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Research Article

Comparison of the Effectiveness of Allopurinol and Methylprednisolone in Reducing Reperfusion Injury in Coronary Artery Bypass Surgery

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Abstract

Background: Reperfusion injury due to the release of ROS when using CPB and the return of oxygen-rich blood flow to ischemic myocardium after the release of aortic clamps, can cause myocardial dysfunction. Allopurinol as an inhibitor of xanthine oxidase and methylprednisolone is used to reduce the effects of inflammation and reperfusion injury.

Method: A double-blind randomized clinical trial study was conducted on 42 patients undergoing coronary artery bypass surgery using CPB between October 2019 and March 2020, which was allocated to the allopurinol group or the methylprednisolone group. Examination of biomarkers of reperfusion injury is carried out by examination of a blood sample of MDA which is performed shortly after the installation of a central venous catheter and 5 minutes after the aortic clamp are removed. MDA examination is done by the ELISA method. Assessment of VIS was carried out in the first 24 hours of postsurgical treatment. While the assessment of the incidence of postoperative arial fibrilation was performed during the first 48 hours after surgery.

Results: MDA post reperfusion levels increased significantly in the administration of methylprednisolone (p=0.041) and increased not significantly in the administration of allopurinol (p=0.251). The postoperative VIS value in the administration of allopurinol was significantly lower than in the administration of methylprednisolone (median 6 vs. 22, p = 0.009). The incidence of POAF in the two groups showed no differences were statistically significant (p = 0.231).

Conclusion: Allopurinol is more effective than methylprednisolone and can be used in efforts to reduce reperfusion injury in coronary artery bypass surgery.

Keywords

Reperfusion injury, Allopurinol, Methylprednisolone, Malondialdehyde, Vasoactive-inotropic score, Postoperative atrial fibrillation

Abbreviation

CPB: Cardiopulmonary bypass; MDA: Malondialdehyde; POAF: Postoperative atrial fibrillation; VIS: Vasoactive-inotropic score; ROS: Reactive oxygen species

1. Introduction

Myocardial ischemia-reperfusion (I/R) injury was first described by Jennings et al in 1960 using the dog's heart as a coronary ligation model [1]. The study authors observed that reperfusion appeared to accelerate the development of necrosis. Histological changes found after only 30 to 60 minutes of I/R are proportional to the level of necrosis that is usually seen after 24 hours of permanent coronary occlusion. Cardiopulmonary bypass (CPB) starts several processes that have an impact on the cellular and non-celluler levels of the blood content. Repetition of blood flow through nonendothelial extracorporeal circuits triggers the activation of polymorphonuclear leukocytes (especially neutrophils) that are believed to be sources of reactive oxygen species (ROS) during cardiac surgery [2-4]. CPB is also associated with systemic inflammatory response syndrome (SIRS) with activation of the complement and granulocyte systems [5].

One of the enzymes involved in free radical formation is xanthine oxidase. Xanthine oxidase is involved in the catabolism of adenine nucleotides, specifically hypoxanthine. As long as myocardial perfusion is under normal conditions, xanthine oxidase is present in small amounts and hypoxanthine is oxidized by xanthine dehydrogenase to xanthine, a process that does not produce free radicals [6]. Conversely, during the period of ischemia, xanthine dehydrogenase is converted to xanthine oxidase. This conversion facilitates the production of oxygen radicals [6,7]. The evolution of oxygen free radicals begins because, unlike xanthine dehydrogenase which uses nicotinamide adenine dinucleotide as its substrate, xanthine oxidase uses oxygen [6,7]. As a result, during periods of oxygen deprivation, xanthine oxidase cannot catalyze the conversion of hypoxanthine to xanthine, causing the accumulation of hypoxanthine [6]. Furthermore, when

oxygen is available during reperfusion, xanthine oxidase can function, resulting in the generation of significant toxic oxygen species.

A meta-analysis study has also been reported by Singh et al regarding the efficacy of allopurinol in reducing the incidence of myocardial infarction after coronary artery bypass. With limited evidence available, the results of the study showed that allopurinol has a cardioprotective effect with a significantly lower incidence of myocardial infarction compared to the control group (1.77% vs. 12.07%) [8].

