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Role of neutrophil gelatinase-associated lipocalin (NGAL) as an acute prerenal kidney injury marker: exploring factors associated with its postoperative levels in hypotension-controlled otorhinolaryngology surgery

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ABSTRACT

Introduction: Acute kidney injury (AKI) is a sudden decrease in kidney function due to damage within seven days or less, thus inducing an early stress response that can be promptly detected by biomarkers, such as Neutrophil Gelatinase-Associated Lipocalin (NGAL). This study aimed to analyze the role of NGAL level as a biomarker of postoperative prerenal AKI in patients who underwent otorhinolaryngology surgery with controlled hypotension.

Methods: A prospective study was conducted among patients that underwent otorhinolaryngology surgery with controlled hypotension. Patients were selected with purposive sampling. NGAL level was measured using enzyme-linked immunosorbent assay (ELISA) from venous blood collected 1-hour pre- and 2-hour post-surgery. NGAL levels were compared between preoperative and postoperative states. Wilcoxon and Spearman test were used to determine the correlation between NGAL levels and parameters of AKI.

Results: A total of 30 patients underwent a varies of otorhinolaryngology surgeries were recruited in this study. Our data suggested no significant difference between the level of NGAL during preoperative and postoperative (184.73±120.09 ng/mL vs 175.80±129.97 ng/mL). Pre-operative laboratory parameters of AKI such as blood urea nitrogen (BUN), serum creatine (SCr), BUN/SCr ratio, and GFR had no correlation with postoperative NGAL level. In addition, systolic blood pressure, diastolic blood pressure, MAP, heart rate, $EtCO_2$, surgery duration and controlled hypotension had no correlation with postoperative NGAL.

Conclusion: NGAL levels have nonsignificant role as biomarker of incidence of postoperative prerenal AKI in patients who receiving otorhinolaryngology surgery with controlled hypotension. However, further study with the bigger sample size is warrant to confirm the findings of this study.

Keywords: Neutrophil gelatinase-associated lipocalin, AKI, controlled hypotension, otorhinolaryngology surgery.

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INTRODUCTION

Acute kidney injury (AKI) is common after major surgery, with similar risk factor and outcome associations across surgery type, one of which are otorhinolaryngology surgery.[1] Management of bleeding that occurs during otorhinolaryngology surgery is often done by surgeons using adrenaline as a local vasoconstrictor. Controlled hypotension is a state of hypotension that is controlled during surgery to reduce bleeding and to increase the visibility of the operating field that is adjusted to the patient's age, preoperative blood pressure, and past medical history.[2] Controlled hypotension has been recommended to reduce bleeding and the duration of surgery. It is recommended to reduce the mean arterial blood pressure (MAP) by 30% from the patient's baseline MAP. As a result, systolic blood pressure is reduced to 80-90 mmHg and MAP is reduced to 50-65 mmHg in normotensive patients.[3]

AKI is a sudden decrease in kidney function due to damage within seven days or less.[4] AKI is characterized by increased serum creatinine (SCr) concentration of 0.3 mg/dL (26.5 mmol/L) within 48 hours, a relative increase in SCr of 50% above the baseline value prior to seven days and/or urine output of <0,5mL/kg/hour within 6 hours.[5] Currently, there are three diagnostic criteria that are widely used in the diagnosis of kidney injury: Risk, Injury, Failure, Loss, End-Stage Kidney Disease (AKI-RIFLE), AKI Network (AKIN), and Kidney Disease Improving Global Outcomes (KDIGO).[6,7]

The incidence of AKI ranges from 1-7% of all hospitalized cases, and approximately 30–50% of patients in the intensive care unit (ICU) with a 50% mortality rate.[8] Based on its pathogenesis, AKI aetiologies could be classified in three, namely (1) diseases that cause renal hypoperfusion without renal parenchyma damage (prerenal AKI, ~55%); (2) diseases that cause direct renal parenchyma disruption (renal/intrinsic AKI, ~40%); and (3) disease associated with urinary tract obstruction (postrenal AKI, ~5%). AKI incidence is strongly dependent on its localization.[9]

