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Comparative Study Between Action Vitamin C vs. Action of Nitric Oxide in Prolonged Ventilation in Respiratory Failure Patients Due to ARDS

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ABSTRACT

Introduction: Recent meta-analysis prove that vitamin C shorten the duration of mechanical ventilation and accelerate weaning from ventilator especially in prolonged ventilated patients. Nitric oxide considered a relatively old drug used for long time in this issue.

Aim: To compare the effect of either vitamin C or nitric oxide on improvement of general condition of the patients, improvement lung mechanics, early weaning from prolonged ventilation and mortality rates.

Material and Methods: This a prospective double-blind study done in King Abdul-Aziz specialist hospital between September 2020 and December 2021 in the intensive care unit on 60 patients had difficult weaning after ventilation for >10 days due to Acute Respiratory Distress Syndrome (ARDS) and still showing full criteria of ARDS. Allocated randomly in two groups 30 patients in each. All patients in both groups continued on the same protocol of ventilation. Group A received Nitric Oxide (NO) while group B received vitamin C intravenous. The duration of the study last 16 days. during this period, APCH II score, Hemodynamics, Chest X-ray, hypoxic index, lung compliance, Recruitment maneuver, arterial blood saturation, Lactic Acid Dehydrogenase (LDH), C-reactive protein used as indicator for improvement. Number of patients weaned from the ventilator and patients died also recorded.

Results: Showed significant improvement in the general condition between patients of group B compared to group A which monitored by number of patients had both APACH II score <10 and had normal core temperature. Significant improvement in lung condition between patients of group B compared to group A which monitored clinically by number of patients had arterial oxygen saturation >95, hypoxic index >300, better lung compliance, responder to recruitment maneuver. And monitored radiologically by significant higher number of patients in group B had parenchymatous lung infiltrate in chest X-ray less than one quadrant infiltration compared to group A. And monitored laboratory by significant higher number of patients had lower level of LDH from (100-200 U/L) and CRP (201-300) mg/L in group B compared to group A. There was significant higher number of patients weaned from the ventilator in group B compared to group A. There was significant lower morbidity between patients of group B compared to group A. No significant difference was found in mortality rates.

Conclusion: Vitamin C significantly improve the general condition of the patients, improve all parameters of lung mechanics and accelerate weaning from ventilators in prolonged ventilated patients compared to nitric oxide.

Keywords:

Vitamin C, Nitric Oxide (NO), Ventilation, Respiratory failure, Inflammatory, X-ray, Acute Respiratory Distress Syndrome (ARDS)

Introduction

Recent met-analysis proven that vitamin C improve endothelial function, lower blood pressure to its normal range in hypertensive patients, increase left ventricular ejection fraction, decrease the incidence of atrial fibrillation, decrease bronchoconstriction especially in hyperactive airways as Chronic Obstructive Pulmonary Disease (COPD) and bronchial asthma, prevent pain and it may also have beneficial effects against pneumonia [1-4]. Those unique feature put him as competitor to nitric oxide in its use in prolonged ventilation in ARDS patients for acceleration of weaning and shorten the Intensive Care Unit (ICU) stay. The average person, in good health, maintains normal plasma vitamin C levels with a daily intake of about 0.1 g/day. However, much higher doses, in the order of grams per day, are needed for critically ill patients

to reach normal plasma vitamin C levels [5-7]. Without supplementation, plasma vitamin C levels are particularly low in critically ill patients, indicating that the body may have a greater need for vitamin C when under severe stress such as illness requiring intensive care [8-10]. It seems evident that there are gradual changes in vitamin C metabolism according to the severity of disease, in that the sicker patient is the greater the consumption of vitamin C. This further suggests that the sicker a patient is, the more they are likely to benefit from additional vitamin C [11].

Nitric Oxide (NO) has been used successfully in patients with severe Acute Respiratory Distress Syndrome (ARDS) who had poor response to the standard way of management and ventilated for a long time [12-14]. The main mechanism of NO in ARDS is pulmonary vasodilatation and bronco-dilation. thus improve ventilation perfusion ratio. This led to more blood flow and better aeration in inflamed area of the lung with concomitant increase local immunity of the lungs and decreased levels of inflammatory mediators in the inflamed area of the lung which can be proved clinically by decrease inflammatory mediators in bronco-alveolar lavage fluid [15-17]. Moreover Inhaled nitric oxide increases right ventricular ejection fraction and decreases right end-systolic volume and thus prevents the de-compensation of acute cor-pulmonale [18-20]. Nitric oxide also alters immune function and inhibits platelet aggregation and thus decrease the risk of development of micro-thrombi. All these help in preventing right ventricular strain and inhibit pulmonary hypertension in ARDS [21-24].

