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Extra Corporal Membrane Oxygenation (ECMO) *vs.* Conventional Ventilation with Nitric Oxide in ARDS due to Infected Contused Lung

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Abstract

Introduction: Lung contusion due to severe chest trauma considered major problem in the critical care. Not only because of common ARDS (Acute Respiratory Distress Syndrome) but also the devitalized lung tissue due to trauma is major cause of superadded infection. Especially if this lung ventilated for a long time. Ventilator associated pneumonia (VAP) occur in this lung characterized by being developed in short time (early VAP after 4 days only ventilation). And also very resistant to the conventional line of treatment compared to other causes of VAP. As the devitalized lung tissue full with proteinicious material from exudative and infiltrative phase of traumatic inflammation make the lung tissue highly susceptible for bacterial growth. The question is can ECMO be useful in this critical situation? or the conventional way of management of severe VAP is better.

Aim of the work: To compare the efficacy and safety of usage ECMO compared to conventional ventilation with nitric oxide using protective strategy in patients with ARDS due to severe lung contusion following severe chest trauma complicated by VAP as regards controlling all parameters of both Murray and CPIS score and early weaning from the ventilator.

Patients and methods: This a prospective double blind study done in King Abdulaziz specialist hospital between January 2015 and September 2018 in the intensive care unit on 60 patients chosen after 10 days from conventional ventilation due to ARDS from severe lung contusion those who had more than 3 on Murray score and 6 on CPIS allocated randomly in two groups. Group A (30 patients) continued on the same conventional ventilation but broad spectrum antibiotics according to qualitative sputum culture and nitric oxide were added on the management while group B (30 patients) put on ECMO and started antibiotics. The duration of the study last 16 days during this period the clinical parameters of both Murray score and CPIS were compared between the patients of both groups and recorded. Also both mortality and morbidity recorded. Morbidity considered in our study by no improvement in any or all clinical parameters of both Murray and CPIS scores and failure of weaning of patients from the ventilator at the studied period.

Results: By comparing the clinical parameters of both Murray and CPIS scores in both groups all over the studied periods showed significant improvement in the APACH II score <10 of patients of group B (0 patient in group A and 7 patients in group B), significant improvement in arterial oxygen saturation >95 of group B (0 patient in group A, 8 patients from B), significant improvement in hypoxic index >300 of patients of group B (0 patient in group A and 9 patients in B), significant improvement in parenchymatous lung infiltrate in chest X-ray with less than one quadrant infiltration of group B (3 patients in group A and15 patients in B), significant improvement in lung compliance with >80 ml for 1 cm H_2O pressure of group B (3 patients in group A and 20 patients in B), significant improvement in response of the lung to recruitment maneuver of group B (14 patients in group A and 20 patients in B), significant improvement in return core temperature to normal in group B (4 patients in group A and 12 patients in B), significant return of tracheal secretion to normal in group B (6 patients in group A and 22 patients in B), significant return leucocytic count to normal in group B (10 patients in group A and 19 patients in B), significant improvement in the number of patient had lower level of LDH from 100-200 U/L in group B (6,8,12 and 19 patients in group B compared to 0,0,1 and 4 patients) in group A in the studied periods, significant improvement in the number of patient had higher CRP 201-300 mg/L in group B (8,10,13 and 17 patients in group B compared to 9,8,7and 5 patients in group A) significant improvement in the number of patient had negative sputum culture in group B (6 patients in group A and 17 patients in B), significant higher number of weaned patients in group B (15 from 27 patients in group A and19 from 26 patients in B), but unfortunately mortality rate was higher in group B (4 patients died) compared to group A (3 patients died).

Conclusion: ECMO significantly improve all clinical parameters of both Murray and CPIS score and significantly increase number of weaned patients from ventilator but with higher mortality.

Keywords: ECMO in infected contused lung; Trauma

Introduction

Severe lung contusion due to chest trauma is a significant source of morbidity and mortality all over the world. Especially if complicated by ventilator associated pneumonia (VAP) from prolonged ventilation and depressed local immunity from devitalized lung tissue. It is considered a major challenge for the intensivists [1-4].

The percent of chest trauma in United States 12 per million populations per day. Approximately 33% of these injuries required intensive care admission and overall blunt thoracic injuries are directly responsible for 20-25% of all deaths in USA [5,6].

The most common cause of blunt chest trauma is motor vehicle accidents which account for 70-80% of such injuries. Direct lung injuries such as pulmonary contusions occur in 80-90% with blunt chest trauma [6-8].

