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Lidocain Effect on Inflammation seen from sICAM-1 in Patients with Coronary Artery Bypass Graft Surgery

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Research Article

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ABSTRACT

About 9.3 percentage over 1000 per year coronary artery disease in Asia-Pacific needs coronary artery bypass grafting. Coronary artery bypass grafting is an aggressive surgery that may lead to damage of vascular endothelia. Inflammatory response on coronary artery bypass grafting are induced by ischemic condition during aortic cross-clamping which is followed by reperfusion, causing oxidative stress that increase production of reactive oxygen species (ROS) which can stimulate formation of intercellular adhesion molecule-1 (ICAM-1). This study aims to analyze whether administration of intravenous lidocaine in coronary artery bypass grafting utilizing cardiopulmonary bypass machine may inhibit formation of sICAM-1. This randomized double blind controlled experimental study with permutation block randomization involves 30 patients who were underwent coronary artery bypass grafting. Patients were divided into two groups, 15 patients on lidocaine group and 15 patients on placebo group. Blood tests of sICAM-1 level were performed during pre-induction, 8 and 12 h post utilization of cardiopulmonary bypass machine. Data was analyzed using unpaired T-test and Chi-squared method, with p value <0.05 assuming a significant result. Statistical analysis showed sICAM-1 level in lidocaine group on 8 and 12 h post utilization of cardiopulmonary bypass machine was lower than placebo group with significant difference ($p<0.05$). Conclusion: Administration of intravenous lidocaine in coronary artery bypass grafting utilizing cardiopulmonary bypass machine may inhibit formation of sICAM-1.

INTRODUCTION

Life style change and fast urbanization have increased incidence of cardiac diseases in Asia [1]. According to American Heart Association (AHA), prevalence of coronary artery disease in Asia-Pacific range about 4.3 percent of all population and around 9.3 percent of the particular population needs to undergo coronary artery bypass grafting [2,3].

Incidence rate of Systemic Inflammatory Response Syndrome (SIRS) in patients who undergo coronary artery bypass grafting is still extremely as high as 90 percent [4]. Beside Systemic Inflammatory Response Syndrome (SIRS) marker such as TNF-α, IL-6 and IL-8 cytokines, Left Ventricle Ejection Fraction (LVEF) is also a strong predictor of outcome for patients with cardiovascular disease, in correlation with mortality and morbidity rate [5].

Coronary artery bypass grafting is an aggressive surgery that may lead to damage of vascular endothelia and most of the procedures are still utilizing cardiopulmonary bypass machine [6-8]. Inflammatory response on coronary artery bypass grafting are induced by ischemic condition during aortic cross-clamping which is followed by reperfusion [6,9]. Ischemic condition causes oxidative stress that increase production of reactive oxygen species (ROS) which can stimulate formation of intercellular adhesion molecule-1 (ICAM-1) [9,10]. Elevation of ROS activates a transcription factor called nuclear factor kappa B (NFκB) which stimulates release of TNF-α, IL-6 and IL-8 cytokines [10] and formation of adhesion molecules Inter Cellular Adhesion Molecule-1 (ICAM-1), Vascular Cell Adhesion Molecule-1 (VCAM-1), integrin and E-selectin [8,11].

Release of inflammatory cytokines, mainly IL-2 and TNF-α, causes endothelial activation [8,9]. Activated endothelial expresses cellular surface adhesion molecules such as E-selectin, P-selectin, Intercellular Adhesion Molecule (ICAM) and Vascular Cell Adhesion Molecule (VCAM). Those adhesion molecules regulate leucocytes extravasations, causing increment in leukocyte's

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rolling, adhesion, and migration [11,12]. ICAM-1 will bind with leukocyte's integrin LFA-1 and VCAM-1 will bind with antigen 4 (VLA-4). ICAM-1's peak of expression happens 12 h after stimulation of cytokines [7,13]. After stimulated, endothelial starts to produce adhesion molecules which can detached from endothelial surface in to blood circulation and known as a soluble form. Increment of adhesion molecules in plasma indicates endothelial activation during reperfusion on ischemic cardiac muscles [14].

