Association of fluid balance during first 48 hours and length of mechanical ventilation in pediatric intensive care unit

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Abstract

***Background*: Prolonged mechanical ventilation can increase mortality and morbidity rate. Study shows that positive fluid balance associated with prolonged mechanical ventilation, longer hospital length of stay, and higher mortality rate in acute lung injury. We conducted this study to show the association of fluid balance and duration of mechanical ventilation in the pediatric intensive care unit.**

***Methods*: This was an analytic observational study in children one month to 18 years old who admitted to Pediatric Intensive Care Unit (PICU) Haji Adam Malik General Hospital Medan during April-November 2019. Fluid balance was recorded during first 48 hours in PICU. Bivariate analysis was done to analyse association of fluid balance and length of mechanical ventilation with logistic regression analysis for the mortality.**

***Results*: One hundred and seventy-one children were included in this study. Positive fluid balance was found in 102 children (59.6%) with length of mechanical ventilation mostly under seven days (64.3%). Chi-square test showed significant association between fluid balance and duration of mechanical ventilation (p<0.001). Univariate logistic regression analysis showed that fluid balance had no significant association with mortality, but Pediatric Logistic Organ Dysfunction-2 (PELOD-2) and Pediatric Index of Mortality 2 (PIM2) had significant association with OR 2.6 (1.6-4.4) and 1.05 (1.02-1.08), respectively. Multivariate model also indicated that PELOD-2>8.5 and PIM2>30% showed significant association with mortality (OR 2.6 [1.6-4.4] and OR 1.05 [1.02-1.08], respectively).**

***Conclusion*: Fluid balance was associated with length of mechanical ventilation, but no effect on mortality. Multivariate model showed independent association of PELOD-2>8.5 and PIM2>30% with mortality.**

Key words: Fluid balance, mechanical ventilation, pediatric intensive care unit.

Introduction

Mechanical ventilation is one of the most common therapy in the intensive care unit. (1) Prolonged mechanical ventilation is associated with increasing risk of morbidity and mortality. Prolonged mechanical ventilation also associated with various complications such as ventilator-associated lung injury and ventilator-associated pneumonia. (2) Risk factors associated with prolonged mechanical ventilation in children undergoing pediatric congenital heart surgery include prolonged cardiopulmonary bypass time, delayed sternal closure, healthcare-associated infections, noninfectious pulmonary complications, and the need for reintubation. It may contribute to increased resource utilization and worse neurodevelopmental outcomes in children. (3)

The incidence of pneumonia increases among patients in the intensive care unit compared to wards. Ventilator pneumonia can increase mortality 24-50%, and 76% for infection caused by high-risk pathogens. (4) Acute lung injury (ALI) has a mortality rate 22-65% and almost 2500-9000 children die annually in America. (5) One of the approaches to prevent the injury caused by mechanical ventilation is by decreasing the duration of mechanical

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ventilation. Strategies that are used to control it are sedation protocol and ventilation weaning by using spontaneous breathing. (6,7) Measured outcomes such as fluid balance also associated with the duration of mechanical ventilation. (8)

Observational study showed positive fluid balance within 24 hours increased the risk of ALI and mortality rate. (5) Another study showed an association of positive fluid balance in the first three days with increased length of mechanical ventilation and mortality in children with ALI and 15% fluid overload stated to be associated with poor oxygenation, increased length of mechanical ventilation. (9,10) We conducted this study to show the association of fluid balance and duration of mechanical ventilation in the pediatric intensive care unit.

Methods

An analytic observational study was conducted on children who admitted in the Pediatric Intensive Care Unit (PICU) H. Adam Malik General Hospital Medan in April to November 2019. All subjects have been asked for parents' approval after an explanation about the condition of the disease. The study was conducted after approval of the Health Ethics Committee from the Faculty of Medicine, Universitas Sumatera Utara and Ethics Committee H. Adam Malik Hospital Medan. Patients with renal replacement therapy, burn injury, and patients who already use mechanical ventilation prior transferred to the hospital were excluded.

Demographic data such as age, gender, weight, height, previous medical history, physical examination, and diagnosis were recorded. Blood samples were taken for a complete blood count, blood gas analysis, kidney function test, lactate, with additional blood pressure, and PaO2/FiO2 to calculate Pediatric Logistic Organ Dysfunction-2 (PELOD-2) and Pediatric Index of Mortality 2 (PIM2) scores. Sputum culture was taken after 48 hours of mechanical ventilation. Duration of mechanical ventilation and calculation of fluid balance during 48 hours of mechanical ventilation were recorded.

Univariate analysis was done to determine the distribution of characteristics of researched subjects with mechanical ventilation. Numeric variables were expressed as median (minimal-maximal) because of non-normality data distribution and categorical variables were expressed as frequency and percentage. Bivariate analysis was done using chi-square and Mann-Whitney test. Multivariate analysis was done using logistic regression. Data were analyzed using Statistical Package for Social Sciences (SPSS) version 22.

