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Correlation of Tracheal Amylase and Ventilator-Associated Pneumonia in Mechanically Ventilated Pediatric Patients

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ABSTRACT

Introduction: *To determine the correlation between tracheal amylase level and ventilator-associated pneumonia (VAP); and evaluate whether tracheal amylase level is associated with pre-intubation aspiration risk factors.*

Methods: *This was a cohort study at Queen Sirikit National Institute of Child Health, Bangkok, Thailand, during April 2019 – March 2020. Intubated and mechanically ventilated pediatric patients aged 1mo – 15 years were included. Tracheal amylase levels were measured at time of enrollment and day of suspected VAP.*

Results: *Tracheal amylase levels were measured at the time of enrollment and on the day of suspected VAP diagnosis. Eighty-eight patients were enrolled in this study, 22 (25%) of which were diagnosed as VAP; and 56 (63.6%) were male. Median initial amylase levels in non-VAP and VAP groups were 165.5 U/L and 108.5 U/L respectively (p=0.82). Median amylase level when VAP was diagnosed decreased to 63 U/L. Median initial amylase level significantly increased in patients with pre-intubation risk factors for aspiration compared to those without (320 U/L and 56 U/L respectively, $p < 0.001$).*

Conclusions: *There was no association between initial tracheal amylase level and VAP but increased tracheal amylase level was associated with pre-intubation risk factors for aspiration.*

Keywords

Ventilator-associated pneumonia, Mechanically ventilated patients, Tracheal amylase, Aspiration.

Introduction

Ventilator-associated pneumonia (VAP) is the second most common cause of hospital-acquired infection in pediatric intensive care unit (PICU) [1-3] resulting in increased ventilator days, length of hospital stays, morbidity and mortality [4-5]. However, the pathogenesis of VAP is still unclear. One of the most important mechanisms for VAP is the aspiration of oropharyngeal and gastric contents into airway [6-7]. In recent years, some biomarkers have been studied for the diagnosis of aspiration such as pepsin and amylase [8-12].

Amylase is an enzyme found in saliva and pancreas. It has been used as a biomarker of aspiration because it is usually not found in respiratory tract. If amylase is detected in lower respiratory secretion, macro or micro aspiration should be considered [13-15]. The advantage of using this biomarker is that the measurement is inexpensive, easy to perform, and available [13].

The objective of this study is to determine the correlation between tracheal amylase level and VAP; and to evaluate associations between tracheal amylase level and pre-intubation risk factors for aspiration.

Materials and Methods

This research was a cohort study conducted in patients admitted

to PICU of the Queen Sirikit National Institute of Child Health, Bangkok from April 2019 to March 2020. The patients included in the study met the following criteria: (1) children aged 1 month to 15 years; and (2) intubated and on mechanical ventilation. Patients were enrolled within 24 hours after intubation. The exclusion criteria included severe hypoxemia (PaO_2/FiO_2 < 100) and bleeding tendency (thrombocytopenia, coagulopathy). The study was approved by the Institutional Review Board.

Tracheal amylase specimens were collected at the time of enrollment and on the day of suspected VAP diagnosis. The specimen was diluted by normal saline (1:1). The measurement of tracheal amylase concentrations was conducted in the laboratory using enzymatic colorimetric assay (COBAS INTEGRA 400 plus; Roche). The research personnel performing the measurement were blinded to the clinical information.

Baseline characteristics, medical comorbidities and pre-intubation risk factors for aspiration (vomiting, swallowing dysfunction, altered consciousness and cardiac arrest) were assessed at the time of enrollment. Clinical suspicion of VAP was based on the following criteria: mechanical ventilation for at least 48 hours, new or evolving radiological infiltrates, and at least three of the following criteria: body temperature greater than or equal to 38°C (100.4°F) or less than 36°C (97°F), WBC count greater than 15,000/μL or less than 4,000/μL, signs of respiratory distress (including apnea in patients aged less than 12 months), abnormal breath sounds, gas exchange degradation and purulent respiratory secretions [16]. Physicians providing VAP diagnosis were independent of this study.

