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Effect of Captopril Rapid Uptitration to Plasma Aldosterone level in Patients with Acute Myocardial Infarction

Verry Gunawan Sohan[1)], Niniek Purwaningtyas[2)], Ari Natalia Probandari [2)]

[1)]Family Medicine Master Program, Post Graduate Program
of Sebelas Maret University of Surakarta
[2)]Faculty of Medicine, Sebelas Maret University of Surakarta

ABSTRACT

Background: Acute myocardial infarction is a myocardial necrosis associated with acute myocardial ischemia of which the incidence keeps increasing over time. Appropriate management of acute myocardial infarction is very important in order to determine the efficacy of the therapy and also to prevent further complications due to acute myocardial infarction. Captopril is essential in the management of acute myocardial infarction to inhibit the renin-angiotensin-aldosterone system whereby aldosterone may increase the probability of heart failure and increase mortality up to approximately 10 times compared to patients with acute myocardial infarction without heart failure. The administration of captopril should be uptitrated the doses in order to obtain optimal results, however there is no such fixed standard on how fast the doses of captopril should be uptitrated in order to obtain a more optimal effect, especially in order to suppress the plasma aldosterone level. This study examined the effect of rapid uptitration of captopril in the first 3 days of treatment of patients with acute myocardial infarction on plasma aldosterone levels compared to the increase in the captopril standard uptitration.
Subjects and Method: This is an experimental research with Randomized Controlled Trial (RCT). 28 patients with Acute Myocardial Infarction on Cardiovascular Intensive Care Unit (ICVCU) and Cardiovascular wards of RSUD Dr. Moewardi hospital Surakarta were sequentially involved as research subjects and then randomly divided into a control group who received standard captopril uptitration and treatment group who received captopril rapid uptitration. The blood plasma was taken on the first day before the administration of captopril and on the last day of treatment. The plasma aldosterone level was tested by ELISA. Independent t-tests were carried out for data that qualified the normality test and mann whitney test if not qualified in the normality test with kolmogorov smirnov. It was considered statistically significant if the value of $p < 0.05$.
Results: Plasma Aldosterone levels in treatment group was lower than control group and statistically significant (1133.54 ± 748.81 pg/dl vs 512.16 ± 444.81 pg/dl; p= 0.013)
Conclusion: Treatment with captopril rapid uptitration can decrease aldosterone plasma levels lower than captopril with standard uptitration in patient with acute myocardial infarction.

Keywords: Acute myocardial infarction, plasma aldosterone, captopril, captopril rapid uptitation.

Correspondence :
Verry Gunawan Sohan. Family Medicine Master Program. Post Graduate Program of Sebelas Maret University of Surakarta.

BACKGROUND

Acute Myocardial infarction is a term for the occurrence of necrosis within a consistent definition related to acute myocardial ischemia. Acute myocardial infarction is indicated by the increasing of biomarker especially heart troponin. Acute myocardial infarction itself can be divided into acute myocard infarction with ST segment elevation on at least 2 electrocardiography (EKG) leads that are connected and acute myocardial infarction without ST segment ele-

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vation (Thygesen K, 2012). The frequency are getting increasing by time, based on data of Riskesdas 2013, Coronary Heart Disease prevalence in Indonesia based on diagnosis also symptoms is around 0.5%-1.5% (Kementerian Kesehatan RI, 2013).

The right management of acute myocardial infarction is very important in determining the success of therapy and also preventing further complication as the result of acute myocardial infarction (Hamm, 2012). ACE inhibitor is very important in the management of acute myocardial infarction to hamper renin angiotensin aldosterone system in which it is identified that the activation of renin angiotensin aldosterone system may increase the possibility of heart failure occurrence and on the patients of acute myocardial infarction that coincides with heart failure it will increase the mortality rate about 10 times compared to patients of acute myocardial infarction without heart failures (Juilliere, 2012).

