RESEARCH ARTICLE

Curcumin's Antioxidant Properties in Stable Coronary Artery Disease Patients Undergoing Percutaneous Coronary Intervention: A Randomized Controlled Trial

Todung Silalahi[1,2,*], Idrus Alwi[2,3], Frans Suyatna[4,5], Katarina Dewi Sartika[1], Christopher Surya Suwita[6]

[1]Division of Cardiovascular, Department of Internal Medicine, Faculty of Medicine, Krida Wacana Christian University, Jl. Arjuna Utara No.6, Jakarta 11510, Indonesia
[2]Division of Cardiovascular, Department of Internal Medicine, Cipto Mangunkusumo National General Hospital, Jl. Pangeran Diponegoro No.71, Jakarta 10430, Indonesia
[3]Division of Cardiovascular, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Jl. Salemba Raya No.6, Jakarta 10430, Indonesia
[4]Department of Pharmacology, Faculty of Medicine, Universitas Indonesia, Jl. Salemba Raya No.6, Jakarta 10430, Indonesia
[5]Department of Pharmacology, Cipto Mangunkusumo National General Hospital, Jl. Pangeran Diponegoro No.71, Jakarta 10430, Indonesia
[6]Division of Cardiovascular, Department of Internal Medicine, Jakarta Heart Center, Jl. Matraman Raya No.23, Jakarta 13140, Indonesia

*Corresponding author. E-mail: todungdsilalahi@gmail.com

Received date: Oct 13, 2021; Revised date: Jan 10, 2022; Accepted date: Jan 26, 2022

Abstract

BACKGROUND: Percutaneous coronary intervention (PCI) is the most common intervention for coronary artery disease (CAD) with very low complications. High oxidative stress post-PCI is associated with further atherosclerosis progression. Curcumin, extracted from a specific type of herbs, exhibits anti-oxidant properties by acting as hydrogen and electron donor for superoxide radicals. The aim of this study is to determine the effect of curcumin's antioxidant properties in reducing oxidative stress of post-PCI in stable CAD.

METHODS: This study was a double-blind parallel randomized controlled trial among 50 stable CAD patients undergoing PCI in Cipto Mangunkusumo General Hospital and Jakarta Heart Center. The subjects received either 45 mg/day curcumin or placebo 7 days pre-PCI until 48 hours post-PCI. Reduced oxidative stress markers (decreased MDA or increased GSH) were measured in 3 phases (7 days pre-PCI, 24 hours post-PCI, 48 hours post-PCI).

RESULTS: Curcumin group showed increased MDA from baseline to 24 hours (Δ1=0.01 *vs.* 0.03; *p*=0.3) and decreased MDA from baseline to 48 hours (Δ2=-0.06 *vs.* 0.03; *p*=0.9). While, curcumin group showed decreased GSH from baseline to 24 hours (Δ1=-49.7% *vs.* 12.2%; *p*=0.4) and from baseline to 48 hours (Δ2=-19.09% *vs.* 11.4%; *p*=0.6). However, no significant changes were found in malondialdehide (MDA) and glutathione (GSH) level after the intervention.

CONCLUSION: The 45 mg/day curcumin supplementation from 7 days pre-PCI until 48 hours post-PCI had no significant antioxidant effect in stable CAD post-PCI.

KEYWORDS: coronary artery disease, curcumin, antioxidant, percutaneous coronary intervention

Indones Biomed J. 2022; 14(1): 66-73

Introduction

Coronary artery disease (CAD) is one of the leading causes of death and disability worldwide. Around 17.5 million people died due to cardiovascular disease in 2012 and about 7.4 millions of death were caused by CAD which dominated in developed countries.(1) The prevalence of CAD in Indonesia during in 2013 was 1.5% of total population.(2)

Percutaneous coronary intervention (PCI) is the most common intervention for revascularization of blocked arteries with very low complications less than 1-2%.(3,4)

PCI is associated with excessive of reactive oxygen species (ROS), which cause the pathogenesis of atherosclerosis post-procedural, including restenosis, thrombosis, endothelial dysfunction and ischemia-reperfusion injury that leading to death.(5) Increased oxidative stress post-PCI occur besides given standard treatment such as clopidogrel and statin before procedure that reduce stress oxidative levels.(6-10)

Curcumin, a yellow polyphenolic pigment from *Curcuma longa* (turmeric), is a type of herbs widely grown in Asia with well-recognized as antioxidant properties. Curcumin has a conjugate structure that includes 2 methoxylated phenols and 1 β-dicetone. Phenol methoxylation component acts as a hydrogen atom donor while the β-dicetone component is an electron donor. These two components play a role in cutting the reaction between the chain of the formation of superoxide radical (SOR). Curcumin has more oxygen groups much more than β-tocopherol, so that curcumin is easier to enter cells to inhibit SOR production.(11) Curcumin reduced the oxidative stress process by elimination of ROS.(12) The cardiovascular potential benefits of curcumin have been indicated in several studies.(13)

Direct measurement of oxidative stress levels and free radicals are very difficult, because they are highly reactive and have an extremely short half-life. Therefore, *in vivo* levels of oxidative stress were assessed by measuring endogenous antioxidant molecules and molecules of damage products from oxidative stress. Malondialdehyde (MDA) is a form of end product of lipid hydroperoxide degradation which shows an increased level free radical, while glutathione (GSH) is one of the endogenous antioxidant defense molecules that can measure the level of oxidative stress indirectly.