Material and Methods

This a prospective cohort study done in King Abdu el Aziz specialist hospital between September 2020 and December 2021 in the intensive care unit on patients with respiratory failure and showed failure of weaning from ventilator due to medical and/or surgical causes of ARDS. Inclusion criteria include; aged >18-<65 years, patients had all laboratory and radiological parameters of ARDS which include, Uncompensated hyper-capnia with PH <7.25, and/or Hypoxic index less than 200 (PaO2/FIO2) and/or bilateral parenchymatous lung infiltration on the chest X-ray (4 quadrant infiltration on Murray score). While exclusion criteria were: Post-cardiac arrest which could be a cause of failure of weaning from the ventilator, diabetes mellitus, hypertension and permanent organic brain insult.

Included patients started on the slandered way of ventilation for 10 days with Controlled Mechanical Ventilation (CMV) mode, Fraction Inspired Oxygen (FIO2) of 100%, Positive End Expiratory Pressure (PEEP) of >10 cm H2O to achieve target arterial oxygen saturation (SPO2) of >90% with sedation by midazolam infusion to achieve Richmond Agitation- Sedation Scale (RASS) -2 to -3 (Table 1) and fentanyl infusion for pain control between 50-100 mg/min. All patients nursed in head elevation >30°, received broad spectrum antibiotics according to our antibiotic regimen, with daily assessment for both analgesic and sedative dose, NasoGastric Tube (NGT) feeding given according to our protocol with daily evaluation of weaning criteria and sedation dose. After 10 days only 60 patients selected who had ARDS criteria mentioned before [Uncompensated hyper-capnia with PH <7.25, and/or Hypoxic index less than 200 and/or bilateral parenchymatous lung infiltration on the chest X-ray (4 quadrant infiltration on Murray score)], Included in our study. Tracheostomy done for all patients who were randomly allocated in one of the two groups. Randomization sequence was created using Excel 2007 (Microsoft, Redmond, WA, USA). Each group included 30 patients. Patients of group A received inhalation of nitric oxide stared by 50 parts/billion (ppb) as starting dose titrated according to patient's saturation reaching to 90 ppb as a maximum dose. While patients of group B received 4 gram of vitamin c slowly intravenous once daily for 4 days duration. Improvement of global tissue oxygenation and reduction of toxemia assessed by APACH II score (acute physiological assessment and chronic health evaluation) and core body temperature. improvement of local tissue immunity (lungs) assessed clinically by following: SpO2, hypoxic index, compliance and response to recruitment maneuver (Recruitment maneuver is considered clinical test of lung compliance and start by increase the peak inspiratory pressure to 40 cm/H2O for 40 sec and observe the saturation (SpO2) if improved to more than 95% considered responder in our study) [18], radiologically by area of lung infiltration on chest X-ray using Murray score Table 2, and laboratory by following markers of tissue destruction both levels of Lactic Acid Dehydrogenase (LDH) and C-Reactive Protein (CRP) used for this issue. The study last for sixteen days. If patient showed no cure in one or all measured parameters it considered morbidity. Patients weaned from the ventilator recorded and compared at the end of the studied duration. patients died during the studied period recorded and compared.

We took approval from our research and ethical committee approved the project.

Table 1: Richmond Agitation-Sedation Scale (RASS) [25].

Richmond Agitation-Sedation Scale (RASS)		
Score	**Term**	**Description**
+4	Combative	Violent, immediate danger to staff
+3	Very agitated	Pulls catheters, tubes (aggressive)
+2	Agitated	Aimless movement, fights ventilator
+1	Restless	Anxious but movements not aggressive
0	Alert and calm	
-1	Drowsy	Not fully alert but has eye Contact and opening >10 second
-2	Light sedation	Briefly awakens with eye contact <10 Second

-3	Moderate sedation	Movement or eye opening to voice with no eye Contact
-4	Deep sedation	No response to voice responds to physical Stimulation either by movement or eye opening
-5	Un-arousable	No response to voice or physical stimulation

Table 2: Murray score for severity and evaluation of parenchymatous lung infiltration by chest X ray [26].

Score of severity	0	1	2	3	4
Chest X-ray	Non	1 quadrant infiltrated	2 quadrants infiltrated	3 quadrants infiltrated	4 quadrants infiltrated

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 measured based on a previous study and by using Med Calc statistical software.