The final product renin angiotensin aldosterone system is aldosterone in which aldosterone may give effect directly to cardiovascular system. Aldosterone directly may lead to proliferation of heart myocyte and fibroblast that will give inflammation response through TGF-β and cell death (White, 2003). Study about aldosterone on acute myocardial infarction firstly conducted in 2006 by Beygui et al, in which high level of plasma aldosterone on patients who are diagnosed with acute myocardial infarction with ST segment elevation is related to the increasing number of death which is not related to age, heart failure, and reperfusion status (Beygui, 2006).

The higher level of plasma aldosterone on patients of coronary heart disease and acute myocardial infarction have a relationship with the increasing number of death and the occurrence of acute ischemia incidents in which it shows the big effect of of Coronary Heart Disease incidents (CHD) plasma aldosterone level in the process of hearth disease especially coronary heart disease (Mignano, 2014). The negative effect of aldosterone itself has been identified that can be inhibited by medication that may hamper renin angiotensin aldosterone system among others are renin inhibitor such as aliskiren, ACE inhibitor such as captopril, inhibitor of AT1 receptor such as valsartan, as well as inhibitor of mineralocorticoid receptor such as spironolactone (Pitt, 2012).

Inhibition of renin angiotensin system and aldosterone within the management of myocardial infarction since aldosterone is the main mineralocorticoid hormone which is secreted by adrenal cortex and as the key modulator of neurohormonal hemodynamic arrangement (Udell, 2013). The previous study obtained the increasing of plasma aldosteron post acute myocardial infarction will increase the risk of heart failure and death in the future (Ivanes, 2012).

The guidelines of acute myocardial infarction management according to AHA as well as ESC suggests the administration of ACE inhibitor as a therapy given to acute myocardial infarction patients and the administration of ACE inhibitor should be conducted with gradual dosage increasing to attain optimal result in the inhibition of renin angiotensin aldosterone system, yet there is no standard regulation how fast the dosage increasing of ACE inhibitor shoulf be conducted to get more optimal effect especially in keeping down the level of plasma aldosterone (Hamm, 2012; O'Gara, 2013). Up to currently Captopril is still recommended by AHA in the regular management of acute myocardial infarction which is started with initial dosage of 6.25 mg or 12.5 mg and it is possible to be titrated up to 25 mg or 50 mg in accordance with patients' tolerance limit (O'Gara, 2013).

SUBJECTS AND METHOD

This study was conducted in Intensive Cardiovascular Care Unit and ward of RSUD Dr. Moewardi Surakarta during Februari 2016-Maret 2016. The type of the study was Randomized Controlled Trial. Patients who came consecutively, were put into two different groups. Treatment group wasa group of acute myocardial infarction patients who got the rapidly increased titration of captopril with optimal dosage ≥75 mg/ day within three day treatment in ICVCU and control group that got standard increased titration of captopril 37.5 mg/day in the third day of treatment in ICVCU. Intervention was conducted with undercover technique called single blind, in which subjects did not know the type of treatment, whereas researchers knew the type of treatment. Subjects were AMI patients with ST segment elevation and without ST segment elevation in RSUD Dr. Moewardi Surakarta and the administration of captopril with 28 subjects.

Inclusion Criteria :

1. All AMI patients (killip 1-3)
2. Level of creatinine ≤2.5 mg/dl, level of potassium ≤5.0 mmol/l, TDS ≥90 mm Hg with stable hemodynamic
3. Did not get inhibitor of RAA system previously

Exclusion Criteria :

1. Patients with history of heart failure or AMI previously
2. Creatinine level >2.5 mg/dl, potassium level >5.0 mmol/l
3. Cardiogenic shock (killip IV), TDS <90 mmHg, hemodynamic was not stable
4. Obtain RAA system inhibitor prior to attack or need other RSS system inhibitor or in addition to captopril during the treatment
5. Die within 6 days of treatment

Definition of Operational Variables

1. Standard uptitration: it starts with dosage 6.25 mg of captopril 3 times a day and titrated into 12.5 mg 3 times a day for 3 days of treatment.
2. Rapid uptitration it starts with dosage 12.5 mg 3 times a day and titrated into optimal dosage 25 mg or 50 mg 3 times a day for 3 days of treatment.