This study aims to determine the effect of curcumin's antioxidant properties in reducing oxidative stress of post-PCI in stable CAD. This is the first clinical study that investigated the effects of curcumin's antioxidant properties in stable CAD patients undergoing PCI.

Methods

Study Design and Sample Collection

We conducted a double-blind parallel randomized controlled trial in Cipto Mangunkusumo General Hospital and Jakarta Heart Center, Jakarta, Indonesia, with consecutive sampling method among 50 stable CAD patients undergoing PCI. Inclusion criteria were patients with range of age 30 to 75 years, stable CAD with stenosis >70% and non-calcified lesion. Exclusion criteria were stable CAD with history of myocardial infarct or unstable angina within the last three months, total occlusion in angiography, new Left Bundle Branch Block (LBBB), use of steroids or immunosuppressants, those with condition of increased inflammatory parameters (high-sensitivity C-reactive protein (hsCRP) and sCDL40) and free radicals such as acute or chronic infection, malignancy, hyperthyroidism, and acute or chronic kidney disease.

Based on previous study, the standard deviation (SD) for MDA change was 9.5.(14) To detect this difference, 25 participants recruited to each group would provide 80% power with 5% probability of type 1 error (0.05). All procedures performed in this study was approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia (No. 101/UN2.F1/ETIK/2015).

Intervention

Subjects were allocated in a 1:1 to the 2 groups used computerized random number generator sequence (google random generator) with range of number were 1 to 50, first sequence was curcumin group and the second sequence was placebo group. Randomization and allocation concealment was prepared by third party (research promotor) with no involvement in trial. They wrote patient number on the outside of brown envelope and the drug code (A or B) were sealed inside the brown envelope. Placebo or curcumin was prepared by drug company using identical taste, color of the powder and the capsules. The capsules were put in plastic bottle, each bottle contain 27 capsules placebo or curcumin. Bottles were coded A or B. Then, subjects were given a plastic bottle according to the serial number of the patient and the drug code inside the brown envelope. The drug code was recorded by the researchers after recruitment was completed and the brown envelope was opened by the research promoter, after all data and laboratory examinations were completed. Researchers and patients were blinded in this study. Either placebo or 15 mg curcumin were given three times a day from 7 days pre-PCI until 48 hours post-PCI, besides standard medication using 100 mg aspirin, 300 mg clopidogrel and 20 mg simvastatin/atorvastatin. Volume contrast of PCI was around 100 mL. We used intravascular ultra sound (IVUS) to assess before and after stent placement. Blood samplings for MDA, GSH were taken 7 days pre-PCI before used curcumin/placebo, 24 hours and 48 hours post-PCI.

MDA Examination

All samples were examined in Prodia Laboratory, Jakarta, Indonesia. The principle of measuring MDA serum was

based on the reaction of the chromogenic reagent N-methyl-2-phenylindole (NMPI). The procedure for examining GSH serum was based on the formation of thione chromophoric formation. Tris (2-carboxyethyl) phosphine (TCEP) reduced oxidized GSSH to GSH. Addition of base to specimen created a specific β-elimination towards GSH-thioether that produced a chromophoric compound.

Statistical Analysis

After normality test Kolmogorov-Smirnov revealed normal data spread (p>0.05). All categorical data were presented as frequency (%) and numeric data with normal distribution were presented as mean±SD while abnormal distribution were presented as median (minimum–maximum). The comparison between curcumin and placebo group was analyzed using Mann Whitney test, the comparison between 3 times of measurement was analyzed using Friedman test and the comparison within baseline to 24 hours post-PCI, 24 hours to 48 hours post-PCI and baseline to 48 hours post-PCI was analyzed using Wilcoxon test. All data were analyzed using SPSS statistics for Windows version 21 (IBM Corporation, Armonk, NY, USA). The p-value<0.05 was considered significant.

