Role of Colchicine in Reducing Reperfusion Injury in STEMI Patients Who Undergo Primary Percutaneous Coronary Intervention: A Randomized Clinical Trial

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ABSTRACT

Background: *Inflammation plays a role in ST-segment elevation myocardial infarction (STEMI), especially in reperfusion injury (RI). Colchicine, an anti-inflammatory drug, can suppress inflammation during RI. We assessed the effectiveness of administering colchicine to STEMI patients undergoing primary percutaneous coronary intervention (PPCI) in suppressing RI events.* ***Methods:*** *This study was a randomized, double-blind, placebo-controlled clinical trial conducted in a multicenter manner at two hospitals in Jakarta with IKPP facilities from December 2022 to April 2023. STEMI patients that underwent PPCI received 2 mg of colchicine as a loading dose and a maintenance dose of 0.5 mg every 12 hours for two days or amylum at a similar dose. Patients were observed for RI events (low-flow thrombolysis in myocardial infarction (0–2) during angiography procedure, reperfusion arrhythmia, cardiogenic shock, or persistent chest pain).* ***Results:*** *Seventy-seven STEMI patients with a mean age of 55.2 ± 9.9 years underwent PPCI. Of these patients, 37 received colchicine, and 40 received a placebo. Most subjects were male (77.5%), suffered three-vessel disease (44.15%), and occlusion in left anterior descending coronary artery (53.24%). Colchicine was found to fail to reduce the incidence of ischemia-RI (51.5% vs. 42.4%; p = 0.437). Analysis of comorbidities (hypertension, chronic kidney disease, diabetes mellitus, and obesity) and angiography results (vessel disease, lesion diameter, and culprit artery) failed to demonstrate a statistical difference in RI. Side effects were similar in the colchicine and placebo groups (21.6% vs. 15%).* ***Conclusion:*** *Colchicine administration in STEMI patients undergoing PPCI failed to reduce RI.*

Keywords: *Colchicine, inflammation, reperfusion injury, PPCI, STEMI.*

INTRODUCTION

ST-segment elevation myocardial infarct (STEMI) is one form of acute coronary syndrome (ACS) that occurs when coronary artery occlusion results in prolonged cardiomyocyte ischemia and, subsequently, necrosis of myocardium. The prevalence of cardiovascular disease in Indonesia, according to the 2018 National Heart Survey, is 1.5%,[1] a figure that increased from the reported 0.63% of 2013.[2] The global prevalence of STEMI varied from 3.8% in individuals <60 years of age to 9.5% in the ≥ 60 years of age group.[3] STEMI incidence from South Asia, Latin America, and Eastern Europe exhibit rising trends attributable to smoking, obesity, and physical inactivity.[4]

Despite significant advances and innovations in STEMI management, including the development of the STEMI code, double antiplatelet therapy, fibrinolytic, and primary percutaneous coronary intervention (PPCI), STEMI-associated mortality remains high. The in-hospital case fatality rate ranges from 9.7 to 13.5%, whereas 30-day, 1-year, and 5-year all-cause mortality rates for STEMI patients undergoing PPCI were 7.9%, 11.4%, and 23.3%, respectively.[5,6] However, when STEMI patients experienced cardiogenic shock, admission to an intensive cardiac care unit (ICCU) and 30-day mortality reached 43.7% and 50.5%, respectively.[7]

High mortality rates in STEMI patients may be associated with reperfusion injury (RI), manifested as reperfusion arrhythmia, myocardial stunning, microvascular obstruction, and intramyocardial hemorrhage.[8] RI is mediated by various proinflammatory cytokine or biological agents, such as IL (interleukin)-1, IL-1β, IL-6, tumor necrosis factor-alpha (TNF-α), eicosanoids, and nitric oxide.[9,10] One of the main intracellular effectors of RI is the NLRP3-ASC-caspase inflammasome pathway, which is stimulated by DAMP and PAMP and increases IL-1β synthesis.[11] Despite numerous pharmacological agents and various interventions developed to reduce RI, an effective treatment has not yet been established.

Colchicine is an anti-inflammatory drug extracted from the *Colchicum* plant. Colchicine anti-inflammatory effects are exerted through various mechanisms, such as disruption of microtubule formation in inflammatory cells, anti-mitotic effect, inhibition of neutrophil chemotaxis, adhesion, recruitment, and mobilization, inhibition of reactive oxygen species (ROS) formation, and inhibition of the NLRP3 inflammasome pathway.[12] Colchicine has been effectively used in the treatment of pericardial disease and prevention of post-operation atrial fibrillation. Colchicine also significantly reduces the rate of major adverse cardiovascular events in stable coronary artery disease. Nevertheless, data on the efficacy of colchicine in ACS are still conflicting.[13] Our study aims to analyze colchicine's effect on RI in STEMI patients undergoing PPCI.

