the 3rd 4 Days	**(n=86 Patients)**	**%**	**(n=87 Patients)**		0.001*
<6	9	10.5	0	0.0	
6-9	10	11.6	4	4.6	
10-12	16	18.6	8	9.2	
>12	51	59.3	75	86.2	

Note:* Represent Significant P value

Table 8. Mean arterial blood pressure of all patients in the studied period.

MAP by mmHg	Group A		Group B		*P value*
End of the 1st 5 Days	**(n=95 Patients)**	**%**	**(n=96 Patients)**	**%**	0.0001*
<70 or with inotrope	43	45.3	18	18.8	
70-85	27	28.4	20	20.8	
86-95	14	14.7	24	25.0	
>95	11	11.6	34	35.4	
End of the 2nd 5 Days	**(n=90 Patients)**	**%**	**(n=91 Patients)**		0.0001*
<70 or with inotrope	15	16.7	6	16.7	
70-85	25	27.8	10	27.8	
86-95	25	27.8	15	27.8	
>95	25	27.8	60	27.8	
End of the 3rd 4 Days	**(n=86 Patients)**	**%**	**(n=87 Patients)**		0.0005*
<70 or with inotrope	10	11.6	0	0.0	
70-85	11	12.8	3	3.4	
86-95	15	17.4	10	11.5	
>95	50	58.1	74	85.1	

* Represent Significant P value

Table 9. Bilirubin levels in all patients in the studied period.

Bilirubin level in mg/dL	Group A		Group B		*P value*
End of the 1st 5 Days	**(n=95 Patients)**	**%**	**(n=96 Patients)**	**%**	
≥12	30	31.6	12	12.5	
6-11.9	24	25.3	19	19.8	0.011*
2-5.9	22	23.2	25	26.0	
≤1.9	19	20.0	40	41.7	
End of the 2nd 5 Days	**(n=90 Patients)**	**%**	**(n=91 Patients)**		
≥12	15	16.7	4	4.4	
6-11.9	18	20.0	5	5.6	0. 001*
2-5.9	23	25.6	15	16.7	
≤1.9	34	37.8	66	73.3	
End of the 3rd 4 Days	**(n=86 Patients)**	**%**	**(n=87 Patients)**		
≥12	11	12.8	0	0.0	
6-11.9	12	14.0	4	4.6	0.005*
2-5.9	15	17.4	11	12.6	
≤1.9	48	55.8	72	82.8	

Note: * Represent Significant P value.

Table **10** compares the creatinine levels of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied durations as (44, 65 and 75 patients) had creatinine <1.9 mg/dL at the end of 5,10,14 days consecutively, while (20,32and 45 patients) in group A achieved same creatinine level at the same time of the study.

Table **11** compares the platelets count of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied durations as (66, 78 and 82 patients) had platelets > 100.000 at the end of 5, 10, and 14 days consecutively, while (35, 43 and 54 patients) in group A achieved same platelets count at the same time of the study.

Table **12** compares the nature of the tracheal secretion of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied durations as (55, 71 and 83 patients) had normal tracheal secretion at the end of 5, 10 and 14 days consecutively, while (19, 34 and 48 patients) in group A achieved same tracheal secretion at the same time of the study.

Table 10. Creatinine levels in all patients in the studied period.

Creatinine Level in mg/dL	Group A		Group B		*P value*
End of the 1st 5 Days	**(n=95 Patients)**	**%**	**(n=96 Patients)**	**%**	
≥5	28	29.5	12	12.5	
4.9-3.5	25	26.3	17	17.7	0.007*
3.4 -2	22	23.2	23	24.0	
≤1.9	20	21.1	44	45.8	
End of the 2nd 5 Days	**(n=90 Patients)**	**%**	**(n=91 Patients)**		
≥5	11	12.2	5	5.6	
4.9-3.5	19	21.1	8	8.9	0.003*
3.4 -2	28	31.1	13	14.4	
≤1.9	32	35.6	65	72.2	
End of the 3rd 4 Days	**(n=86 Patients)**	**%**	**(n=87 Patients)**		
≥5	11	12.8	0	0.0	
4.9-3.5	12	14.0	3	3.4	0.002*
3.4 -2	18	20.9	9	10.3	
≤1.9	45	52.3	75	86.2	

Note: * Represent Significant P value

Table 11. Platelet count in all patients in the studied period.