Results

From 54 subjects, 4 subjects were excluded. We randomized the subjects to curcumin group (n=25) and placebo group (n=25) (Figure 1). There were 28 male and 22 female with average age was 61 years, median of BMI was 25.6 5kg/m2, which 26 patients were smoking, 26 patients had history of myocardial infarct, 1 patient had history of stroke and 20 patients had history of PCI. According to echocardiography data, median of right ventricle function (TAPSE) was 16 mm and mean of left ventricle function was 55.6%. Lipid profile test showed median of total cholesterol was 176.1mg/dL, High Density Lipoprotein (HDL) was 48.1 mg/dL, Low Density Lipoprotein (LDL) was 107.6 mg/dL, and triglyceride was 165.9 mg/dL. PCI characteristics showed there were 35 patients who had left artery descending (LAD) occlusion, 11 patients had right coronary artery (RCA) occlusion and 4 patients had left circumflex (LCx) occlusion.

All patients were given 1 drug-eluting stent based on the lesion. Table 1 showed general and clinical characteristics of the subjects. We found no complications during procedure PCI and no side effects of curcumin such as nausea or vomiting.

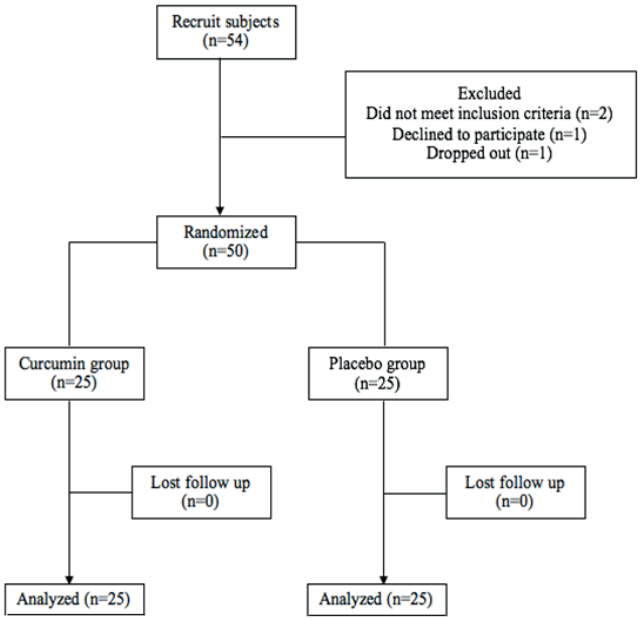

Figure 1. Diagram of trial subjects.

MDA Change

MDA change in both group were not statistically significant. Similarly, test results of MDA change between baseline, 24 hours post-PCI, and 48 hours post-PCI were not substantial in both group (p=0,6; 0,7; 0,7, in each episode, respectively). The level of MDA transformation was also not significant between curcumin (p=0.6) *vs.* placebo group (p=0.3). Table 2 and Figure 2A showed that supplementation with curcumin for 48h can decrease MDA level although not statistically significant, compared to placebo (Δ2=-0.06 *vs.* 0.03; p=0.9). The level of MDA transformation in curcumin group from baseline to 24 hours post-PCI, 24 hours to 48 hours post-PCI and baseline to 48 hours post-PCI were also not significant (p=0.3; 0.2; 0.9 *vs.* p=0.2; 0.3; 0.9) compared with placebo group (Figure 3).

GSH Change

While curcumin groups showed contradictory result, in which GSH level decreased post-PCI, this result was not statistically significant. Likewise, test results of GSH change between baseline, 24 hours post-PCI, and 48 hours post-PCI were not substantial in both group (p=0.9; 0.3; 0.3, in each episode, respectively). The level of GSH transformation was also not significant between curcumin (p=0.3) *vs.* placebo group (p=0.1). Table 2 and Figure 2B showed detailed data for these changes. GSH level in curcumin group contradictory with placebo group from baseline to 48 hours (Δ2=-19.09% *vs.* 11.4%; p=0.6). GSH level was decreased

Table 1. Clinical subject and procedure characteristics.