The kidneys can locally regulate their vascular resistance, due to their ability to independently control afferent and efferent arteriolar tone. Hypoperfusion is often accompanied by vasodilation of the afferent arteriole and vasoconstriction of the efferent arteriole, thereby maintaining a constant hydraulic pressure and glomerular filtration rate (GFR).[5] Prerenal renal failure is mainly caused by renal hypoperfusion. AKI will induce an early stress response that biomarkers can promptly detect.[10] Substances secreted by damaged renal tubules are interleukin 18, tubular enzymes, N-acetyl-B-glucosamidase, alanine aminopeptidase, kidney injury molecule 1, and Neutrophil Gelatinase-Associated Lipocalin (NGAL).[6] These components are potentially to be used as biomarkers. Assessing the sensitive specific biomarkers or predictors is critical to diagnosing the disease prognosis not only related to AKI.[11-16] Some studies have been conducted to assess the markers associated with AKI in different conditions.[17-21] However study on NGAL as biomarker of postoperative prerenal AKI in patients who underwent otorhinolaryngology surgery is limited. This study aimed to analyze the role of NGAL as a biomarker of postoperative prerenal AKI in patients who underwent otorhinolaryngology surgery with controlled hypotension.

METHODS

Study design and sample collection

A prospective study was conducted at the Integrated Surgery Center of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Patients were selected with purposive sampling. The inclusion criteria of the sample were: (1) patients aged 18-60 years; (2) patients that underwent elective tympanoplasty, mastoidectomy, septoplasty, rhinoplasty, and functional endoscopic sinus surgery (FESS) surgery; and (3) patients with physical status classification results of I-II according to the American Society of Anaesthesiologists (ASA). All patients with history of hypertension, cerebrovascular disease, acute or chronic renal failure, and hemodialysis, infection or sepsis, use of anticoagulant drugs, or with severe visual or hearing impairment were excluded. All patients with a severe decrease in condition resulting in laboratory tests that cannot be carried out or not willing to undergo laboratory examination or those with incomplete research data were considered as drop-out cases.

Study variables

This present study used primary data that included postoperative NGAL levels as independent variable and preoperative laboratory AKI parameters as dependent variable. Patients who met the inclusion were enrolled in the study. NGAL levels were collected and assessed one hour before surgery and two hours after surgery. Preoperative laboratory AKI parameters (blood urine nitrogen (BUN), serum creatinine (SCr), BUN/SCr ratio and glomerular filtration rate (GFR)) were assessed before the surgery.

Demographic data such as gender, age, height, body mass index (BMI), ASA score, and types of surgical procedures were also collected. Hemodynamic parameters (systolic blood pressure, diastolic, and mean arterial pressure (MAP), and heart rate were measured every 15 minutes after the surgery started until the surgery was complete. During the surgeries the MAP was maintained in the range of 60–80 mmHg.

NGAL measurement

NGAL level was using ELISA against blood. Human Neutrophil Gelatinase-associated Lipocalin, NGAL ELISA Kit was used to measure the NGAL following the manufacture procedure (Cat. No: E1719HU, Bioassay Technology Laboratory, Zhejiang, China). The measurement unit of test was ng/mL. To measure the NGAL, venous blood samples collected one hour before surgery and two hours after surgery.

Statistical analysis

All data on demographic characteristics were summarized using descriptive statistics. All measurement data were presented in the form of mean ± standard deviation (SD). Normality statistical test was conducted with Kolmogorov-Smirnov test. Paired difference test was conducted; normal distribution data was conducted with paired Student t-test, non-normal distribution data was conducted with Wilcoxon signed rank test. Correlation test was also carried out; since the data had non-normal distribution Spearman correlation was conducted. All analyses were conducted using SPSS (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 30 patients underwent otorhinolaryngology surgery with controlled hypotension were included in this study. The characteristics of patients are presented in Table 1. Among all patients, preoperative laboratory found that the mean BUN was 8.88±2.33 mg/dL; mean SCr 0.80±0.17 mg/dL; mean BUN/SCr ratio 11.42±3.72; and mean GFR value 103.77±24.09 mL/min. There were four types of surgical procedures in this study, consisting of seven patients (23.3%) of FESS, eight patients (26.7%) of mastoidectomy, five patients (16.7%) for septoplasty + turbinoplasty, and ten patients (33.3%) for tympanoplasty.