Severe lung contusion can lead to ARDS (acute respiratory distress syndrome) and respiratory failure. ARDS occur in 25-30% of these lung injuries especially if complicated by VAP which easily complicate devitalized lung due to prolonged ventilation [9-11].

The golden standard lines of management in severe pulmonary contusion are conventional invasive ventilation with the application of protective lung strategy, pain control, pulmonary toilet and oxygen therapy [12-14]. Oxygenation of the lung is very important line of management as it cause vasodilatation in the pulmonary vessels and accelerate the process of healing. Especially in those who developed ARDS and had superadded VAP [15-17]. Complete sedation and relaxation considered one of the adjuvant lines of treatment in invasive ventilation [18]. The main component of lung protection strategy are low tidal volume to keep peak inspiratory pressure less than 35 cm/H_2O, high PEEP, 1:1 IE rate, high FIO_2 to ensure well oxygenation of the lungs, elevate the head 30 degree or more, and the use of selective digestive decontamination therapy (oral paste containing antibiotics and antifungal agent put in early morning and spread by finger in the mouth cavity) to decrease the possibility of ventilator associated pneumonia [19,20].

Using high frequency oscillatory ventilator in the management of this cases obsolete now a days due to uncontrolled complications such as (hypercabnia, recorded organic brain insult, respiratory acidosis and non-improvement of the lung condition) [21,22].

ECMO is now considered one of major line of treatment of severe ARDS, respiratory failure due to severe lung contusion in chest trauma especially for cases showing no improvement with conventional ventilation. Only the veno-venous type used in these situations not the veno-arterial type which used only if there is cardiac problem [23-28].

Aim of work

To compare the efficacy and safety of usage ECMO compared to conventional ventilation with nitric oxide using protective strategy in patients with ARDS due to severe lung contusion following severe chest trauma complicated by VAP as regards controlling all parameters of both Murray and CPIS score and early weaning from the ventilator.

Patients and Methods

Patients who had severe chest trauma with massive lung contusion and admitted to surgical intensive care unit at King Abdulaziz specialist hospital between January 2015 and September 2018 those who showed the following inclusion criteria of ARDS, respiratory failure due to severe lung contusion complicated by VAP enrolled in our study.

King Abdulaziz research and ethical committee approved the project

Inclusion criteria

- Adult patients aged >18-<65 years
- No any cardiac injury either acute due to cardiac contusion or chronic with history of ischemic heart disease
- No history of systemic diseases (diabetes mellitus, hypertension)
- Uncompensated hypercapnea with PH<7.25
- Hypoxic index less than 200 (PaO_2/FIO_2)

All selected patients received conventional ventilation with protective lung strategy for 10 days with Controlled mechanical ventilation mode(CMV), fraction inspired oxygen (FIO_2) of 100%, Positive end expiratory pressure(PEEP) of 10 cm H_2O or more to achieve target arterial oxygen saturation(SPO_2) of 90% or more with sedation by midazolam infusion to achieve Richmond Agitation-Sedation Scale (RASS) -2 to -3 and fentanyl infusion for pain control between 50-100 mg/min. Protective lung strategy was strictly applied in form of head elevation more than 30°, daily assessment for both analgesic and sedative dose were given to patients, early naso-gastric feeding started to prevent ventilator associated pneumonia and daily trial was done to reduce PEEP to prevent more lung injury from ventilation also qualitative sputum culture was taken after one week from ventilation. After 10 days from the conventional ventilation those who showed no improvement subjected to both Murray score for diagnosis of severe ARDS and CPIS (clinical pulmonary infection score) for diagnosis of VAP and 60 patients from those who get 3 or more on Murray score and had 6 or more on CPIS were included in our study and randomly allocated in 2 groups. Group A included 30 patients continued the same conventional ventilation with protective lung strategy as mentioned above with inhalation of nitric oxide stared by 50 parts/billion(ppb) as starting dose titrated according to patients saturation and broad spectrum antibiotics were given according to qualitative sputum culture collected after week from ventilation while group B included 30 patients were put on veno-venous ECMO which involves venous blood from the patient being accessed from the large central veins (via the "access line") and returned to the venous system near the right atrium (via the "return line") after it has passed through an oxygenator. When flow through a single access cannula is insufficient to support the high ECMO flow rate that may be required in severe respiratory failure, a second venous access cannula may be required. V–V ECMO improves the patient's oxygenation by reducing the amount of blood that passes through the lung without being oxygenated and in addition, removes CO_2 from the patient's blood. This allows the level of ventilatory support to be reduced-which reduces ventilator-induced lung injury (Figure 1).