Platelets count in 10^3 /microL	Group A		Group B		*P value*
End of the 1st 5 Days	**(n=95 Patients)**	**%**	**(n=96 Patients)**	**%**	0.001*-
≤20	16	16.8	6	6.3	
21-<50	20	21.1	10	10.4	
50-≤100	24	25.3	14	14.6	
>100	35	36.8	66	68.8	
End of the 2nd 5 Days	**(n=90 Patients)**	**%**	**(n=91 Patients)**		0.001*
≤20	4	4.4	0	0.0	
21-<50	18	20.0	5	5.6	
50-≤100	25	27.8	8	8.9	
>100	43	47.8	77	85.6	
End of the 3rd 4 Days	**(n=86 Patients)**	**%**	**(n=87 Patients)**		0.002*
≤20	7	8.1	0	0.0	
21-<50	8	9.3	1	1.1	
50-≤100	17	19.8	4	4.6	
>100	54	62.8	82	94.3	

Note: * Represent Significant P value.

Table 12. The number and percentage of patients who had either a score of 0,1 or 2 for all CPIS parameters in the studied period.

	Group A (n=95 Patients)						Group B (n=96 Patients)						*P value*
CPIS Score	**0**		**1**		**2**		**0**		**1**		**2**		
End of1ST 5 Days	No	%	No	%	No	%	No	%	No	%	No	%	
Tracheal secretion	20	21.1	35	36.8	40	42.1	55	57.3	26	27.1	15	15.6	0.001*
Chest x-ray infiltrate	23	24.2	40	42.1	32	33.7	61	63.5	19	19.8	16	16.7	0.001*
Temperature	25	26.3	51	53.7	19	20.0	50	52.1	40	41.7	6	6.3	0.002*
Leucocytic count/mm^3	27	28.4	50	52.6	18	18.9	51	53.1	38	39.6	7	7.3	0.009*

(Table 12) contd.....

	Group A (n=95 Patients)						Group B (n=96 Patients)						*P value*
CPIS Score	**0**		**1**		**2**		**0**		**1**		**2**		
$PAO2/FIO_2$ mmHg	57	60.0	----	----	38	40.0	69	71.9	----	----	27	28.1	0.046*
Microbiology	59	62.1	----	----	36	37.9	75	78.1	----	----	21	21.9	0.045*
End of 2nd5 Days	**Group A (n=90 Patients)**						**Group B (n=91 Patients)**						
	NO	%	**NO**	%	**NO**	%	NO	%	NO	%	NO	%	
Tracheal secretion	37	41.1	31	34.4	22	24.4	71	78.0	19	20.9	1	1.1	0.001*
Chest x-ray infiltrate	38	42.2	32	35.6	20	22.2	75	82.4	13	14.3	3	3.3	0.001*
Temperature	42	46.7	29	32.2	19	21.1	77	84.6	14	15.4	0	0.0	0.001*
Leucocytic count/mm^3	35	38.9	33	36.7	22	24.4	70	76.9	21	23.1	0	0.0	0.001*
$PAO2/FIO_2$ mmHg	61	67.8	----	----	29	32.2	76	83.5	----	----	15	16.5	0.039
Microbiology	62	68.9	----	----	28	31.1	80	87.9	----	----	11	12.1	0.007*
End of 3rd 4 Days	**Group A (n=86 Patients)**						**Group B (n=87 Patients)**						
	0		**1**		**2**		**0**		**1**		**2**		
	NO	%	NO	%	NO	%	NO	%	NO	%	NO	%	
Tracheal secretion	59	68.6	19	22.1	8	9.3	83	95.4	4	4.6	0	0.0	0.006*
Chest x-ray infiltrate	65	75.6	12	14.0	9	10.5	85	97.7	2	2.3	0	0.0	0.003*
Temperature	60	69.8	17	19.8	9	10.5	81	93.1	5	5.7	1	1.1	0.003*
Leucocytic counts/mm^3	63	73.3	15	17.4	8	9.3	83	95.4	4	4.6	0	0.0	0.006*
PAO_2/FIO_2 mmHg	72	83.7	----	----	14	16.3	83	95.4	----	----	4	4.6	0.042*
Microbiology	70	81.4	----	----	16	18.6	86	98.9	----	----	1	1.1	0.0005*