In several studies it was found that administration of steroids can reduce the effects of reperfusion injury in adult open heart surgery, thereby reducing the release of free radical oxygen. Research by Volk et al. on coronary artery bypass surgery provided results that administering 15 mg/kg of methylprednisolone 1.5 hour before CPB use significantly reduced MDA levels compared to placebo [9]. It is known that the examination of ROS and nitrogen species in human blood samples is very difficult because of its very short half-life, so what we can examine as a marker of oxidative stress is an increase in MDA levels, which is a product of oxidative stress induced lipid peroxidation [10,11]. Another similar study was conducted by Dandona et al, where intravenous administration of hydrocortisone is effective in inhibiting the formation of ROS [12]. Corticosteroids are known to work as inhibitors of the enzyme phospholipase A2, which acts to facilitate the formation of ROS [13]. Subsequent research has shown that in certain cell lines, glucocorticoids can induce the expression of the IκB protein, which binds to the Nuclear Factor κß (NFκB), which, in turn, is involved in the inflammatory pathway caused by endotoxin and tumor necrosis factor-alpha (TNFα) [14].

The release of free radical oxygen or ROS as well as inflammatory mediators in coronary artery bypass surgery using CPB and aortic cross clamps have been known to cause reperfusion injury which can further cause myocardial damage through lipid peroxidation, postoperative atrial fibrillation, and stunning. One of the efforts to prevent reperfusion injury at our institution so far has been to use methylprednisolone. There are no studies comparing the administration of allopurinol and methylprednisolone in reducing the effects of reperfusion injury in coronary artery bypass surgery, seen from the levels of malondialdehyde, inotropic and vasoactive requirements (vasoactive-inotropic scores) and postoperative atrial fibrillation.

2. Methods

2.1 Participants

The study was conducted for 6 months, and was a randomized and experimental controlled intervention study aimed at comparing the effectiveness of administration of allopurinol and methylprednisolone to reduce reperfusion injury in coronary artery bypass surgery marked by malondialdehyde levels, vasoactive-inotropic scores, and postoperative atrial fibrillation. The patients and anesthesia operator did not know the type of drug given, whether allopurinol or methylprednisolone. All patients who underwent coronary artery bypass surgery were recruited between October 2019 and March 2020 at the Haji Adam Malik General Hospital. All patients included in the study were randomized via block randomization. Patients included in the study were over 18 years old and undergoing coronary artery bypass surgery using CPB. Patients were classified as drop-out criteria if they died during the intervention and observation within 48 hours postoperative. Patients who refused to participate in the study were excluded from the study. This study protocol was approved by our Institutional Review Board of the Medical Faculty of the University of Sumatera Utara and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

Patients who met the inclusion and exclusion criteria were selected as research subjects. At 8:00 pm, one day before surgery, all patients received oral medications in the form of 600 mg allopurinol (allopurinol group) and oral placebo drugs (methylprednisolone group). In the morning, one hour before surgery, all patients received another 600mg allopurinol (allopurinol group) and an oral placebo drug (methylprednisolone group). Anesthetic preparation was carried out according to standard procedures in Haji Adam Malik General Hospital. An arterial line was inserted before induction of anesthesia. Anesthesia induction was performed by co-induction of midazolam 0.05 mg/kg, fentanyl 3-5 μg/kg and sevofluran 1-2 vol% until the eyelid reflex disappeared. Endotracheal intubation was then carried out facilitated with rocuronium 1 mg/kg. All patients received intravenous methylprednisolone 15 mg/kg (for the methylprednisolone group), and placebo injections (for the allopurinol group). Venous blood samples were taken from central venous catheters for examination of basal malondialdehyde levels. All patients received intravenous morphine 10-20 μg/kg/hour continuously during surgery. CPB priming fluids were given according to standard procedures at the Haji Adam Malik General Hospital. All patients received 300-400 IU of heparin before cannulation with an activated clotting time (ACT) target above 480 seconds before CPB was used. Increased blood sugar level (BSL) was treated by administering insulin drip by maintaining the BSL 140-180 mg/dl. Five minutes after the aortic clamp was removed, venous blood samples were taken through a central venous catheter for examination of the postreperfusion malondialdehyde level. After termination of CPB and decanulation, all patients received protamine at a dose of 1 mg for every 100 IU of heparin used. The use of inotropic and vasoactive drugs in all patients was recorded 24 hours postsurgery. The incidence of postoperative atrial fibrillation was recorded up to 48 hours.

2.2 Methylprednisolone

Patients were given intravenous methylprednisolone 15 mg/kg at the time of induction of anesthesia.

2.3 Vasoactive-Inotropic Score

The scale shows the amount of support inotropic and other vasoactive drugs needed by the patients.

VIS formula (all doses in µg/kg/min):

VIS score: (dopamine dose + dobutamine dose) + (100 × adrenaline dose) + (10 × millrinone dose) + (100 × dose norepinephrine)

2.4 Malondialdehyde

ELISA (Enzyme-Linked Immunosorbent Assay) was used for quantitative measurement of MDA levels in serum where a solid phase ELISA sandwich was needed to determine qualitative and quantitative MDA in the supernatant.

