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The Utility of Neutrophil Gelatinase-Associated Lipocalin in the Detection of Emerging Lung Injury due to Mechanical Ventilation in Children: A Preliminary Study

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What is already known on this topic?

- *Although neutrophil gelatinase-associated lipocalin (NGAL) has been reported as a promising marker for the early detection of acute kidney injuries in various studies, the data related to the benefits of NGAL are limited, especially for the cases with lung injuries.*

What this study adds on this topic?

- *This study showed that NGAL may be a useful biomarker for emerging lung injuries developing due to mechanical ventilation in children and deserves to be investigated.*

ABSTRACT

Objective: Lung injuries are mostly ignored in patients supported by mechanical ventilation. Neutrophil gelatinase-associated lipocalin has come into prominence as an early sensitive and highly predictive biomarker of inflammation. The purpose of the study was to assess the capability of neutrophil gelatinase-associated lipocalin in recognizing lung injuries in children requiring mechanical ventilation.

Materials and Methods: This prospective case-controlled study was carried out in a tertiary pediatric intensive care unit. The entire study group consisted of a total of 45 patients, 15 in the patient group (supported by invasive mechanical ventilation) and 30 in the control group (self-breathing). Whether lung injuries developed or not was investigated by measuring serum-neutrophil gelatinase-associated lipocalin and urine-neutrophil gelatinase-associated lipocalin levels in the course of ventilation support.

Results: In the patient group supported by mechanical ventilation, mean levels of serum-neutrophil gelatinase-associated lipocalin and urine-neutrophil gelatinase-associated lipocalin were measured as 192 ± 136.7 ng/mL and 43.7 ± 57.5 ng/mL, respectively. In the control group (self-breathing patients), mean levels of serum-neutrophil gelatinase-associated lipocalin and urine-neutrophil gelatinase-associated lipocalin were found as 144.8 ± 95 ng/mL and 39.3 ± 85 ng/mL, respectively. The levels of serum-neutrophil gelatinase-associated lipocalin were higher in those ventilated mechanically, compared to self-breathing patients. Although urine-neutrophil gelatinase-associated lipocalin levels were higher among mechanically ventilated patients than the controls, the difference was not statistically significant.

Conclusion: Based on our study findings, we consider that neutrophil gelatinase-associated lipocalin may be a useful biomarker for emerging lung injuries due to mechanical ventilation in critically ill children and deserves to be investigated.

Keywords: Diagnostic biomarker, lung injury, neutrophil gelatinase-associated lipocalin, pediatric intensive care unit.

INTRODUCTION

Children admitted to a pediatric intensive care unit (PICU) are at a high risk of dysfunction in vital organs, such as kidneys, liver, and lungs. However, lung injuries are mostly ignored in patients supported by mechanical ventilation. Considering that the lungs are filled with air due to negative pressure under normal physiologic conditions, the fact that the lungs are filled with a positive pressure during mechanical ventilation is an opposite process of physiology. The mechanisms, such as volume trauma, recurrent alveolar opening–closure, oxygen toxicity, and biotrauma are considered the main causes of lung injuries due to mechanical

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ventilation.[1,2] The lack of an early and non-invasive biomarker for lung injuries delays the ability of medical professionals to promptly initiate preventive and therapeutic measures. Therefore, a novel reliable marker is required for an accurate and rapid diagnosis of lung injuries to initiate early treatment. In this context, neutrophil gelatinase-associated lipocalin (NGAL) may be a promising biomarker in the detection of lung injuries.

Neutrophil gelatinase-associated lipocalin is a member of the lipocalin family and is known to exhibit protective properties against bacterial infections, apoptosis, and oxidative stress. Neutrophil gelatinase-associated lipocalin is also considered a component of the innate immune system.[3,4] Biochemically, NGAL is a small, 25 kDa protein discovered for the first time in activated neutrophils.[5] Neutrophil gelatinase-associated lipocalin is expressed in colon, liver, lung epithelial, and kidney tubular cells, as well as in neutrophils.[6,7] Under physiological conditions, NGAL is present at very low levels in the human bloodstream.[3] Serum-NGAL (s-NGAL) is freely filtered by the glomerulus and almost entirely reabsorbed by the proximal tubules. Therefore, urine-NGAL (u-NGAL) is detected only in the presence of a concomitant proximal tubular injury precluding NGAL reabsorption and/or increasing NGAL synthesis.[8,9] The expression of NGAL is markedly increased in epithelial cells after an ischemic/toxic injury.[10] This increase in the expression can provide an advantage in the determination of the severity of the injury in the affected tissue. Based on the literature, the duration of increase was reported to occur between 2 and 6 hours in general.[11,12] So, NGAL can be a promising biomarker in the detection of lung injuries at an early stage. As in many cases, the early detection of the injuries before the manifestation of signs and symptoms is of vital importance to take measures and determine an ideal therapeutic approach.