From the hemodynamic state during surgery (Table 2), the lowest mean systolic blood pressure was 93.5 ± 8.9 mmHg at 75 minutes, while the highest average was 104.1 ± 14.0 mmHg at 15 minutes. The lowest average diastolic blood pressure was 54.2 ± 5.4 mmHg at 225 minutes, while the highest average was 62.1 ± 10.6 mmHg at 15 minutes. The lowest mean MAP pressure was 67.7 ± 5.0 mmHg at 225 minutes, while the highest average was 76.9 ± 12.4 mmHg at 15 minutes. Meanwhile, the lowest mean heart rate is 68.8 ± 10.7 bpm at 45 minutes, while the highest average is 83.9 ± 17.9 bpm at 15 minutes.

The mean preoperative NGAL level was 184.73±120.09 ng/mL, and 2 hours postoperative was 175.80±129.97 ng/mL. Statistical analysis using the Wilcoxon test suggested there mean preoperative NGAL levels were not significantly different between preoperative and postoperative (p=0.13) (Figure 1).

We assessed factors associated with postoperative NGAL level among the patients. Our data suggested that preoperative AKI parameters (BUN, SCr, BUN/SCr ratio, and GFR) have no correlation with postoperative NGAL levels (p>0.05) (Table 3). Intraoperative hemodynamic parameters (systolic, diastolic, MAP, heart Rate, end-tidal carbon dioxide ($EtCO_2$)) also had no correlation with postoperative NGAL levels (p>0.05) (Table 3). Our data also suggested that duration of surgery and duration of controlled hypotension had no correlation with postoperative NGAL levels with p=0.27 and p=0.15, respectively (Table 3).

Table 1. Demographic characteristics of the included patients underwent otorhinolaryngology surgery (n=30).

Variable	n (%)
Gender	
Male	16 (53.3)
Female	14 (46.7)
Age, mean ± SD (years)	32.53 ± 11.47
Height (cm), mean ± SD	161.93 ± 8.05
Mass (kg), mean ± SD	59.03 ± 11.35
BMI (kg/m^2), mean ± SD	22.39 ± 3.71
ASA score	
ASA I	10 (33.3)
ASA II	20 (66.7)
Preoperative laboratory results, mean ± SD	
Blood urine nitrogen (BUN, mg/dL), mean ± SD	8.88 ± 2.33
Serum creatinine (SCr, mg/dL), mean ± SD	0.80 ± 0.17
BUN / SCr ratio, mean ± SD	11.42 ± 3.72
Glomerular filtration rate (mL/min) mean ± SD	103.77 ± 24.09
Types of surgical procedures*	
Functional Endoscopic Sinus Surgery (FESS)	7 (23.3)
Mastoidectomy	8 (26.7)
Septoplasty and Turbinoplasty	5 (16.7)
Tympanoplasty	10 (33.3)
Intraoperative	
Surgery duration (minutes), mean ± SD	183.00 ± 49.45
Anesthesia duration (minutes), mean ± SD	198.17 ± 48.55
Bleeding volume (mL), mean ± SD	55.9 ± 23.1

Table 2. Intraoperative hemodynamic characteristics of the included patients underwent otorhinolaryngology surgery (n=30).

