International Journal of Cardiovascular Research

Research article A SCITECHNOL JOURNAL

Effectiveness of Colchicine in the Treatment of Acute Myocardial Infarction

Rizwan Munir*

Department of Medical Sciences, The Aga Khan University, Stadium Road, Karachi, Pakistan

***Corresponding author:** Rizwan Munir, Department of Medical Sciences, The Aga Khan University, Stadium road, Karachi, Pakistan; E-mail: riz_187@hotmail.com

Received date: 04 April, 2022, Manuscript No. ICRJ-22-59384;
Editor assigned date: 07 April, 2022, PreQC No. ICRJ-22-59384 (PQ);
Reviewed date: 21 April, 2022, QC No. ICRJ-22-59384;
Revised date: 03 June, 2022, Manuscript No. ICRJ-22-59384 (R);
Published date: 13 June, 2022; DOI: 10.4172/2324-8602.1000471

Abstract

Background: The global burden of cardiovascular and cerebrovascular events is increasing. Addition of Colchicine can be beneficial and more effective in reducing adverse events in STEMI patients. Therefore, we planned this study to get evidence for Colchicine in STEMI patients to improve their outcome and avert adverse outcomes.

Objective: To compare the effectiveness of colchicine in addition to conventional treatment after primary episode of acute ST-elevation Myocardial Infarction (STEMI).

Study design: Randomized controlled trial.

Study place and duration: Department of Medicine, KEMU and Mayo Hospital, Lahore for 3 months.

Material and methods: In this trial, 92 patients (46 patients in each group) were included with primary STEMI and randomly divided in two groups. Baseline investigations were done. Group A: Standard treatment plus placebo were given. Group B: Along with standard treatment plus tablet Colchicine 0.5 mg once daily were given. Follow up at the end 01 month and then at 03 months to see Major Adverse Cardiovascular Events (MACE) and adverse events were noted. Data were entered into SPSS-26.

Results: In patients taking standard treatment, the mean age was 54.67 ± 13.41 years. In patients given Colchicine with standard treatment, the mean age was 48.83 ± 14.42 years. Within 1 month, cardiovascular deaths were noted as 9 (19.6%) *vs.* 2 (4.3%) cases and within 3 months, cardiovascular deaths were noted as 10 (21.7%) *vs.* 3 (6.5%). Hospitalization was noted as 13 (28.3%) *vs.* 3 (6.5%) within 1 months while 15 (32.6%) *vs.* 4 (8.7%) cases within 3 months. Ischemic stroke was 8 (17.4%) *vs.* 2 (4.3%) within 1 months while 12 (26.1%) *vs.* 2 (4.3%) within 3 months and difference was significant. Diarrhea was reported as 3 (6.5%) *vs.* 4 (8.7%) within 1 month while 8 (17.4%) *vs.* 5 (10.9%) within 3 months.

Conclusion: Thus addition of Colchicine in standard treatment for primary STEMI is more effective in reducing MACE, while having no significant adverse effects were noted.

Keywords: Colchicine; Major adverse cardiovascular events; ST-segment elevation myocardial infarction; cardiovascular deaths; Ischemic stroke

Introduction

In the year 2015, the global burden of cardiovascular disease CVD was predicted to be 422 million instances, with roughly 7 million cases of acute myocardial infarction AMI and around 18 million deaths attributable to CVD [1]. Although the global burden of Coronary Artery Disease (CAD) and its associated morbidity and mortality is decreasing, it is increasing in certain developing countries [2]. According to the inter heart study, which evaluated CAD risk factors in 52 countries, the average age of persons suffering from acute myocardial infarction in South Asia is ten years younger than in Europe, China, and Hong Kong [3]. As a result, there is a rise in morbidity and death, as well as an economic strain on Pakistan's poor health infrastructure.

One of the fundamental causes of CAD is atherosclerosis, and inflammation plays a key role in all stages of the disease, from initiation through progression and finally post-Acute Myocardial Infarction (AMI) consequences [4]. Due to its significant anti-inflammatory characteristics, colchicine has lately emerged as a unique therapeutic option for cardiovascular disease [5,6]. Colchicine is an inexpensive anti-inflammatory medicine that works by decreasing microtubule polymerization and perhaps by affecting cellular adhesion molecules, inflammatory chemokines, and the nucleotide-binding oligomerization domain-like receptor protein 3 inflammasome, also known as NLRP3 [7].

The NLRP3 protein complex is an intracellular protein that triggers a powerful inflammatory response in response to threat signals. NLRP3 dependent inflammation promotes negative left ventricular remodeling and recurrent thromboembolic atherosclerotic episodes after an AMI. NLRP3 or its downstream effectors (interleukin-1 and interleukin-18) inhibitors, both selective and nonselective, may prevent unfavourable left ventricular remodeling and recurrent atherosclerotic events [8-11].