Variable	Group		*p*- value
	Placebo (n=25)	Curcumin (n=25)	
Age (years), mean±SD	60.60±7.99	62.7±6.46	0.3§
Gender, n (%)			
Male	13 (52.0)	15 (60.0)	0.6*
Female	12 (48.0)	10 (40.0)	
History of myocardial infarct, n (%)			
Yes	11 (44.0)	15 (60.0)	0.3§
None	14 (56.0)	10 (40.0)	
History of ischemic stroke / transient ischemic stroke, n (%)			
Yes	0 (0.0)	1 (4.0)	1.0¶
None	25.0 (100)	24 (96.0)	
Smoking, n (%)			
Yes	11 (44.0)	15 (60.0)	0.3*
None	14 (66.0)	10 (40.0)	
History of percutaneous coronary intervention, n (%)			
Yes	7 (28.0)	13 (52.0)	0.09*
None	18 (72.0)	12 (48.0)	
History of coronary artery bypass grafting, n (%)			
Yes	0 (0.0)	0 (0.0)	-
None	25 (100)	25 (100)	
Body weight (kg), median (min–max)	66 (38–127)	67 (54–84)	0.2¥
Body height (cm), mean±SD	160.5±7.15	161.7±8.72	0.6§
Body mass index (kg/m^2) , median (min–max)	25.7 (16.9–47.8)	25.6 (21.2–32.7)	0.5¥
Right ventricle function/TAPSE (mm), median (min–max)	16 (11–22)	16 (11–22)	0.3¥
Left ventricle function (%), mean±SD	55.6±8.17	56.3±7.56	0.8§
Systolic (mmHg), mean±SD	134.8±14.96	134.9±13.31	0.9§
Diastolic (mmHg), mean±SD	76.3±8.21	77.7±9.89	0.6§
Hemoglobin (g/dL), mean±SD	14.1±3.39	13.6±1.21	0.3§
Hematocrit (%), mean±SD	40.3±4.12	41.1±3.39	0.5§
Leukocyte (x10^3/mL), median (min–max)	8.2 (4.8–16.5)	8.2 (3.9–10.5)	0.6¥
Thrombocyte (x10^3/mL), median (min–max)	262.4 (135.0–405.0)	262.0 (116.0–438.0)	0.6¥
Estimated glomerular filtration rate, median (min–max)	68.8 (20.3–111.7)	68.8 (24.0–98.7)	0.9¥
Triglyceride (mg/dL), median (min–max)	165.9 (61.0–346.0)	165.9 (40.0–897.0)	0.7¥
Total cholesterol (mg/dL), median (min–max)	176.1 (100.0–437.0)	176.1 (97.0–265.0)	0.8¥
HDL (High density lipoprotein), median (min–max)	48.1 (29.0–82.0)	48.1 (32.0–75.0)	0.4¥
LDL (Low density lipoprotein), median (min–max)	107.6 (37.0–339.0)	107.6 (39.0–172.0)	0.9¥
HbA1c (Hemoglobin A1c) (%), median (min–max)	7.2 (5.2–11.1)	7.2 (5.0–10.2)	0.3¥
Blood vessel, n(%)			
Left artery descending (LAD)	14 (56.0)	21 (84.0)	1.0*
Left circumflex (LCx)	3 (12.0)	1 (4.0)	
Right coronary artery (RCA)	8 (32.0)	3 (12.0)	
Before dilatation, median (min–max)			
Balloon inflation (seconds)	15 (15–20)	15 (15–20)	1.0§
Balloon length (mm)	15 (15–20)	15 (15–20)	1.0§
Balloon pressure (atm)	12 (8–12)	12 (8–14)	0.264§
Amount of stent	1	1	1.0§
Stent placement, median (min–max)			
Stent length (mm)	38 (20–38)	38 (20–38)	0.625§
Stent diameter (mm)	3 (2.5–3.5)	2.75 (2.5–3.5)	0.314§
Drug eluting stent, n (%)			
Yes	25 (100)	25 (100)	-
None	0 (0)	0 (0)	
Deploy stent pressure (atm), median (min–max)	14 (12–16)	16 (10–16)	0.286§
Deploy stent duration (seconds), median (min–max)	20 (18–22)	20 (15–20)	0.984§

*Chi-square test; §Unpair t-test; Fisher exact test; ¥Mann-Whitney test.

Table 2. Median of serum level in patients with CAD before PCI, 24 hours, 48 hours post-PCI and delta of serum level between baseline *vs.* 24 hours post-PCI and baseline *vs.* 48 hours post-PCI.

	Serum Markers, Median of Serum Levels*				Delta of Serum Levels			
MDA (mM)	**Baseline**	**24 hours**	**48 hours**	***p*-value[2]**	**Δ1**		**Δ2**	
Curcumin	0.28 (0.4 - 119)	0.29 (0.2 - 155)	0.22 (0.4 - 68.2)	0.6	0.01	3.40%	-0.06	21.40%
Placebo	0.27 (0 - 68.4)	0.3 (0.4 -18.2)	0.3 (0.5 -13.9)	0.3	0.03	9.20%	0.03	0%
***p*-value[1]**	0.6	0.7	0.7					
GSH (mM)	**Baseline**	**24 hours**	**48 hours**	***p*-value[2]**	**Δ1**		**Δ2**	
Curcumin	200.1 (32.2 - 359.8)	150.4 (43.1 - 570.2)	161.9 (27.1 – 425.9)	0.3	-49.7	24.80%	-38.2	19.09%
Placebo	164.8 (43.4 - 328.1)	176.9 (66.2 - 583.3)	183.6 (88.1 - 659.3)	0.1	12.2	7.40%	18.8	11.40%
***p*- value[1]**	0.9	0.3	0.3					

Δ1 indicates the intra-group difference between baseline and 24 hours post-PCI; Δ2 indicates the intra-group difference between baseline and 48 hours post-PCI; *p*-value[1] for comparison between curcumin and placebo (Mann Whitney test); *p*-value[2] for intra-group comparisons between baseline, 24 hours and 48 hours post-PCI (Friedman test).

after 24h of curcumin supplementation (Δ1=-49.7) but then slightly increased after 48h (Δ2=-38.2). While in placebo group the level of GSH keep slightly increasing (Δ1=12.2 and Δ2 =18.8). (Figure 3).