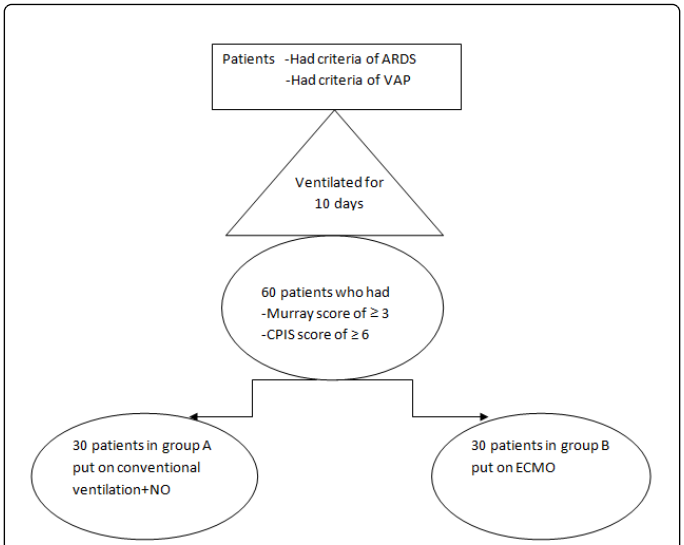

Figure 1: VAP diagnosed in our study by CPIS 6 or more while indication of ECMO diagnosed by Murray score 3 or more.

The efficiency of oxygenation by the ECMO circuit depends on the pump flow relative to the patient's cardiac output. The patient's oxygenation should increase with increasing ECMO flow. The ECMO machine applied and maintained by experienced team. This study conducted for 16 days and heparin was given on the access cannula (arterial cannula) and reversed by the equivalent dose of protamine sulphate on return cannula (inferior vena cava cannula) to minimize its systemic effect on the trauma patients. And also broad spectrum antibiotics were given according to qualitative sputum culture collected Tables 1 and 2.

Clinical parameter of Murray score	**0**	**1**	**2**	**3**	**4**
Hypoxic index PaO_2/FIO_2 On FIO_2 100%	≥ 300	299-225	224-175	174-100	<100
Chest X-ray	Non	1 quadrant infiltrated	2 quadrant infiltrated	3 quadrant infiltrated	4 quadrant infiltrated
PEEP	≤ 5	6-8	9-11	Dec-14	≥ 15
Compliance ml /1 cm H_2O	≥ 80	79-60	59- 40	39-20	≤ 19

Table 1: Clinical parameter of Murray score.

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

Table 2: Modified clinical-pulmonary infection score (CPIS). Any patient having score of 6 or more is considered having VAP

VAP diagnosed in our study by CPIS 6 or more [29] while indication of ECMO diagnosed by Murray score 3 or more [30].

Exclusion criteria

Any patient had contraindications to the use of V-V ECMO was excluded from the study such as:

- Any patient had uncontrolled cardiac problem either acute cardiac contusion or Chronic heart disease (with history of IHD, Cardiomyopathy)
- Any patient had uncontrolled systemic disease (DM, HTN)
- Any patient had active intracerebral bleeding because this affects the decision of weaning
- Un-Witnessed cardiac arrest or CPR>60 min prior to commencement of ECMO or deeply comatose patient with Glasgow coma scale 3/15 due to severe head trauma.

Survey done to all patients once admitted to our ICU according to our hospital protocol including. All laboratory work were done daily including (complete blood count, blood chemistry, cardiac enzyme to exclude cardiac contusion, coagulation profile, liver function testes, kidney function tests and arterial blood gases to calculate the hypoxic index done for all the patients during admission and daily Radiological study for the brain and spinal cord (computerized tomography) to exclude active intracerebral haemorrhage or spine fracture.

All the patients in both groups were followed for 16 days by both parameters of both Murray score and of CPIS:

1-APACHE II score

2-Oxygen saturation recorded by pulse oximetry

3-Hypoxic index

4- Response to recruitment maneuver

5- Chest X-ray

6- Compliance (measured by ml/cm H_2O) from the lung dynamics on screen of the ventilator

7- Core body temperature.

8- Nature and amount of tracheal secretion.

9- Total leucocytic count

10- Laboratory marker of lung tissue destruction both lactate dehydrogenase (LDH) and C-reactive protein (CRP) used in our study.

