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Proinflammation and Anti Inflammation in Contrast Induced Nephropathy Patient after Administration of Contrast Media; Analysis of Interleukin 18 and Interleukin 37 Levels

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Abstract

Background/Objective : Contrast induced nephropathy is potential side effect of contrast administration. A good marker is required in order to synergize with the creatinine marker so that CIN can be handled more quickly. This study aimed to compare the levels of interleukin 18 as a marker of inflammation and interleukin 37 as an anti-inflammatory marker in patients with CIN after administration of contrast media.

Material and Method: It was as crosssectional study, subject of study were were all affordable populations who underwent Percutaneous Coronary Intervention (PCI) at the Cardiac Installation Center of Wahidin Sudirohusodo Makassar (as many as 30 patients). Healthy people used as control of study (10 people) and also AKI patients (10 people).

Results: Data indicated that both Non CIN and CIN groups had statistically significant IL-18 increases but decrease IL-37 even unsignificantly Data after media contrast administration showed that IL-18 of the control group differed significantly with CIN and AKI groups and did not differ significantly with non-CIN groups. After media contrast administration also showed that the IL-37 of control group differed significantly with AKI groups only and did not differ significantly with non-CIN and CIN groups.

Conclusion: Proinflammation activity, marked by IL-18 increased significantly after contrast administration but anti-inflammatory, marked by IL-37 decrease even unsignificantly.

Keywords: Contrast, Contrast Induced Nephropathy, IL-18, IL-37

Introduction

Contrast Induced nephropathy (CIN) is side effect of giving contrast media that has become one of the main causes of kidney failure and causes a critical condition in patients ¹⁻³. It has been a major determinant of Acute Kidney injury (AKI) and its incident has varied time after contrast media delivery, there are fast only 2 days and there are up to 30 days ^{4,5}. Although a recent meta-analysis study found that no significant difference between renal of patients given and those not given contrast many studies has indicated different result ⁶.

Marker of CIN traditionally still used increasing of creatinine serum within 24-48 hours after exposure but some studies have tried used inflammatory response as biomarker because delayed response of creatinine serum

could reach 30 days and it was too late for patients to treat and prognostic will deteriorate ⁷. A good marker is required in order to synergize with the creatinine marker so that CIN can be handled more quickly even if the serum creatinine condition is still under normal conditions

Pathophysiology of CIN-AKI is still being studied to gain a good understanding and consensus on prevention is not present yet ⁸. Inflammatory processes are involved in the CIN mechanism that occurs after administration of contrast media, some studies use C-reactive protein (CRP) levels as an inflammatory marker and predictor ⁹⁻¹¹. Proinflammation cytokine, interleukin 18 (IL-18) has been one of the early detection of AKI events, it can be detected at 24 hours and 48 hours after exposure. It

suppose as strong biomarker and moderate diagnostic IL-18 also has potential as a biomarker for CIN events¹²⁻¹⁴.

Before being used as a biomarker in CIN events, it must first be ascertained whether there is indeed a difference in IL-18 levels in CIN and non-CIN patients and should also be comparable to patients with AKI. Response to inflammation by antiinflammation cytokine should be considered to be biomarker together with proinflammation cytokine. One of the most infrequently studied but important anti-inflammatory cytokines is interleukin 37 (IL-37). Clinicians need an early biomarker of CIN diagnostic and also an appropriate decision regards inflammation.

Interleukin-18 stimulates infiltration and activation of T lymphocytes and Natural killer (NK) and interferon-production. Interleukin-18 is released in²⁴ the urine 6 hours after the onset of a kidney injury¹⁵. Interleukin 37 (IL-37) is a family of IL-1 that has a close relationship as well as a natural inhibitor for Interleukin 18 (IL-18), this cytokine is also a suppressor for TNF- α that induces neutrophil activation¹⁶.

¹ This study aimed to compare the levels of interleukin 18 as a marker of inflammation and interleukin 37 as an anti-inflammatory marker in patients with CIN after administration of contrast media. This study will also compare between IL-18 and IL-37 in patients with CIN and AKI patients.