Increment of soluble VCAM-1 (sVCAM-1) and soluble ICAM-1 (sICAM-1) as a marker of endothelial activation due to inflammation in patients underwent coronary artery bypass grafting has been published in several studies [7,13-19]. In a prospective study on 60 patients, it was found that only patients who underwent coronary artery bypass grafting experienced elevation of P-selectin, sVICAM-1 and sICAM-1 level between 2 to 4 h after surgery [8].

A study in 25 patients who underwent coronary artery bypass grafting showed that level of cytokines and adhesion molecules were significantly elevated after coronary artery bypass grafting. Mean level of sICAM-1 was 2.4 times higher on day 6 after surgery. Patient underwent hypothermic technique shows significantly higher level of sICAM-1, SE-selectin, IL-6 and IL-8 in 24 h after surgery, compared to patients underwent norm thermic techniques [13].

A study in 25 patients who underwent coronary artery bypass grafting utilizing cardiopulmonary bypass machine assessed concentration of sICAM-1 and sVCAM-1 in patients' blood serum. There were elevations on both adhesion molecules in the end of surgery if compared to before surgery, showing coronary artery bypass grafting affected endothelial function [8].

Administration of lidocaine is one of many methods utilized to reduce inflammatory responses. This drug is commonly used by anesthesiologist as anti-arrhythmic agent in cardiac surgeries, but its effect as anti-inflammatory agent has not been studied in many research on patients underwent coronary artery bypass grafting utilizing cardiopulmonary bypass machine. Lidocaine is a local anesthetic agent from amide group which has strong anti-inflammatory effect, probably due to similarity of its chemical structures with steroid and anti-histamine [20,21]. In a study about continuous infusion of lidocaine in same dosage usually administered to adult patient, it inhibited all inflammatory process due to peritonitis in rabbits [22].

The ability of lidocaine as an anti-inflammatory agent is marked with decrement on both *in vivo* and *in vitro* pro-inflammatory cytokines level. Lidocaine also stimulates secretion of anti-inflammatory IL-1 cytokine. Lidocaine in its role as anti-inflammatory agent can inhibit activation of NFκB and T-cell proliferation. Lidocaine lowers defect on epithelial cells. Lidocaine inhibits secretion of pro-inflammatory cytokines taken from culture of intestinal epithelial cells, which is stimulated by TNF-α [19]. *In vitro*, amide local anesthetic agent, for example lidocaine, inhibits release of IL-1α from lipopolysaccharide-stimulated human peripheral blood mononuclear cell [23]. *In vitro*, lidocaine also inhibits release of histamine from leukocytes, basophils and mast cells in high concentration, therefore lidocaine able to inhibit release of several other inflammatory mediators, besides its direct effect to PMN and macrophage [21,22].

MATERIALS AND METHOD

This study is a randomized double blind controlled experimental study with permuted block randomization which was performed after receiving approval from Ethical Committee of Padjadjaran University, Rumah Sakit. Dr. Hasan Sadikin Bandung. The study was performed in Rumah Sakit, Dr. Hasan Sadikin Bandung. Subjects which include the study were patients underwent coronary artery bypass grafting that match to the inclusion criteria, which are the patient had never undergone any coronary artery bypass grafting procedure utilizing cardiopulmonary bypass machine before, ejection fraction >40%, age ranges from 18 to 64 years old, and BMI<40. Exclusion criteria are patient has undergone other type of coronary bypass surgery, on anti-inflammatory medications, on immunosuppressive therapy, has immunological disease based on anamnesis and clinical condition. Sample would be dropped out if there was any severe hemodynamic disturbance which was difficult to handle during surgery or any massive bleeding, patient must underwent repeated surgery after the first and patient drew back.