Statistics

Demographic data, continuous variables and categorical variables were analyzed by median, interquartile range and percentage respectively. Chi square tests were performed for the comparison between groups of categorical variables, and Mann-Whitney U tests were used for non-normally distributed variables. Group differences associated with a p-value of ≤ 0.05 were considered statistically significant.

Statistical analysis was performed using SPSS 26.0 statistical software (SPSS Inc., Chicago, IL).

Results

A total of 88 mechanically ventilated patients were recruited in this study. The median age of the subjects was 22 months (7-74), and 63.6% were male. VAP rate was 26 rates per 1,000 ventilator-days. The most common diagnosis was pneumonia (46.6%), followed by seizure (13.6%). Baseline characteristics are shown in Table 1. Patients with VAP had higher PRISM III scores, higher number of ventilator days, longer PICU length of stays, and higher mortality rate. Gender, age, diagnosis and underlying diseases were not different between the two groups. Median initial tracheal amylase level in non-VAP group was higher than those in VAP group but there was no statistical significance (165.5 vs. 108.5, p=0.82). Median amylase level when VAP was diagnosed decreased to 63 U/L (Table 2).

Table 1: Baseline characteristics of patients.

Variables	Non-VAP group (n=66)	VAP group (n=22)	p-value
Male, n (%)	44 (66.7)	12 (54.5)	0.31
Age (months), median (IQR)	17 (7, 70)	34.5 (17, 84)	0.11
Cuffed ET-tube, n (%)	33 (50)	18 (81.8)	0.012*
Diagnosis, n (%)			
- Pneumonia	31 (47)	10 (45.5)	1.00
- Seizure	10 (15.2)	2 (9.1)	0.72
- Post-operation	4 (6.1)	1 (4.5)	1.00
- Upper airway obstruction	3 (4.5)	1 (4.5)	1.00
- Sepsis/ septic shock	2 (3)	1 (4.5)	1.00
- Others	16 (24.2)	7 (31.8)	0.57
Underlying disease, n (%)			
- Neurological	13 (19.7)	2 (9.1)	0.33
- Cardiovascular	8 (12.1)	1 (4.5)	0.44
- Respiratory	6 (9.1)	1 (4.5)	0.67
- Immunocompromised	6 (9.1)	3 (13.6)	0.40
- Genetic syndrome	5 (7.6)	4 (18.2)	0.22
PRISM III, median (IQR)	3 (0, 7)	7 (3, 9)	0.04*
Ventilator day (days), median (IQR)	5 (3, 9)	13 (10, 19)	< 0.001*
PICU stay (days), median (IQR)	7 (4, 11)	14.5 (10, 20)	< 0.001*
PICU mortality, n (%)	4 (6.1)	6 (27.3)	0.01*
Initial amylase (U/L), median (IQR)	165.5 (35, 572)	108.5 (35, 320)	0.82

Table 2: Tracheal amylase levels in VAP group.

	Initial	suspected VAP diagnosis
Tracheal amylase (U/L), median (IQR)	108.5 (35, 320)	63(16, 158)

Patients with seizure and other diagnoses significantly had greater risk factors for aspiration (p< 0.001 and p=0.002). Meanwhile, underlying diseases were not associated with pre-intubation risk factors (Table 3).

Table 3. Diagnosis and underlying disease classified by pre-intubation risk factors for aspiration

Variable	Pre-intubation risk factors for aspiration		p-value
	No (n=43)	Yes (n=45)	
Diagnosis, n (%)			
- Pneumonia	30 (69.8)	11 (24.4)	0.003
- Seizure	0 (0)	12 (26.8)	< 0.001*
- Post-operation	5 (11.6)	0 (0)	< 0.001*
- Upper airway obstruction	2 (4.7)	2 (4.4)	1.00
- Sepsis/ septic shock	2 (4.7)	1 (2.2)	0.56
- Others (cardiac arrest, drowning, encephalitis)	4 (9.3)	19 (42.2)	0.002*
Underlying disease, n (%)			
- Neurological system	4 (9.3)	11 (24.4)	0.07
- Cardiovascular system	5 (11.6)	4 (8.9)	0.73
- Respiratory system	4 (9.3)	3 (6.7)	0.70
- Immunocompromised condition	6 (13.9)	3 (6.7)	0.17
- Genetic syndrome	5 (11.6)	4 (8.9)	0.73

Patients with risk factors for aspiration had higher tracheal amylase levels compared to those without (320 vs. 56 U/L, p<0.001) (Figure 1).