11-Qulitative sputum culture took at the end of 1st 8 days and another at the end of 16th days

Ventilator associated pneumonia (VAP) considered in our study by 6 or more in CPIS. And routine percutaneous tracheostomy was done to all patients in both groups at the end of the first week. 3 patients from group A died from ARDS with multiple organ failure. Two after 5 and 7 days consecutively and the third died after 14 days from starting the study while 4 patients died in group B from progressive hypoxemia and respiratory failure 2 after 9 days and 2 after 13 days from connection to ECMO machine.

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013. For qualitative data it represented as number and percentage inferential analyses for independent variables were done using Chi square test for differences between proportions and student t-test for continuous variables.

The level of significance was taken at P value <0.050 is highly statistically significant, otherwise is non-significant.

Sample size

Sample size was calculated based on a previous study and by using Med Calc statistical software.

Assuming area under ROC to be 0.80, an alpha of 0.05 and power of study 90.0%. A minimum sample size required was at least 60 patients will be required for this study.

Results

Recruitment maneuver is considered clinical test of lung compliance and started by increase the peak inspiratory pressure to 40 cm/H_2O for 40 min and observe the saturation (SpO_2) if improved to more than 95% considered responder in our study.

Table 3 represent the demographic data of patients in both groups and showed no significant difference between the two groups as regard age and sex.

	Group A		Group B		p
	(n=30)	%	(n=30)	%	
Age by years					
18-30	10	33.3	9	30	0.362
31- 45	8	26.7	9	30	
46- 55	8	26.7	7	23.3	
56- 65	2	6.7	4	13.3	
>65	2	6.7	1	3.3	
Sex in both groups					
Female	8	26.7	6	20	0.254
Male	22	73.3	24	80	

Table 3: Demographic data of the patients in the two groups.

Table 4 compared the APACH II score of patients in both groups all over the duration of the study and showed significant higher number of patients had score of 10 or less in group B compared to group A. As 1,3,5 and 7 patients in group B had this score at the end of 4,8 12 and 16 days consecutively while no patients in group A had this score all over the duration of the study.

	1st 4 day		2nd 4 day		3rd 4 day		4th 4 day	
Group A	(n=30)	%	(n=28)	%	(n=28)	%	(n=27)	%
Above 25	28	93.3	20	71.4	16	57.1	15	55.6
15-25	2	6.7	8	28.6	10	35.7	6	22.2
11-14	0	0	0	0	2	7.1	6	22.2
≤ 10	0	0	0	0	0	0	0	0
Group B	(n=30)		(n=30)		(n=28)		(n=26)	
Above 25	14	46.7	10	46.7	7	25	4	14.8
15-25	10	33.3	12	33.3	8	28.6	7	25.9
11-14	5	16.7	5	16.7	8	28.6	8	29.6
≤ 10	1	3.3	3	3.3	5	17.9	7	25.9
P Value	0.028*		0.023*		0.013*		0.002*	

Table 4: APACH II score for both groups all over the study.

Table 5 compared the arterial oxygen saturation (SPO_2) of patients in both groups all over the duration of the study and showed significant higher number of patients had SPO_2>95% in group B compared to group A. As 2,3 and 8 patients in group B had SPO_2>95% at the end of 8,12 and 16 days consecutively while no patients in group A had this saturation all over the duration of the study.

O_2 saturation	1st 4 days		2nd 4 days		3rd 4 days		4th 4 days	
Group A	(n=30)	%	(n=28)	%	(n=28)	%	(n=27)	%
≤ 80%	27	90	20	71.4	16	57.1	11	40.7
81%-85%	3	10	8	28.6	7	25	5	18.5
86%-90%	0	0	0	0	5	17.9	5	18.5
91%-94%	0	0	0	0	0	0	6	22.2
≥ 95%	0	0	0	0	0	0	0	0
Group B	(n=30)		(n=30)		(n=28)		(n=26)	
≤ 80%	19	63.3	6	21.4	0	0	0	0
81%-85%	5	16.7	8	28.6	9	32.1	0	0
86%-90%	6	20	11	39.3	10	35.7	10	37
91%-94%	0	0	3	10.7	6	21.4	8	29.6
≥ 95%	0	0	2	7.1	3	10.7	8	29.6

p	0.021*	0.0013*	0.001*	0.001*

Table 5: Oxygen saturation recorded by the pulse oximeter for both groups all over the study period.

Table 6 compared the hypoxic index of patients in both groups all over the duration of the study and showed significant higher number of patients had hypoxic index of >300 in group B compared to group A. As 4 and 9 patients in group B had this hypoxic index at the end of 12 and 16 days consecutively while no patients in group A had this index all over the duration of the study.