Discussion

Fifty participants were randomly assigned to receive curcumin or placebo. The primary outcomes of this study were examined curcumin's antioxidant properties in reducing oxidative stress of post-PCI in stable CAD. Compared with placebo, curcumin was not statistically significant. The result of this study showed no complications during procedure PCI and no side effects of curcumin. The curcumin intoxication was indeed rare and the symptoms are mild.(15-17)

MDA is a product of lipid peroxidation resulted from the breakdown of polyunsaturated fatty acids (PUFA) contained within the endothelial membrane by ROS. MDA increase is not only found in CAD, but also after PCI because of ischemia-reperfusion injury. This type of

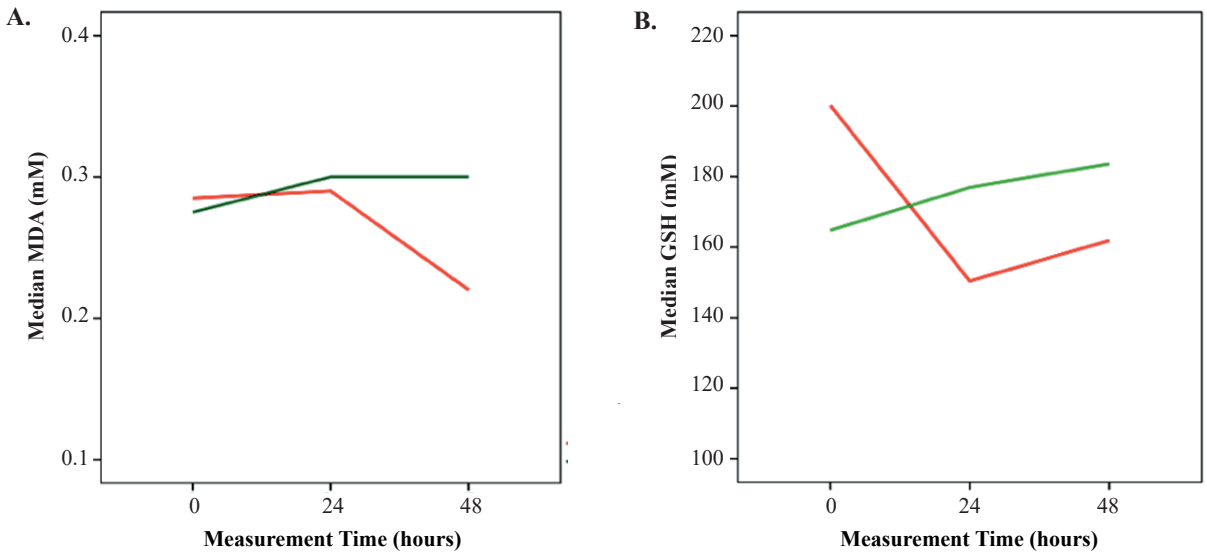

Figure 2. Trend of MDA serum level (A) and GSH serum level (B) in curcumin and placebo groups. Red line: curcumin; Green line: placebo. Data are presented in median (minimum-maximum).