Note: * Represent Significant P value

Table 13. The course of lung compliance in all patients in the studied period.

Lung compliance in ml/1cmH_2O	**Group A**		**Group B**		*P value*
End of the 1st 5 Days	**(n=95 Patients)**	**%**	**(n=96 Patients)**	**%**	
≤19	39	41.1	14	14.6	
20-40	25	26.3	22	22.9	0.007*
41-79	17	17.9	28	29.2	
≥80	14	14.7	32	33.3	
End of the 2nd 5 Days	**(n=90 Patients)**	**%**	**(n=91 Patients)**		
≤19	21	23.3	7	7.7	
20-40	22	24.4	11	12.1	0.001*
41-79	23	25.6	16	17.6	
≥80	24	26.7	57	62.6	
End of the 3rd 4 Days	**(n=86 Patients)**	**%**	**(n=87 Patients)**		
≤19	12	14.0	0	0.0	
20-40	18	20.9	9	10.3	0.001*
41-79	21	24.4	10	11.5	
≥80	35	40.7	68	78.2	

Note: * Represent Significant P value.

Table **12** compares parenchymatous lung infiltrates on the chest X-ray of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied durations as (61, 75 and 85 patients) had almost normal chest X-ray at the end of 5, 10 and 14 days consecutively, while (23, 38 and 65 patients) in group A achieved same chest X-ray at the same time of the study.

Table **12** compares the core temperature of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied durations as (50, 77 and 81 patients) had core temperature > 36.5 and < 38.4 at the end of 5, 10 and 14 days consecutively, while (25, 42 and 60 patients) in group A achieved same core temperature at the same time of the study.

Table **12** compares the total leucocytic count of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied durations as (51, 70 and 83 patients) had leucocytic count > 4000 and < 11000 thousand/mL at the end of 5,10 and14 days consecutively, while (27, 35 and 63 patients) in group A achieved same leucocytic count at the same time of the study.

Table **12** compares the hypoxic index ($PaO2/FIO_2$) of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied duration as (69, 76 and 83 patients) had hypoxic index >240 at the end of 5,10 and14 days consecutively, while (57, 61 and 72

patients) in group A achieved same hypoxic index at the same time of the study.

Table **12** compares the microbiological results of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied durations as (75, 80 and 86 patients) had negative qualitative BAL culture at the end of 5,10 and14 days consecutively, while (59, 62 and 70 patients) in group A had negative qualitative sputum culture at the same time of the study.

Table **13** compares lung compliance in both groups all over the studied duration and shows significant improvement in patients of group B in all studied durations as (32, 57 and 68 patients) had measured lung compliance of > 80 ml/ 1 cm H_2O at the end of 5, 10 and 14 days consecutively, while (14,24and 35 patients) in group A achieved same measured lung compliance at the same time of the study.

Table **14** compares the number of patients who responded to the recruitment maneuver in both groups all over the studied duration and shows a significantly higher number of patients who responded to this maneuver in group B in all studied durations as (35, 71 and 82 patients) were responders at the end of 5, 10 and 14 days consecutively, while (14, 24 and 35 patients) in group A were responders in the same time of the study.