METHODS

This randomized double-blind controlled clinical trial was conducted from December 2022 to April 2023 in Cipto Mangunkusumo Hospital (CMH) and Jantung Jakarta Hospital (JJH). The eligibility criteria for the patients enrolled in this trial were a STEMI diagnosis based on clinical signs and electrocardiography findings, 18–80 years of age, PPCI in the catheterization laboratory at CMH or JJH, and written informed consent by patients and their families to enroll in this clinical trial. Patients with a history of malignancy, allergy to contrast media, stroke in the last three months, coronary artery bypass graft in the last three years, inflammatory bowel disease, chronic diarrhea, chronic kidney disease (CKD) with eGFR < 30 ml/minute, chronic liver disease, autoimmune, or steroid usage were excluded.

The study subject was divided into two arms: the intervention arm and the placebo arm. Each arm received standard medical therapy for STEMI treatment (oxygen, double antiplatelet therapy, and statin) and underwent PPCI. The intervention arm received 2 mg of colchicine as the initial loading dose (four tablets) and 0.5 mg (one tablet) every 12 hours for two days. The placebo arm received 2 mg of amylum as the initial dose (four tablets) and 500 mg of amylum (one tablet) every 24 hours for two days. After PPCI was performed, subjects were monitored for two days to observe the incidence of RI. The patient was admitted to the ICCU for 48 hours and assessed clinically and through an

ICCU monitor. The subject was assessed for RI as the primary outcome, including reperfusion arrhythmia, cardiogenic shock, persistent chest pain, or low flow TIMI 0–2 during the angiography procedure. Demographic data, including age, sex, body mass index, onset of STEMI, history of diabetes, hypertension, dyslipidemia, coronary artery disease, smoking, and CKD, were collected at the initial evaluation. Results of PPCI, including culprit artery and number of vessels affected, were also retrieved.

A computer-assisted randomization technique of random block allocation technique with a combination of four blocks was used by the Epidemiology Unit of the Internal Medicine Department. Until the end of the study, the assignment of patients to each arm remained blinded to patients, investigators, nurses, pharmacists, emergency medical officers, field officers, and attending physicians who performed PPCI. Both arms received drug pills of the same size, number, and appearance. Data analysis was carried out using the SPSS 20 program. Descriptive data are displayed in table form. The Kolmogorov–Smirnov test was carried out to determine the normality of the data. Differences in the proportion of RI events between the two intervention groups were calculated using the Chi-square test.

The implementation of this research complied with the principles of the "Declaration of Helsinki" and the principles outlined in the "Guideline for Good Clinical Practice" from the ICH Tripartite Guideline (ICH-GCP) as well as local regulations applicable in Indonesia. This research has received a letter of passing ethical review from the Permanent Committee for Medical Research Ethics, FKUI-RSCM, Jakarta, No. KET-1057/UN2.F1/ETIK/PPM.00.02/2022. This study was registered in the clinical trials database registry at www.clinicaltrials.gov with the identification number NCT05734612.

RESULTS

This study enrolled 104 patients with STEM. Among them, 20 patients were excluded based on exclusion criteria; three declined to participate, and the attending physician of one patient refused to collaborate. The remaining 80 patients were evenly randomized into two groups: the intervention arm (n = 40) and the placebo arm (n = 40). Unfortunately, three patients in the intervention group inadvertently received incorrect drugs. Thus, 37 patients in the intervention arm and 40 in the placebo arm successfully completed the study without dropouts. The recruitment, allocation, follow-up, and analysis process are illustrated in **Figure 1**.

