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Research Article

The Effect of N-Acetylcysteine on Glomerulus Filtration Rate in Patients with Chronic Kidney Disease Post Percutaneous Coronary Intervention

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Abstract
The use of contrast for percutaneous coronary intervention (PCI) procedures in chronic kidney disease (CKD) patients can worsen kidney function. N-Acetylcysteine is widely used as a preventive therapy for contrast-induced nephropathy (CIN). However, previous studies have shown inconsistent results, so that further research regarding the effectiveness of N-Acetylcysteine to prevent CIN is needed. This study aimed to determine the effect of N-Acetylcysteine on glomerulus filtration rate (GFR) in patients with CKD who underwent PCI. This research was conducted at Jakarta's national central general hospitals from July to December 2019 with a retrospective study design. Through the purposive sampling method, we obtained 72 data. The sample was patient data selected from the patient's medical records in the period January-June 2019. Patients who underwent PCI and had a history of CKD were included in the study. The data were analyzed by t and chi-square tests to determine the effect of N-Acetylcysteine on the patient's GFR. The results showed that CKD patients underwent PCI were dominated by male (61.11% vs 38.89%) and 33.33% of patients aged 55-64 years. Most patients had GFR values between 30-59.99 ml/min/1.73m2 with 100 ml of contrast administration. The ratio of contrast amount to GFR > 3.7 was found in 47.22% of patients. The administration of N-Acetylcysteine as a preventive therapy for CIN post-PCI increased the GFR value of CKD patients by 2.69±5.72. N-Acetylcysteine had a significant effect on the GFR of post-PCI CKD patients (p=0.000).

Keywords: Chronic Kidney Disease (CKD), Effect, Glomerulus Filtration Rate (GFR), N-Acetylcysteine, Percutaneous Coronary Intervention (PCI)

Efek Pemberian N-Asetilsistein terhadap Laju Filtrasi Glomerulus Pasien Gagal Ginjal Kronik Pasca Intervensi Koroner Perkutan

Abstrak
Penggunaan kontras pada pasien gagal ginjal kronik (GGK) dengan intervensi koroner perkutan (IKP) dapat memperburuk fungsi ginjal pasien. N-Asetilsistein sering digunakan sebagai terapi preventif contrast-induced nephropathy (CIN). Namun berbagai penelitian terdahulu menunjukkan ketidak-konsistenan hasil sehingga penting dilakukan penelitian terkait efektivitas N-Asetilsistein. Penelitian ini bertujuan untuk mengetahui efek N-Asetilsistein terhadap laju filtrasi glomerulus (LFG) pasien GGK pasca IKP. Penelitian ini dilakukan di salah satu rumah sakit di Jakarta dari Juli-Desember 2019 dengan rancangan studi retrospektif. Melalui metode purposive sampling diperoleh 72 data. Data yang digunakan merupakan data sekunder dari rekam medik pasien GGK yang menjalani IKP pada bulan Januari-Juni 2019. Data kemudian dianalisis dengan uji-t dan chi-square untuk mengetahui efek N-Asetilsistein terhadap LFG pasien. Hasil penelitian meunjukkan bahwa pasien GGK yang menjalani IKP lebih banyak laki-laki daripada perempuan (61,11% vs 38,89%) dan 33,33% pasien berusia 55-64 tahun. Sebagian besar pasien memiliki LFG antara 30,00-59,99 ml/min/1,73m2 dengan jumlah pemberian kontras sebanyak 100 ml. Rasio antara jumlah kontras dengan LFG > 3,7 ditemui pada 47,22% pasien. Pemberian N-Asetilsistein sebagai terapi preventif CIN pasca IKP meningkatkan nilai LFG pasien GGK sebesar 2,69±5,72. N-Asetilsistein memberikan efek yang signifikan terhadap LFG pasien GGK pasca IKP (p=0,000).

Kata kunci: Efek, N-Asetilsistein, Gagal Ginjal Kronik (GGK), Laju Filtrasi Glomerulus (LFG), Intervensi Koroner Perkutan (IKP)