2.5 Statistical analyses

All data were analyzed using the SPSS 25.0 package program. Hypothesis testing for numerical comparative 2-time measurement (on the MDA content variable) used the paired t-test if the data distribution was normal. Hypothesis testing for numerical comparative 1-time measurement (on vasoactive-inotropic score variable) used the unpaired T-test if the data distribution was normal and the Mann Whitney test if the distribution was not normal. Meanwhile, hypothesis testing for categorical comparative (on POAF event variable) used the chi-square test (if the ×2 condition was met) or the fisher test (if the ×2 condition was not met).

3. Results

3.1 Sample

Forty-two samples were analyzed in this study. A CONSORT diagram depicting the allocation of patients is presented in Figure 1. Of 46 patients, 42 met the inclusion criteria and were randomized. One patient in the intervention group and 1 in the control group were drop out due to dead during observation postoperative, therefor only 40 patient include in this study (Table 1). Characteristics of the sample in this study were spread homogeneously in both groups. All patients included in the study were randomized using a computer-generated list of random numbers (randomizer.org). The inclusion criteria of the study were patient's age more than 18 years, underwent coronary artery bypass surgery using CPB. Patients were underwent immediate or emergency coronary artery bypass surgery, treatment with allopurinol and methylprednisolone before surgery, allergy to allopurinol and methylprednisolone, and patient suffers atrial fibrillation on preoperative examanination were excluded from this study. Study protocol was approved by our Institutional Review Board Medical Faculty of University of Sumatera Utara (No 685/ TGL/ KEPK FK USU RSUP HAM/2019) was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

3.2 Basal Malondialdehyde Levels and Malondialdehyde Levels 5 Minutes Post Aox Off

There was an increase in MDA levels 5 minutes after AoX off compared to basal MDA levels in both groups. In the methylprednisolone group, the increase in MDA levels was statistically significant ($p < 0.05$), whereas in the allopurinol group, the increase was not statistically significant, $p = 0.251$ (Table 2 and Table 3)

3.3 Vasoactive-inotropic Scores

The need for inotropic and vasoactive drugs was higher in the Methylprednisolone group than in the Allopurinol group. Lower vasoactive-inotropic score in the Allopurinol group with a median VIS 6 were statistically

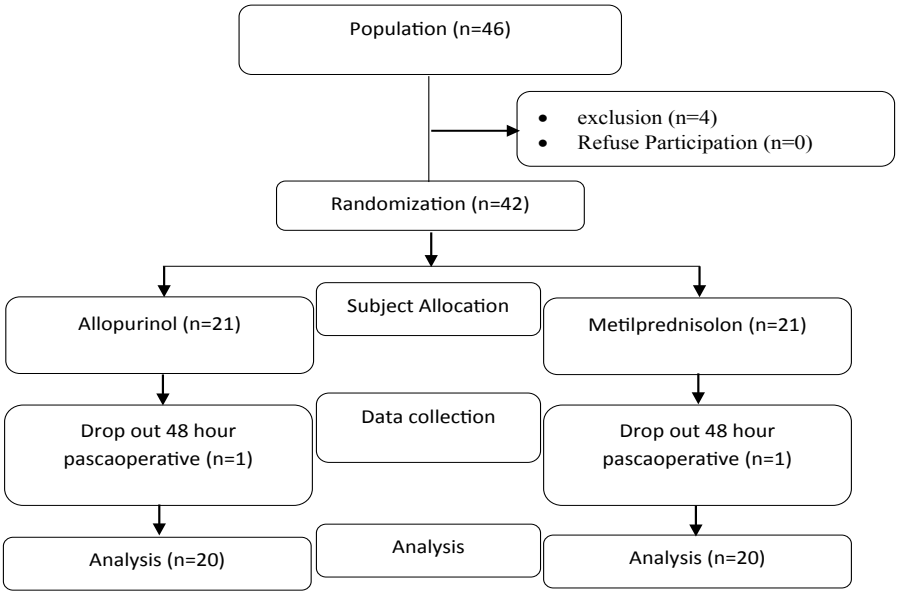

Figure 1: Consort flow study diagram.

Table 1: Sample Characteristics.