Time (minutes)	Blood pressure (mmHg), mean ± SD			Heart rate (bpm) mean ± SD
	Systolic	Diastolic	MAP	
Baseline	122.8 ± 7.8	76.9 ± 6.1	92.1 ± 4.9	83.7 ± 12.1
15'	104.1 ± 14.0	62.1 ± 10.6	76.9 ± 12.4	83.9 ± 17.9
30'	94.8 ± 5.5	57.1 ± 7.6	69.7 ± 5.8	73.4 ± 13.7
45'	95.4 ± 6.9	55.7 ± 6.2	69.0 ± 5.6	68.8 ± 10.7
60'	94.9 ± 6.8	56.3 ± 7.1	69.1 ± 6.3	70.8 ± 12.6
75'	93.5 ± 8.9	56.1 ± 8.6	68.6 ± 8.2	71.0 ± 13.1
90'	97.5 ± 11.4	57.5 ± 8.3	70.8 ± 8.9	75.2 ± 15.8
105'	98.1 ± 9.9	60.1 ± 8.3	72.7 ± 8.1	73.7 ± 13.5
120'	95.3 ± 6.6	57.2 ± 6.3	70.0 ± 5.6	72.3 ± 11.4
135'	95.7 ± 9.9	55.4 ± 7.7	68.9 ± 8.0	69.9 ± 10.7
150'	94.4 ± 7.2	56.5 ± 6.2	69.1 ± 5.9	69.8 ± 9.1
165'	95.6 ± 6,8	57.5 ± 6.0	70.1 ± 5.8	69.8 ± 10.0
180'	97.8 ± 9.0	60.4 ± 8.8	72.9 ± 8.2	75.1 ± 12.2
195'	97.0 ± 10.7	58.0 ± 7.1	71.0 ± 7.7	71.6 ± 9.8
210'	97.2 ± 10.4	54.5 ± 2.5	68.8 ± 4.3	73.1 ± 12.3
225'	94.5 ± 7.4	54.2 ± 5.4	67.7 ± 5.0	70.3 ± 10.6
240'	94.7 ± 7.1	56.7 ± 5.9	69.4 ± 5.4	70.7 ± 6.1

DISCUSSION

Our data suggest that NGAL levels have no correlation to the incidence of postoperative prerenal AKI in patients who underwent otorhinolaryngology surgery with controlled hypotension. Laboratory results for AKI parameters (BUN, SCr, BUN/SCr ratio, and GFR) have no correlation with postoperative NGAL levels (r value > 0.05). The results showed no significant difference between the preoperative and postoperative NGAL levels. Based on the statistical test of normality using the Kolmogorov-Smirnov test on the distribution of preoperative and postoperative NGAL levels, it is known that the distribution of data is normal with a p-value of 0.00, while the Wilcoxon test showed p-value of 0.13. This means that there was no statistically significant difference between the preoperative and postoperative NGAL levels. In contrast, several other studies showed some correlations in different degree.

There were no previous studies or consensus on the cut-off value of NGAL for the diagnosis of AKI at microscopic surgery, in particular otorhinolaryngology surgery. Several studies found that the cut-off value varies based on the disease's case or cause.[22,23] As it was known that the NGAL levels describe the injury to the kidney, its value is also influenced by several factors including inflammatory, infection, intoxication, ischemia, and neoplasia.[24]

The majority of existing studies state that the cut-off value of NGAL was in cases of intensive care sepsis and very rarely in postoperative cases.[25-27] Some studies used a cut-off of 150 ng/mL to predict AKI in sepsis patients in the ICU, which has high

Table 3. **Correlation of preoperative laboratory, intraoperative hemodynamic, and Procedure parameters with postoperative NGAL level.**

Variables	Postoperative NGAL level	
	r coefficient*	p-value
Preoperative laboratory parameters		
Blood urine nitrogen (BUN, mg/dL), mean ± SD	0.08	0.67
Serum creatinine (SCr, mg/dL), mean ± SD	0.22	0.24
BUN / SCr ratio, mean ± SD	0.07	0.72
Glomerular filtration rate (mL/min) mean ± SD	0.26	0.17
Intraoperative hemodynamic parameters		
Systolic	0.12	0.50
Diastolic	0.08	0.65
MAP	0.04	0.83
Heart rate	0.01	0.97
End-tidal carbon dioxide ($EtCO_2$)	0.01	0.96
Procedure parameters		
Surgery duration	0.21	0.27
Controlled hypotension duration	0.27	0.15

*Spearman's rho correlation test.
Weak correlation r< 0.4; medium 0.4 < r < 0.59; strong 0.6< r<0.7