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Introduction

Coronary heart disease leads the cause of death in Indonesia. Data from the Ministry of Health Republic of Indonesia shows that the prevalence of heart disease in Indonesia reaches 7.2% of the population and is predicted to increase because of increased risk factors such as hypertension and obesity.[1] However, advances in imaging technology, especially in the heart and arteries in the last 70 years, can reduce morbidity, mortality and improve patients' quality of life. One of the most common procedures for patients with coronary heart disease is percutaneous coronary intervention (PCI). The data shows that the highest number of hospitalized patients at Harapan Kita Jakarta, National Heart Center Hospital in 2018, underwent percutaneous cardiovascular procedures, reaching 2569 cases. PCI was the most performed procedure (2009 cases).2 Besides the benefits provided by PCI, some complications can harm the patient. One of them is contrast-induced nephropathy (CIN). CIN is an acute kidney disease characterized by an increased serum creatinine ≥ 25% or ≥ 0.5 mg/dl within 48-72 hours after contrast media administration.[3,4] CIN is the third cause of acute renal failure in hospitalized patients (5). The incidence of CIN in post-PCI patients increases by up to 40% in patients with high-risk factors, such as patients with a history of chronic kidney disease.[6,7]

Prevention of post-PCI CIN in patients with chronic kidney disease is a top priority. One of the recommended therapy to prevent post-PCI CIN is hydration and administration of N-Acetylcysteine 2 x 600 mg.[8,9] However, according to the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (ESC/EACTS), the administration of N-Acetylcysteine in post-PCI CKD patients to prevent CIN does not yet have robust evidence.[10] This statement is also supported by a systematic review and meta-analysis conducted by Renfan Xu et al. (2016), who concluded that the use of N-acetylcysteine as a preventive therapy for CIN in patients who underwent angiography is still unclear. Some previous studies significantly affected the prevention effect of CIN, but other studies produced the opposite effect. The inconsistency of the results of those studies was caused by several factors, including differences in patient demographics/characteristics, the dose of N-Acetylcysteine administration, inclusion criteria, and the quality of the study.[11]

In Indonesia, data regarding the effectiveness of N-Acetylcysteine as prevention of CIN is still limited. Based on the description above, it is essential to research the effect of N-Acetylcysteine on Glomerulus Filtration Rate (GFR) in Patients with Chronic Kidney Disease (CKD) Post Percutaneous Coronary Intervention (PCI).

Methods

The study used secondary data and was collected from patient medical records. The population in this study was patients who underwent PCI for the January-June 2019 period. We collected patient characteristics data such as age, gender, dosage of NAC, baseline GFR value, amount of contrast given, and changes in GFR values before and after PCI.

This study was a preliminary and retrospective study, conducted at one of the central general hospitals in Jakarta with Ethical Approval Number: KET-811/UN2. F1/ETIK/PPM.00.02/2-19. Ethical Approval was issued by the Faculty of Medicine, the University of Indonesia, on July 8, 2019. Data collection was carried out from July-December 2019. Seventy-two data were selected by purposive sampling method with inclusion criteria of patients with a

Table 1. The characteristics of CKD patient underwent PCI

No	Characteristics	Frequency (n)	Percentage (%)
1	Age (years)		
	35-44	1	1.39
	45-54	21	29.17
	55-64	24	33.33
	65-74	16	22.22
	≥ 75	10	13.89
	Total	72	100
2	Gender		
	Male	44	61.11
	Female	28	38.89
	Total	72	100
3	GFR (ml/min/1,73m2)		
	30-59.99	34	47.22
	15-29.9	21	29.17
	< 15	17	23.61
	Total	72	100
4	Contrast Amount (ml)		
	100	54	75
	> 100	18	25
	Total	72	100
5	Ratio Contrast to GFR		
	< 3.7	38	52.78
	> 3.7	34	47.22
	Total		100

history of CKD who underwent PCI, were given N-acetylcysteine before PCI, and had complete data on patient characteristics and GFR.

Paired t-test was used to compare the GFR values between before and after administration of N-Acetylcysteine in CKD patients who underwent PCI. P-value < 0.05 indicates the significant change of GFR value. Patients categorized as having CIN after 48-72 hours post PCI procedure (administrating contrast) experience a 25% increase in serum creatinine or a 20% decrease in GFR value (with the Cockcroft-gault formula). If the patient has an increase in serum creatinine value more than 25% after PCI, but the GFR is still in a normal range (still in the same stage of CKD before PCI), then the patient is categorized as having CIN. Meanwhile, to examine the comparison of the effect of N-Acetylcysteine on the incidence of CIN based on risk factors for age, gender, baseline GFR, the amount of contrast given, and the ratio between the amount of contrast given and the GFR, we used the chi-square test.

Results

The characteristics of CKD patients who underwent PCI are shown in table 1. Based on table 1, it was known that patients who underwent PCI were at risk of CIN incidence.