Table **14** compares the number of patients who failed to be weaned in both groups at the end of the studied duration and shows a significantly lower number of patients in group B (only 2 patients out of 87 patients) compared to group A (17 patients out of 86 patients.

Table **14** compares the total number of patients discharged from the ICU at the end of the studied period and shows a significantly higher number of patients discharged from group B (85 patients) compared to group A (69 patients .(

Table **15** compares LDH levels of patients in both groups all over the studied duration and shows significant improvement in patients of group B in all studied durations as (45, 66 and 73 patients) had LDH < 200 U/L at the end of 5,10 and14 days consecutively, while (21, 33 and 40 patients) in group A achieved same LDH level at the same time of the study.

Table **16** compares C-reactive protein levels in both groups all over the studied duration and shows significant improvement in patients of group B in all studied durations as (68, 79 and 80 patients) had C-reactive protein levels <100 mg/L at the end of 5, 10 and 14 days consecutively, while (33, 39 and 49 patients) in group A achieved same C-reactive protein level at the same time of the study.

Table **17** compares the morbidity recorded in all patients between the two groups in all studied periods.

Table 14. The response to the recruitment maneuvers in all patients, patients who had a failure of weaning from the ventilator and the number of patients discharged from ICU at the end of the studied period.

Days **No response to recruitment**	**Group A**		**Group B**		***P value***
	NO	**%**	**NO**	**%**	
End of 1st. 5 Days	19/95 patients	20.0	35/96 patients	36.5	0.036*
End of 2nd. 5 Days	38/90 patients	42.2	71/ 91 patients	78.0	0.011*
End of 3rd. 4 Days	60/86 patients	69.8	82/87 patients	94.3	0.0036*
Failure of weaning	17 from 86 patients	19.8	2 from 87 patients	2.3	0.001*
N. discharged from ICU	69 from 100 patients	69.0	85 from 100 patients	85.0	0.037*

Note: * Represent Significant P value.

Table 15. LDH levels recorded for all patients in the studied period.

LDH level in U/L	**Group A**		**Group B**		***P value***
End of the 1st 5 Days	**(n=95 Patients)**	**%**	**(n=96 Patients)**	**%**	
>600	29	30.5	12	12.5	
400-600	25	26.3	16	16.7	0.004*
200-400	20	21.1	23	24.0	
<200	21	22.1	45	46.9	
End of the 2nd 5 Days	**(n=90 Patients)**	**%**	**(n=91 Patients)**		
>600	16	17.8	5	5.5	
400-600	18	20.0	6	6.6	0.001*
200-400	23	25.6	14	15.4	
<200	33	36.7	66	72.5	
End of the 3rd 4 Days	**(n=86 Patients)**	**%**	**(n=87 Patients)**		
>600	10	11.6	0	0.0	
400-600	11	12.8	3	3.4	0.001*
200-400	25	29.1	11	12.6	
<200	40	46.5	73	83.9	

Note: * Represent Significant P value

Table 16. C reactive protein levels recorded for all patients in the studied period.

CRP in mg/L	Group A		Group B		*P value*
End of the 1st 5 Days	**(n=95 Patients)**	**%**	**(n=96 Patients)**	**%**	
>300	17	17.9	5	5.2	
201-300	20	21.1	10	10.4	0.001*
100-200	25	26.3	13	13.5	
<100	33	34.7	68	70.8	
End of the 2nd 5 Days	**(n=90 Patients)**	**%**	**(n=91 Patients)**		
>300	4	4.4	0	0.0	
201-300	17	18.9	2	2.2	0.001*
100-200	30	33.3	10	11.0	
<100	39	43.3	79	86.8	
End of the 3rd 4 Days	**(n=86 Patients)**	**%**	**(n=87 Patients)**		
>300	0	0.0	0	0.0	
201-300	12	14.0	0	0.0	0.001*
100-200	25	29.1	7	8.0	
<100	49	57.0	80	92.0	

Note: * Represent Significant P value.

