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A Study of Inflammatory Response and Lung Injury Induced by Variable Tidal Volumes in Mechanically Ventilated Children

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Abstract

Background

We aimed to compare the effects of high tidal volume (Vt) versus low Vt mechanical ventilation (MV) on systemic interleukin-8 (IL-8), and tumor necrosis factor alpha (TNF- α) cytokines production and induction of lung injury in mechanically ventilated children.

Materials and Methods: This prospective observational study was performed on 60 critically ill mechanically ventilated children from 2018 to 2019, at PICU of South Valley University and Minia University hospitals, Qena and Minia cities, Egypt. After application of the inclusion and exclusion criteria, we compared MV with high Vt of 9-11 ml (group I) versus low Vt of 5-7ml (group II) per kilogram of predicted body weight in critically ill children. Plasma levels of IL8 and TNF- α cytokines were estimated at the onset of MV and after 24 hours in both groups. Lung injury development was evidenced by change in oxygenation parameters.

Results: Sixty patients on MV (30 with high Vt versus 30 with lower Vt) were enrolled in the study. Plasma levels of interleukin-8 and TNF- α were increased in both groups 24 hours after initiation of MV, but this rise was significantly higher in high Vt group ($p<0.05$). There were significant positive correlations between tidal volume and oxygenation index (p-value <0.05, r=0.32), and with plasma IL-8 (r=0.34, p= 0.01), while negative correlation between tidal volume and change in PaO2/fiO2 ratio after 24 hours MV (r= -0.34, p <0.05).

Conclusion

Mechanical ventilation with high Vt was associated with increased IL-8, and TNF- α cytokines production, and will induce lung injury as evidenced by acute hypoxemia and deterioration in oxygenation parameters (PaO2/FiO2 ratio less than 300 mmHg).

Key Words: Children, Cytokines, Lung injury, Tidal volume, Mechanical ventilation.

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1- INTRODUCTION

Application of mechanical ventilation (MV) in pediatric intensive care units (PICUs) is an essential and pivotal life-saving therapy for patients with critical illness and respiratory failure whether acute or chronic (1). In spite of being a life-saving intervention in frequent critical illnesses, MV can result in serious drawbacks ranging from airway complications, equipment failure and endotracheal tube blockage during the intubation period to laryngotracheal stenosis during the post-extubation period (2). MV may lead to substantial damage for both previously healthy and diseased lungs through a process called ventilator-induced lung injury (VILI) that could end with multi-organ failure and death. The basic pathophysiological components of VILI can be barotrauma and volutrauma due to alveolar overdistension by excessive tidal or end-expiratory volume, atelectrauma due to ventilation at low lung volumes below the lower inflection point; and biotrauma by released inflammatory mediators in the lung (3).

Lung inflammation and acute injury is a critical process in which cytokines play a crucial role. Cytokines including interleukin-8 (IL-8), and tumor necrosis factor alpha (TNF- α) are produced and released by airway epithelial cells of bronchioles and bronchi in addition to neutrophils and alveolar macrophages (4). Non-protective ventilation strategies may lead to release of cytokines and even microbes from the lungs into systemic circulation and induce damage to other organs in addition to the lungs. The remote effects of released inflammatory mediators on subsequent development of multi-organ dysfunction syndrome (MODS) gave researchers a theoretical base explaining serious effects of injurious ventilator strategies in cases of adult respiratory distress syndrome (ARDS) (3, 5). Protective MV with lower Vt can attenuate the systemic inflammatory response, improve lung function and hasten earlier weaning and extubation (6). The purpose of this study was to compare the effects of high Vt versus low Vt mechanical ventilation (MV) on systemic production of IL-8 and TNF- α, cytokines and induction of lung injury evidenced by acute hypoxemia (PaO2/FiO2 ratio less than 300 mmHg), in mechanically ventilated children.

2- MATERIALS AND METHODS

2-1. Study design and population

Prospective observational study was performed on 60 critically ill mechanically ventilated children during the period from June 2018 to March 2019**,** in double-centers tertiary institutions, at pediatric intensive care units (PICU) of South Valley University and Minia university hospitals, Qena and Minia cities, Egypt. The two units had similar guidelines for sedation and mechanical ventilation.