The levels of both s-NGAL and u-NGAL have been frequently studied, especially in urinary tract infections (UTI) and acute kidney injuries (AKI) recently.[13-15] Although NGAL has been reported as a promising marker for the early detection of AKI in various studies, the data related to the benefits of NGAL are limited, especially for the cases of lung injuries.[16,17] Our study aimed to assess the capability of NGAL in recognizing lung injuries in children requiring mechanical ventilation. For this purpose, we investigated whether s-NGAL or u-NGAL would be a beneficial marker for lung injuries in children supported by mechanical ventilation in PICU.

MATERIALS AND METHODS

Study Design and Setting

In this prospective case-control study, 15 patients admitted to PICU were investigated (Table 1). The mechanically ventilated patients at the age of ≤16 years constituted our inclusion criteria. Those with disorders such as liver insufficiency, severe chronic pulmonary disease, pre-existing renal disease, and any known cardiac pathologies or metabolic diseases were excluded from the study. Thirty children, admitted to PICU but not ventilated mechanically, were enrolled into the study as the control group.

Study Participants

Our study group consisted of 40 participants. Five of the patients took part in both groups. There were no patients with acute respiratory distress syndrome or overt pulmonary disease in both the mechanically ventilated group and the control group.

Data Collection

All patients were followed up routinely through pulse oximetry and blood gas monitorization. Venous blood samples were drawn simultaneously for the analysis of blood gas parameters (BGPs) (pH, partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), bicarbonate, lactate levels) and s-NGAL. The levels of s-NGAL and u-NGAL were measured by the enzyme-linked immunosorbent assay (ELISA) method using the chemiluminescence microparticle immunoassay according to the instructions of the manufacturer (Human NGA, ELISA Kit, ARCHITECT immunoassay analyzer i2000 SR; Abbott Diagnostics Division, Abbott Laboratories, Abbott Park, IL, USA).

We performed serial measurements of u-NGAL and s-NGAL at 7-day intervals to detect the changes in the course of ventilation support and to assess the correlation between NGAL and BGPs. In order that the changes at s-NGAL levels were followed up more definitely, the patients were divided into 3 categories based on the ventilation day (group 1: ≤7 days, group 2: >7-≤14 days, and group 3: >14 days).

Statistical Analyses

The statistical analyses were performed using the Statistical Package for Social Sciences for Windows, release 22.0 (SPSS, Chicago, Ill, USA). The normality of data was tested using the Kolmogorov–Smirnov test. While the Mann–Whitney *U* test was used to compare the mean values of non-parametric data, the *t*-test was utilized to compare the parametric data.

The correlations between s-NGAL, and both BGPs and ventilation days were assessed using the Spearman correlation test. The results were expressed as mean ± SD or median interquartile range (IQR), and a *P*-value of < .05 was accepted as statistically significant.

RESULTS

The study group consisted of a total of 45 patients, 15 in the patient group (supported by invasive mechanical ventilation) and 30 in the control group (self-breathing). The measurements were repeatedly performed in some patients. As a result, s-NGAL levels were measured in 113 patients, while the levels of u-NGAL were measured in 98 patients.

In the patient group (n = 15), median age was 15 months (min 4, max 192) (IQR 7.5-118.5). Sixty percent (n = 9) were male and 40% (n = 6) were female (Table 1). In this group (66 measurements), the mean levels of s-NGAL and u-NGAL were 192 ± 136.7 ng/mL (min 30.9, max 747.7), 95% CI 158.4-225.6 and 43.7 ± 57.5 ng/mL (min 0.6, max 306.2), 95% CI 27.5-59.9, respectively.