Table 2. Comparison of GFR patients before and after administration of N-Acetylcysteine

GFR			p-value
Before	After	Δ (After-Before)	
28.97±15.37	31.67±16.99	2.69±5.72	0.000*

*significant result (analyzed by two-tailed paired t-test)

The risk indicated by age, GFR value, and the amount of contrast administered for PCI. The sample was dominated by patients aged 55-64 years and male. About 47.22% of patients had a GFR between 30-59.9 ml/min/1.73m2, and most of them (75%) received 100 ml of contrast. It also showed that almost half of the patients had a total contrast ratio to GFR > 3.7.

Before the PCI procedure, patients were administered with N-Acetylcysteine capsule 2x600 mg per-oral to prevent the incidence of CIN. The effect of N-Acetylcysteine on patients before and after PCI can be seen in table 2. N-Acetylcysteine increased the GFR value significantly.

Only a few patients (8.33%) had CIN after the PCI procedure. The prevalence of CIN based on risk factors is shown in table 3. Table 3 showed that no difference in the effect of N-Acetylcysteine on GFR of CKD patients who underwent PCI based on age, sex, baseline GFR, administration of total volume, and proportion of contrast to GFR (p>0.05).

Discussion

This study showed that CKD patients who underwent PCI were dominated by the late elderly and males. In Indonesia, the elderly are categorized into: early elderly (46-55 y.o), late elderly (56-65 y.o) and elderly > 65 y.o. This result was similar to the research conducted by Opitasari and Lutdah (2021), which reported that most of the patients hospitalized with a diagnosis of cardiovascular disease were male and the age range between 56-65 years.[12] Dewi et al. (2015) also showed that 75% of patients who underwent PCI at Gatot Subroto Hospital were male, and 66.7% were aged 45-64 years.[13] Age and gender are often associated with the incidence of coronary and arterial disease. The incidence of coronary disease increases with age. Atherosclerotic plaque buildup in blood vessels is known as a significant cause of coronary disease. This plaque starts to build up slowly from 20 and causes stiffness and narrowing of blood vessels. This situation can increase blood pressure and reduce the supply of blood flow that carries oxygen to the heart.[14] At the same time, the male gender is associated with smoking habits, excessive consumption of alcohol, sedentary life, and obesity that cause coronary heart disease.1 In addition to age and gender, the kidney condition also has a close relationship with the incidence of coronary heart disease. Sagita et al. (2018) mentioned that the severity of kidney disease was related to the incidence of cardiovascular disease. The more severe degree of chronic kidney failure, the higher the incidence of coronary heart disease.[15] Other studies also found that CKD stages 3a, 3b and 4 are more at risk of developing cardiovascular disease than CKD stages 1 and 2. The odd ratios and 95% confidence intervals for these risk factors were 2.07 (1.28-3.34) for CKD stage 3a, 1.66 (1.00-2.62) for CKD stage 3b and 2.74 (1.72-4.36) for CKD stage 4.[16] In a study in Brazil involving 581 patients it was found that CKD was confirmed as an independent risk factor for CVD (OR= 2,42; p=0,003).1[7]

High osmolarity contrast with a large volume can also increase CIN incidence. Patients with

Table 3. Effect comparison of N-Acetylcysteine on the incidence of CIN in patients with CKD post PCI based on risk factors

No	Risk Factors	CIN+ (n (%))	CIN– (n (%))	p-value*
1	Age (years)	0 (0)	1 (1.39)	0.992
	35-44	2 (2.78)	19 (26.39)	
	45-54	2 (2.78)	22 (30.55)	
	55-64	1 (1.39)	15 (20.83)	
	65-74	1 (1.39)	9 (12.5)	
	≥ 75	6 (8.33)	66 (91.67)	
	Total			
2	Gender	2 (2.78)	42 (58.33)	0.1449
	Male	4 (5.56)	24 (33.33)	
	Female	6 (8.33)	66 (91.67)	
	Total			
3	GFR (ml/min/1,73m2)	2 (2.78)	32 (44.44)	0.28
	30-59.99	1 (1.39)	20 (27.78)	
	15-29.9	3 (4.17)	14 (19.44)	
	< 15	6 (8.33)	66 (91.67)	
	Total			
4	Contrast Amount (ml)	1 (1.39)	17 (23.61)	0.622
	100	5 (6.94)	49 (68.06)	
	> 100	6 (8.33)	66 (91.67)	
	Total			
5	Ratio Contrast to GFR	2 (2.78)	30 (41,67)	0.319
	< 3.7	4 (5.56)	36 (50)	
	> 3.7	6 (8.33)	66 (91.67)	
	Total			

CKD undergoing PCI are advised to give low osmolarity contrast with a maximum volume of 100 ml.3 In this study, Iodixanol was used as a contrast. Iodixanol is a nonionic hydrophilic compound with an osmolarity similar to the blood (290 mOsm/l).[18] The ratio between the amount of contrast to GFR has an impact on the incidence of CIN. The ratio > 3.7 increases the incidence of CIN .[2] In this study we found 47.22 % patient had a ratio > 3.7. They are at risk of CIN, but only 5,56% had CIN after PCI and it was not statistically significant.

