ORIGINAL ARTICLE

Title

Plasma Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Creatinine Levels after Percutaneous Coronary Intervention

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Editor:
I Gde Raka Widiana

Received 9 April 2019, revised 28 July 2019, accepted 21 October 2019, published 2 December 2019

Abstract

Background. Contrast-induced nephropathy (CIN) is defined as an increase in serum creatinine ≥ 25% or ≥0.3 mg/dl in 48 hours after the administration of a contrast agent in the absence of other causative factors (KDIGO 2012). Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a substance produced by the kidneys in acute kidney injury (AKI) caused by various insults, from ischemia to toxin-induced nephropathy. NGAL is known to increase earlier than serum creatinine levels. NGAL is also a protease-resistant polypeptide; it is released from the distal tubule, secreted to the urine or returned to the plasma (back leak), freely filtered in the glomerulus, reabsorbed in the proximal tubule through the megalin receptor endocytosis or secreted to urine. This makes NGAL detectable both in the blood and urine.

Aim. To elucidate the effect of contrast administration to serum NGAL and serum creatinine levels in patients undergoing PCI.

Methods. The study was done in the Cardiovascular Care ward in M. Djamil General Hospital, Padang, West Sumatra, Indonesia. Through consecutive random sampling, 21 subjects were selected. The subjects' serum NGAL and creatinine levels were tested before PCI and 6 hours after contrast administration.

Results. The mean serum NGAL and creatinine levels of the subjects before and after contrast administration were 52.26 ng/mL vs 64.78 ng/ml and 1.1 mg/dl vs 1.09 mg/dL, respectively. The serum NGAL level difference before and after contrast administration was statistically significant (p=0.003) whereas the serum creatinine level was not (p>0.05).

Conclusion. There is an increase of serum NGAL levels before and after contrast administration in patients undergoing PCI, whereas serum creatinine level was not. Future studies should be done to determine the usefulness of NGAL as an early diagnostic marker for CIN.

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Background

Neutrophil Gelatinase Associated Lipocalin (NGAL) is a protein from the lipocalin group, a polypeptide chain consisting of 178 amino acids with a molecular weight of 25-kDa which is bound to gelatinase from neutrophils. NGAL molecules contain 8 β-strands that form a barrel shape structure with hydrophobic calyx which can bind to small lipophilic molecules. NGAL is expressed by neutrophils and various epithelial cells. In normal kidneys, NGAL is produced at very low levels; NGAL will increase if epithelial damage occurs.[1] Alongside other biomarkers such as Cystatin C, Kidney Injury Molecule-l (KIM-l), and urinary IL-18, NGAL has been profusely studied as an early diagnostic marker for acute kidney injury (AKI) caused by many conditions; cardiac surgery, sepsis, contrast administration, and kidney transplant surgery.[2]

In AKI, NGAL is mainly produced by the kidneys. NGAL production is caused by an array of insults to the kidney, from ischemia to renal toxicity. NGAL is also a protease-resistant polypeptide, released from the distal tubule. It is secreted to the urine or returned to the plasma (back leak), freely filtered in the glomerulus, reabsorbed in the proximal tubule through the megalin receptor endocytosis or secreted to urine. Therefore, NGAL can be detected both in the blood and urine.

Acute kidney injury (AKI) can be diagnosed with a small change in the value of serum creatinine or an acute decrease in urine production. However, when creatinine increase in diagnosis is established, kidney damage continues and some interventions will be less satisfying because the golden period of therapy has passed. For this reason, early detection of kidney damage (before a functional abnormality) is needed, to be able to initiate therapy at the beginning of the process of ongoing kidney damage. [3]

Based on the aforementioned background, it is important to examine the NGAL as a potential early marker of AKI compared to creatinine as a traditional marker in patients who undergo procedures involving contrast administration.

Methods

This study is an observational study on patients who underwent PCI in M. Djamil General Hospital. The subjects were selected through consecutive sampling. The inclusion criteria were serum creatinine level < 1.5 mg/dl and able to give verbal and written consent for the study. Exclusion criteria were the presence of unstable hemodynamic such as shock, presence of malignancy, and the presence of sepsis. The number of subjects needed for this study was 20.25, which was rounded to 21. In this study, the contrast agent used was Iso-Osmolar Contrast Media (IOCM), Visipaque with a dose of 100 ml contrast agent.