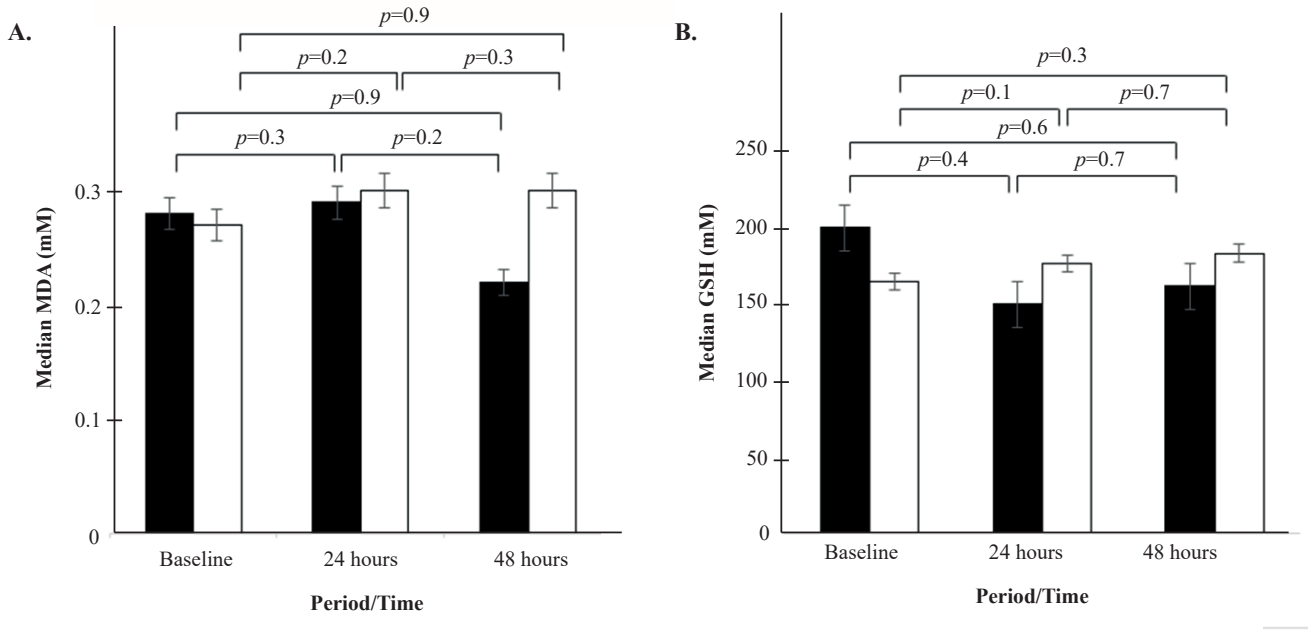

Figure 3. Analysis delta of MDA serum level (A) and GSH serum level (B) in curcumin and placebo groups. Black bar: curcumin; White bar: placebo. *Comparison within group was analyzed using Wilcoxon test.

injury triggers ROS production, causing lipid peroxidation. Based on that fact, MDA can be used as a mean of oxidative stress measurement caused by ischemia-reperfusion injury.(18) A study enrolled 10 stable ACS patients undergoing PCI. This study compared baseline MDA (before balloon inflation) with right after balloon deflation (60 seconds of balloon occlusion) and 60 seconds after balloon deflation. A significant increase of MDA level happened right after deflation and returned back to baseline after 60 seconds post deflation.(19) Another study on 120 post-PCI patients categorized its population into rosuvastatin group (n=55) and control group or without statin (n=65). These groups had increased MDA 2 hours post-PCI and then decrease up to 4 weeks post-PCI.(20) Our study showed decreased MDA from baseline to 48 hours post PCI compared with placebo group. Decreased MDA level in curcumin group was considered caused by curcumin's antioxidant properties as it effectively takes ROS and inhibits lipid peroxidation. The mechanism of curcumin's antioxidant properties revealed curcumin has conjugated structures consisting of 2 methoxylated phenol and 1 β-diketon. Methoxylated phenol acts as hydrogen donor and β-diketon acts as an electron donor.

MDA change was attributed to GSH serum level change. Our study showed decreased stress oxidative level in curcumin group not statistically significant. It was thought that lipid peroxidation activity in these subjects was already repressed by simvastatin/atorvastatin, making MDA changes no longer significant post-PCI. The reduction of stress oxidative by curcumin supplementation was dependent on the dose of curcumin and the duration of treatment. This study showed that curcumin supplementation supported antioxidant properties in simvastatin/atorvastatin that given to patient before PCI. Previous study results reported proven reduced activity of lipid peroxidation using statin in humans.(21) A study about atorvastatin effect on MDA serum concentration enrolled 12 subjects with 40 mg of atorvastatin daily. They measured MDA level at 1 month and 6 months of treatment and compared the results with their level before treatment. This resulted in significant reduction of MDA level after 1 month of treatment ($p<0.05$) and 6 months of treatment ($p<0.01$).21 Similar result was also showed significant reduction of MDA level after 1 week ($p<0.05$) and 4 weeks post-PCI ($p<0.05$) in the group with rosuvastatin.(20)

Oxidative stress is an imbalance of pro- and anti-oxidants which has the potency to cause tissue injury.(22) PCI causes a short ischemic episode of myocardium when the balloon is inflated that cause oxidative stress in endothelial tissue.(19,23,24) Direct measurement of oxidative stress and free radicals are very difficult because they are highly reactive and have an extremely short half-life. Although *in vitro*, oxidative stress can be measured using endogenous antioxidant molecules, such as GSH. Serum GSH shows endogenous defense activity.(25) Curcumin reduced the oxidative stress process by elimination of ROS.(12) Curcumin's role in eliminating free radicals is not just by its direct antioxidant effect, but also by increasing intracellular

defense against oxidants. Decreased GSH has a major role in cellular defense and in the detoxification of reactive oxygen radicals in acute malathion toxicity in rats.(26)

GSH has important role in changing NADPH into $NADP^+$. NADPH donors a hydrogen ion to neutralize radical oxygen and radical OH coming from Fenton and Haber-Weise reaction, which will then be modified into H_2O. GSH also modifies H_2O_2 into H_2O with the help of catalase. H_2O_2 is a molecule produced from ROS with catalysis by superoxide dismutase (SOD) in the event of ischemia-reperfusion trauma.