Materials and Method

Design and Subject

It was as cross sectional study, subject of study were all affordable populations who underwent Percutaneous Coronary Intervention (PCI) at the Cardiac Installation Center of Dr. Wahidin Sudirohusodo Makassar and meet the inclusion criteria.

Inclusion criteria were serum creatinine levels were normal before contrast administration, adults aged 30 and above and willing to participate in research by signing Informed consent. Criteria of control were healthy young adults 20-40 years old who are not getting contrast and have no history or are not suffering from kidney disease and other illnesses based on serum history and serum creatinine. Subject was drop out when the patient's condition worsened, patients refuse

blood collection after 24-48 hours after contrast medium delivery. Patient categorized as CIN when a patient who after contrast has a serum creatinine increase of ≥ 0.5 mg / dl or an increase of 25% from baseline within 24-48 hours.

The contrast agent in¹⁵ this study was a type of iodine contrast, nonionic with Low-Osmolar Contrast Media (LOCM) or Iso-Osmolar Contrast Media (IOCM) and injected into the patient's body either through an artery or vein.

Ethic

Each action was conducted by the consent and knowledge of the patient who was sampled by the informed consent sheet and stated¹⁷ fulfill the ethical requirements to be implemented from the Medical Research Ethics Committee of Hasanuddin University Medical Faculty²¹. Ethical clearance has been accepted before study from Medical Research Ethics Committee of Hasanuddin University Medical Faculty (UH16080614).

Procedures

Procedure conducted was:

1. Record the identity of patients who meet the inclusion criteria and provide a full explanation of what will be done to them and if agreed they will fill out and sign the informed consent.
2. The subjects who met the inclusion criteria were taken venous blood sampling before and after contrast administration as many as 3 ml. The serum was obtained¹⁶ after the tube containing the blood was allowed to freeze for 30 minutes at room temperature and centrifuged for 20 minutes at a rate of 3000 rpm. Samples are stored at -80 ° C until sufficient samples, at most 12 months, when the sample will be diluted at 25 ° C before analysis.
3. Serum level of IL-18 and IL-37 examination was performed at the Biomolecular Laboratory and Immunology of the Faculty of Medicine, Hasanuddin University based on Human ELISA KIT Instruction.

Statistics Analysis

Data presented with table using mean, deviation standard (SD), mean difference and probability value

value). Analysis of pre and post administration of contrast data used paired T test and comparison of group used independent T-test for normal distribution data and Mann Whitney U for data have not normal distribution. Level of significance was 0.05.

Results

Interleukin 18

Data indicated that both Non CIN and CIN groups had statistically significant IL-18 increases (p-value=0.000), although the increase in the CIN group was much higher than in the non-CIN group (86.11 pg/ml versus 127.15 pg/ml) (Table 1).

Table 1. Level of IL-18 before and after contrast administration

Group	Frequency (n)	IL-18 (pg/ml) level based on time administration of contrast Mean±SD		Mean difference	P-Value
		Pre	Post		
Non CIN	20	114.422±10.972	200.532±24.065	86.11	0.000 ^a
CIN	10	89.410±9.254	216.560±35.071	127.15	0.000 ^a
*Paired T-test					

Data after media contrast administration showed that the control group differed significantly with CIN and AKI group and did not differ significantly with non-CIN groups. Analysis of the differences between the groups showed that the largest difference in the control group was with the group experiencing CIN even higher when compared with patients with AKI but AKI and CIN group did not differ significant (Table 2).