PaO_2/FIO_2	1st 4 days		2nd 4 days		3rd 4 days		4th 4 days	
Group A	(n=30)	%	(n=28)	%	(n=28)	%	(n=27)	%
<100	25	83.3	20	71.4	16	57.1	11	40.7
100-174	3	10	5	17.9	5	17.9	6	22.2
175-224	2	6.7	3	10.7	5	17.9	4	14.8
225-299	0	0	0	0	2	7.1	6	22.2
≥ 300	0	0	0	0	0	0	0	0
Group B	(n=30)		(n=30)		(n=28)		(n=26)	
<100	19	63.3	10	35.7	5	17.9	0	0
100-174	3	10	2	7.1	5	17.9	4	14.8
175-224	4	13.3	8	28.6	6	21.4	6	22.2
225-299	4	13.3	10	35.7	8	28.6	7	25.9
≥ 300	0	0	0	0	4	14.3	9	33.3
P	0.0251*		0.001*		0.003*		0.001*	

Table 6: Hypoxic index for both groups all over the period of study.

Table 7 compared parenchymatous lung infiltrate on the chest X-ray of patients in both groups all over the duration of the study and showed significant higher number of patients had less than one quadrant infiltration in group B compared to group A. As 4,10 and 15 patients in group B had this finding at the end of 8,12 and 16 days consecutively while only 3 patients in group A had same result at the end of the duration of the study.

	1st 4 day		2nd 4 day		3rd 4 day		4th 4 day	
Group A	**(n=30)**	**%**	**(n=28)**	**%**	**(n=28)**	**%**	**(n=27)**	**%**
Bilateral lung infiltrate (all quadrant)	30	100	26	92.9	22	78.6	16	59.3
≥ 4 quadrant infiltrate	0	0	2	7.1	4	14.3	4	14.8
3-1 quadrant infiltrate	0	0	0	0	2	7.1	4	14.8
Less than 1 quadrant infiltrate	0	0	0	0	0	0	3	11.1
Group B	(n=30)		(n=30)		(n=28)		(n=26)	
Bilateral lung infiltrate (all quadrant)	22	73.3	16	57.1	2	7.1	1	3.7
≥ 4 quadrant infiltrate	6	20	6	21.4	6	21.4	4	14.8
3-1 quadrant infiltrate	2	6.7	4	14.3	10	35.7	6	22.2
Less than 1 quadrant infiltrate	0	0	4	14.3	10	35.7	15	55.6
P	0.042*		0.001*		0.001*		0.0026*	

Table 7: Chest X-ray taken in both groups all over the duration of the study.

Table 8 compared lung compliance of patients in both groups all over the duration of the study and showed significant higher number of patients had >80 cm/1 cm H_2O pressure in group B compared to group A. As 2,14,16 and 20 patients in group B had this compliance at the end of 4,8,12 and 16 days consecutively while only 2,3 patients in group A had same compliance at the 12 and 16 days consecutively.

$ml/1cmH_2O$	1st 4 days No (30)		2nd 4 days No (28)		3rd 4 days No (28)		4th 4 days No (27)	
Group A	(n=30)	%	(n=28)	%	(n=28)	%	(n=27)	%
≤ 19	22	73.3	17	60.7	7	25	7	25.9
20-39	8	26.7	6	21.4	8	28.6	7	25.9
40-59	0	0	5	17.9	6	21.4	5	18.5
60-79	0	0	0	0	5	17.9	5	18.5
≥ 80	0	0	0	0	2	7.1	3	11.1
Group B	(n=30)		(n=30)		(n=28)		(n=26)	
≤ 19	16	53.3	3	10.7	1	3.6	0	0
20-39	5	16.7	2	7.1	3	10.7	0	0
40-59	5	16.7	3	10.7	4	14.3	2	7.4
60-79	2	6.7	8	28.6	4	14.3	4	14.8
≥ 80	2	6.7	14	50	16	57.1	20	74.1

P Value	0.048*	0.0036*	0.0025*	0.005*

Table 8: Compliance by (ml/1 cm H_2O) for both groups all over the duration of the study.

Table 9 compared number of patients respond to recruitment maneuver in both groups all over the duration of the study and showed significant higher number of patients had positive response to recruitment maneuver of group B compared to group A. As 8,13,15 and 20 patients in group B had this response at the end of 4,8,12 and 16 days consecutively while only 2,8,9 and 14 patients in group A had same results at the 4,8, 12 and 16 days consecutively.

