The Effect of Chronic Usage of Renin-Angiotensin-Aldosterone System Blocking Agents on Incidence of Contrast-Induced Nephropathy in Patients with Diabetes Mellitus and Renal Insufficiency: a Retrospective Cohort Study.

Astika Widy Utomo1, Dwi Aris Agung Nugrahaningsih2, Iwan Dwiprahasto2,

Abstract

Background: This study was to investigate the effect of long term use of Renin-Angiotensin-Aldosterone System (RAAS) blocking agents on the Incidence of Contrast-Induced Nephropathy (CIN) on patients with Diabetes Mellitus (DM) and renal insufficiency underwent Percutaneous Coronary Intervention (PCI).

Methods: A total 281 of subjects were included in this study and divided into two groups based on prior use of RAAS blocking agents (RAAS +, n = 146; RAAS -, n = 135). CIN was defined as an increase of ≥25% in creatinin over baseline value 48-72 hours after PCI.

Results: Total incidence of CIN was 14.95%. There was no difference in the incidence of CIN between 2 study groups (p = 0.952) and relative risk for CIN was 1.02. Left Ventricular ejection Fraction (LVEF) ≤ 40 % (OR 2.300; 95% CI 1.028 – 5.143; p = 0.043), anemia (OR 2.628; 95% CI 1.274 – 5.422; p = 0.009) and Glomerular Filtration rate (GFR) pre PCI ≤ 60 mL/minute (OR 2.782; 95% CI 1.293 – 5.987; p = 0.009) were important predictors of CIN.

Conclusion: Long term use of RAAS blocking agents do not increase the incidence of CIN in patients with DM and renal insufficiency underwent PCI.

Keywords: DM, CIN, PCI, RAAS blocking agents, renal insufficiency

Introduction

Contrast-Induced Nephropathy (CIN) is one of a serious complication of Percutaneous Coronary Intervention (PCI) whose incidence varies from 2% - 25% based on population and risk factors1,2. CIN is usually defined as an increase in serum creatinine by 25% or by 0.5 mg/dL (44 mmol/L) from a baseline value by 48 – 72 hours post-contrast administration3. Renal insufficiency, diabetes mellitus (DM), congestive heart failure (CHF),

1Department of Pharmacology and Therapy, Faculty of Medicine, Diponegoro University, Indonesia
2Department of Pharmacology and Therapy, Faculty of Medicine, Universitas Gadjah Mada, Indonesia

Correspondence:
Astika Widy Utomo, MD, M.Sc
Department of Pharmacology and Therapy, Faculty of Medicine, Diponegoro University, E-mail: astikautomo@gmail.com
dehydration, elderly, anemia, and nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs (NSAID) are known risk factors for CIN. The development of CIN has been associated with increased length of hospitalization and 3x incidence of MACCE (Major Adverse Cardiac and Cerebrovascular Events) at 1 year follow up i.e: death, stroke, myocardial infarction (MI), and end-stage renal disease.

The role of the Renin-Angiotensin-Aldosterone System (RAAS) blocking agents in CIN is still controversial. Data from available literature are conflicting and discordant. Some study concluded that it was effective in the prevention of CIN, but other studies concluded that it was a risk factor. The reason behind these conflicting results is the pathomechanism of CIN that remain unclear. There is two main mechanisms leading to CIN, renal vasoconstriction induced medullary hypoxia, and direct toxicity of contrast media. It has been speculated that RAAS blocking agents may decrease the vascular tone of efferent arteriole used to maintain glomerular hydrostatic pressure. The lower the hydrostatic pressure, the less glomerular filtration. Experimental data suggest that increased endothelin-1, and reactive oxygen species are vital in the development of CIN, and can be inhibited using RAAS blocking agents.

### Methods

#### Study Population

An observational study with historical cohort design using medical records was performed in patients who were referred to National Cardiac Center “Harapan Kita” Hospital Jakarta for non-emergent PCI between January 2012 and December 2013. Inclusion criteria were age > 18 years old, diagnosed with DM and renal insufficiency (GFR 30-89 mL/min) at least 3 months prior to PCI, and Mehran score > 5. Patients were excluded if they had the following criteria: prior condition leading to renal hypoperfusion (i.e hypovolemia, systolic pressure < 90 mmHg, cardiogenic shock, cardiac arrest, sepsis, obstructive uropathy), administration of contrast load within 7 days, severe renal impairment (GFR < 30 mL/min), subsequent surgery following PCI, nephrotoxic agent administration within 48 hours before the procedure (NSAIDs, amphotericin B, aminoglycosides, cyclosporine), and severe anemia require blood transfusion. All patients received normal saline at rate 1 mL/kg/h–maximum 100 mL/h for 6 h before and 6 h after PCI. A total of 281 subjects met the inclusion criteria and divided into two groups: the RAAS (+) group (n = 146), who received any type of RAAS.
blocking agents at least 3 months before admission, and the RAAS (-) group (n = 135), who did not received any RAAS blocking agents before admission.