2-2. Inclusion and exclusion criteria

The study included all patients admitted to the PICU with acute respiratory failure aged between 1 month and 16 years and continued on MV for at least 24 hours. Acute respiratory failure was considered if PaO2 was lower than 60 mmHg and/or PaCO2 higher than 50 mmHg. We excluded all cases aged less than 1 month or more than 16 years, those without respiratory failure, children on immunosuppressive therapy, cases with evidence of acute lung injury, restrictive pulmonary disease, ex-premature with chronic lung disease, children with sepsis and those with previous lobectomy.

2-3. Method

Demographic data including age, sex, and the underlying condition causing respiratory failure were recorded in addition to complete physical examination, and chest radiography. Data

of arterial blood gas analyses, ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2 ratio), and oxygenation index (OI) where OI= mean airway pressure (MAP) × FiO2 × 100÷PaO2 where MAP was measured by ventilator were calculated at onset and after 24 hours of MV. The children were assigned to receive mechanical ventilation in volume controlled mode according to their clinical status, oxygenation parameters, and tidal volume was adjusted according to the patients need. Acute lung injury was evidenced by acute hypoxemia (PaO2/FiO2 ratio less than 300 mmHg), and bilateral infiltrates seen on chest X-ray (7). Moreover, pediatric risk of mortality (PRISM), pediatric logistic organ dysfunction score (PELODS), duration of MV, length of hospital stay and mortality rate were also recorded.

2-4. Intervention

Patients were ventilated with intermittent positive pressure ventilation using Evita 2 dura intensive care ventilator, Drager Medical AG and CO KGaA, Germany. Respiratory rate and fraction of inspired oxygen were adjusted to keep arterial oxygen saturation of > 90%, paco2 of 35-45 mmHg and pH> 7.25. Positive end-expiratory pressure (PEEP) was kept at (5 to 8 cm H2O), and inspiratory: expiratory (I: E) ratio at 1:2 and further adjustments were carried out based on lung compliance (6, 7). All ventilator circuits were equipped with a heat-moisture exchanger. Variables of tidal volume, inspiratory time, expiratory time, PEEP, MAP and peak inspiratory pressure were measured at onset and after 24 hours of MV. The critically ill children were classified into 2 groups:

Group I: received high Vt of 9 to 11 ml/kg of predicted body weight (high Vt group).

Group II: received low Vt of 5 to 7 ml/kg of predicted body weight (low Vt group).

2-5. Laboratory measurements

Baseline blood samples for IL-8 and TNF-α measurement were taken and additional samples were obtained after 24 hours of MV for comparison. After, 2 ml of fresh blood sample was obtained from each patient, immediately centrifuged for 10 minutes then plasma was aspirated and stored at -40 ℃. Commercially available ELISA assay was used to measure plasma levels of human IL-8, TNF-α in duplicate according to manufacturer's instructions with the detection limit for IL-8 25pg/ml and TNF-α 10 pg/ml. Difference between baseline and 24 hours samples were calculated in both groups.

2-6. Ethical consideration

Institutional ethics committee approval was obtained for the study, and written informed consent was taken from parents.

2-7. Statistical Data Analyses

Statistical analyses of the data collected from the two outcome groups (high Vt group and low Vt group) were compared using SPSS version 20.0 for Windows (Chicago, IL. USA). Continuous variables were expressed as mean (standard deviation), and categorical variables were expressed as frequency. Pearson's Chi-square test was used for comparison of categorical data between groups and t-test was used for comparison of means. A p-value<0.05 was considered statistically significant. Pearson's correlation was used to assess the correlation between different variables.

3- RESULTS

Our study included 60 mechanically ventilated patients who met the inclusion criteria. Their age ranged from 1month to 16 years; there were 30 males and 30 females. The patients were divided into 2 groups; the demographic characteristics of both groups and admission diagnosis of patients are reported in **Table.1.**

Table-1: Demographic characteristics of studied groups of patients.