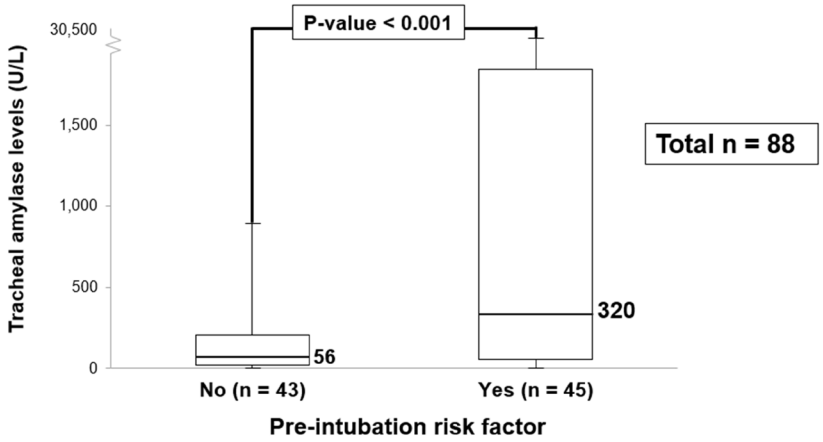

Figure 1: Initial tracheal amylase level in association with pre-intubation risk factors for aspiration.

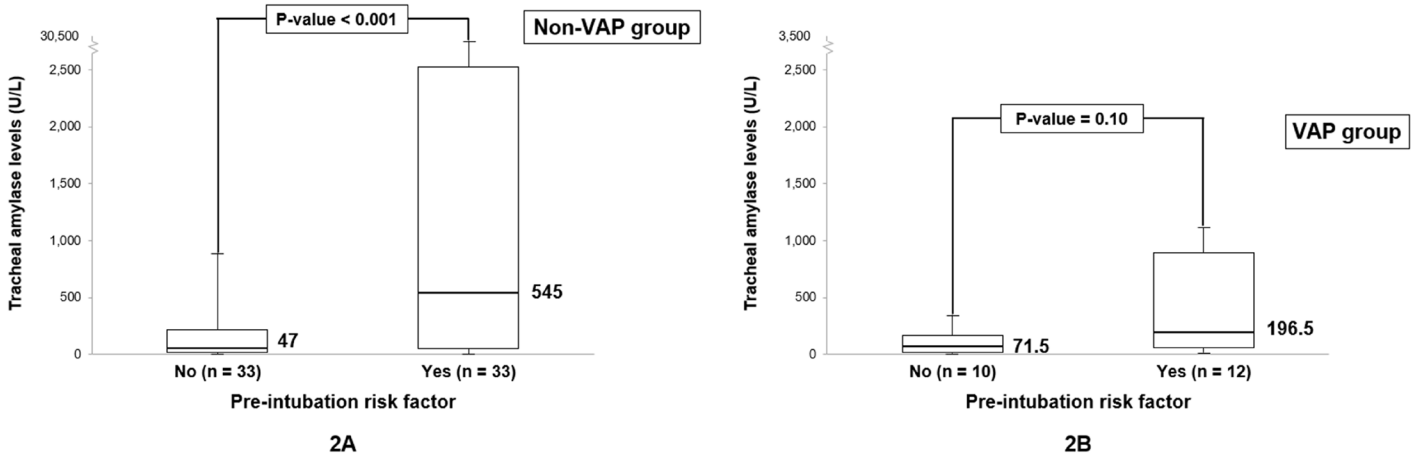

Figure 2: Association between pre-intubation risk factors for aspiration and tracheal amylase level (2A: non-VAP group, 2B; VAP group).