Table 17. Morbidity recorded for all patients in the studied period.

The Morbidity	Number of Patients in Group A (86)		Number of Patients in Group B (87)		*P value*
	No.	**%**	**No.**	**%**	**0.002***
APACH II Score >25	**19**	**22.1**	**5**	**5.7**	
GCS <6	9	10.5	0	0.0	0.013*
MAP <70 mmHg +or- inotropes	10	11.6	0	0.0	0.011*
Bilirubin level ≥ 12 mg/dL	11	12.8	0	0.0	0.010*
Creatinine level ≥ 5 mg/dL	11	12.8	0	0.0	0.01*
Platelets count >100.000 10^3/microL	7	8.1	0	0.0	0.021*
Hypoxic index <100	14	16.3	4	4.6	0.002*
X-ray chest (all quadrant lung infiltrate)	9	10.5	0	0.0	0.013*
Lung compliance ≤19 ml/ cmH_2O	12	14.0	0	0.0	0.006*
NO response to recruitment	26	30.2	5	5.7	0.001*
Core temp.2 on CPIS	9	10.5	1	1.1	0.013*
Tracheal secretion 2 on CPIS	8	9.3	0	0.0	0.021*
Leucocytic count 2 on CPIS	8	9.3	0	0.0	0.021*
High LDH >600 U/L	10	11.6	0	0.0	0.011*
C-reactive protein 201-300 mg/L	12	14.0	0	0.0	0.006*
Positive microbiology results after 10 days	28	32.6	11	12.6	0.017*
Positive microbiology results after 14 days	16	18.6	1	1.1	0.001*
Failure of weaning from the ventilator at the end of the study period	17	19.8	2	2.3	0.001*
Mortality	14	16.3	13	14.9	0.211 N.S.

Note: * Represent Significant *P value*

4. DISCUSSION

As regard, improving the general condition of the patients [13]:

There was a significant improvement of APACH II, GCS, and hemodynamics stability between patients in group B compared to patients in group A in all periods of the study due to more rapid and efficient control of all local lung parameters of infection measured in our study by CPIS score and more rapid and efficient control of all general parameters of severe sepsis measured in our study by SOFA scores. The pathophysiological mechanism of this finding is explained in detail later.

As regard controlling all parameters of sepsis (SOFA) score:

There was a significant improvement in the total leucocytic count, core body temperature, creatinine level, bilirubin level,

and platelet count between patients in group B compared to group A in all periods of the study. This could be due to better control of systemic manifestations of both VAP and sepsis by removing the purulent discharge from the small airways. This purulent discharge might be the primary cause of sepsis. Also, this purulent discharge might be responsible for spreading a resistant bacteria to blood, causing septicemia and triggering a systemic immunological cascade of septic reactions that end by marked local and systemic tissue destruction. Moreover, patients of group B were given antibiotics according to BAL results which were considered more reliable than sputum culture. As sputum culture is associated with higher bacterial contamination than BAL, yielding of bacteria in BAL is better than sputum. All those aspects increased the success rate of antibiotic action and accelerated the bacteriological cure between patients of group B compared to group A. Also, those aspects might be the cause of a higher percentage of unsuitable antibiotics usage among patients of group A. The rapid bacteriological cure in patients of group B might be the main cause of rapid control of systemic manifestation of sepsis and septic shock. This might be the main cause of rapid recovery from a low tissue perfusion state and rapid restoration of the MAP with satisfactory tissue perfusion pressure in all organs. Therefore in those patients, there was a more rapid improvement of GCS, creatinine level, bilirubin level, and platelets count due to improvement of perfusion pressure of brain (recovery from septic encephalopathy) kidneys, liver and bone marrow, respectively. Also, there was a more rapid improvement in APACHI II score, leucocytic count and core temperature due to a more rapid improvement of global tissue perfusion and decrease/stop the release of systemic toxins and pyrogens.