Determination of sample count was performed using formula to test differentiation between two means, by choosing confidence interval 95% (Zα=1.645) and power test 80% (Zβ=0.842). Minimal number of sample needed was 13 patients in each group. Samples were divided into two groups using permuted block randomization with 15 patients on each group. Group I was treated with lidocaine and group II was untreated and received placebo instead. Treated group received intravenous 1.5 mg/kg body weight of lidocaine during anesthetic induction, followed by continuous maintenance infusion with dosage 2 mg/kg body weight/hour during surgery, and discontinued when surgery had been done. Control group received placebo with same form, color, smell, and packaging. 10 ml of blood was drawn from each patient in both groups in order to examine sICAM-1 level. Blood tests of sICAM-1 level were performed based on three observations time, which are during pre-induction, 8 and 12 h post utilization of cardiopulmonary bypass machine (post on by pass).

Descriptive statistical data analysis was performed to obtain mean, median, standard deviation, lowest value and highest value. Data normality test on sICAM-1 in both groups utilized Shapiro Wilk method (for n<50), in which data was stated as normally distributed if p value exceeded 0.05. sICAM-1 level on lidocaine group was compared to level on placebo group, during initial (pre-test) and final condition (post-test), using Mann Whitney U test if data distribution was not normal, and unpaired t-test if data distribution was normal. Meanwhile, to compare level of sICAM-1 between pre-test and post-test, Wilcoxon test would be used in case data distribution was not normal, or paired t-test if data distribution was normal.

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RESULTS

Result of the study in a total of 30 patients with 15 patients on lidocaine group and 15 other patients on placebo group will be described based on general characteristics, comparison analysis of alteration of sICAM-1 level from pre-induction, 8 h post on by pass, until 12 h post on by pass **(Table 1)**.

Table 1. General characteristic of study subjects.

Variables	Group		P Value
	Lidocaine (n=15)	Placebo	
Age (in years)			
Mean (SD)	57.2 (5.71)	60 (5.04)	0.161b
Median (Range)	58 (49- 64)	62 (47- 64)	
Ejection fraction			
Mean (SD)	54.13 (2.23)	54.27 (1.62)	0.853a
Median (Range)	54 (50- 58)	55 (52- 57)	
Duration of cardiopulmonary bypass machine usage			
Mean (SD)	255.33 (36.23)	265.33 (25.32)	0.388a
Median (Range)	240 (200- 320)	270 (220- 300)	
Duration of aortic cross-clamping			
Mean (SD)	79.13 (6.21)	79.93 (6.34)	0.730a
Median (Range)	79 (71- 89)	82 (70- 89)	
Bleeding volume			
Mean (SD)	1760 (501.14)	1680 (478.39)	0.658a
Median (Range)	2000 (1000- 2500)	1700 (1000- 2600)	
Complication (f, %)			
Yes	-	-	1.000c
No	15 (100%)	15 (100%)	

Note: P value was calculated from a) unpaired t-test, b) Mann Whitney test, and c) Chi-square test. Differentiation was assumed as significant if p value<0.05 and highly significant if p<0.01

According to **Table 1**, it was known that general characteristics from both groups were not significantly different or could be classified as homogen. This can be seen from comparison of all characteristic which showed value above 0.05. Therefore, these two groups were comparable.

Level of sICAM-1 on groups on three observation period which were pre-induction, 8 h post on by pass and 12 h post on by pass. First, data was tested for its distribution normality, which results are presented in annex, then comparison was performed with results as described below:

Table 2. Comparison of sICAM-1 on both groups.

Variable (ng/ml)	Group		P value
	Lidocaine (n=15)	Placebo (n=15)	
sICAM-1 pre-induction			
Mean (SD)	15.1 (9.44)	14.06 (9.77)	0.512b
Median (Range)	14.11 (5.01- 45.13)	11.72 (5.1- 45.87)	
sICAM-1 8 h post on by pass			
Mean (SD)	19.78 (10.67)	38.24 (12.67)	0.000**b
Median (Range)	17.21 (9.79- 54.87)	35.37 (24.33- 74.13)	
sICAM-1 12 h post on by pass			
Mean (SD)	34.41 (11.28)	66.32 (16.05)	0.000**a
Median (Range)	33.51 (17.18- 63.9)	67.3 (41.02- 103.9)	
P-value	0.000**b	0.000**b	