Subgroup analysis: Patients in non-VAP group with risk factors for aspiration significantly had higher initial tracheal amylase compared to those without risk factors (545 vs. 47 U/L, $p < 0.001$) (Figure 2A). However, in VAP group, there was no significant difference between patients with risk factors and those without. (196.5 U/L vs. 71.5 U/L, $p= 0.10$) (Figure 2B).

Discussion

This cohort study aims to assess the correlation between tracheal amylase level and VAP; and to determine the association between tracheal amylase level and pre-intubation risk factors for aspiration. To our knowledge, this is the first report regarding the association of tracheal amylase and VAP in pediatric patients. The result showed that there was no correlation between tracheal amylase level and VAP.

There are two main mechanisms of aspiration in patients undergoing mechanical ventilation: the first mechanism is through the gastroesophageal reflux, where gastric contents are aspirated; the second one is the aspiration of oropharyngeal secretions through the surrounding area of endotracheal tube [8]. According to adult studies, aspiration is one of the most important causes of VAP. Previous study revealed that tracheal amylase level was significantly higher in VAP patients than in non-VAP patients, with the cut-off value 4,681.5 U/L; and sensitivity, specificity, and AUC figures equaling to 80.1%, 79.3%, and 0.81 respectively [21]. In another study, the accuracy of α-amylase in diagnosing micro aspiration was moderate. Higher tracheal amylase levels were found to be higher among patients with micro aspiration [11,22]. Weiss et al. indicated that bronchoalveolar lavage amylase was elevated in patients with bacterial pneumonia. Bronchoalveolar lavage amylase < 125 units/L was significantly associated with lower incidence of bacterial pneumonia (OR 0.39, 95% CI 0.21–0.71, $p = 0.002$) [23]. Samanta et al. studied the association between the amylase in mini-bronchoalveolar lavage and VAP, and found that patients who developed VAP within 72 hours from intubation significantly had increased mini-bronchoalveolar lavage fluid amylase concentrations [24].

On the contrary, this study did not show any association between tracheal amylase level and VAP. Aspiration is the most important cause of pneumonia in the elderly [17-18]. A plausible explanation is different physiologic condition between children and adults. Elderly people suffer various chronic diseases leading to a decrease in swallowing function and cough reflex [19-20]. Meanwhile, meta-analysis in pediatric population demonstrated that genetic

syndrome, reintubation or self-extubation, steroids, bloodstream infection, prior antibiotic therapy and bronchoscopy were risk factors for VAP in PICU [25]. We also found that tracheal amylase level on the day of suspected VAP diagnosis had lower compared to initial tracheal amylase level. The most likely mechanism is aspiration of oropharyngeal secretions or gastrointestinal contents before or during intubation procedure. Furthermore, pediatric VAP bundle (comprehensive oral hygiene program, suctioning techniques and elevating the head of the bed by 30-45°C) is to be employed in clinical setting, which could help to reduce risk of oropharyngeal aspiration [1].

A recent study suggests that amylase level in bronchoalveolar lavage can help identify children who have a risk of pulmonary aspiration [26]. In this study, initial tracheal amylase concentration was found to correlate with pre-intubation risk factors for aspiration. Patients at risk for aspiration had higher tracheal amylase concentration than patients at no risk. Similar results were reported by Qu GP et al., who discovered that tracheal amylase level was positively correlated with the number of pre-intubation risk factors for aspiration in elderly patients [21]. In non-VAP group, we also found significant difference in tracheal amylase levels between patients with risk factors and those without. Though the patients in VAP group with risk factors for aspiration had higher tracheal amylase levels compared to those without risks, there was no significant difference.

This study has several limitations to be considered. Firstly, this study was a single-center study and the sample size was small. Secondly, VAP was diagnosed based on clinical suspicion. Therefore, the accuracy of the relationship between tracheal amylase level and VAP would be affected to a certain extent. Third, repeated amylase measurements were not conducted in patients without VAP. There was no time matched control group to compare the VAP samples to, making its interpretation very difficult.

Conclusions

Initial tracheal amylase level is not associated with VAP in pediatric patients but there is a correlation between tracheal amylase level and pre-intubation risk factors.

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