As regards controlling all parameters of CPIS score, ARDS, VAP and improved lung mechanics [13]: There was significant improvement between patients in group B compared to patients in group A in oxygen saturation, hypoxic index, compliance, and response to recruitment maneuver during all periods of the study. Moreover, radiologically [13], patients of group B showed significant improvement in parenchymatous lung infiltrate on chest X-ray all over the duration of the study compared to patients of group A. This could be due to better aeration of small airways after washing and removing the purulent discharge and debris which improve lung compliance by removing the physical obstruction of pus from the small airways (as good lung aeration is one of the most important parameters of normal lung compliance). Better lung aeration also causes better lung tissue oxygenation and pulmonary vasodilation (as increased lung tissue oxygenation causes reflex pulmonary vasodilatation and increases blood supply of the lungs and thus improves local immunity of the lungs). Both improvement in lung compliance and local immunity of the lung accelerate the rapid healing from VAP and rapid control of sepsis, and thus accelerate the weaning from the ventilator.

As regards controlling laboratory markers of tissue destruction [13]:

There was a significant decrease in the markers of tissue destruction (LDH and C reactive protein) in patients of group B compared to group A. This could be due to better control of both general and local parameters of VAP, ARDS, sepsis, and/or septic shock by the same mechanism described above, which stops the cascade of sepsis and thus stops tissue destruction and rapidly reverses the state of low tissue perfusion in sepsis and accelerates the global tissue reperfusion.

As regards lowering morbidity and shortening the duration of ICU stay [13]:

The number of patients who showed no improvement of one/or all parameters of both CPIS score and SOFA score was significantly higher in group A compared to group B, as illustrated in Table **17**, and this could be explained by the lower number of weaned patients from the ventilator in group A compared to group B. And prolonged ventilation is the main cause of morbidity in all patients in the critical care; moreover, patients of group B showed shorter duration of ICU stay compared to group A due to higher number of weaned patients from the ventilator. No significant difference was found in the mortality rate between both groups.

Our study supports those studies done on this aspect as Fagon *et al*., in 2000 [14] demonstrated lower short-term mortality and decreased Sequential Organ Failure Assessment Scores at three days (6.1 – 4.0 *vs*. 7.0 – 4.3 points; p = 0.33) and seven days (4.9 – 4.1 *vs*. 5.8 – 4.4 points; p = 0.04) for their group that had a diagnosis via BAL versus a non-invasive technique. This finding suggests that bronchoscopy has some short-term therapeutic benefits. Michetti *et al*., in 2012 [15] did a study on 137 patients with VAP due to lung contusion following chest trauma; they compared BAL-based microbiological results versus endotracheal sputum-based microbiological results, and they found improvement in signs of both VAP and lung contusion and this was associated with low overall mortality and VAP-attributable mortality. Christopher A *et al*., in 2014 [16] did a trial on 360 patients with VAP, and they compared the invasive diagnosis of VAP by bronchoscopy with the noninvasive traditional way of diagnosis. They found that diagnostic bronchoscopy was associated with a shorter length of stay and shorter duration of antibiotics. Qiao, Zhihao MM *et al*., in 2018 [17] did a study on 107 patients with respiratory failure patients due to acute exacerbation of COPD and compared daily suction of sputum by bronchoscope with general suction by the traditional way. They found that the bronchoscopic sputum suction group showed the earlier appearance of normal sputum color, lesser viscosity, scanty in amount, shorter time of invasive ventilation, total time of ventilation and hospital stay, lower reintubation rate, and fatality rate, and higher weaning success rate than the general sputum suction group (all $P < .05$). On the other hand, Sanchez-Nieto *et al*., in 1998 [18] and Ruiz *et al*., in 2000 [19] found no statistical difference between the culture results obtained from BAL and those obtained from sputum aspirated from the endotracheal tubes in both short-term and long-term results of VAP as regards the duration of antibiotics, duration of ventilation, duration of ICU and mortality rates. Shorr *et al*., in 2005 [20] and Berton *et al*., in 2012 [21] did two meta-analyses (including a Cochrane review) and found no statistical difference between microbiological results obtained from BAL and those obtained from sputum on the duration of