Note: P value was calculated from a) unpaired t-test, b) Mann Whitney test, c) Friedman test, and d) ANOVA repeated measure. Differentiation was assumed as significant if p value<0.05 and highly significant if p<0.01

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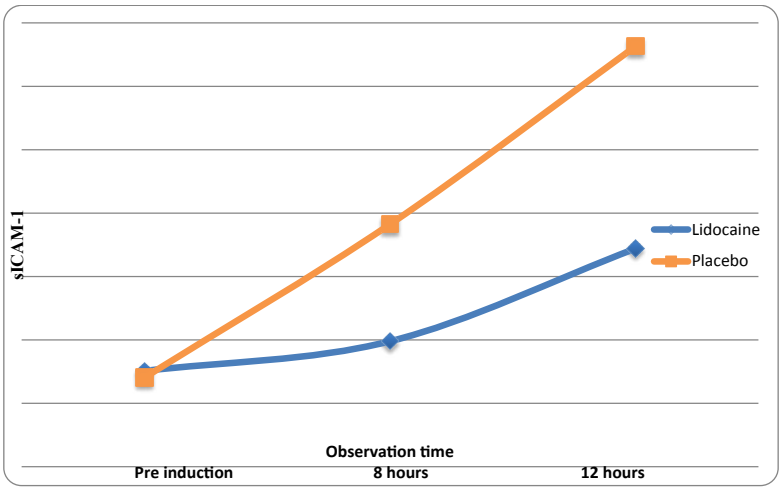

Figure 1. Comparison of sICAM-1 on both groups.

Table 2 and **Figure 1** above show comparison of sICAM-1 level on both groups. During pre-induction, sICAM-1 level on placebo group was not significantly different in comparison to lidocaine group (p>0.05). During 8 h post on by pass, an extremely significant difference was noted between two groups, in which elevation of sICAM-1 level on lidocaine group was lower than on placebo group. Entering 12 h post on by pass, elevation of sICAM-1 level on lidocaine group was still lower than on placebo group. Alterations of sICAM-1 levels were analyzed further in the following description.

Table 3. Comparison of sICAM-1 level alteration on both groups.

sICAM-1 alteration (ng/ml)	Alteration (Mean & SB)		P value
	Lidocaine (n=15)	Placebo (n=15)	
Pre-induction and 8 h post induction (1 vs. 2)	4.68 (2.41)	24.18 (5.44)	0.000**
Pre-induction and 12 h post induction (1 vs. 3)	19.31 (4.6)	52.26 (10.8)	0.000**
8 and 12 h post induction (2 vs. 3)	14.63 (5.06)	28.08 (7.99)	0.000**

Note: P value was calculated from unpaired t-test, differentiation was assumed as significant if p value<0.05 and highly significant if p<0.01

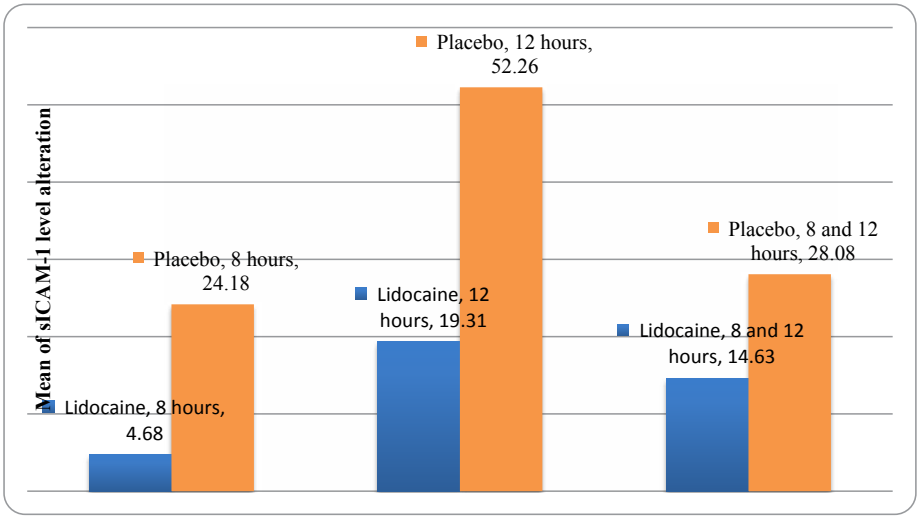

Figure 2. Comparison of sICAM-1 level alteration on both groups.