Characteristics	Groups	
	Allopurinol (n=20)	**Metilprednisolon (n=20)**
Age (years), Average (SD)	55.15 ±4.603	56.80 ±5.718
Gender, n (%)		
Male	17 (85.0)	18 (90.0)
Female	3 (15.0)	2 (10.)
Number of graft, n (%)		
1	0 (0.0)	0 (0.0)
2	0 (0.0)	0 (0.0)
3	3 (15.0)	9 (45.0)
4	17 (85.0)	10 (50.0)
5	0 (0.0)	1 (5.0)
Preoperative ejection fraction (%), Average (SD)	52.9 ±12.9	56.1±12.3
Duration of CPB (minute), Average (SD)	115.8±15.773	119.5 ±18.819
Duration of AoX (minute), Average (SD)	89.10±12.161	89.95 ±17.309

Table 2: Data of Basal MDA Levelsa.

Variable	Groups		p
	Allopurinol (n=20)	**Metilprednisolon (n=20)**	
Basal MDA Level			
(nmol/ml), Average (SD)	2.187 ± 0.489	1.902 ± 0.528	0.085

Note: t-independent test

Table 3: Change in MDA Levels.

Groups	MDA Level		p
	Basal (nmol/ml), Average (SD)	5 minutes after *AoX off* (nmol/ml), Average (SD)	
Allopurinol	2.187 ±0.489	2.416 ±0.711	0.251
Metilprednisolon	1.902 ±0.528	2.396 ±0.856	0.041*

Note: t-independent test, *significant statistical difference p<0.05.

Table 4: Inotropic and Vasoactive Scores.

Variable	Groups		p
	Allopurinol (n=20)	**Metilprednisolon (n=20)**	
Inotropic and Vasoactive Scores, Median (Min-Max)	6 (0-25)	22 (3-50)	0.009*

Note: Mann Whitney test, *significant statistical difference p<0.05.

Table 5: Post-operative Atrial Fibrillation.

Variable	Groups		p
	Allopurinol (n=20)	**Metilprednisolon (n=20)**	
Post-operative atrial fibrillation, n (%)			
Yes	0 (0.0)	3 (15.0)	0.231
No	20 (100.0)	17 (85.0)	

Note: Fisher Exact test, *significant statistical difference p<0.05.

significant (p <0.05) compared to the Methylprednisolone group which had a median value of VIS 22 (Table 4).

3.4 Postoperative Atrial Fibrillation

No statistically significant differences were found (p = 0.231) in the incidence of postoperative atrial fibrillation in the two groups (Table 5). Three patients experienced postoperative atrial fibrillation in the methylprednisolone group and no patient experienced postoperative atrial fibrillation in the Allopurinol group.

4. Discussion

In both groups there was an increase in MDA levels at reperfusion which was measured at 5 minutes after AoX off (postreperfusion) compared to basal levels, where the allopurinol group showed a smaller increase in MDA levels compared to the methylprednisolone group. The increase in MDA levels in the allopurinol group was statistically not significant (p = 0.251), where the mean basal MDA level was 2.187 ± 0.489 nmol/ml and increased to 2.416 ± 0.711 nmol/ml at 5

minutes postreperfusion. Another case was shown in the methylprednisolone group where there was a statistically significant increase (P = 0.041), where the mean basal MDA level was 1,902 ± 0,528 nmol/ml and increased to 2,396 ± 0,856 nmol/ml at 5 minutes postreperfusion. Previously, Mohaved et al had conducted a study of 36 patients who underwent coronary artery bypass surgery, giving the result that there was a significant increase in MDA levels 1 minute postreperfusion, where MDA levels at the start of reperfusion in the allopurinol group were significantly lower than in the placebo group (mean ± SEM; 5.54 ± 0.77 vs. 8.0 ± 0.75 nmol/mL; p <0.05) [7].

Furthermore, in 2017, Talwar et al. also succeeded in proving that the use of allopurinol in cardiac surgery was more effective in reducing MDA increase post CPB compared to placebo (11.8 ± 2.94 pg/ml in the placebo group *vs.* 9.16 ± 3.02 in the allopurinol group, P < 0.001) [15]. Another study that tried to measure the effectiveness of using methylprednisolone in preventing an increase in oxidative stress in coronary artery bypass surgery was conducted by Volk et al. The results showed that administration of methylprednisolone 15mg/kgbb 1.5 hours before the use of CPB significantly reduced post-MDA levels reperfusion compared to placebo (p <0.05) [9]. Another study that measured the effectiveness of methylprednisolone in reducing the effects of reperfusion injury after CPB in open heart surgery was conducted by Yavuz Enc et al. The results showed that giving a single dose of methylprednisolone 25mg/kg 1 hour before ischemia was effective in reducing myocardial ischemia-reperfusion injury compared to placebo [16]. From all the previous studies, to the best of the authors' knowledge, no one had compared the administration of allopurinol and methylprednisolone associated with changes in MDA levels post reperfusion in coronary artery bypass surgery.