Result

In this study, the age range of the subjects was 40 - 71 years with a mean age of 57.57 years. The subjects were mostly male (90.46%). The body mass index (BMI) of the subjects in this study were categorized into normal (28.6%), overweight (52.4%), and obese (19%) The diagnosis of patients undergoing PCI in this study were stable angina pectoris (42,9%), ST-elevated myocardial infarct (STEMI) (28,6%), non-ST elevated myocardial infarct (NSTEMI) (9,5%), dan unstable angina pectoris (UAP) 19%.

The plasma NGAL levels before PCI were 52.26 ng/mL, and the level 6 hours after contrast agent administration was 64.78 ng/mL. The results of the Kolmogorov-Smirnov test showed data on plasma NGAL levels both before and after intervention were normally distributed. The lowest and highest levels of plasma NGAL before PCI were 32.20 ng/ml and 89.74 ng/ml, whereas the lowest and highest plasma NGAL levels

at 6 hours after administration of contrast agents were 32.32 ng/mL and 133.31 ng/mL. Paired T-test results showed significantly increased plasma NGAL 6 hours after PCI from baseline(p=0.003).

Table 1. Baseline characteristics of subjects (n=21)

Subject characteristic	N (%)	Mean (SD)
Age (years)		57.57 (8.95)
Gender		
Male	19 (90.46%)	
Female	2 (9.54%)	
Body Mass Index		
Normoweight	6 (28.6%)	
Overweight	11 (52.4%)	
Obese	4 (19%)	

Table 2. Serum creatinine and NGAL levels prior and 6 hours after contrast administration

Variable	Mean (SD)		p
	Pre-PCI (n=21)	6 hours post-contrast agent administration (n=21)	
Serum creatinine (mg/dl)	1.10 (0.22)	1.09 (0.19)	0.57
Plasma NGAL (ng/dl)	52.26 (14.96)	64.78 (24.50)	0.003

Discussion

The majority of the study's subjects were male, and the mean age of the subjects was 57.5 years old. This result is not much different from the report submitted by Shylaja et al (2017) who conducted a study of 60 patients who underwent PCI and had a higher proportion of males than female subjects (90% vs 10%). In the study by Shlaja et al, the average age of patients was 35.75 years. In the study conducted by Peer et al (2017) on 222 patients, the proportion of male subjects was higher than the female (men 55.8% vs women 44.2%), and the average age of patients in this study was 48.96 years. The study by Marenzi et al (2009) also found a higher proportion of male (83% vs 17%), with a mean age of 61 years in patients in their study.[3,4]

In contrast-induced nephropathy (CIN), kidney damage usually ensues during 12-24 hours after contrast administration. The characteristic of AKI in CIN is non-oliguric, and the kidney injury is usually mild. However, some patients' creatinine reached 5 mg/dl and require dialysis. The patients susceptible to this condition is usually patients with pre-existing chronic kidney disease (CKD) and diabetes mellitus. The creatinine levels will then return to normal after 3-5 days. Despite the process of renal injury that occurs, the diagnosis of AKI in CIN is done after observation of increased creatinine levels in 24 hours, after the aforementioned period of injury. This will lead to a missed golden period of intervention to protect kidney function. It is important to detect kidney injury before functional abnormalities are present, so intervention can be done to improve renal outcome.