Statistical Analysis

Data were presented in a form of mean ± SD afterward they were analyzed by using SPSS 22.0 for windows with value $p<0.05$ was considered statistically significant. Test for differences between means was employed. To know the differences of mean between control group and treatment group also before and after the treatment, independent t sample test was used if the data distribution was normal (if it was not normal Mann Whitney test was employed).

RESULTS

The study aimed to know the influence of rapid uptitration of captopril toward the level of plasma aldosterone on acute myocardial infarction patients. The study was conducted from February 2016 up to March 2016 on 28 patients of acute myocardial infarction who got captopril in ICVCU and ward of RSUD Dr. Moewardi Surakarta. The number of research subjects was 28, divided into two groups of samples that were treatment group which consists of 14 people and control group which consists of 14 people. In this study treatment group was given captopril with rapid titration during the treatment in ICVCU, whereas

control group got captopril with standard titration which was regularly given in RSDM.

Data of research subjects' basic characteristics that were constant in nature were tested in term of their normality using Kolmogorov-Smirnov test to assess data normality and followed by test for mean differences by suing independent t-test if the data were normal in nature to test whether there was significant difference between two groups of samples. If the data were not normal in nature, then to test whether there was significant difference between two groups of sample, a test for mean differences was conducted by using Mann Whitney. To test whether there was a significant difference between two groups of sample that were binominal in nature then non-parametric comparative test was conducted using Chi-Square. Basic characteristics of patients can be seen in Table 1.

Table 1. Basic characteristics of research subjects

Variables	Treatment(n = 15) (mean, SD)	Control (n = 15) (mean, SD)	p
Age (year)	61.50 ± 9.73	57.71 ± 11.51	0.356
Male, n (%)	9 (64)	10 (71)	0.686
Risk Factors			
Hypertension, n (%)	7 (50)	6 (43)	0.705
DM, n (%)	10 (71)	5 (38)	0.058
Dyslipidemia, n (%)	9 (64)	8 (57)	0.699
Smoking, n (%)	10 (71)	9 (64)	0.686
Hemoglobin	13.51 ± 1.23	12.82 ± 1.36	0.170
Total cholesterol	180.14 ± 28.6	185.50 ± 44.07	0.706
Triglyceride	134.76 ± 47.7	141.64 ± 46.41	0.703
LDL	113 ± 32.85	115.79 ± 29.82	0.816
HDL	37.5 ± 7.41	33.36 ± 9.37	0.206
STEMI, n (%)	11 (76)	10 (71)	0.663
Creatinine before	1.18 ± 0.4	1.36 ± 0.56	0.320
Creatinine after	0.99 ± 0.28	1.11 ± 0.38	0.345
Potassium before	3.81 ± 0.54	3.71 ± 0.77	0.694
Potassium after	3.94 ± 0.24	3.8 ± 0.27	0.153
Troponin before	11.57 ± 12.23	6.25 ± 9.86	0.232
Troponin after	9.04 ± 7.93	7.50 ± 8.24	0.890
Delta troponin	-2.54 ± 8.82	1.25 ± 8.62	0.261

To measure the level of plasma aldosterone towards captopril on control group and treatment group can be seen in table 2-5.

Table 2. Level of plasma aldosterone before captopril administration on treatment group and control group

Variable	Treatment	Control	Mean Difference	Std. Error Difference	p	95% CI	
						Lower	Upper

Aldosterone (pg/dl)	1400.18 ± 820.37	1202.81 ± 869.69	-197.37	319.53	0.542	-854.16	459.43

Table 3. Level of plasma aldosterone after and before the administration of captopril with rapid uptitration on treatment group

Variable	After captopril	Before captopril	Mean Difference	Std. Error Difference	p	95% CI	
						Lower	Upper
Aldosterone (pg/dl)	356.8 ± 258.95	1400.18 ± 820.37	1043.37	172.11	<0.001	671.55	1415.2