In the controls (n = 30), median age was 52 months (min 1, max 192) (IQR 16-132), and 63.3% (n = 20) were male and 36.7% (n = 10) were female, respectively. Also, in the control group

Table 1. Clinical Features of Children in Patient Group Supported by Invasive Mechanical Ventilation

Patients	Age (Month)	Gender	Diagnosis
1	6	Male	Aspiration pneumonia
			Cleft palate
			Ambiguous genitalia
2	9	Male	Hypotonic infant
			Inborn metabolic disorders
			Congenital hypothyroidism
3	138	Male	Cerebral palsy
			Pneumonia
4	192	Male	Undefined mental disorders
			Pneumonia
			Patient with tracheostomy
5	5	Female	Hydrocephalic patient
			Bronchopneumonia
			Patient with tracheostomy
6	4	Female	Hypotonic infant
			Respiratory failure
			Patient with tracheostomy
7	192	Male	Cerebral palsy
			Pneumonia
			Sepsis
			Acute renal failure
8	8	Female	Early myoclonic encephalopathy
			Infant with epilepsy
			Bronchopneumonia
9	12	Female	Epileptic encephalopathy
			Hypotonic infant
			Sepsis
10	63	Male	Neuronal ceroid lipofuscinosis
			Pneumonia
11	112	Female	Canavan disease
			Patient with tracheostomy
			Viral pneumonia
			Respiratory failure
12	51	Female	Aspirated foreign body in respiratory tract
			Acute respiratory distress
			Cardiac arrest
13	14	Male	Bronchopulmonary dysplasia
			Pneumonia
			Respiratory failure
14	18	Male	Rickets
			Hypocalcemic convulsion
			Cardiac arrest
			Respiratory failure
15	16	Male	Cerebral palsy
			Pneumonia
			Respiratory failure

Table 2. Distribution and Comparison of Neutrophil Gelatinase-Associated Lipocalin Levels in Groups

	Participants (n = 45)		
	Patient Group (n = 15)	Control Group (n = 30)	*P*
s-NGAL (ng/mL)	192 ± 136.7	144.8 ± 95	<.05
Number of measurements	66	47	
u-NGAL (ng/mL)†	43.7 ± 57.5	39.3 ± 85	>.05
Number of measurements	51	47	

†Erasable.
NGAL, neutrophil gelatinase-associated lipocalin; s-NGAL, serum- neutrophil gelatinase-associated lipocalin; u-NGAL, urine-neutrophil gelatinase-associated lipocalin.

(47 measurements), mean s-NGAL and u-NGAL levels were found as 144.8 ± 95 ng/mL (min 38, max 451.2), 95% CI 116.9-172.6 and 39.3 ± 85 ng/mL (min 0.2, max 523.9), 95% CI 14.3-64.3, respectively.

The levels of s-NGAL were higher in those mechanically ventilated, compared to self-breathing patients (Table 2). In addition, while 20 (36.4%) of 55 measurements with s-NGAL levels >145 ng/mL belonged to the self-breathing patients, the remaining 35 (63.6%) belonged to those supported by ventilation. Although the levels of u-NGAL were higher in those mechanically ventilated than the self-breathing patients, the difference was not statistically significant.

We performed serial u-NGAL and s-NGAL measurements at 1-week intervals to show the changes in the course of ventilation support. In the patient group, a weak correlation was observed between the number of days on ventilation and both s-NGAL and u-NGAL levels (Table 3). In addition, we obtained blood gas measurements simultaneously for u-NGAL and s-NGAL samples to show the correlation between NGAL and blood gas parameters (BGPs). There was a weak correlation between s-NGAL and BGPs.

Two patients had u-NGAL levels above 1500 ng/mL. Of 2 patients, the first had septic shock and multi-organ failure and so underwent peritoneal dialysis due to renal failure. The urea and creatinine values of this patient were 170 mg/dL and 5.14 mg/dL, respectively. The second patient had acinetobacter

Table 3. Correlations Between Neutrophil Gelatinase-Associated Lipocalin Levels, and Blood Gas Parameters, Number of Ventilation Days, and Age in Patients Supported by Mechanical Ventilation*

Blood Gas Parameters	s-NGAL	u-NGAL
pH	0.037	0.083
CO_2	0.160	−0.061
O_2	−0.221	0.060
HCO_3	0.212	0.065
Lactate	0.206	0.143
Number of ventilation days	−0.088	0.191
Age	0.205	−0.009

*The results were given as *r* value.
s-NGAL, serum- neutrophil gelatinase-associated lipocalin; u-NGAL, urine-neutrophil gelatinase-associated lipocalin.

sepsis and renal failure. For this patient, the urea and creatinine values were 147 mg/dL and 4.31 mg/dL, respectively. Urea and creatinine levels of all remaining patients were within normal limits. In performing statistical analyses, we ignored the data concerning u-NGAL for these 2 patients. In addition, 3 patients also underwent tracheostomy, and the average of 8 s-NGAL measurements before tracheostomy was 173.25 ng/mL, while the average of 5 s-NGAL measurements performed after tracheostomy was 91.24 ng/mL.