Table 3 and **Figure 2** above show comparison of sICAM-1 level alteration on both groups. Changes in sICAM-1 level from pre-induction to 8 h post on by pass showed that lidocaine group experienced lower elevation (4.68) in comparison to placebo group (24.18) and the difference was highly significant (p<0.01). Changes in sICAM-1 level from pre-induction to 12 h post on by pass showed that lidocaine group experienced lower elevation (19.31) in comparison to placebo group (52.26) and the difference was also highly significant (p<0.01). Meanwhile, changes in sICAM-1 level from 8 h post on by pass to 12 h post on by pass showed that lidocaine group experienced lower elevation (14.63) in comparison to placebo group (28.08) and the difference was highly

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significant ($p<0.01$). Based on the mentioned results, it can be concluded that lidocaine has been proven to be able to reduce increment of sICAM-1 more effectively than placebo, with an extremely significant result.

DISCUSSION

This study was performed in 30 patients underwent coronary artery bypass grafting utilizing cardiopulmonary bypass machine. General characteristics that were used in this study were age, ejection fraction, duration of cardiopulmonary bypass machine utilization, duration of aortic cross clamping, volume of bleeding and complications. p-value not significant, there are many studies performed in patients underwent coronary artery bypass grafting utilizing cardiopulmonary bypass machine due to its high incidences of inflammation which caused high morbidity and mortality rate. Incidence of inflammation during coronary artery bypass grafting utilizing cardiopulmonary bypass machine has lots of causes, such as conversion to laminar flow, blood contact with synthetic by pass surface, cardiac ischemic during aortic cross clamping, and hypothermia. Inflammatory reaction may cause SIRS which relates to serious morbidity and mortality. Current strategies to depress inflammation does give beneficial effects, but do not able to control SIRS [3,6-8]. Various techniques has been performed by surgeons, anesthesiologists and perfusionists, to lower inflammatory reaction. Medications to lower inflammatory process during coronary artery bypass grafting utilizing cardiopulmonary bypass machine has been studied, such as leukocyte filtration, corticosteroid, aprotinin, heparin and Nitric Oxide donor compounds [9].

Repression of inflammatory process has been performed pharmacologically using medications, such as lidocaine. Assessment of effects of lidocaine administration in this study was done by analyzing sICAM-1 level on study subjects who were divided into two groups, treatment group and control group.

In **Table 1**, it was known that general characteristics (age, ejection fraction, duration of cardiopulmonary bypass machine utilization, duration of aortic cross clamping, volume of bleeding) from both groups were not significantly different or could be classified as homogen. This can be seen from comparison of all characteristic which showed value above 0.05. Therefore, these two groups were comparable.

If age, ejection fraction, duration of cardiopulmonary bypass machine utilization, duration of aortic cross clamping, volume of bleeding and complications were significantly different, then one group would experience more severe inflammatory process. This would lead to more severe inflammatory reaction which includes activation of endothelial cells, leucocytes, platelets, complement system, and coagulation cascade [24-27]. Group with more severe inflammation would experience more severe SIRS compared to another group, therefore those groups were not comparable.

Histologically, typical sign of acute inflammation is interstitial tissue infiltration by leucocytes, which in initial phase are mainly consisting of neutrophils and mononuclear leucocytes. Leukocyte's ability to perform extravasations on inflamed location has been known since one century ago, but only during the last decade, the responsible molecule for migration of trans-endothelial adhesion leukocytes, also called as diapedesis (emigration) was identified and its mechanism of action described [10,15].