	Group A		Group B		P value
days		%		%	
1st 4 days	2/30	6.7	8/30	26.7	0.0021*
2nd 4 days	8/28	28.6	13/ 30	43.3	0.005*
3rd 4 days	9/28	32.1	15/28	53.6	0.016*
4th days	14 /27	51.9	20 / 26	76.9	0.026*

Table 9: Number of patients responds to recruitment maneuver in both groups. Recruitment maneuver is considered clinical test of lung compliance and start by increase the peak inspiratory pressure to 40 cm/H_2O for 40 sec and observe the saturation (SpO_2) if improved to more than 95% considered responder in our study (34).

Table 10 compared core temperature recorded in both groups all over the duration of the study and showed significant higher number of patients had normal core temperature in group B compared to group A. As only 0,2,3 and 4 patients had normal core temperature at the end of 4,8,12 and 16 days consecutively in group A while 7,8,10 and 12 patients in group B had the same temperature in the same periods.

	1st 4 days		2nd 4 days		3rd 4days		4th 4 days	
Group A	(n=30)	%	(n=28)	%	(n=28)	%	(n=27)	%
0 in CPIS	0	0	2	7.1	3	10.7	4	14.8
1 in CPIS	0	0	4	14.3	6	21.4	8	29.6
2 in CPIS	30	100	22	78.6	19	67.9	15	55.6
Group B	(n=30)		(n=30)		(n=28)		(n=26)	
0 in CPIS	7	23.3	8	28.6	10	35.7	12	44.4
1 in CPIS	4	13.3	12	42.9	11	39.3	9	33.3
2 in CPIS	19	63.3	10	35.7	7	25	5	18.5
P Value	0.016*		0.0035*		0.027*		0.002*	

Table 10: The core temperature according to CPIS in both groups.

Table 11 compared nature and amount of tracheal secretion in both groups all over the duration of the study and showed significant higher number of patients had normal tracheal secretion in group B compared to group A. As only 0,2,6 and 6 patients in group A had this result at the end of 4,8,12 and 16 days consecutively while 10,14,18 and 22 patients in group B had the same result in the same periods.

	1st 4 days		2nd 4 days		3rd 4days		4th 4 days	
Group A	(n=30)	%	(n=28)	%	(n=28)	%	(n=27)	%
0 in CPIS	0	0	2	7.1	6	21.4	6	22.2
1 in CPIS	18	60	16	57.1	14	50	18	66.7
2 in CPIS	12	40	10	35.7	8	28.6	3	11.1
Group B	(n=30)		(n=30)		(n=28)		(n=26)	
0 in CPIS	10	33.3	14	50	18	64.3	22	81.5
1 in CPIS	10	33.3	8	28.6	6	21.4	4	14.8
2 in CPIS	10	33.3	8	28.6	4	14.3	0	0
P Value	0.0036*		0.0021*		0.005*		0.0001*	

Table 11: The amount and nature of tracheal secretion according to CPIS in both groups.

Table 12 compared total leucocytic count in both groups all over the duration of the study and showed significant higher number of patients had normal leucocytic count in group B compared to group A. As 0,0,8 and 10 patients had normal tracheal secretion at the end of 4,8,12 and 16 days consecutively in group A while 10,12,17 and 19 patients in group B achieved the same result in the same periods.

	1st 4 days		2nd 4 days		3rd 4days		4th 4 days	
Group A	(n=30)	%	(n=28)	%	(n=28)	%	(n=27)	%
0 in CPIS	0	0	0	0	8	28.6	10	37
1 in CPIS	12	40	17	60.7	14	50	14	51.9
2 in CPIS	18	60	11	39.3	6	21.4	3	11.1
Group B	(n=30)		(n=30)		(n=28)		(n=26)	
0 in CPIS	10	33.3	12	42.9	17	60.7	19	70.4
1 in CPIS	10	33.3	10	35.7	9	32.1	7	25.9

2 in CPIS	10	33.3	8	28.6	2	7.1	0	0
P value	0.0036*		0.001*		0.025*		0.007*	

Table 12: Total leucocytic count according to CPIS in both groups.

Table 13 compared LDH level in both groups all over the duration of the study and showed significant higher number of patients had LDH level <200 U/L in group B compared to group A. As 6,8,12 and 19 patients in group B had this result at the end of 4,8,12 and 16 days consecutively while only 0,0,1 and 4 patients in group A had the same result at the same period.