DISCUSSION

Recently, NGAL has come into prominence as a sensitive and highly predictive early biomarker of inflammation.[16-19] Neutrophil gelatinase-associated lipocalin may increase in blood and urine due to the inflammation through the release from neutrophils, macrophages, and other immune cells. Therefore, we consider that it will be reasonable to assess NGAL as an acute phase reactant. The benefit of u-NGAL was first recognized in a prospective study performed by Mishra et al.[20] In the study, it was reported that the diagnosis of AKI can be established via the monitorization of NGAL levels before the observation of the increase in serum creatinine level after cardiopulmonary bypass surgery. Also, NGAL has been the subject of various researches as an early biomarker of inflammation to investigate different tissue injuries.[3,13,21] Our study aimed to assess whether NGAL is capable of identifying lung injuries in children requiring mechanical ventilation. To the best of our knowledge, our study is the first to examine the association between NGAL and lung injuries in mechanically ventilated patients.

Although NGAL has been reported as a useful biomarker in the diagnosis of AKI, there is limited information on the role of NGAL in the follow-up of lung injuries.[22] Our results showed that s-NGAL levels were higher in those ventilated mechanically, compared to the self-breathing patients. Additionally, while 20 of 55 measurements with s-NGAL levels >145 ng/mL were in the self-breathing group, the remaining 35 belonged to those supported by ventilation. In light of these findings, we consider that elevated s-NGAL levels are associated with lung injuries and thus may be the sign of the worsened pulmonary function. The fact that the mechanically ventilated patients had a higher rate of s-NGAL levels above the average than the self-breathing controls supported the above-mentioned consideration. However, we found no statistically significant correlation between NGAL levels and BGPs. It is obvious that BGPs are directly related to ventilator settings and may show instant changes. So, it may be asserted that while BGPs can change in a far shorter time, the level of NGAL is kept for longer periods because of its long half-life. This may have prevented us from finding a clear correlation between NGAL levels and BGPs. However, the lung injuries associated with mechanical ventilation can only be determined with histopathological examination. Therefore, NGAL can be used as a beneficial biomarker in the determination of lung injuries without any need for an invasive procedure.

In the study performed by Krawczeski et al[23], it was found that both s-NGAL and u-NGAL levels were higher in the patients with AKI, compared to the control group.[23] However, some authors believe that the increase in the u-NGAL level is more specific than that of its serum concentration for the early detection of AKI.[24,25] Likewise, Kim et al[13] also suggested that the level of u-NGAL is more useful than that of s-NGAL in screening for UTI. Based on the findings in these reports, an increase in the level of u-NGAL can give us a clue about whether the problem is due to the urinary system or not. In our study, we examined no relationship between NGAL and AKI or UTI. Nevertheless, the fact that 5 measurements of u-NGAL levels were >1500 ng/mL in our 2 patients supported the findings reported in the literature. Another intriguing finding in our study was that a nearly 2-fold difference was found between mean pre-and post-operative s-NGAL levels in 3 patients undergoing tracheostomy. It can be suggested that tracheostomy constitutes a lower risk for lung injuries in mechanically ventilated patients. We consider this is an issue deserving to be investigated.

It was reported that NGAL measured by ELISA revealed a marked increase within 2 to 6 hours in both urine and serum and the level of u-NGAL peaked at 6-12 hours in the patients with AKI.[11,12] The increase of NGAL level within hours may be an advantage for clinicians to follow up the patients. In our study, there was no correlation between ventilation time and s-NGAL levels. In addition, no difference was also found between s-NGAL levels of the patient groups classified according to ventilation day (group 1: ≤7 days, group 2: >7- ≤ 14 days, and group 3: >14 days). We consider that healthcare workers can predict lung injuries accurately by using s-NGAL when s-NGAL is measured closer to the time of the injury developing due to mechanical ventilation. In order to achieve this, it is necessary to perform serial NGAL measurements at shorter intervals. Unfortunately, because of ethical concerns, our study was not carried out in accordance with such a design.