In this study, curcumin supplementation is aimed as an antioxidant. In oxidative stress conditions, GSH level will be reduced because of increased consumption or disruption in its synthesis. Studies about oxidative stress and antioxidant level in group burst fracture and hepatocellular carcinoma showed increased MDA level and decreased GSH level caused by different biological response, in which oxidative stress insult results in faster MDA change than that of GSH level.(27-28) Our study showed decreased GSH level from baseline to 48 hours post-PCI caused by slow protective response from curcumin to oxidative stress induced by PCI. Our finding is in line with a study about oxidative stress level post-PCI that revealed while MDA level increased immediately after the procedure, GSH level would have not increased until 14 days post-PCI.(29) Therefore, GSH level is unable to describe oxidative stress post-PCI rather than MDA in the acute phase. Curcumin supplementation 45mg/day for 14 days greatly reduced ischemia-reperfusion injury in children undergoing Tetralogy of Fallot surgery.(30,31) Meanwhile, current study had less significant antioxidant effect due to lower period of treatment.

Limitation of our study was varied stress oxidative level in myocardial infarction history have potential to cause bias because there was no matching on the subject. Further study can be done to observe the GSH level in longer supplementation of curcuma in post-PCI subjects. Large-scale and multicenter study are also required to verify and expand on our conclusions.

Conclusion

Supplementation of 45 mg/day curcumin for 48h could decrease MDA level but not enough to increase the GSH level in post-PCI. Therefore curcumin supplementation could be useful, however RCT with matched subjects, longer period of treatment and 1-month follow-up is necessary to evaluate the potential effect of curcumin's antioxidant properties.

Acknowledgements

We would like to thank the translators, patients, and the expert committee for their participation in this study.

Authors Contribution

TS, IA, and FS were involved in concepts, design, the definition of intellectual content, literature search, and clinical studies. TS performed data acquisition, data analysis, and statistical analysis. KDS, CSS performed the manuscript preparation and manuscript editing. All authors discussed the results and commented on the manuscript review.

References

1. World Health Organization. Global health estimates: Leading causes of DALYs. Disease burden, 2000–2019 [cited Jul 1, 2021]. Available from: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/global-health-estimates-leading-causes-of-dalys.
2. Kementrian Kesehatan RI. Basic Health Research 2013. Jakarta; Kementrian Kesehatan RI; 2013.
3. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. Lancet. 1978; 1(8058): 263. doi: 10.1016/s0140-6736(78)90500-7.
4. Means G, End C, Kaul P. Management of percutaneous coronary intervention complications. Curr Treat Options Cardiovasc Med. 2017; 19(4): 25. doi: 10.1007/s11936-017-0526-6.
5. Cicek D, Tamer L, Pekdemir H. Coronary angioplasty induced oxidative stress and its relation with metoprolol use and plasma homocysteine levels. Anadolu Kardiyol Derg. 2006; 6(4): 308-13.
6. Ferns GA, Raines EW, Sprugel KH. Inhibition of neointimal smooth muscle accumulation after angioplasty by an antibody to PDGF. Science. 1991; 253(5024): 1129-32.
7. Holmes DR, Vlietstra RE, Smith HC. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA Registry of the National Heart, Lung, and Blood Institute. Am J Cardiol. 1984; 53(12): 77C-81C.
8. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, *et al.* 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011; 124(23): e574-651.
9. Nobuyoshi M, Kimura T, Nosaka H. Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients. J AM Coll Cardiol. 1988; 12(3): 616-23.
10. Serruys P, Lutijen H, Beatt K, Geuskens R, Feyter Pd, Brand Mvd. Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon. A quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months. Circ J. 1988; 77(2): 361-71.