**Study Variables and Definitions**

CIN was defined as an increase of ≥ 25% or ≥ 0.5 mg/dL (≥ 44 mmol/L) in serum creatinine over the baseline value within 48 – 72 h of PCI. DM was defined as a fasting plasma glucose ≥ 126 mg/dL, and or an oral glucose tolerance test ≥ 200 mg/dL, and or an AIC ≥ 6.5%, and or clinical diagnosis of diabetes with dietary, oral or insulin treatment. GFR was calculated using Cockcroft Gault: (140 – age) x weight (kg)/ serum creatinine (mg/dL) x 72 (x 0.8 in female). Patients with blood pressure ≥ 140/90 mmHg were regarded as having hypertension. The presence of anemia was defined as a hemoglobin concentration < 12.0 g/dL in female or < 13.0 g/dL in male. Hypercholesterolemia was defined as having a total cholesterol concentration > 200 mg/dL. LVEF ≤ 40% was examined using echocardiography before PCI. CHF was defined as NYHA III-IV criteria with LVEF ≤ 40%. Mehran score was calculated according to the assessment of the associated risk factors, including volume of contrast media, baseline GFR, age, presence of hypotension, CHF, presence of anemia, and diabetes mellitus. A cutoff value of 60 mL/min – 89 mL/min and 30 mL/min – 59 mL/min in GFR were used to define mild and moderate renal insufficiency, respectively.

**Statistical Analysis**

Continuous variables were given as mean ± standard deviation, and the comparisons of these variables were performed using student’s t-test. Within-subjects comparisons of continuous variables i.e GFR and sCr were completed using the paired t-test. Categorical variables were analyzed using chi-square and were presented as absolute value and percentage. We performed bivariate analysis with CIN as dependent variables and potential risk factors as follow: age, BMI, LVEF, duration of PCI was performed, contrast amount, Mehran score, variance of contrast media, use of RAAS blocking agent, hypertension, anemia, hypercholesterolemia, gender, CHF, use of NAC, GFR, and sCr. Variables that were statistically significant in bivariate analysis were included in the final multivariate model to identify predictors of CIN. P-value ≤ 0.05 was considered for statistical significance. A 2 x 2 table was used to calculate the relative risk of CIN. We performed statistical analysis using statistical analysis software.

**Results**

Two hundred and eighty-one (281) subject were included in the final analysis. Baseline characteristic is shown in table 1.

**Markers of renal functions and incidence of CIN**

Mean GFR before PCI was 50.85 mL/min with range 30.05 – 89.27 mL/min. Mean sCr before PCI was 1.47 mg/dL with 0.7 mg/dL as minimum value and 3.0 mg/dL as maximum value. Before PCI the two groups had comparable renal markers (table 2). After PCI, RAAS (-) groups had significantly higher GFR compare to RAAS (+) (p = 0.026), as shown on absolute change (p = 0.007).

### Table 2. Post PCI changes in renal parameters in two study groups

<table>
<thead>
<tr>
<th></th>
<th>RAAS +</th>
<th>RAAS -</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (mL/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>49.85 ± 14.34</td>
<td>51.92 ± 14.40</td>
<td>-2.07 (-5.46 – 1.31)</td>
<td>0.229</td>
</tr>
<tr>
<td>Post PCI</td>
<td>51.28 ± 15.77</td>
<td>56.52 ± 20.78</td>
<td>-5.23 (-9.86 - 0.62)</td>
<td>0.026</td>
</tr>
<tr>
<td>Absolute change</td>
<td>1.43 ± 13.71</td>
<td>4.60 ± 19.50</td>
<td>-3.17 (-7.10 – 0.77)</td>
<td>0.114</td>
</tr>
<tr>
<td>sCr (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.49 ± 0.42</td>
<td>1.45 ± 0.42</td>
<td>0.04 (-0.06 – 0.14)</td>
<td>0.429</td>
</tr>
<tr>
<td>Post PCI</td>
<td>1.52 ± 0.58</td>
<td>1.45 ± 0.66</td>
<td>0.07 (-0.08 – 0.22)</td>
<td>0.345</td>
</tr>
<tr>
<td>Absolute change</td>
<td>0.03 ± 0.47</td>
<td>-0.003 ± 0.58</td>
<td>0.03 (-0.09 – 0.156)</td>
<td>0.626</td>
</tr>
</tbody>
</table>