Variables		High Vt (n= 30) Group I	Low Vt (n= 30) Group II	P-value
Age (years)	< 1 year (n= 21) ≥1y<5y(n= 20) ≥5 years(n= 19)	10(33.3%) 11(36.7%) 9(30%)	11(36.7%) 9(30%) 10(33.3%)	0.79
Gender (male/female)		17/13	13/17	0.31
Weight (kg)		17.51 (4.84)	19.31 (6.32)	0.07
Length (cm)		93.95 (11.7)	94.63 (15.64)	0.13
Body mass index (kg/cm)		16.42 (1.57)	18.08 (3.2)	0.08
Heart rate (beats/minute)		133.3 (14.94)	126.59 (17.13)	0.15
Respiratory rate (breaths/minute)		38.93 (7.1)	40.68 (6.1)	0.12
Systolic blood pressure (mmHg)		91.62 (14.97)	89.18 (19.62)	0.16
Diastolic blood pressure (mmHg)		58.31 (12.89)	55.5 (16.75)	0.67
Admission Diagnosis	Neurologic disease	8 (26.7%)	10(33.3%)	0.9
	Respiratory disease	10 (33.3%)	8(26.7%)	
	Cardiac arrest	5 (16.7%)	6(20%)	
	Poisoning& envenomation	4 (13.3%)	4(13.3%)	
	Post-operative#	3 (10%)	2(6.7%)	
Use of sedatives		17/30 (56.7)	19/30 (63.3%)	<0.01*
Use of inotropes		21/30 (70%)	18/30 (60%)	0.28
ICU score (1st 24 hours)	PELOD	14.7(11.31)	12.05 (7.31)	0.60
	PRISM	10.35(6.9)	9.1(4.2)	
Mortality (total 12 =20%)		7 (58%)	5 (42%)	0.13

Vt: tidal volume; PELODS: Pediatric logistic organ dysfunction score; PRISM: Pediatric risk of mortality, Significant P-value at P <0.05; # two of them operated for congenital heart (VSD), and one for intussusception. *significant P value<0.05.

Table.2 shows comparison between the two groups: group I (high Vt group), and group II (low Vt group). There was no significant difference between the two groups concerning the blood gases analysis and oxygenation parameters at admission but there are significant higher levels of Vt and PIP in group I compared to group II (p-value <0.01 and <0.015, respectively).

Table-2: ABG and Ventilatory parameters of both groups at admission.

Variables		High Vt (n= 30) Group I	Low Vt (n= 30) Group II	P-value
Blood gases parameters	PH	7.25 (0.17)	7.22 (0.14)	0.59
	PaO2 (mmHg)	73.96 (51.11)	79.91 (55.46)	0.58
	PaCO2 (mmHg)	51.2 (25.44)	50.99 (31.89)	0.59
	O2 saturation (%)	82.93(15.02)	79.35 (21.43)	0.54
Ventilatory parameters	Tidal volume	9.83 (1.17)	6.64 (1.14)	<0.01*
	RR (breaths/minute)	26.55 (5.32)	27.05 (4.77)	0.75
	PIP (cmH2O)	21.05 (4.16)	17.75 (4.04)	0.015*
	PEEP (cmH2O)	6.2 (1.2)	5.7 (0.86)	0.13
	MAP (cmH2O)	8.24 (1.72)	7.06 (2.1)	0.06
	FiO2 (%)	67.2 (10.81)	65.75 (10.58)	0.71

PEEP: Positive end-expiratory pressure; PIP: Peak inspiratory pressure; PaO2: Partial pressure of oxygen; PaCO2: Partial pressure of carbon dioxide; Vt: tidal volume; MAP: Mean airway pressure; *significant P-value<0.05.

Table.3 shows comparison between the two groups regarding blood gases analysis and oxygenation parameters at admission and after 24 hours. There was significant deterioration in oxygenation parameters in group I as proved by decrease in PaO2/FiO2 and increased oxygenation index (p-value <0.05); while significant improvement was observed in group II (p-value <0.05). When comparing the same parameters between the two groups after 24 hours, significant increase in PaO2/FiO2 and decrease in oxygenation index were observed in low tidal volume group than in high Vt group (p-value <0.001).

Table-3: Comparison between the two groups regarding blood gases analysis and oxygenation parameters at admission and after 24 hours.