Results

During study period, 171 eligible children were included in the study based on inclusion and exclusion criteria. Ninety-four children (55%) were boys and 59 children (34.5%) were under one-year-old. The nutritional status assessment was carried out based on World Health Organization (WHO) and Center for Disease Control and Prevention (CDC) growth chart, and majority were well nourished (n=78, 45.6%). Postoperative management was the most common indication for mechanical ventilation, contributing to 31% with mortality rate 42.1%. All baseline characteristics of children with mechanical ventilation can be seen in **Table 1**.

Duration of mechanical ventilation that was observed had a median 4 days (range 2 to 35 days) and mostly under 7 days (n=110, 64.3%). Ventilator-associated pneumonia (23.4%) was the major complications observed in our study. The fluid balance assessment showed large variation with range from -31.7% to +10.2%. Positive fluid balance was found in 61 subjects (56%) and negative fluid balance in 48 subjects (44%) (**Table 2**). All patients that using mechanical ventilation were checked for sputum culture to isolate microorganism and to diagnose ventilator-associated pneumonia (VAP). The most common organisms isolated from sputum culture were Acinetobacter baumanii and Klebsiella pneumonia (n=13, 7.6%) (**Table 3**).

Table 4 shows that in patient with positive fluid balance, most children had length of mechanical ventilation more than 7 days (53.9%). Length of mechanical ventilation under 7 days was found mostly in children with negative fluid balance (91.3%). Bivariate analysis using chi-square test showed significant association between fluid balance and length of mechanical ventilation ($p<0.001$). Probable outcome using PELOD-2 and PIM2 scores was analysed using Mann-Whitney test and each score showed significant association with mortality ($p<0.001$ and $p<0.001$, respectively) (**Table 5**). Cutoff value of fluid balance, PELOD-2 score, and PIM2 score for mortality in this study were 2.5%, 8.5, and 30%, respectively. Univariate logistic regression analysis showed that fluid balance was unsignificant to mortality, but significant association was found for PELOD-2 (OR 2.6 [1.6-4.4]) and PIM2 (OR 1.05 [1.02-1.08]). Multivariate model also showed that PELOD-2 and PIM2 scores were associated with mortality ($p<0.001$) (**Table 6**).

Discussion

Indication for mechanical ventilation in this study mostly was post operative care. Each pediatric intensive care unit has different majority indication for mechanical ventilation. Samaddar, et al study showed most mechanical ventilation indication was sepsis (49.2%) and followed by respiratory failure (24.6%). (11) Study by Vidal, et al did not distinguish whether the disorder happened before or after post operative care with respiratory and cardiovascular disorder contributed to 28.8% and 27.6%, respectively, with total post operative mechanical ventilation 42.9%. (12)

Study by Chen, et al showed that non-survivor patients had long period of mechanical ventilation (ranged from 3.5 until 79.5 days). (13) This study had shorter ventilation duration that ranged from 2 until 35 days. VAP was common complication that can further prolong mechanical ventilation. Vedavathy, et al said that pneumonia incidence was higher in intensive care unit and VAP could increase mortality by 24%-50%, even until 76% if the infection was caused by high-risk pathogen. (4) VAP in this study was found in 40 children (23.4%).

Fluid balance was used as a marker to assess length of mechanical ventilation. Mueller, et al conducted a study in PICU showed that fluid balance associated with mortality was quite high with value 51.9% (range 9.71%-64.12%). Mortality rate in that study was 30%. (14) Ketharanatha, et al also showed that positive fluid balance with value 3.5% (range 2.1%-4.9%) was found in non-survivor patients with mortality rate 10%. (15) Vidal, et al showed that fluid balance in the first 48 hours had an average of 5.75%±5.86 and 50.3% patients had mechanical ventilation more than 7 days. (12) Our study also showed positive fluid balance in 59.6% patients with median value 2.3% (range -31.7%-10.2%) and high mortality rate until 41.2%

Arikan, et al conducted a retrospective cohort study with result that positive fluid balance more than 15% had longer mechanical ventilation time. (10) Flori, et al stated that total fluid balance during 72 hours of acute lung injury was associated with higher mortality rate in bivariate analysis (OR 1.12 [1.02-1.2]) and correlation with mechanical ventilation time (r=0.41). Multivariate analysis also showed that increased fluid balance significantly associated with mortality (OR 1.08 [1.01-1.12]). (9) This study showed different result that fluid balance did not have a significant effect with mortality (OR 0.9 [0.8-1.02]).