PCI procedure in patients with a history of CKD can cause CIN, which can worsen kidney function. Previous research recommends giving N-Acetylcysteine to prevent CIN. N-Acetylcysteine could significantly reduce serum creatinine and the incidence of CIN post angiography.[19] Similar results were also demonstrated in this study. The GFR values in CKD patients who underwent PCI after administering N-Acetylcysteine 2x600 mg as preventive therapy for CIN were increased significantly. The mechanism of action of N-acetylcysteine as a preventive therapy for CIN is still not clearly understood. However, it is thought to be related to its antioxidant

activity, which can bind oxygen radicals. A prospective, randomized and a clinical trial study was compared the antioxidant effect of NAC in infusion group and placebo in 60 critically ill patient with sepsis. They found that NAC considerably increased total antioxidant capacity (TAC) level and decreased malondialdehyde (MDA) significantly. In intermittent infusion, TAC was increased 0.68 ± 0.60; P value = .036 and in continuous infusion group was 0.69 ± 0.64; P value = .015, compared to placebo (0.61 ± 0.10); Likewise, NAC infusion decreased MDA levels in intermittent infusion (19.45 ± 4.18; P value = 0.001) and continuous infusion group (22.47 ± 6.68; P value = .002), compared to placebo (31.76 ± 11.06) (20). A systematic review also found that NAC may reduce the incidence of acutely increased serum creatinine after administration of intravenous contrast, (relative risk was 0.65 (0.43-1.00, P= 0.049)), but there was significant heterogeneity between trials (21).
N-Acetylcysteine is also a precursor of glutathione which is an endogenous antioxidant. Another mechanism is related to the ability of N-Acetylcysteine to increase Nitric oxide (NO) expression, causing vasodilation and facilitating blood flow to the kidneys.5
Advanced age, female gender, GFR < 60 ml/min/1.73m2, amount of contrast, and the ratio between the amount of contrast and GFR are the risk factors that significantly increase the incidence of CIN after angiography.3 Based on this study, N-Acetylcysteine could prevent the incidence of CIN. It was only 8.33% of CKD patients who underwent PCI had CIN. There was no difference in the effect of N-Acetylcysteine on GFR of CKD patients who underwent PCI based on age, sex, baseline GFR, administration of total volume, and proportion of contrast to GFR (p>0.05). According to the description above, these results proved that N-Acetylcysteine effectively prevented CIN incidence in CKD patients who underwent PCI.
The limitation of this study is the lack of other supporting data such as urea, BUN, urine output, and urinalysis. These data are needed to complete monitoring kidney function in patients with CKD post PCI as a whole. For further research, it is recommended to use other parameters with a larger sample size in evaluating the effect of N-Acetylcysteine to prevent the incidence of CIN.

Conclusions

There was an effect of N-Acetylcysteine on GFR value in patients with chronic kidney disease post-PCI. N-Acetylcysteine could prevent the incidence of CIN and significantly increased the GFR. There was no difference in the effect of N-Acetylcysteine as a preventive therapy for CIN in post-PCI chronic kidney disease patients based on risk factors for age, gender, GFR value, amount of contrast, and proportion of contrast to GFR.

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Conflict of Interest

We declared no potential conflicts concerning the research, authorship, and publication of this article.

References

1. Ministry of Health Republic of Indonesia. National Report of Basic Health Research 2018. Jakarta: Health Research and Development Agency Ministry of Health Republic of Indonesia; 2019. 674 p.
2. The Indonesian Heart Association. National Guidelines for Percutaneous Coronary Intervention Medicine Services.