	1st 4 days	2nd 4 days	3rd 4 days	4th 4 days
Group A	(n=30)	(n=28)	(n=28)	(n=27)
100-200 U/L	0	0	1	4
201-400 U/L	0	3	5	9
401-600 U/L	9	8	9	5
>600 U/L	21	17	13	9
Group B	(n=30)	(n=30)	(n=28)	(n=26)
100-200 U/L	6	8	12	19
201-400 U/L	6	14	10	7
401-600 U/L	6	8	6	0
>600 U/L	12	0	0	0
P value	0.452	0.021*	0.006*	0.017*

Table 13: LDH level in both groups in the studied period

Table 14 compared CRP level in both groups all over the duration of the study and showed significant higher number of patients had CRP level of 201-300 mg/L in group B compared to group A. As 13 and17 patients in group B had this result in 12 and 16 days consecutively compared to 7 and 5 patients in group A had the same level in the same period.

	1st 4 days	2nd 4 days	3rd 4 days	4th 4 days
Group A	(n=30)	(n=28)	(n=28)	(n=27)
0-100 mg/L	17	13	12	8
101-200 mg/L	4	7	9	14
201-300 mg/L	9	8	7	5
>300 mg/L	0	0	0	0
Group B	(n=30)	(n=30)	(n=28)	(n=26)
0-100 mg/L	11	9	7	2
101-200 mg/L	11	11	8	7
201-300 mg/L	8	10	13	17
>300 mg/L	0	0	0	0

P value	0.068	0.103	0.045*	0.038*

Table 14: C-reactive protein in both groups in the studied period.

Table 15 compared the qualitative sputum culture of patients in both groups took at 8 and 16 days and showed significant lower number of patient had positive sputum culture in group B compared to group A. As only 4 and 9 patients in group B had this result at 8 and16 days consecutively while 12 and 21 patients in group A had positive culture at the same periods.

	Group A		Group B		P Value
		%		%	
Number of patients with positive sputum culture after 1st 8 days	12/28	42.9	4/30	13.3	0.0041*
at the end of 16 days	21/27	77.8	9/26	34.6	0.003*
Weaned from ventilator	15/27	55.6	19/26	73.1	0.026*

Table 15: Number of qualitative positive sputum culture after 8 and 16 days consecutively from starting our study and patients weaned from the ventilator.

Table 15 compared number of patients weaned from the ventilator in both groups at the end of the study and showed significant higher number of weaned patients in group B (19 from 26 patients) compared to group A (15 from 27 patients).

Table 16 compared number of patients had morbidity in both groups at the end of the study and showed significant lower number of patients who showed no improvement in one or all measured parameters of both Murray and CPIS score at the end of studied duration.

The Morbidity	Number of patients in Group A (27)		Number of patients in Group B (26)		P Value
	No.	%	No.	%	
APACH II score above 25	15	55.6	4	15.4	0.002*
Desaturation SPO2 ≤ 80%	11	40.7	0	0	0.001*
Hypoxic index less than 100	11	40.7	0	0	0.001*
X-ray chest (all quadrant lung infiltrate)	19	70.4	2	7.7	0.001*
Lung compliance >19 ml/ cmH2O	7	25.9	0	0	0.003*
NO response to recruitment	13	48.1	6	23.1	0.013*
Core temp.2 on CPIS	15	55.6	5	19.2	0.005*
Tracheal secretion 2 on CPIS	3	11.1	0	0	0.042*
Leucocytic count 2 on CPIS	3	11.1	0	0	0.042*
High LDH >600 U/L	9		0		0.003*
C-reactive protein lower than 100 mg/L	8		2		0.0026*

Positive sputum culture After 8th day	12	44.4	4	15.4	0.0036*
After 16th day	21	77.8	9	34.6	0.014*
Failure of weaning from ventilator at the end of the study period	12	44.4	7	26.9	0.009*
Mortality	3	11.1	4	15.4	0.231

Table 16: Morbidity and mortality recorded at the end of the period of the study in both groups

Table 16 compared mortality rate in both groups at the end of the studied period and showed of no significant deference between the two groups. As 3 patients died from group A while 4 patients died from group B.

Discussion

As regard improvement of general condition of the patients

By comparing the results of both groups there were significant improvement of APACH II score ,total leucocytic count and core body temperature in group B compared to group A. This could be due to better tissue oxygenation by ECMO than the devitalized infected lungs and thus better systemic immunity which controls the bacteremia and toxins from bacteria caused VAP and thus controlling all general signs of inflammation as fever, leucocytic count and APACH II. Wu et al. [24] studied the effect of ECMO on severe traumatic lungs injuries and found marked improvement in patients oxygenation and general condition of them but with high mortality. Same results was found 4 years back by Brodie et al. [25] in 2011 they studied the effect of ECMO in acute lung injury in adult during epidemic of influenza (H1N1 virus) and had almost the same results.