This study shows that allopurinol can better prevent the increase in oxidative stress after reperfusion as seen from the smaller increase in MDA levels and the statistically significant increase in post-reperfusion MDA levels compared to the methylprednisolone group in coronary artery bypass surgery. Literature studies reveal that the enzyme systems that play the most role in accelerating the production of ROS in postiskemic anemia are xanthine oxidase, NADPH oxidase, the mitochondrial electron transport chain and nitric oxide synthetase [17]. However, it is not yet clear whether, among the enzyme systems, it is xanthine oxidase or NADPH oxidase that has a greater role in producing ROS in postischemia of open heart surgery. There are several factors that can increase the activity of NADPH oxidase, including activation of phospholipase A2, release of proinflammatory cytokines (TNF-α, IL-1β), activation of the complement system and angiotensin II [6,7]. Corticosteroids are known to inhibit the activation of phospholipase A2 and inhibit the release of proinflammatory cytokines such as TNF-α and IL-1β, but are ineffective against two other factors activating NADPH oxidase [18,19].

This is probably the reason why methylprednisolone is less effective in inhibiting the activation of NADPH oxidase, and further research is needed to ensure the effectiveness of methylprednisolone in inhibiting the activation of NADPH oxidase. As for allopurinol, it is not only a drug that has been shown to work as an inhibitor of xanthine oxidase, but also has the ability as an antioxidant (oxygen free radical scavenging) [20]. It seems that this may explain why allopurinol is more effective in preventing post-reperfusion MDA increase than methylprednisolone.

In this study, there was a statistically significant difference (p <0.05) in the vasoactive-inotropic scores in both groups, with the allopurinol group showing a median value of SIV 6 (0-25), lower than the methylprednisolone group which had a median value of SIV 22 (3-50). Therefore, in this study it can be concluded that the administration of preoperative allopurinol is more effective than methylprednisolone in reducing the need for inotropic and vasoactive drugs after cardiac surgery. These results are consistent with several other studies, including those by Rashid et al on coronary artery bypass surgery, which showed that the administration of allopurinol versus controls was associated with a lower percentage of patients requiring inotropic drugs (4.4% *vs.* 26.6%, p <0, 01) [21].

The difference in POAF incidence between the two groups in this study was not statistically significant (p = 0.231). However, clinically, 3 out of 20 patients (15%) in the methylprednisolone group experienced POAF, whereas none of the patients (0%) in the allopurinol group experienced POAF. Study by Rashid et al on 90 cases of coronary artery bypass surgery showed that administration of allopurinol was more effective in reducing the incidence of POAF compared to placebo (2.2% *vs.* 11.1%) [21]. In a study conducted by Zul Efendi et al., comparing the administration of allopurinol 600 mg daily and placebo in coronary artery bypass surgery resulted in a significantly decreased incidence of POAF in the allopurinol group (12 (26.7%) vs. 22 (48.9%), p = 0.030) [22]. Then the study on adult cardiac surgery by Talwar et al. showed that administration of allopurinol comparing placebo was associated with a significantly decreased POAF incidence, where there was no POAF was found in the allopurinol group and 7 out of 25 patients (28%) had POAF in the placebo group [15].

The resumption of blood flow when the aortic clamp is removed is the most important time in ROS production in open heart surgery, and studies have shown that ROS formation occurs maximum within 3 to 5 minutes after reperfusion and lasts up to 3 hours, which significantly contributes to myocardial depression [23-25]. The difficulty of measuring ROS in human blood samples because of its very short half-life makes MDA an alternative marker of oxidative stress ,which is a product of oxidative stress induced lipid peroxidation [10,11]. And MDA becomes the oxidative stress biomarker

most often used in cases of cardiac surgery (52% of the total publications conducted from 1990 to 2016) on a systematic review conducted by Romano et al. [7,9]. In the systematic review, MDA values in several studies varied greatly both in basal MDA levels and post-reperfusion MDA levels, and there were no provisions regarding the normal cut-off value of basal MDA or what was the significant cut-off of an increase in MDA after reperfusion, so a significant increase was assessed through statistical analysis comparing basal MDA levels and MDA levels after reperfusion [26].

5. Conclusion

Allopurinol is more effective than methylprednisolone and can be used in efforts to reduce reperfusion injury in coronary artery bypass surgery. The availability of allopurinol which is quite easy to obtain and more economical than methylprednisolone.

6. Acknowledgement

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7. Conflict of Interest

The authors declare that there is no conflict of interest.

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