Variables	Group I		P-value
	At admission	After 24 hours MV	
PH	7.25 (0.17)	7.31 (0.07)	0.59
PaO2 (mmHg)	73.96 (51.11)	86.6 (27.83)	0.20
PaCO2 (mmHg)	51.2 (25.44)	44.74 (8.33)	0.06
O2 saturation (%)	82.93(15.02)	87.21(2.54)	0.16
PaO2/ FiO2 (mmHg)	268.81 (52.91)	237.06 (63.07)	<0.05*
Oxygenation index	3.07 (0.75)	3.7(1.43)	<0.05*
Group II			
Variables	At admission	After 24 hours MV	P-value
PH	7.22 (0.14)	7.26 (0.13)	0.50
PaO2 (mmHg)	79.91 (55.46)	86.75 (57.22)	0.54
PaCO2 (mmHg)	50.99 (31.89)	34.02 (9.39)	0.08
O2 saturation (%)	79.35 (21.43)	86.93 (4.25)	0.41
PaO2/FiO2 (mmHg)	276.28 (59.93)	305.71 (126.16)	<0.05*
Oxygenation index	2.94 (0.91)	2.64(1.1)	<0.05*
Group I versus Group II			
Variables	At admission	After 24 hours MV	
PH	0.59	0.67	
PaO2(mmHg)	0.58	<0.05*	
PaCO2(mmHg)	0.59	0.74	
O2 saturation (%)	0.54	0.58	
PaO2/FiO2(mmHg)	0.67	<0.001*	
Oxygenation index	0.09	<0.001*	

MV: mechanical ventilation; PaO2: Partial pressures of oxygen; PaCO2: Partial pressures of carbon dioxide; PaO2/FiO2 ratio PaO2:FiO2: Oxygenation ratio; *significant P-value<0.05.

Table.4 shows comparison between baseline and 24 hours plasma cytokines in each group. There was significant increase in plasma IL8 and TNF-α cytokines levels after 24 hours in group I (p-value <0.01 and <0.05, respectively); while, non-significant increase in plasma IL-8 and TNF-α levels after 24 hours was detected in group II. When comparing the same parameters between the two groups after 24 hours, significant increase in IL-8 and TNF-α level was detected in group II than group I (p-value <0.001 and <0.01, respectively).

Table-4: Comparison between baseline and 24 hour plasma cytokines in each group.

Variables	Group I		P-value
	At baseline	After 24 hours MV	
IL-8 (pg/ml)	25.5 (15.05)	35.8 (24.5)	<0.01*
TNF-α (pg/ml)	29.5 (7.6)	34.8 (6.8)	<0.05*
Group II			
Variables	At baseline	After 24 hours MV	P- value
IL-8 (pg/ml)	23.9 (15.9)	25.6 (18.3)	0.29
TNF-α (pg/ml)	26.3 (8.2)	28.6 (10.7)	0.76
Group I versus Group II			
Variables	At baseline	After 24 hours MV	
IL-8 (pg/ml)	0.09	<0.001*	
TNF-α (pg/ml)	0.08	<0.01*	

MV: mechanical ventilation; TNF-α: Tumor necrosis factor α; IL: Interleukin. *Significant P value at P <0.05.

Table.5 shows correlation between tidal volume and changes in oxygenation parameters and cytokines levels. There were significant positive correlations between tidal volume and oxygenation index (p-value <0.05, r=0.32), and with plasma IL-8 (r=0.34, p-value 0.01) after 24 hours MV, while negative correlation between tidal volume and change in PaO2/fiO2 ratio in 24 hours MV was observed (r= -0.34, p-value <0.05).

Table-5: Correlation between tidal volume and changes in oxygenation parameters and cytokines levels.

Variables	Tidal volume	
	R	P-value
Change in PaO2/fiO2 ratio in 24 hours MV	-0.34	<0.05
Change in oxygenation index in 24 hours MV	0.32	<0.05
Change in plasma IL-8 in 24 hours MV	0.34	0.01
Change in plasma TNF-α in 24 hours MV	0.32	0.07

R: Pearson's correlation; RR: Respiratory rate; PaCO2: Partial pressures of carbon dioxide; PaO2/FiO2 ratio: Oxygenation ratio; TNF-α: Tumor necrosis factor α; IL: Interleukin. Significant P-value at P <0.05.