As regard improvement of the lungs condition

Could be divided to clinical improvement by comparing the results of the 2 groups regard oxygen saturation, hypoxic index, compliance and response to recruitment maneuver in both groups which revealed significant improvement in group B compared to group A in all those parameters all over the duration of the study.

Also radiologically group B showed significant improvement of parenchymatous lungs infiltrate on chest X-ray all over the duration of the study compared to group A. This could be due to better improvement of the local immunity of the lungs following better oxygenation as increase lung tissue oxygenation cause pulmonary vasodilatation and increase blood supply and thus improve local immunity of the lungs more over ECMO protecting the lungs from the injurious effect of mechanical ventilation (especially PEEP) and help in accelerating healing of lung tissue from both septic inflammation (VAP) and traumatic inflammation (lung contusion). This local improvement of the lung tissue could also be proved by following the laboratory marker of tissue destruction LDH and CRP as group B showed significant reduction of LDH level in group B compared to group A all over the studied period also there was inverse proportion between the level of the CRP and improved of lung condition in group B compared to group A in all the studied periods. Ednan et al. [31] found inverse relation between level of CRP and improvement of patients oxygenation and weaning they proved that high CRP carried a good prognosis in severe ARDS. While Aoki et al. [32] found significant reduction in the LDH level in the bronch-alveolar lavage fluid with improvement of oxygenation of patients with ARDS and for rapid weaning.

As regard bacteriological improvement

This very important issue as the severely contused lung considered devitalized lung easy to get infected from ventilation this could be assessed by comparing the chest X-ray as above and qualitative sputum culture which showed significant reduction in number of patients in group B had positive sputum culture compared to patients of group A. This could be due to better oxygenation of both lung tissue and all tissue perfusion which improve both local and systemic immunity and thus better control of both lung infection and bacteremia.

As regard morbidity and mortality

APACH II score above 25, Desaturation $SPO_2 \leq 80\%$, Hypoxic index less than 100, X-ray chest (all quadrant lung infiltrate), Lung compliance>19 ml/cm H_2O, no response to recruitment, Positive sputum culture After 8^{th} day and After 16^{th} day and Failure of weaning from the ventilator at the end of the studied duration significantly higher in group A than group B. While mortality is higher in group B than group A. There was non-significant higher mortality rate in ECMO group compared to conventional ventilation group this could be attributed to effect of heparin which not fully reversed by protamine sulfate as one of this patients develop intracerebral haemorrhage while remaining three patients developed progressive hypoxemia in spite of increasing the machine flow on the other hand all (three) cases from group A died from ventilator associated pneumonia and acute respiratory distress syndrome with multi-organ failure. But still the higher mortality rate in ECMO not well under stood it may be due to systemic effect of heparin used even with the reversal with protamine sulfate or may be to progressive hypoxemia due to increase right to left shunting due to pulmonary vasodilatation from inflammatory cytokines (prostaglandin A and interlukin-6) even with increasing flow of the machine, or micro air thrombi passed from the oxygenator even with presence of micro filters, cases of unexplained deaths on ECMO reported in all the studies done and need more researches [33,34].

This result support results done by Peek et al. [35] at 2009 in united kingdom on 90 patients had ARDS and put on ven-venous ECMO for 6-16 days their mortality rate was 37% but the rest of patients improved and discharged from hospital earlier than those received conventional ventilation. In 2011 Noah et al. [36] used ECMO in ARDS due to H1N1influenza in 69 patients and showed marked improvement of lung condition with lower mortality rate 24% with 6-12 days of ECMO use. Same results were found by Pham et al. [37] 123 patients had severe ARDS due to epidemic of H1N1 influenza and get mortality rate of 36% on 8-22 days ECMO on his study. Bréchot et al. [38] in the same year 2013 did ECMO but veno-venous in ARDS due to septic shock on 140 patients but he had higher mortality 40% on 8-30 days use of ECMO. And lastly Schmidt et al. [39] in 2014 did same study on larger scale 2355 patients with 57% mortality on 4-13 days.

All those study showed improvement of ARDS on ECMO and early weaning from ventilator and less hospital stay whether this ARDS was due to viral pneumonitis or septic shock or trauma but still mortality rate considered high. Further research needed on causes of high

mortality on ECMO and uses of ECMO in all kind of hypoxemia e.g. cardiogenic pulmonary edema and in pediatric ARDS.

Conclusion

ECMO significantly improve all clinical parameters of both Murray and CPIS score and significantly increase number of weaned patients from ventilator but with higher mortality.

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