2021. 41 p.
3. Anwar MR, Hai ANMA, Debnath DK, Faraji MAH, Hasan KM. Incidence and Risk Factors of Contrast Induced Nephropathy in Patients Following Coronary Angiography. Journal of Science Foundation. 2017;15(1):20–5.
4. Hossain MA, Costanzo E, Cosentino J, Patel C, Qaisar H, Singh V, et al. Contrast-induced nephropathy: Pathophysiology, risk factors, and prevention. Saudi Journal of Kidney Diseases and Transplantation. 2018 Jan 1;29(1):1.
5. Kovar F, Knazeje M, Mokan M. Contrast-Induced Nephropathy: Risk Factors, Clinical Implication, Diagnostics Approach, Prevention [Internet]. What Should We Know About Prevented, Diagnostic, and Interventional Therapy in Coronary Artery Disease. IntechOpen. https://doi.org/10.5772/54036.
6. Parlindungan HW, Hasan R, Andra CA, Akbar NZ, Nasution AN, Hasan H, et al. CHA2DS2-VAS-HSF Score as a Predictor for Contrast- Induced Nephropathy in Acute Coronary Syndrome Patients Undergoing Percutaneous Coronary Intervention. Indonesian Journal of Cardiology. 2018;39(2):60-67. doi: 10.30701/ijc.v39i2.766
7. Pintaningrum Y. Percutaneous Coronary Intervention Complications. Medical Journal of Mataram University. 2016;5(4):32-37. https://doi.org/10.29303/jku.v5i4.9
8. Eskandarian R, Yarmohamadi M, Zaker-Tavalae M, Mirmohammadkhani M, Biglari M, Tamadon MR, et al. The standard dose versus double dose of N-acetylcysteine to prevent contrast-induced nephropathy; a randomized controlled clinical trial. J Nephropathol. 2018 May 25;7(3):145–50.
9. Simatupang LD, Susalit E, Wijaya IP. The Role of the Combination of Hydration and N-Acetyl Cysteine in Contrast-induced Nephropathy 48 Hours After Percutaneous Coronary Intervention in Stage 3 Chronic Kidney Disease Patients. Jurnal Penyakit Dalam Indonesia. 2016 Sep 30;3(3):125–30. doi: 10.7454/jpdi.v3i3.22
10. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019 Jan 7;40(2):87–165.
11. Xu R, Tao A, Bai Y, Deng Y, Chen G. Effectiveness of N-Acetylcysteine for the Prevention of Contrast-Induced Nephropathy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc. 2016 Sep 23;5(9):e003968.
12. Opitasari C, Rif'ati L. Cardiovascular Diseases in Adult Hospitalized Patients: a Case Study of BPJS Claims Data for Government Hospitals in Jakarta. Health Research and Development Media. 2021 Mar 31;31(1) https://doi.org/10.22435/mpk.v31i1.3291
13. Dewi VA, Musthafa Z, Bustamam N. Comparative Analysis of Vascular Access to Hematoma Post Percutaneous Coronary Intervention with Stent Installation in Acute Coronary Syndrome Patients at Gatot Subroto Central Army Hospital. Jurnal Profesi Medika: Jurnal Kedokteran dan Kesehatan. 2015. http://dx.doi.org/10.33533/jpm.v9i1.821
14. The Indonesian Heart Association. Guidelines for the Management of Acute Coronary Syndromes. 4th ed. 2018. 94 p.
15. Sagita TC, Setiawan AA, Hardian H. Relationship Between the Severity of Chronic Kidney Failure and Coronary Heart Disease. Diponegoro Medical Journal. 2018;7(2):472–84. https://doi.org/10.14710/dmj.v7i2.20689.
16. Yuan, J., Zou, XR., Han, SP. et

al. Prevalence and risk factors for cardiovascular disease among chronic kidney disease patients: results from the Chinese cohort study of chronic kidney disease (C-STRIDE). BMC Nephrol. 2017;18(23). https://doi.org/10.1186/s12882-017-0441-9

17. Greffin, Suzana et al. Chronic kidney disease and metabolic syndrome as risk factors for cardiovascular disease in a primary care program. Jornal Brasileiro de Nefrologia. 2017;39(03):246-252. https://doi.org/10.5935/0101-2800.20170040
18. Wijaya AT, Atmadja B. Risk Identification and Prevention of Contrast-induced Nephropathy. Jurnal Radiologi Indonesia. 2016;2(1):52–8.
19. Xie W, Liang X, Lin Z, Liu M, Ling Z. Latest Clinical Evidence About Effect of Acetylcysteine on Preventing Contrast-Induced Nephropathy in Patients Undergoing Angiography: A Meta-Analysis. Angiology. 2021 Feb;72(2):105–21.
20. Peivandi Yazdi A, Razavi M, Sheikh S, Boroumand N, Salehi M, Hashemy SI. Clinical Trial Assessment of Intermittent and Continuous Infusion Dose of N-Acetylcysteine on Redox Status of the Body in Patients with Sepsis Admitted to the ICU. Journal of Intensive Care Medicine. 2020;35(12):1383-1388. doi:10.1177/0885066618823152
21. Pannu N, Manns B, Lee H, Tonelli M. Systematic review of the impact of N-acetylcysteine on contrast nephropathy. Kidney Int. 2004;65(4):1366-1374. doi:10.1111/j.1523-1755.2004.00516.x