In this study, the increase of creatinine serum levels obtained 6 hours after the administration of contrast agent was not statistically significant. This is consistent with multiple studies available. The study by Kafkas et al (2016) obtained a mean serum creatinine levels before and after PCI was 0.92 mg/dl and 0.93 mg/dl in the group experiencing impaired renal function whereas in the group that did not experience impaired renal function, serum creatinine levels averaged before PCI and after PCI were 0.96 mg/dl and 0.88 mg/dl.[5] The same results were obtained by Peer et al (2016) in their study stating that the mean serum creatinine levels before PCI and 6 hours after PCI were 0.91 mg/dl and 0.98 mg/dl, respectively.[4]

A relatively novel biomarker, NGAL has been studied as a potential biomarker to foretell renal injury before any functional abnormalities were observed. In healthy individuals, NGAL is usually very low and can only be detected in 67% of the population. The baseline value of this study population's NGAL level was similar to the study by Otto et al (2015), who conducted a study to see plasma NGAL levels in healthy populations, and obtain a mean plasma NGAL rate of 35 ng/ml and stated the normal NGAL plasma level is ≤ 100 ng / ml.[5] A study by Mishra et al (2003) on animals found that the renal epithelium expresses large amounts of NGAL within 30 minutes after damage due to ischemia and reperfusion, nephrotoxins, sepsis, and progressive chronic changes.[6]

In this study, the increase of NGAL after 6 hours of contrast administration was statistically significant. Shylaja et al (2018) conducted a study of 60 subjects undergoing PCI and observed the NGAL levels before and 6 hours after PCI also found similar results: plasma NGAL levels before PCI were 71.2 ng/ml and increased at 6 hours after PCI to 156 ng/ml in the group experiencing impaired kidney function after PCI. Similar results were also obtained by Shaker et al (2010) who conducted a study of 30 non-diabetic patients with normal creatinine levels who underwent PCI with mean NGAL levels plasma before PCI and after PCI are 52.5 ng/ml and 88.5 ng/ml, respectively.[7,8] Filiopoulos et al (2014) also conducted a study to evaluate plasma NGAL levels for detection of impaired renal function after intravenous administration of contrast substances and obtain plasma NGAL levels after 6 hours of use of contrast agents can be measured to see kidney cell injury.[1,9]

In predicting renal functional abnormality, Nusca et al (2018) who conducted a study of 97 patients who underwent PCI found plasma NGAL levels ≥ 96 ng/ml can predict an increase in serum creatinine >0.24 mg/dl with a sensitivity of 53% and specificity 74%.[10] The same was found by Ling et al (2008) who conducted a study in China in adult patients with normal kidney function who underwent coronary angiography, getting NGAL levels increased significantly after 24 hours of angiographic procedures.[11]

In this study, the contrast agent used was different from the study by Peer et al (2016) which conducted a study of LOCM and IOCM contrasts with a dose average used was 115 ml and 76 ml and it was found that more impaired renal function occurred in the use of contrast substances with a dose of 115 ml. Briguori et al. (2006) found that kidney dysfunction occurred in about 6.5% of PCI with 122 IOCM contrast substances. [4,12] Based on the hypothesis that kidney injury is dose-dependent to the amount of contrast agent administered, Mehran et al (2004) performed a retrospective analysis of patients who underwent procedures with contrast agents and found that the total dose of contrast substances 30 mL for diagnostic measures and <100 mL for intervention procedures reduce the risk of CIN. Freeman et al (2002) also found in their study that a dose of contrast agent >5 m per kilogram of body weight was associated with the need for postoperative dialysis. From several other studies, the average number of LOCM contrast agents injected and considered safe ranged between 30 - 140 mL. Further research is needed to identify safe dosages of contrast agents.[13]

This study has a limitation that is the level of NGAL and creatinine was not measured 48 hours after contrast administration. Therefore, whether the increase of NGAL is followed by the increase of serum creatinine level cannot be assessed.

The limitation that should be taken into account is that NGAL has already increased 6 hours after the kidney insult (a good marker for AKI) but creatinine levels just increase 48 to 72 hours after kidney insult. NGAL is immediately produced by the kidney, however, creatinine is produced by the turnover of muscular tissue, and will achieve equilibrated plasma level in a longer period. In this study, plasma creatinine levels were

measured in 6 hours after PCI, may explain why creatinine levels have not yet increased, while NGAL levels have already increased

Conclusion

Serum NGAL levels increase 6 hours after administration of contrast agent for PCI, whereas serum creatinine did not. The increase of NGAL after contrast agent administration should further be studied to elucidate whether NGAL is a good marker for CIN before the onset of increased serum creatinine levels.

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