Table 4. Level of plasma aldosterone after and before the administration of captopril with standard uptitration on control group

Variable	After captopril	Before captopril	Mean Difference	Std. Error Difference	p	95% CI	
						Lower	Upper
Aldosteron (pg/dl)	697.8 ± 555.92	1202.81 ± 869.68	505.01	122.91	<0.001	239.48	770.55

Table 5. Level of plasma aldosterone after the administration of captopril on treatment and control groups

Variable	Treatment	Control	Mean Difference	Std. Error Difference	p	95% CI	
						Lower	Upper
NO (μM)	356.80 ± 258.95	697.8 ± 55.,92	340.99	163.9	0.047	4.09	677.9

Table 6. Inhibition on the increase of plasma aldosterone level on treatment group and control group

Variable	Treatment	Control	Mean Difference	Std. Error Difference	p	95% CI	
						Lower	Upper
Aldosterone (pg/dl)	1133.54 ± 748.81	512.16 ± 444.81	-621.38	232.77	0.013	-1099.86	-142.91

The result shows that test for mean difference by using independent t-test indicates or can be implied that the reduction of plasma aldosterone level on treatment group is lower than the reduction of plasma aldosterone level on control group and the difference is statistically significant.

DISCUSSION

The study was an experimental study that aimed to seek the effect of rapid uptitration of captopril toward plasma aldosterone level on acute myocardial infarction patients. Acute myocardial infarction is an incident of myocardium necrosis within a situation which is consistent with acute myocardial ischemia (Thygesen, 2012). A proper management of acute myocardial infarction is very important in determining therapy

accomplishment and also preventing further complication as the result of acute myocardial infarction (Hamm, 2012).

Captopril administration to patients with acute myocardial infarction has been proven in reducing the occurrence of dilatation on left ventricle without having significant hypotension effect (Ray, 1993), captopril is also able to prevent extension of infarction and maintaining electrical stability post acute myocardial infarction compared to regular therapy with nitroglycerine and thrombolysis (Bussmann, 1995). Captopril up to currently is still recommended by AHA in regular management of acute myocardial infarction patients started from initial dosage of 6.25mg or 12.5 mg and it is possible to be titrated up to 25mg or 50mg in accordance with patients' tolerance limit (O'-Gara, 2013).

Aldosterone is a mediator of vascular and myocardial remodeling also contributes in preventing synthesis of *nitric oxide* (NO), endothelium dysfunction and myocardial stiffness. Activation of renin angiotensin aldosterone system both locally and systemically will lead to the significant increase of aldosterone and generate deterioration of heart function because of the effect which is caused by aldosterone.

High dosage of captopril is told to be able to reduce the level of aldosterone plasma on heart failure patients better than low dosage of captopril. High dosage of captopril is defined as ≥75mg/ day and low dosage of captopril is defined as <75mg/ day. The inhibition of plasma aldosterone level is found in the administration of high dosage of captopril (Pacher, 1993). Dosage of captopril should be increased by titration, so far the guidelines of captopril uptitration only occurs on heart failure which by standard is increased after 2-4 weeks on outpatients, however it can be increased faster on inpatients (Siswanto, 2015), though, there is no standard on how fast the increase of captopril titration on acute coronary syndrome.

So far captopril is a type of ACE inhibitor which is always available in RDM and also a formulation of ACE inhibitor which is available in peripheral hospitals in Indonesia so that the administration of captopril with rapid uptitration is extremely possible to be applied in other hospitals in Indonesia. In the guideline of captopril administration it is mentioned that according to AHA there is no specific regulation on the best practice for captopril uptitration for arriving at the optimal dosage that patients can tolerate (O'Gara, 2013). The guidelines give privilege to each doctor to conduct titration in accordance with patients' condition however if it is possible the study is expected to be consideration to conduct captopril rapid titration as long as it is within patients' tolerance.