antibiotics, duration of ventilation and duration of ICU stay. Another randomized trial done on 740 patients who had VAP in 28 ICUs in Canada and the United States published by the Canadian Critical Care in 2006 in this study compared bacteriological results taken by BAL versus sputum taken from the endotracheal tube and found no significant difference as regards the duration of antibiotics, duration of ventilation, APACHII score and mortality rate between the bronchoalveolar-lavage group and the endotracheal-aspiration group [22].

Von Essen *et al*. in 1991 [23], Lawrence *et al*. in 1996 [24], Sato *et al*. in1998 [25], and Takeshi *et al*. in 2001 [26] did trials on the use of bronchoscopy in pneumonia and had significant signs of deterioration of their patients after bronchoscopy and they did not recommend its use in pneumonia.

From all previous studies, we can divide the authors' opinion on this aspect into three main categories, a group of authors proved that bronchoscopy in VAP is very beneficial and significantly improves both short-term outcomes (shortening the duration of antibiotics therapy, ventilation and ICU stay) and long-term outcomes, (morbidity and mortality rate of VAP) another group of author found no significant difference between the use of bronchoscopy in both diagnostic and/or therapeutic management of VAP, following the traditional way of management of VAP. The last group of authors found significant deterioration signs in patients who had bronchoscopy with VAP, which could be due to the breaking of the localizing mechanism of the body to isolate the inflamed area of the lung and spread the infection to the adjacent lung segments, facilitate the systemic spread of the infection to the blood stream, increase the ventilation perfusion mismatch through obstructing the small airway with the wash during bronchoscopy, and aggravate the systemic cascade of sepsis through flooding the systemic circulation with purulent discharge from the inflamed lung areas. We found bronchoscopy very beneficial in our center when used in VAP and septic patients and had significant results proving improvement in both short- and long-term outcomes of both VAP and sepsis except for mortality rate, which showed no significant difference between both groups.

There were many limitation points in our study, including small sample size, predominantly male sex in our sample, exclusion of pediatric age group, using only SOFA score for sepsis, not all parameters of sepsis, selecting only VAP, type of health care acquired pneumonia and not all types of health care acquired pneumonia, and only 4 lung diseases (traumatic lung contusion, COPD with bronchitis, Bronchiectasis and aspiration pneumonia) were used in our sample size which are widespread to cause ARDS in our locality. However, still, our study is considered a unique study that follows the effect of bronchoscopy in both severe sepses with VAP as this combination has never been recorded before. We recommend more research work on the role of bronchoscopy in all types of pneumonia, not only VAP, and emphasise a regimen for its use in this aspect. Moreover, the same study is needed in pediatric patients as our study was done only in the adult age group.

CONCLUSION

The use of bronchoscopy can improve general conditions, control all signs of severe sepsis and VAP, improve lung mechanics, improve ARDS, accelerate weaning from the ventilator, and shorten the ICU stay but has no effect on mortality rate in those patients with severe sepsis with ARDS and complicated by VAP from prolonged ventilation.

LIST OF ABBREVIATIONS

ICU	=	Intensive Care Units
ARDS	=	Acute Respiratory Distress Syndrome
BAL	=	Broncho-Alveolar Lavage
RASS	=	Richmond Agitation-Sedation Scale
SOFA	=	Sequential Organ Failure Assessment

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by King Abdul-Aziz Specialized Hospital Research and Ethical committee.

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. All the humans were used in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Written consent from all patients was taken from the first-degree relatives of the patients.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the finding of this study will be available upon reasonable request from the corressponding author [M.A].

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CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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