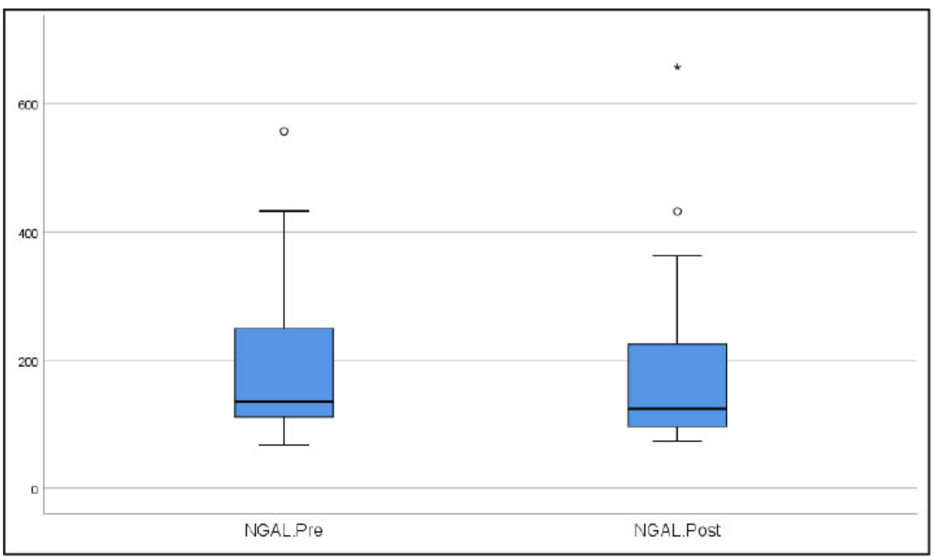

Figure 1. Comparison of mean NGAL levels during preoperative and postoperative of patients underwent otorhinolaryngology a surgery (*n*=30).

sensitivity.[25,26] A systematic review and meta-analysis conducted by Zhang et al. (2019) reported the diagnostic ability of plasma NGAL to predict AKI in septic patients, using a cut-off value of 150 ng/mL had an area under curve (AUC) of 0.94 (95% CI, 0.88-0, 97) and 0.92 (95% CI, 0.84-0.96).[27] Meanwhile, using the same cut-off, another study reported an AUC of 0.81 (95% CI 0.74-0.87).[28] Among pediatric septic patients after 48-72 hours of hospitalization at Dr. Soetomo General Academic Surabaya, the cut-off value of 1,242 ng/ml was found with a sensitivity of 76.5% and specificity of 61.5%.[19]

Based on a case series report at Dr Soetomo General Academic Surabaya, it was found that although the clinical results were very good, the incidence of AKI after coronary artery bypass graft (CABG) surgery was relatively high. Most patients only experienced AKI for a short time and then recovered.[29] The incidence of AKI after CABG with CPB in Dr Soetomo General Academic Surabaya was more than half of the total cases worked on, and most of them occurred on the first postoperative day.[29]

This study had several limitations. The number of patients might be relatively small to determine the correlation, which might explain our study's result. Patients diagnosed with AKI postoperative surgery were not clearly analyzed and should have been a comparison group to understand the correlation. Further development of the study should be conducted in order to strengthen the results.

CONCLUSION

Our data suggested no significant difference between the preoperative and postoperative NGAL levels in patients underwent otorhinolaryngology a surgery. Preoperative laboratory parameters of AKI such as BUN, SCr, BUN/SCr ratio, and GFR had no correlation with postoperative NGAL levels. Our data suggested that there was no correlation between systolic blood pressure, diastolic blood pressure, MAP, pulse and $EtCO_2$ and postoperative NGAL. The duration of surgery and the duration of controlled hypotension also had no correlation with postoperative NGAL.

ETHICAL APPROVAL

The Medical Research Ethical Committee approved the study protocol of Dr Soetomo General Academic Hospital, Indonesia (No. 128/EC/KEPK/FKUA/2021).

COMPETING INTERESTS

All authors declared no conflict of interest.

GRANT INFORMATION

This study received no external funding.

AUTHORS CONTRIBUTION

ANS contributed in concepting and designing the study, literature search, data collection, data analysis, manuscript preparation and editing. PSA, EK, PK, CS were responsible in concepting and designing the study, contributed in intellectual content, manuscript editing and final editing. BAR helped in data collection, data analysis, manuscript preparation and editing.

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