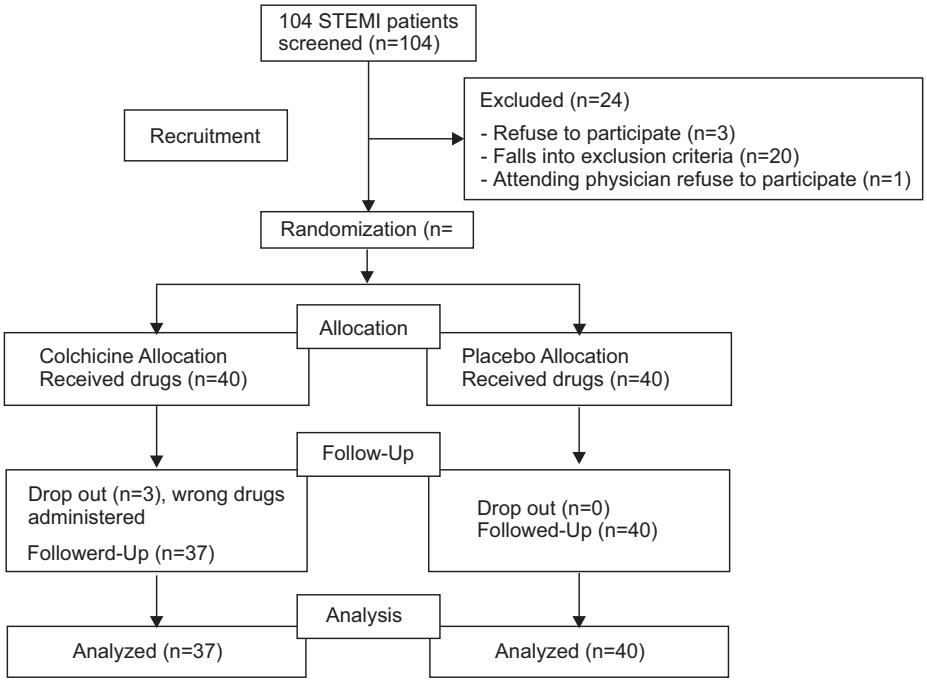

Figure 1. Study subject recruitment, randomization, allocation, follow-up, and analysis flow chart.

The mean age of the participants was 55.2 ± 9.9 years, with the majority being male (76.6%). There were no statistically significant differences in demographic characteristics between the intervention and control arms (**Table 1**). Each participant had comorbidities, such as diabetes, hypertension, dyslipidemia, a history of smoking, obesity, CKD, and coronary artery disease. Smoking history was the most prevalent comorbidity (71.42%). The majority of subjects had two risk factors (27.27%). A considerable number of participants (44.15%) experienced three-vessel disease (3VD), with the left anterior descending artery (LAD) being the most frequently affected infarct-related artery (53.24%).

RI was observed in 18 (48.6%) of the subjects of the intervention arm and 17 (42.5%) of the placebo arm (**Table 2**), which was not statistically significant ($p = 0.588$). Analysis of the relationship between various comorbidities, such as diabetes mellitus, hypertension, smoking, obesity, CKD, and RI incidence shows no difference ($p > 0.05$). Subsequent analysis of the angiography results reports, such as culprit artery, number of the lesions, and lesion diameter, also shows no statistical difference ($p > 0.05$).

During follow-up, adverse events were monitored. No serious adverse events occurred. Non-serious adverse events were found in a total of eight subjects in the colchicine drug intervention group, as listed in **Table 3**. Of the eight side effects, the most common complaint was diarrhea in six patients (16%). Meanwhile, other side effects include gastrointestinal bleeding in the form of melena (2.7%) and hematemesis (2.7%).

Table 1. Baseline Subject Characteristics

Subject characteristics	Colchicine n = 37	Placebo n = 40	p-value
Age (mean ± SD)	55.3 ± 10.01	55.15 ± 9.88	0.930*
Sex, n (%)			
Male	27 (72.9)	32 (80)	0.467*
Female	10 (22.1)	8 (20)	
STEMI onset (mean ± SD)	6.0 ± 2.78	7.19 ± 3.34	0.10*
Comorbidities, n (%)			
Diabetes mellitus	15 (40.5)	13 (32.5)	0.464*
Dyslipidemia	22 (59.4)	29 (72.5)	0.227*
Hypertension	23 (62.1)	25 (62.5)	0.976*
Smoking	25 (67.6)	30 (75.0)	0.471*
Obesity	17 (45.9)	23 (57.5)	0.311*
Chronic kidney disease	1 (2.7)	1 (2.5)	0.733*
Coronary artery disease	2 (5.4)	1 (2.5)	0.470*
Coronary angiography, n (%)			
CAD 1VD	7 (18.91)	14 (35.00)	0.260*
CAD 2VD	11 (29.72)	11 (27.5)	
CAD 3VD	19 (51.35)	15 (37.50)	
Infarct location, n (%)			
LAD	18 (48.64)	23 (57.5)	0.388*
LCx	6 (16.21)	2 (5.00)	
RCA	13 (35.13)	15 (37.5)	

*= Chi-square test, †= Independent t-test, SD= standard deviation, CAD = coronary artery disease, VD= vessel disease, LAD = left anterior descending artery, LCx = left circumflex artery, RCA= right coronary artery

Table 2. Relation of Intervention, Comorbidities, and Angiography Results and Reperfusion Injury