The study also conducted evaluation to discover the safety level of captopril rapid uptitration administration. In accordance with the guidelines of AHA (O'Gara, 2013) that during the administration of captopril, an evaluation toward kidney function and potassium level should be performed to discover the reduction of kidney function and electrolyte disorder since captopril is mainly discarded through kidney (Brown, 1998).

The study proved that captopril administration with captopril rapid titration on treatment group did not have any significant difference statistically towar kidney function reduction and potassium increase compared to captopril standard titration on control group. The result of the study is important considering that the optimal dosage administration of captopril is difficult to attain for the side effect that make doctors often limit captopril up to standard dosage 3x12.5mg which does not fit with

the recommended guidelines by AHA. Previous study had proven that captopril is safe in term of the effect on blood pressure so it will not lead to significant hypotension effect on acute myocardial infarction patients (Ray, 1993) and the study added that captopril rapid uptitration did not generate kidney disorders potassium increase effect on acute myocardial infarction patients. The study also attempted to give description on whether there was a correlation between captopril rapid uptitration toward troponin level. Troponin is acknowledged as heart biomarker that may become projection of heart muscle damage so it is also possibly affected by the administration of captopril. The study proved that there was no significant correlation between captopril administration with rapid uptitration toward troponin level. It is possibly caused by patients' characteristics differences in patients who receive reperfusion therapy and those who do not will have different changes in troponin level (Makam, 2015) so that there will be extremely various dissimilarity of troponin level alteration on acute myocardial infarction patients and also varied onset presentation of acute myocardial infarction attack on patients in this study generated invalid troponin level to be compared with captopril uptitration. It may need other studies that focus to evaluate troponin toward captopril with homogen samples who have received reperfusion therapy. Aldosterone has an advantage in evaluating therapy administration on acute myocardial infarction patients compared to other biomarkers such as troponin. It happens since the troponin level can not be evaluated if it exceeds acute heart attack phase in which the level of troponin is decreasing to normal after 7 days and will rapidly decrease if receives reperfusion therapy (Mahajan, 2011), it is different with aldosterone level that will remain assessable although it has past acute myocardial infarction phase, it is because aldosterone is hormone within circulation whose level remain measurable when it pasts acute phase, it will remain increasing even when the patient endures heart failure (Pitt, 2012; Hurwitz, 2004).

The administration of ACE inhibitor in which the study used captopril is acknowledged as capable of reducing plasma aldosterone well by administrating captopril with either rapid uptitration or standard uptitration. It proves that the administration of captopril is proven to have good effect in the inhibition of renin angiotensin aldosterone, so that it meets both AHA and ESC guidelines that catopril administration should be given with recommendation class 1A to patients of STEMI anterior, heart failure, and fraction ejection <40%, recommendation class IIa LoE B to all STEMI excluding anterior, and recommendation IB to NSTEMI.

The previous study had showed that the optimal dosage of captopril administration ≥75 mg/day is able to reduce the level of plasma aldosterone better than dosage which is not optimal <75 mg/ hari (Bussmann, 1995; Pacher, 1993). The study showed that optimal dosage which is immediately given with rapid uptitration of captopril is able to reduce the level of plasma aldosterone better compared to captopril administration with standard uptitration. The researchers expect that the study may open new insights and becomes the consideration to the importance of optimal dosage captopril administration on acute myocardial infarction patients the faster catopril is increased up to optimal dosage the faster it reduces the level of plasma aldosterone. The study is quite easy to conduct and possible to be applied in all

heart centers that employ captopril as ACE inhibitor post acute myocardial infarction.

The study had a limit that did not distinguish whether patients received reperfusion therapy or not, thus it did not discover whether reperfusion also affected on the reduction of plasma aldosterone level. The study was only on one center, it needs to conduct on multicenter especially on center which still use captopril, as ACE inhibitor, with more number of sample so that can enhance the influence of the study. Captopril administration with rapid uptitration will better reduce the level of plasma aldosterone compared to standard uptitration of captopril on acute myocardial infarction patients.

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