4- DISCUSSION

This study aimed to compare the effects of high Vt versus low Vt mechanical ventilation (MV) on systemic production of IL-8 and TNF- α, cytokines and induction of lung injury in mechanically ventilated children. We found that use of lower Vt might dampen the inflammatory response of the lungs. Our major finding is that both IL-8 and TNF-α concentrations were increased significantly with high Vt than low Vt in mechanically ventilated patients after 24 hours of onset. Mechanical ventilation is known to exaggerate the inflammatory response of previously injured lungs and induce massive release of cytokines from healthy lungs (8, 9), a finding that was noticeable in our current study. The local and systemic inflammatory response to MV is thought to be the central mechanism in the pathogenesis of VILI (5). The occurrence of ALI is commonly explained by the “double hit” phenomenon (10). The "first hit" is the initiating insult for which child was admitted to ICU where both catecholamine storm and inflammatory reaction occur. Catecholamine release leads to increased hydrostatic pressure and capillary permeability in the pulmonary vessels (11). The normal lung becomes a primed lung that is very susceptible to further injurious stimuli like MV "second hit". The potentially injurious ventilation

leads to stress and strain in the primed lung resulting in alveolar inflammation with neutrophil activation and cytokine production; ultimately, ALI develops (12). In a study by Plotz et al. (13), they found that children without lung injury who were ventilated for cardiac catheterization with Vt 10 ml/kg showed a marked pro-inflammatory response in bronchoalveolar lavage (BAL) fluid. A previously published meta-analysis of low Vt ventilation in patients without lung injury documented that low Vt ventilation induces less incidence of lung injury and decreased mortality rate along with reduction of incidence of chest infections and length of hospital stay (14).

In 400 adult patients who underwent major abdominal surgery and who were at risk of pulmonary complications, Futier and colleagues (15) compared protective low Vt (6–8 mL/kg) with conventional high tidal volume ventilation (10–12 mL/kg). They concluded that low Vt patients had less complications in the first 7 days following surgery, less ventilation needs for acute respiratory failure and shorter post-operative hospital stay. Pinheiro de Oliveira et al. (16) observed higher levels of IL-8 and TNF-α in the BAL fluid of patients ventilated with high Vt without significant increase in systemic cytokines. Some clinical studies evaluating short periods of mechanical ventilation in patients without lung diseases did not detect alteration of plasma levels of inflammatory mediators (17-19).

In patients who planned to undergo an elective surgical interventions lasting more than 5 hours, Wolthuis et al. (20) showed that MV with Vt of 12 ml/kg increased inflammatory mediators in the BAL fluid when compared to a Vt of 6 ml/kg without accompanied rise of plasma levels. As there are major differences between child and adult lungs, results obtained from ventilated adults cannot be applied directly to the critically ill child. Remarkably, variable results have been noticed in several pediatric retrospective and prospective observational studies. Some studies showed a beneficial effect of higher Vt, without any effect on patient outcome (21-23); while some investigators observed lower mortality among children ventilated with low Vt ~8 mL/kg compared with ~10 mL/kg (24). In the current study, the incidence of lung injury in high Vt ventilated group reflected by decreased oxygenation ratio (PaO2/FiO2), and increased oxygenation index was more noticeable than low Vt ventilated group. Halbertsma et al. (5) analyzed Vt in children admitted with a normal oxygenation ratio (PaO2 / FiO2 > 300mm Hg), and detected that use of higher tidal volumes contributes to the development of a oxygenation ratio < 300 mm Hg.

They added that in ventilated critically ill children with an initial normal gas exchange, a Vt > 9 ml/kg increases the risk for ALI with negative impact on prolongation of mechanical ventilation duration. Contrary to Wolthuis et al. (20), we noticed more need for sedatives use in low Vt group and this difference can be explained by higher rate of patient-ventilator asynchrony noticed with low Vt ventilation (25). In several studies, in addition to detection of higher plasma cytokine levels during high Vt ventilation (26-28), some studies documented that persistent cytokine elevation is associated with development of Multiple organ dysfunction syndrome (MODS) and poor outcome in patients with Acute respiratory distress syndrome (ARDS) (28).

4-1. Study Limitations

Limitations of this study include: the small number of studied critically ill patients and the short time of follow-up at 24 hours after the onset of MV. Finally, our study did not correlate cytokine levels with the patient's outcome and future research is needed to evaluate long-term effects.

5- CONCLUSION

We concluded that high tidal volume is associated with increased cytokine production and contributes to development of lung injury in mechanically ventilated children and leads to deterioration in oxygenation parameters than low tidal volume ventilation. The significant deterioration in oxygenation parameters with high tidal volumes ventilation was proved by decrease in PaO2/FiO2. As Vt settings are determined by ICU practitioners and physicians, implementation of lung-protective MV with lower Vt can lead to reduction of the incidence of this iatrogenic lung injury and may limit pulmonary inflammation in mechanically ventilated patients.

6- CONFLICT OF INTEREST: None.

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