Assuming area under the curve 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

Three patients died from multi-organ failure from group A. Two from them died after 5 and 7 days from starting our study. and last one died after fourteen days from starting the study. While four patients died in group B from same cause. two from them died after nine days and two died after thirteen days from starting this study. Those patients recorded as mortality.

Table 3: Represent the demographic data of patients in both groups.

	Group A		**Group B**		**P Value**
	(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 4: Represent the causes of ARDS and prolonged ventilation in patients included in our study.

	Group A		**Group B**		**P Value**
	(n=30)	%	(n=30)	%	
Medical causes	22	73.3	24	80	0.362
COPD with infect	10	33.3	13	43.3	
Pneumonia	6	20	7	23.3	
Others	6	20	4	13.3	
Surgical causes	8	26.7	6	20	0.254
Lung contusion	5	16.6	4	13.3	
ARDS pancr.	2	6.7	1	3.3	
Others	1	3.3	1	3.3	
COPD with infect: chronic obstructive lung disease with chest infection ARDS pancr: ARDS due to pancreatitis					

Table 5: Represent the APACH II score in all patients in both groups in the studied period.

	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
15-25	2	6.7	8	28.6	10	35.7	6
11-14	0	0	0	0	2	7.1	6
≤ 10	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
15-25	10	33.3	12	33.3	8	28.6	7
11-14	5	16.7	5	16.7	8	28.6	8
≤ 10	1	3.3	3	3.3	5	17.9	7
P Value	0.028*		0.023*		0.013*		0.002*

Table 6: Represent the recorded core temperature in degree centigrade in all patients in both groups in the studied period.

Temperture by ^{O}C	**1st 4 days**		**2nd 4 days**		**3rd 4 days**		**4th 4 days**	
Group A	(n=30)	%	(n=28)	%	(n=28)	%	(n=27)	%
>36.5-<38.4	0	0	2	7.1	3	10.7	4	14.8
>38.5-<38.9	0	0	4	14.3	6	21.4	8	29.6
>39 or <36	30	100	22	78.6	19	67.9	15	55.6
Group B	(n=30)		(n=30)		(n=28)		(n=26)	
>36.5-<38.4	7	23.3	8	28.6	10	35.7	12	44.4
>38.5-<38.9	4	13.3	12	42.9	11	39.3	9	33.3
>39 or <36	19	63.3	10	35.7	7	25	5	18.5
P Value	0.016*		0.035*		0.027*		0.002*	

Table 7: Represent the Murray score (severity of parenchymatous lung infiltrate in chest X-ray) for all patients in both groups in the studied period.

	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 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 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 Value	0.042*		0.001*		0.001*		0.0026*	

Table 8: Represent arterial oxygen saturation (SPO2) in all patients in both groups in the studied period.

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 value	0.021*		0.0013*		0.001*		0.001*	

Table 9: Represent measured lung compliance in all patients in both groups in the studied period.

ml/1cm H_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 10: Represent measured hypoxic index in all patients in both groups in the studied period.

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 Value	0.0251*		0.001*		0.003*		0.001*	

Table 11: Represent response of all patients in both groups to recruitment maneuver in the studied period.

Response to Recruitment	**Group A**		**Group B**		**P value**
days	Numbers of responders	%	Numbers of responders	%	
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*

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 [18].

Table 12: Represent measured serum LDH in all patients in both groups in the studied 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: Represent measured serum C reactive protein in all patients in both groups in the studied 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: Represent number of patients weaned from the ventilator in both groups at the end of the studied period.

	Group A		Group B		
	Numbers	%	Numbers	%	P value
Weaned from ventilator	15/27	55.6	19/26	73.1	0.026*

Table 15: Represent morbidity recorded between all patients in both groups at the end of the 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*
Core temperature >39^{O}C or <36^{O}C	15	55.6	5	19.2	0.002*
Desaturation SPO_2 ≤ 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/cm H_2O	7	25.9	0	0	0.003*
NO response to recruitment	13	48.1	6	23.1	0.013*
High LDH >600 U/L	9	33.3	0	0	0.003*
C-reactive protein lower than 100 mg/L	8	29.6	2		0.0026*

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

Results

Tables 3 Showed patient's demographic data with no significant difference between the two groups.

Tables 4 Showed the causes of ARDS and prolonged ventilation in patients included in our study.

Table 5 Showed patient's APACH II with significant reduction in the number between patients in group B in first, second, third and fourth durations of the study.

Table 6 Showed patient's core temperature recorded with significant higher number of patients get normal c temperature in group B compared to group A.

Table 7 Showed patient's chest X-ray with significant higher number of patients had improvement of their chest x ray in group B compared to group A.