Table 2. Comparison Level of IL-18 between healthy and AKI subjects After Contrast Administration

Comparison of group	Frequency (n)	IL-18 (pg/ml) level Mean±SD	Mean difference	P-Value
Control vs	10	154.744±50.954		
Non CIN	20	200.532±24.065	45.788	0.039 ^a
CIN	10	216.560±35.071	61.816	0.015 ^a
AKI	10	204.503±90.455	49.759	0.045 ^a
AKI vs		204.503±90.455		
Control 10	10	154.744±50.954	49.759	0.045 ^a
Non CIN 20	20	200.532±24.065	3.971	0.967 ^b
CIN 10	10	216.560±35.071	12.057	0.701 ^b
^a Mann Whitney U test				
^b Independent T-test				

The data show that both non cin group and cin group had decreased levels of IL-37 although not statistically significant (table 3). Decreased levels of IL-37 group cin is higher than non-cin group (2.151 pg/ml versus 5.372 pg/ml).

Interleukin 37

Table 3. Level of IL-37 before and after contrast administration

Group	Frequency (n)	IL-37 (pg/ml) level based on time administration of contrast Mean±SD		Mean difference	P-Value
		Pre	Post		
Non CIN	20	85.152±25.837	83.001±34.841	-2.151	0.313 ^a
CIN	10	79.825±27.949	74.453±20.896	-5.372	0.386 ^a
*Paired T-test					

Data after media contrast administration showed that the IL-37 of control group differed significantly with AKI groups only and did not differ significantly with non-CIN and CIN groups. Analysis of the differences between the groups showed that the largest difference in the control group was with the group experiencing AKI and AKI group has significant difference with other group (Table 4).

Table 4. Comparison Level of IL-37 between healthy and AKI subjects After Contrast Administration

Comparison of group	Frequency (n)	IL-18 (pg/ml) level Mean±SD	Mean difference	P-Value
Control vs	10	85.243±35.003		
Non CIN	20	83.001±34.841	2.242	0.930 ^a
CIN	10	74.453±20.896	10.790	0.545 ^a
AKI	10	240.366±145.463	155.123	0.000 ^a
AKI vs		240.366±145.463		
Control 10	10	85.243±35.003	155.123	0.000 ^a
Non CIN 20	20	83.001±34.841	157.365	0.000 ^a
CIN 10	10	74.453±20.896	165.913	0.000 ^a
^a Mann Whitney U test				
^b Independent T-test				

Discussion

An increase in inflammatory activity characterized by elevated pro inflammation cytokine interleukin 18 appears to suggest that inflammatory activity may be a predictor and at the same time as a diagnostic for CIN incidence for patients who get contrast administration. Although this still needs to be continued with further

research because this study only provides basic data of significant differences.

The pathogenesis of CIN is very complex. Several previous studies have shown that inflammation is important in the prevention of renal impairment. Immune cells of both the natural immune system and the immune system include Dendritic Cells (DC), Natural Killer T

cells, T lymphocytes, B lymphocytes, neutrophils, and macrophages are known to participate in the early stages of injury. Thus, control of inflammation can reduce kidney damage significantly^{17, 18}.

Inflammation is mediated by the adhesion of leukocytes to injured endothelial cells. There is increased escalation of leukocyte adhesion molecules such as ICAM-1, P-Selectin and E-Selectin in endothelial cells in response to injury. Increased chemoattractant factors such as fractalkine (CX3CL1) can be expressed when kidney injury occurs and promote macrophage infiltration. This leads to the activation of leukocytes, capillary obstruction and increased production of proinflammatory cytokines^{19, 20}.

Data also showed that IL-37 level did not increase but decrease even not significantly. It is shown that contrast administration has high risk to develop acute kidney injury. Immune response should increase IL-37 to prevent severe inflammation but it did not happen^{21, 22}.

Study related IL-37 are still very rare, especially those associated with CIN, this study provide a basic data to develop. Increased proinflammatory cytokines, IL-18 and decreased anti-inflammatory cytokines, IL-37 have the potential to be predictors and diagnostics with further study.

Conclusion

Proinflammation activity, marked by IL-18 increased significantly after contrast administration but anti-inflammatory, marked by IL-37 decrease even unsignificantly.

Conflict of Interest : None

Source of Funding : Self

Ethical Clearance: Obtained from Medical Faculty committee member

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