Endothelial activation causes regional capillary endothelial more permeable to substances which normally kept in intravascular [10,15]. Activated endothelial expresses cellular surface adhesion molecules such as intercellular adhesion molecule (ICAM). The adhesion molecule regulates leucocytes extravasations, causing increment in leukocyte's rolling, adhesion, and migration. ICAM-1 will bind with leukocyte's integrin LFA-1. ICAM-1's peak of expression happens 12 h after stimulation of cytokines. After stimulated, endothelial starts to produce adhesion molecules which can detached from endothelial surface in to blood circulation and known as a soluble form. Elevation of adhesion molecules in plasma indicates endothelial activation on ischemic cardiac muscles [4,11-13,28,29].

Increment of soluble ICAM-1 (sICAM-1) acts as a marker of endothelial activation due to inflammation in patients underwent coronary artery bypass grafting. Elevation of this adhesion molecule shows an inflammatory process which may lead to SIRS and organ dysfunctions [3,4].

From **Table 2** and **Figure 1,** it is shown that there were differences in alteration of sICAM-1 level between lidocaine group and placebo group, as well as shown in **Table 3** and **Figure 2**. Reasoning of the result was because lidocaine is a strong anti-inflammatory agent, probably due to similarity of its chemical structures with steroid and anti-histamine. In a study about continuous infusion of lidocaine in same dosage usually administered to adult patient, it inhibited all inflammatory process due to peritonitis in rabbits. Lidocaine in its role as anti-inflammatory agent can inhibit activation of NFκB and T-cell proliferation. Lidocaine also stimulates secretion of anti-inflammatory IL-1 cytokine [19].

Lidocaine lowers release of cytokines in epithelial cells and neutrophils and also lowers defect on epithelial cells. During ischemic reperfusion, endothelial cells hold important roles in activation of cytokines and adhesion molecules, therefore lidocaine able to prevent endothelial injury. Lidocaine inhibits secretion of pro-inflammatory cytokines taken from culture of intestinal epithelial cells, which is stimulated by TNF-α [19].

In vitro, lidocaine also inhibits release of histamine from leukocytes, basophils, and mast cells in high concentration. Therefore, lidocaine able to inhibit release of several other inflammatory mediators, besides its direct effect to PMN and macrophage [21,22].

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Lidocaine also holds important role in production of oxygenized free radicals. Inhibition of oxygenized free radicals, such as superoxide anions, by lidocaine has been clearly shown in clinical studies. Mechanism of action from this direct scavenging effect is caused by interaction between lidocaine and proteins and phospholipids membranes, intervention of free radical formation in mitochondria, and prevention of free radical production [29].

Several *in vitro* and *in vivo* studies have been conducted to learn anti-inflammatory effects of lidocaine. Polymorph nuclear leukocytes' effect on release and mediator of free radicals is the most important effect. Concentration needed to achieve this effect is way lower *in vitro* compared to *in vivo*. Administration of lidocaine via epidural route, in which lidocaine's blood concentration is almost similar to administration via intravenous route, can explain its anti-inflammatory effect. In patients who did not receive epidural analgesic, administration of lidocaine intravenously may also be done to modulate inflammatory response after surgery [21].

Another study on rabbits was performed by administrating bolus of 2 mg/kg body weight lidocaine intravenously, followed by continuous infusion of 2 mg/kg body weight/h, showed that lidocaine was significantly able to repress neutrophils' accumulation and production. Another study was performed by administrating bolus of 1.5 mg/kg body weight lidocaine intravenously followed by continuous infusion of 0.3 mg/kg body weight/min for four hours, showed that lidocaine was able to repress neutrophils' accumulation [21].

These particular reasoning shows that administration of intravenous lidocaine is able as anti-inflammatory agent in coronary artery bypass grafting utilizing cardiopulmonary bypass machine, giving highly significant result seen from alteration of sICAM-1's level.

CONCLUSION

Based on results of the study, it can be concluded that administration of intravenous lidocaine in coronary artery bypass grafting utilizing cardiopulmonary bypass machine may inhibit formation of sICAM-1 and reduce inflammation.

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