11. Kapakos G, Youreva V, Srivastava AK. Cardiovascular protection by curcumin: molecular aspects. Indian J Biochem Biophys. 2012; 49(5): 306-15.
12. Sreejayan N, Rao MN. Free radical scavenging activity of curcuminoids. Arzneimittelforschung. 1996; 46(2): 169-71.
13. Jain SK, Rains J, Croad J, Larson B, Jones K. Curcumin supplementation lowers TNF-alpha, IL-6, IL-8, and MCP-1 secretion in high glucose-treated cultured monocytes and blood levels of TNF-alpha, IL-6, MCP-1, glucose, and glycosylated hemoglobin in diabetic rats. Antioxid Redox Signal. 2009; 11(2): 241-9.
14. Wasserfuhr D, Cetin SM, Yang J, Freitag P, Frede S, Jakob H, *et al.* Protection of the right ventricle from ischemia and reperfusion by preceding hypoxia. Naunyn Schmiedebergs Arch Pharmacol. 2008; 378(1): 27-32.
15. Cheng AL HC, Lin JK, Hsu MM, Ho YF, Shen TS. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res. 2001; 21(4B): 2895-900.
16. Lao CD, Ruffin MTt, Normolle D, Heath DD, Murray SI, Bailey JM, *et al.* Dose escalation of a curcuminoid formulation. BMC Complement Altern Med. 2006; 6: 10. doi: 10.1186/1472-6882-6-10.
17. Sharma RA, McLelland HR, Hill KA, Ireson CR, Euden SA, Manson MM, *et al.* Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. Clin Cancer Res. 2001; 7(7): 1894-900.
18. Ozer MK, Parlakpinar H, Cigremis Y. Ischemia-reperfusion leads to depl etion of glutathione content and augmentation of malondialdehyde production in the rat heart from overproduction of oxidants: can caffeic acid phenethyl est er (CAPE) protect the heart? Mol Cell Biochem. 2005; 273(1-2): 169-75.
19. Roberts MJ, Young IS, Trouton TG, Trimble ER, Khan MM, Webb SW, *et al.* Transient release of lipid peroxides after coronary artery balloon angioplasty. Lancet. 1990; 336(8708): 143-5.
20. Kim TH, Jiang HH, Youn YS, Park CW, Tak KK, Lee S, *et al.* Preparation and characterization of water-soluble albumin-bound curcumin nanoparticles with improved antitumor activity. Int J Pharm. 2011; 403(1-2): 285-91.
21. Murrow JR, Sher S, Ali S, Uphoff I, Patel R, Porkert M, *et al.* The differential effect of statins on oxidative stress and endothelial function: atorvastatin versus pravastatin. J Clin Lipidol. 2012; 6(1): 42-9.
22. Pytel E, Jackowska P, Chwatko G, Olszewska-Banaszczyk M, Koter-Michalak M, Kubalczyk P, *et al.* Intensive statin therapy, used alone or in combination with ezetimibe, improves homocysteine level and lipid peroxidation to a similar degree in patients with coronary artery diseases. Pharmacol Rep. 2016; 68(2): 344-8.
23. Kopff M, Kowalczyk E, Kopff A. Influence of selected cardiological drugs on oxidative status. Pol J Pharmacol. 2004; 56(2): 265-9.
24. Buffon A, Santini SA, Ramazzotti V. Large, sustained cardiac lipid pero xidation and reduced antioxidant capacity in the coronary circulation after brie f episodes of myocardial ischemia. J AM Coll Cardiol. 2000; 35(3): 633-9.
25. Iuliano L, Pratico D, Greco C, Mangieri E, Scibilia G, FitzGerald GA, *et al.* Angioplasty increases coronary sinus F2-isoprostane formation: evidence for in vivo oxidative stress during PTCA. J Am Coll Cardiol. 2001; 37(1): 76-80.
26. Hollman PC, Cassidy A, Comte B, Heinonen M, Richelle M, Richling E, *et al.* The biological relevance of direct antioxidant effects of polyphenols for cardiovascular health in humans is not established. J Nutr. 2011; 141(5): 989s-1009s.
27. Alp H, Aytekin I, Hatipoglu NK, Alp A, Ogun M. Effects of sulforophane and curcumin on oxidative stress created acute malathion toxicity in rats. Eur Rev Med Pharmacol Sci. 2012; 16(Suppl 3): 144-8.
28. Kuyumcu F, Aycan A. Evaluation of oxidative stress levels and antioxidant enzyme activities in burst fractures. Med Sci Monit. 2018; 24: 225-34.
29. Cheng SB, Liu HT, Chen SY, Lin PT, Lai CY, Huang YC. Changes of oxidative stress, glutathione, and its dependent antioxidant enzyme activities in patients with hepatocellular carcinoma before and after tumor resection. PLoS One. 2017; 12(1): e0170016. doi: 10.1371/journal.pone.0170016.
30. Szewczyk-Golec K, Grzelakowski P, Ługowski T, Kędziora J. The effects of percutaneous transluminal coronary intervention on biomarkers of oxidative stress in the erythrocytes of elderly male patients. Redox Rep. 2017; 22(6): 315-22.
31. Sukardi R, Sastroasmoro S, Siregar NC, Djer MM, Suyatna FD, Sadikin M, *et al.* The role of curcumin as an inhibitor of oxidative stress caused by ischaemia re-perfusion injury in tetralogy of Fallot patients undergoing corrective surgery. Cardiol Young. 2015: 26(3), 431-8.