	Reperfusion injury, n = 35	No reperfusion injury, n = 42	p-value
Intervention, n (%)			
Colchicine	18 (51.4)	19 (45.2)	0.588*
Placebo	17 (48.6)	23 (55.8)	
Comorbidities, n (%)			
Diabetes mellitus	9 (25.7)	19 (45.2)	0.076*
No diabetes mellitus	26 (74.3)	23 (55.8)	
Hypertension	22 (62.8)	26 (61.9)	0.932*
No hypertension	13 (38.2)	16 (38.1)	
Obesity	17 (48.5)	23 (55.8)	0.588*
No obesity	18 (51.5)	19 (45.2)	
CKD	1 (2.8)	1 (2.4)	0.896**
No CKD	34 (97.2)	41 (97.6)	
Smoking	22 (62.8)	33 (78.5)	0.129*
No smoking	13 (37.2)	9 (21.5)	
Angiography results			
Culprit artery, n (%)			
LAD	21 (60.0)	20 (47.6)	0.175**
LCX	5 (14.3)	3 (7.2)	
RCA	9 (25.7)	19 (45.2)	
Vessel disease (VD), n (%)			
1VD	7 (20.0)	14 (33.3)	0.425*
2VD	11 (31.4)	11 (26.2)	
3VD	17 (48.6)	17 (41.5)	
Lesion diameter, n (%)			
< 3 mm	14 (40.0)	17 (40.5)	0.966*
≥ 3 mm	21 (60.0)	25 (59.5)	

*= Chi-square test, **= Fisher exact test, CKD = Chronic kidney disease

Table 3. Colchicine Side Effects

Side effects	Colchicine (n = 8)	Placebo (n = 6)
Diarrhea, n (%)	6 (75.0)	3 (50.0)
Hematemesis, n (%)	1 (12.5)	0 (0.0)
Bloating, n (%)	0 (0.0)	2 (33.3)
Nausea and vomiting, n (%)	0 (0.0)	1 (16.7)
Melena, n (%)	1 (12.5)	0 (0.0)

DISCUSSION

One of the limitations of the double-blind, randomized clinical trial research design was that there were many obstacles in some clinical situations due to different clinical aspects, comorbidities, and tolerability to colchicine. Apart from that, several patients refused to participate in the research, and some operators disagreed to participate; these incidents could potentially reduce the validity and integrity of the research. Furthermore, when the research was conducted, it was discovered that the pharmacy on duty provided by mistake incorrect research drugs that did not match the planned randomization sequence, which led to the exclusion of three patients. Nevertheless, this study's results are appropriate to be generalized based on the STEMI patients who received PPCI and did not meet exclusion criteria.

This study is the first to conduct clinical trials on colchicine use in STEMI patients undergoing PPCI. We found that colchicine administration failed to reduce RI. One of the main reasons is that inflammation in STEMI is higher than

in other diseases where colchicine has been shown to be beneficial, such as coronary artery bypas graft, pericardial disease, non-ST-segment elevation myocardial infarction, or stable coronary artery disease. For instance, STEMI has higher high sensitiviry C-reactive protein, interleukin-6, ferritin, and leukocyte median than NSTEMI.[14] Another reason is the high burden of comorbidity demonstrated in the subjects of this study. The majority of the research subjects had multiple risk factors; namely, 6 people (7.79%) had no risk factors, 9 (11.63%) had one risk factor, 21 (27.27%) had two risk factors, 20 (25.97%) had three risk factors, 16 (20.77%) had four risk factors, and 5 (6.49%) had five risk factors. Multiple comorbidities blunt the anti-inflammatory effect of various trials conducted before this study to reduce RI, such as ischemic pre-conditioning or post-conditioning,[15] However, analysis of each cardiovascular risk factor did not yield statistically significant results of RI incidence.

This study's follow-up duration was 48 hours, which was relatively shorter than that of numerous studies conducted to assess colchicine's efficacy. Thus, the duration of the follow-up study might cause non-significant results. Clinical trials of colchicine administration in STEMI patients undergoing PPCI should be conducted with a longer observation duration.

In this study, the side effects of the colchicine drug were found to occur in 21.6% of the colchicine group and 15% of the control group. This is consistent with the study of Ma et al., which found that the most frequent side effects when using colchicine in clinical trial settings were gastrointestinal symptoms. Gastrointestinal side effects increased two-fold when using colchicine (RR: 2.07; IK95%: 1.45–2.95; p = 0.04), and diarrhea side effects increased three-fold (RR: 3.26; IK95%: 1.29–8.25; p = 0.01).[16]

CONCLUSION

There was no difference in RI events between colchicine and placebo administration in STEMI patients undergoing PPCI.

COMPETING INTERESTS

The authors have no conflict of interest to declare related to this study.

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