In the study by Tawfeek et al.[3] it was demonstrated that plasma NGAL levels were significantly higher in children with heart failure caused by idiopathic dilated cardiomyopathy, compared to healthy controls.[3] However, the authors reported no correlation between NGAL and the severity of heart failure. In contrast to the findings by Tawfeek et al.[3] some studies suggest that there is a clear correlation between NGAL levels and clinical severity of heart failure.[26,27] In mechanically ventilated patients, diminished pre-load and correspondingly decreased after-load may result in tubular damage due to perfusion disorder. Since the renal tubular epithelial cells are more vulnerable to hypoxic damage, the hemodynamic changes caused by mechanical ventilation may lead to damage in the tubular epithelium. This can explain the increase in NGAL levels, but the pathophysiology of lung injuries is slightly different. It is likely that in contrast to physiology, the air delivered to the lungs with a positive pressure during mechanical ventilation causes injuries to the bronchial epithelium. In addition, mechanisms such as volume trauma, recurrent alveolar opening–closure, oxygen toxicity, and biotrauma are considered to be the causes of the lung injuries developing during mechanical ventilation.[1,28]

While Tawfeek et al[3] reported that s-NGAL level was about 144.33 ± 5.78 ng/mL in children, the u-NGAL level was reported to be 20 ng/mL in adults in another study by Andreucci et al.[29] Our results were consistent with those reported by Tawfeek et al[3] in terms of the mean level of s-NGAL. However, in the context of

u-NGAL, our results were higher in both patient and control groups as 43.7 ± 57.5 ng/mL and 39.3 ± 85 ng/mL, respectively. The difference may have arisen from the fact that our patients consisted of children only. Even so, this difference cannot be explained to just with age, since there are different studies performed in children and reporting similar results to those in adults. Correspondingly, in a study performed in 232 children by Kim et al.[13] the mean u-NGAL level was reported as 14.32 ng/mL. Also, in another study performed by Zappitelli et al[17] with 34 children, the mean level of u-NGAL was reported as 14.2 ng/mL. In our study, however, the mean u-NGAL levels of both the patient and control groups were higher than the averages of the 2 studies. This may have been because s-NGAL levels in our patient group were higher than those of the control group.

Although the cut-off values for s-NGAL and u-NGAL are reported as 106 ng/mL and 9.8 ng/mL under the manufacturer's manual, Kim et al[13] reported the mean cut-off values as 65.25 ng/mL for s-NGAL and 5.75 ng/mL for u-NGAL in order to predict UTI. Likewise, Hirsch et al[11] also reported a cut-off value of 100 ng/mL for u-NGAL to predict AKI due to contrast administration. In our study, we determined no optimal cut-off values for NGAL, because there was no objective parameter to reveal lung injuries directly. To the best of our knowledge, the present study is the first to demonstrate the significant difference between mechanically ventilated and self-breathing patients in respect to s-NGAL and u-NGAL levels. Given that NGAL is elevated in various clinical situations, a combined assessment of s-NGAL and u-NGAL may improve the follow-up of the patients in PICU, especially for those supported by mechanical ventilation in terms of differential diagnosis.

Our study is the first to examine prospectively the utility of NGAL in both urine and serum as a follow-up marker for lung injuries and so it is superior to other studies where NGAL was assessed only in either urine or serum samples of critically ill children. However, our study has some limitations. We could not evaluate the features of NGAL in different clinical situations such as AKI, sepsis, ventilator-associated pneumonia, drug side effects, and different mechanical ventilation settings since these factors are often witnessed together in the patients in PICU. As another limitation, our study was preliminary and performed in a single center with a small cohort.

CONCLUSION

Given the possible lung injuries, it is sometimes difficult to decide on the ventilator settings. So, we need a new biomarker for the early determination and follow-up of lung injuries. In this context, our study showed that NGAL may be a useful biomarker for emerging lung injuries due to mechanical ventilation in critically ill children and deserves to be investigated. However, more comprehensive studies should be performed before recommending the utility of NGAL as a diagnostic marker for the follow-up of lung injuries in various mechanical ventilation modes and settings.

Ethics Committee Approval: This study was approved by Ethics committee of Necmettin Erbakan University (Approval no:2018/1486).

Informed Consent: Written informed consent was obtained from the parents of all paticipants.

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