Values are means ± SD

Student’s t test was used in statistical analysis between the groups and paired t-test in subject comparison. a p 0.210; b p 0.007; c p 0.471; d p 0.954
CIN occurred in 14.95% (42 of 281) of overall study population, 22 patients (15.07 %) on RAAS (+) group, and 20 patients (14.82%) on RAAS (-) group. There was no statistically significant difference in the incidence of CIN between two study groups (p 0.952). The relative risk of CIN based on chronic usage of RAAS blocking agents was 1.02.

**Bivariate and Multivariate Analysis**

On bivariate analysis, we studied 16 risk factors for the development of CIN. From the analysis, we found 5 risk factors were associated with CIN were LVEF ≤ 40 % (OR 2.421; 95% CI 1.233 – 4.751; p = 0.009), duration of PCI was performed > 65 min(OR 2.021; 95% CI 1.041 – 3.952; p = 0.035), anemia (OR 1.988; 95% CI 1.025 – 3.852; p = 0.040), CHF (OR 1.988; 95% CI 1.023 – 3.863; p = 0.040), and GFR pre PCI ≤ 60 mL/min (OR 2.683; CI 1.312 - 5.485; p = 0.005). Multivariate analysis showed that LVEF ≤ 40 %, anemia, and GFR pre PCI ≤ 60 mL/min were important predictors of CIN (Table 3).

### Table 3. Predictors CIN

<table>
<thead>
<tr>
<th>Predictors</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF ≤ 40%</td>
<td>2,300</td>
<td>1.028 – 5.143</td>
<td>0.043</td>
</tr>
<tr>
<td>Duration of PCI performed &gt; 65 minutes</td>
<td>1,955</td>
<td>0.965 – 3.958</td>
<td>0.063</td>
</tr>
<tr>
<td>Anemia</td>
<td>2,628</td>
<td>1.274 – 5.422</td>
<td>0.009</td>
</tr>
<tr>
<td>CHF</td>
<td>1,567</td>
<td>0.697 – 3.524</td>
<td>0.277</td>
</tr>
<tr>
<td>GFR ≤ 60 mL/min</td>
<td>2,782</td>
<td>1.293 – 5.987</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Discussion

**RAAS blocking agents usage and CIN**

In this study, we found that there is no difference in CIN incidence in subjects with DM and renal insufficiency who were under chronic use of RAAS blocking agents or not. This result was clinically important since previous studies gave inconsistent results. CIN was one of the important complications after contrast administration for medical intervention and associated with an increased hospital stay and cost. Mean Mehran score in this study was 9.52 ± 3.73. This meant that we had a chance to develop CIN as 14%. This exactly predicted a 14.95% CIN incidence in our total study population. Our finding was significantly lower than the previous study in the same center. On the previous study, the incidence of CIN was up to 25%. The reason probably was the difference between our study population, and prevention procedure that was a must in our study design. Some study stated that prevention procedure decreases CIN significantly.

One reason to explain these different results is the complex mechanism of CIN. Medullary hypoxia due to renal blood flow hypoperfusion secondary to arteriole vasoconstriction and direct toxicity of contrast media is widely known as the mechanism of CIN. The imbalance between local vasoconstriction and local vasodilator also play a role in the development of CIN. Local vasoconstriction such as endothelin-1, renin, and angiotensin II compete with nitric oxide as a local vasodilator to maintain renal medullary perfusion. Increase the level of reactive oxygen species (ROS) and decrease the level of nitric oxide is also one mechanism leading to CIN.

In our study, both groups experienced an increase in GFR level after PCI as a result of a progressive preventive procedure. Meanwhile, GFR after PCI was significantly lower in RAAS (+) than on RAAS (-), probably due to a hypothesis that angiotensin II-mediated post glomerular efferent arteriolar vasoconstriction is important to maintain renal to perfusion pressure. Chronic inhibition on angiotensin II will decrease intraglomerular pressure thus decrease GFR. RAAS blocking agents on physiologic condition does not appear to have toxic properties, but these agents will cause serious renal insufficiency in a condition where angiotensin II is important to maintain GFR, i.e: bilateral stenosis of artery renal, severe dehydration, and hyponatremia.