Table 8 Showed patient's SPO2 with significant improvement between patients in group B compared to group A.

Table 9 Showed patient's lung compliance with significant improvement in group B compared to group A.

Table 10 Showed significant increase in hypoxic index in group B compared to group A.

Table 11 Showed significant increase in number of patients responds to recruitment maneuver in group B compared to group A.

Table 12 Showed significant reduction in LDH level in group B compared to group A.

Table 13 Showed significant decrease in CRP level in group B compared to group A.

Table 14 Showed significant higher number of patients weaned from the ventilator in group B compared to group A.

Table 15 Showed non-significant difference in the mortality rates between the two groups.

Discussion

Improvement of global tissue oxygenation and reduction of toxemia

There were significant reduction in APACH II score and normalization of body temperature in patients of group B compared to group A. this could be due to the effect of vitamin C on improvement endothelial function, lower blood pressure, increase left ventricular ejection fraction, decrease the incidence of acute cardiac injury due to stress, abolish or even attenuate bronchoconstriction which considered a natural reflex to infection in the mucosa of the tracheobronchial tree especially in hyperactive airways (COPD, bronchial asthma patients), prevent catecholamine release in response to pain, shorten the duration of exudative phase of inflammation, and decrease the incidence of catching Ventilator Associated Pneumonia (VAP) in ventilated patients, and it may also have beneficial effects against pneumonia by shortened the duration of both exudative and infiltrative phase of VAP [1-4] also, there was considerable improvement in those parameters in group A patients due to better systemic oxygenation from NO as it has direct vasodilator effect on the pulmonary arterioles which may be vaso-constricted from hypoxia. This hypoxia might be from the presence of exudate in the alveoli. Which replace the air in the alveoli and lead to reflex vasoconstriction. Moreover, it has direct broncho-dilatation effect on the bronchi and bronchioles which may be under the effect of bronchoconstriction due to natural response to hypoxic vasoconstriction as a normal inherited reflex in the lungs to maintain ventilation perfusion ratio constant. So, both vitamin C and NO improve systemic oxygenation and improve general condition of the patients. But vitamin C remain significantly better.

Improvement of local tissue immunity (lungs)

Clinical cure as there was significant improvement in patients of group B compared to group A in oxygen saturation, hypoxic index, compliance and response to recruitment maneuver. This could be explained by reverting the vasoconstrictor effect of hypoxia. This hypoxia happened as result of exudative phase of VAP which fill the alveoli. The positive inotropic action of vitamin c could abolish or even decrease this reflex. And thus increase lung tissue perfusion with concomitant rapid healing and better lung mechanics.

Also, radiological cure as there was significant improvement in chest X-ray all over the duration of the study between patients of group B compared to group A. This could be due to higher local immunity of the lungs following better oxygenation. The increase lung tissue oxygenation always concomitant with pulmonary vasodilatation and increase blood supply this is well known physiological rule. and thus improve local immunity of the lungs moreover, both vitamin C and NO increase both local and systemic oxygenation. Which may be of help in accelerating healing of lung tissue from both septic inflammation (VAP) and traumatic inflammation (lung contusion). So, both can be of help in either medical or surgical acute lung injury. Although the mechanism of increase lung tissue perfusion of both drug is different. Vitamin C has more inotropic effect and this increase lung perfusion While NO has vasodilation effect and thus reverting the vasoconstrictor effect of hypoxia and also increases lung tissue perfusion.

Laboratory cure proved by significant reduction in the levels of LDH and C-reactive protein in patients of group B compared to group A. Both considered marker of tissue reduction Improvement of markers of tissue destruction by both vitamin C and NO can be easily understood after the former explanation as improvement of local lung immunity and systemic immunity due to better local lung oxygenation and systemic oxygenation lead to rapid healing of the injured lungs and decrease in the serum level of that markers and restore normal lung compliance, normal parenchymatous appearance in the chest X-ray and accelerate weaning from the ventilator.

As regard morbidity and mortality

Number of patients who showed no improvement in APACH II score, Core temperature, SPO_2 , Hypoxic index, X-ray chest, Lung compliance, LDH, C-reactive protein and Failure of weaning from the ventilator with no response to recruitment at the end of the studied duration, significantly higher in patients of group A compared to group B. While mortality is non-significantly higher in group B than group A. This could be explained by the better effect of vitamin C than NO on controlling all parameters of lung injury and controlling the systemic response of the lung infection. The explanation of non-significant higher mortality may be due to the preexisting disease itself as vitamin C considered a safe drug or may be the metabolic acidosis which may be developed especially in the preexisting acidosis already present from severe hypoxia and septicemia in those patients.