Mortality can also be assessed using predictor scores such as PIM2 and PELOD-2. Study conducted by Ghandi, et al stated that PIM2 score had sensitivity 98.2% with cutoff point 99.8% for mortality. (16) Hariharan, et al also showed that the area under the receiver operating characterictic (ROC) curve (AUC) of PIM2 score was 0.82 (95% CI 0.7-0.92) and supported by Slater, et al with AUC of PIM2 0.90 (95% CI 0.89-0.92). (17,18) PELOD score that assessed by Ketharanatha, et al was associated with mortality where higher PELOD score in non-survivor patients (21.5 [11-30]) than in survivor patients (10 [1-10]). (15) Multivariate analysis done by Vidal, et al showed that PELOD score had significant association with mortality. PELOD score cutoff point was 10 with OR 2.58 (1.17-5.68). (12) In this study, cutoff point of PELOD-2 score was 8.5 with sensitivity 93.1% and PIM2 score was 30% with sensitivity 90.3%. Multivariate model showed that both PELOD-2 and PIM2 scores had significant relationship with mortality. PELOD-2 score had higher risk than PIM2 score with OR 2.5 (1.6-4.1) vs OR 1.04 (1.01-1.07).

There was some limitation in this study: first, cutoff point for fluid balance was lower than other study. Second, this study did not conduct an assessment of other oxygenation factors that affect mechanical ventilation. Third, this study just conducted in one center so that the cutoff point cannot be generalized. It is needed for further research on a larger scale to determine cutoff point in patients with mechanical ventilation.

Table 1. Baseline characteristic of children with mechanical ventilation

Indicator	n=171
Gender, n (%)	
- Boys	94 (55)
- Girls	77 (45)
Age, n (%)	
- Under 1 year old	59 (34.5)
- 1-5 years old	39 (22.8)
- 6-10 years old	20 (11.7)
- 11-18 years old	53 (31)
Body weight (kg), median (min-max)	12 (2.8-80)
Body height (cm), median (min-max)	95 (45-166)
Nutritional status, n (%)	
- Severe malnutrition	51 (29.8)
- Mild-moderate malnutrition	27 (15.8)
- Well-nourished	78 (45.6)
- Overweight	15 (8.8)
Mechanical ventilation indication, n (%)	
- Respiratory disorder	31 (18.1)
- Cardiovascular disorder	10 (5.8)
- Neurological disorder	33 (19.3)
- Circulation disorder	26 (15.2)
- Nephrology disorder	18 (10.5)
- Postoperative management	53 (31)
Outcome, n (%)	
- Move to the ward	99 (57.9)
- Death	72 (42.1)

Table 2. Parameter of mechanical ventilation

Indicator	n=171
Duration of mechanical ventilation, median (min-max)	4 (2-35)
- Less than 7 days, n (%)	110 (64.3)
- More than 7 days, n (%)	61 (35.7)
Fluid balance, median (min-max)	2.3 (-31.7-10.2)
- Positive, n (%)	102 (59.6)
- Negative, n (%)	69 (40.4)
Complication	
- Ventilator-associated pneumonia, n (%)	40 (23.4)
- Atelectasis, n (%)	7 (4.1)

Table 3. The causative organism from sputum culture

Organism	n (%)
- Klebsiella pneumoniae	13 (7.6)
- Acinetobacter baumanii	13 (7.6)
- Stenotropomonas maltophilia	3 (1.8)
- Staphylococcus aureus	2 (1.2)
- Enterobacter cloacae	4 (2.3)
- Pseudomonas aeruginosa	10 (5.8)
- Burkholderia cepacia	2 (1.2)
- No growth	29 (17)

Table 4. Association between fluid balance and length of mechanical ventilation

Fluid balance	Mechanical ventilation, n (%)		p value
	More than 7 days	Less than 7 days	
- Positive	55 (53.9%)	47 (46.1%)	<0.001[a]
- Negative	6 (0.7%)	63 (91.3%)	

Legend: [a]=Chi-square test.

Table 5. Association between PELOD-2 and PIM2 scores with mortality

Parameter	Total (n=171) Median (min-max)	Survivor (n=99) Median (min-max)	Non-survivor (n=72) Median (min-max)	p value
PELOD-2	8 (2-20)	6 (2-14)	12 (6-20)	<0.001[a]
PIM2	23.4 (0.82-96.8)	5.59 (0.82-72.8)	72.4 (2.67-96.8)	<0.001[a]

Legend: PELOD-2=Pediatric Logistic Organ Dysfunction-2; PIM2=Pediatric Index of Mortality 2; [a]=Mann-Whitney test.

Table 6. Univariate and multivariate regression analysis to assess fluid balance, PELOD-2, and PIM2 score with mortality

Parameter	Univariate, OR (CI 95%)	Multivariate, OR (CI 95%)	p value
Fluid balance	0.9 (0.8-1.02)		
PELOD-2	2.6 (1.6-4.4)	2.5 (1.6-4.1)	<0.001[a]
PIM2	1.05 (1.02-1.08)	1.04 (1.01-1.07)	<0.001[a]

Legend: PELOD-2=Pediatric Logistic Organ Dysfunction-2; PIM2=Pediatric Index of Mortality 2; [a]=Logistic regression

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