RAAS blocking agents are integral modalities for treatment of myocardial infarct, hypertension, heart failure. Many studies stated that these agents have
beneficial effects on reducing the progression of renal failure in DM. Nevertheless, a systematic review from 5 RCTs with 678 patients concluded that there is no compelling evidence for stopping or starting ACE I before PCI. The reasons behind this conclusion probably due to the heterogeneity of study designs, small sample size, the difference in a baseline population, prevention procedures, and different definition of CIN itself. In our study, we had younger subjects but with worse renal impairment. These pre-existing renal disease and medical conditions in both groups also helped to explain the result. The other factors were small sample size and wide individual variation. Although our finding did not answer the hypothesis, if we looked at a different view, chronic RAAS blocker usage did not have negative effects on younger subjects with renal impairment.

One thing not to forget is the chemical properties of RAAS blocking agents. Each of these agents has their own lipid solubilities, plasma protein bindings, bioavailabilities, plasma half-lives, and elimination properties which determine different onsets, duration of actions, and the effectivities of RAAS blockade. One to argue, these characteristics would lead to a different result on the development of CIN.

**Risk Factors of CIN**

LVEF ≤ 40% is the main predictor of CIN. Other studies suggested that LVEF ≤ 40% increased the likelihood of developing CIN. Low LVEF are associated with poor hemodynamic and unstable perfusion to a target organ. The kidney is the target organ that suffers much when these conditions occurred since renal blood flow is affected by intrinsic and extrinsic factors. One to remember is pathomechanism of CIN that develop due to the decrease of renal blood flow following contrast administration.

GFR ≤ 60 mL/min is also an independent predictor for CIN and has an important predictive value. GFR ≤ 60 mL/min is clinically important since it’s used as a cutoff value to define patients with renal impairment. Pre-existing renal impairment also an important risk factor for CIN. Duration of PCI > 65 min also included in CIN predictors. Rationally, the longer the duration of PCI, the larger the amount of contrast media being used, and the longer the toxic effect of contrast media are exposed. The accumulation of these factors contributes to the development of CIN. State of anemia prevalence to be found in patients with DM. Studies stated that this condition was an important risk factor for CIN. The outer medullary is prone to hypoxic condition due to high metabolic activities and low oxygen pressure. Contrast media increase the oxygen – hemoglobin affinity, therefore decreasing transfer oxygen to peripheral region.

Our study has some limitations: the new definition of CIN was assigned in 2007 to accommodate a mild increase of serum creatinin that already had clinical implication. Also in 2011, a new guideline stated that every patient prior to PCI need to perform a risk assessment and progressive prevention procedures. CIN decrease respectively with incidence 7.1% - 9.6%. However, we still used the old definition of CIN because of lack of data we had. This was a single-center study with historical cohort design, thus allowed bias on internal validity. On GFR, we still used Cockroft-Gault formulation to calculate renal function, although cystatin C, N-acetyl-glucosaminidase, and inulin clearance may provide a more sensitive estimate renal functions. The heterogeneity duration after PCI to measure creatinine serum were also feared to cause inconsistencies in the study. However, this is the first study that discusses the relationship between chronic used of RAAS blocking agents especially in Indonesia and next study with the design that accommodates prospective or RCT are needed to examine the relationship lack in this study.

**Conclusion**

In conclusion, the present study state that chronic used of RAAS blocking agents do not increase the incidence of CIN. LVEF ≤ 40%, GFR ≤ 60 mL/min, and anemia are important predictors for CIN. A future study that accommodates a lack of finding in this study is needed.

**Ethical Clearance**

This study was approved by the ethic committee of National Cardiac Center “Harapan Kita” Hospital Jakarta no. LB.05.01.1.4/01/2015.

**Conflict Of Interest**

None
Publication Agreement

The authors of this article give permission to Indonesian Journal of Cardiology to publish this article if this article is accepted.

Funding

Self funded

List of Abbreviations

CHF: congestive heart failure
CIN: Contrast-Induced Nephropathy
DM: Diabetes Mellitus
GFR: Glomerular Filtration rate
LVEF: Left Ventricular ejection Fraction
NSAID: nonsteroidal anti-inflammatory drugs
PCI: Percutaneous Coronary Intervention
RAAS: Renin-Angiotensin-Aldosterone System

References

Indonesian Journal of Cardiology