Our result support many published research work done on this field, Bjordahl et al. [27] in his study done in United states in 2012 on 185 patients. In this study they gave vitamin C orally in dose of 2 gram/day and found that length of mechanical ventilation was 28.8 hours in patients received vitamin C group and 33.6 hours in the placebo group, which prove decrease in the ventilation time more than 14% in vitamin C group. Dehghani et al in 2014 [28], Habib et al. in 2017 [29] , Safaei et al. in 2017 [30], Tanaka et al. in 2000 [31], Zabet et al. in 2016 [32], Sadeghpour et al. in 2015 [33]. All those studies found significant difference in the vitamin C group compared to placebo group as regard decrease in the ventilation time and early weaning from the ventilator in either the ICU or CCU.

On the other hand, still many authors showed no significant effect of vitamin C administration on the duration of mechanical ventilation, Amini et al. [34] in 2018 in a study done in Iran and in this study, they gave vitamin C in 3 gram/day orally and they found that no significant difference between vitamin C group and placebo group. Ebade et al. [35] in study done in Egypt in 2014 on 40 patients received 3 gram of vitamin C intravenously once daily. And found no any significant difference between the vitamin C group and placebo group as regard the duration of ventilation.

Table 16: Description of the included trials in our discussion.

Trial [ref.]	N	Site	Vitamin C Route	Dose [g/day]	Length of mechanical ventilation [hours]			
					Vitamin C group		Control group	
					SD	Mean	SD	Mean
Bjordahl et al. [27]	185	CCU	po	2	28.8	19.2	33.6	24
Amini et al. [34]	137	CCU	po	3	7.3	6	6.7	4.3
Dehghani et al. [28]	100	CCU	po	1	13.4	2	15.4	14.3
Habib et al. [29]	100	ICU	iv	6	110	50	189	72
Safaei et al. [30]	58	CCU	iv	2	15.1	5.39	22.9	20.46
Ebade et al. [35]	40	CCU	iv	3	2.04	0.35	1.99	0.31
Tanaka et al. [31]	37	Burns	iv	9	290	211	511	374
Zabet et al. [32]	28	ICU	iv	6	36.6	16.1	46.8	10.1
Sadeghpour et al. [33]	290	CCU	po	1	11.8	3.9	14.1	9.5

The trials are listed by the number of patients (N). The mean age in the trials ranged from 42 to 64 years, with a median of 60 years. The proportion of males varied from 58% to 75%. Five trials were carried out in Iran [34, 28, 30, 29,33], two in Egypt [29,35], one in the USA [27], and one in Japan [31] (Table 16).

*Estimated vitamin C dose.

Iv: Intravenous, po: per oral.

SD and mean were expressed in days.

Site means the place in which the study done. CCU: The Coronary Care Unit, ICU: Intensive Care Unit, Burns: Burn unit.

As regard nitric oxide inhalation results, meta-analysis done on that drug used in prolonged ventilation due ARDS including many numbers of clinical trials done by many authors on various number of patients from 14 to more than 600 included randomized, controlled trials irrespective of publication status, date of publication, blinding status, outcomes reported or language of publication [36]. Those studies compared results of nitric oxide inhalation group versus results of control group and conclude that no any significant difference was found between the two groups as regards mortality rates, duration of ventilation and ICU length of stay [37-42].

The unique point in our study that it compared the results of vitamin C group to results of nitric oxide group as both drugs used in accelerating weaning in prolonged ventilation in intensive care units. We selected a relatively old drug which is nitric oxide to be compared with a relatively new one which vitamin C. This study never done before. As the previous studies compared results of vitamin C patients to placebo group and results of nitric oxide patients compared to results of control group.

The main limitation points in our study were the small sample size and the relative short duration of follow up. Another very important limitation point that we studied the effect of vitamin C in prolonged ventilation in adult not in pediatric patients. Still many studies needed to compare the effect of vitamin C as solo drug compared to control group in prolonged ventilation in both adult and pediatric age group and should be done in larger sample size and should be done in multiple centers to strictly decide its effect in prolonged ventilation. Moreover, vitamin C still considered a new drug used in prolonged ventilation and failure of weaning so more research work needed to emphasis fixed protocol for its use in this field and decide the best time, dose and regimen for given this drug in that condition.

Conclusion

Vitamin C significantly improve the general condition of the patients, improve all parameters of lung mechanics and accelerate weaning from ventilators in prolonged ventilated patients compared to nitric oxide.

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