The increased global prevalence of CAD and its associated morbidity and mortality constitutes the rationale for conducting this trial. The quest for an effective drug to decrease morbidity and mortality associated with CAD, which is both cheaper and more effective than current treatments available, in the subcontinent population, is the foundation stone of this study.

Objective: To compare the effectiveness of colchicine in addition to conventional treatment after primary episode of Acute ST-Elevation Myocardial Infarction (STEMI).

Materials and Methods

Study design: Randomized controlled trial.

Setting: Department of Medicine, KEMU and Mayo Hospital, Lahore.

Duration of study: 3 months after approval of synopsis.

Sample size: The sample size of 92 patients (46 patients in each group) is estimated by using a 95% confidence level, 10% absolute precision with the percentage of colchicine group as 5.5% and placebo group as 7.1% [12].

Sampling technique: Non-probability, consecutive sampling.

Sample selection

Inclusion criteria

- Either gender
- Age between 18 to 85 years
- Primary ST elevation myocardial infarction STEMI
- Myocardial infarction

Exclusion criteria

- Pregnancy or lactation on history
- Diagnose case of cardiomyopathy due to any cause
- Previous contraindications for Colchicine such as hypersensitivity, diarrhea
- Previous usage of chemotherapy or immunosuppressant usage
- Current evidence or previous history of ischemic or hemorrhagic stroke
- Presence of atrial fibrillation
- Inflammatory bowel disease, non-cutaneous cancer within previous 3 years, neuromuscular disease, or raised creatine kinase level greater than three-fold from the normal line.
- Renal disease with a serum creatinine level greater than two-fold from the upper limit of normal.
- Hepatic disease with a ALT greater than two-fold from the upper limit of normal.

Data collection procedure: After obtaining approval from ethical committee of hospital, patients fulfilling inclusion and exclusion criteria were enrolled after taking an informed written consent. After admission in emergency, patients were divided into two groups *i.e.* A and B by computer generated randomization sequence, and each group will contain 46 patients. Details of drug along with side effects were explained to patient. Then investigations including complete blood count, liver function test, renal function test, serum electrolytes, lipid profile, troponin levels, CPK levels, LDH, prothrombin time, and activated partial thromboplastin time were sent.

Group A: Standard treatment plus placebo were given including Tab Aspirin 75 mg 1 × OD, Tab Clopidogrel 75 mg 1 × OD, Tab Atorvastatin 40 mg 1 × HS, ACE Inhibitors and Beta blockers were given to both groups as per requirement according to blood pressure and heart rate up to their safe maximum limits *i.e.* Bisoprolol 10 mg, metoprolol 200 mg, Lisinopril 20 mg, Valsartan 160 mg, amlodipine 10 mg and hydrochlorothiazide 25 mg.

Group B: Along with standard treatment plus Tablet Colchicine 0.5 mg once daily were given. During the study period, nonsteroidal anti-inflammatory drugs except Aspirin, immune modulators and other study drugs were prohibited throughout the study period. Follow up at the end 01 month and then at 03 months to see Major Adverse Cardiovascular Events (MACE) were done telephonically/telemetry or in person. Patients were followed for efficacy and safety of study drug according to operational definitions. Any patient showing adverse/severe adverse reactions including diarrhea, flatulence and abdominal discomfort, skin rashes were excluded from study after stopping the intervention. The primary efficacy end point is the incidence of MACE observed from the start of the study drug administration to one day following discontinuation or completion of study drug. Major adverse cardiovascular events were defined as three point composite MACE *i.e.* (Emergency hospitalizations due to spontaneous MI, ischemic stroke, and cardiovascular death), proven by history, examination, labs and using questionnaire during 03 months surveillance post STEMI. Effectiveness was assessed as decrease in composite MACE during 03 months treatment with colchicine. The primary safety event is the incidence of drug reaction *i.e.* severe allergic reaction or SJS, and clinically significant diarrhea.

Data analysis: Data were entered into SPSS-26. For comparison of both groups, *chi-square* test and independent samples t-test were applied. P-value ≤ 0.05 was kept as significant.

Results

In this trial, we enrolled 92 patients and divided them in two equal groups (46 cases in each group). In patients taking standard treatment, the mean age was 54.67 ± 13.41 years. In patient given Colchicine with standard treatment, the mean age was 48.83 ± 14.42 years. In standard group, there were 22 (47.8%) males and 24 (52.2%) females. In Colchicine+standard group, there were 26 (56.5%) males and 20 (43.5%) females. In standard group, 21 (45.7%) were hypertensive while in Colchicine+standard group, 26 (56.5%) were hypertensive. In standard group, 21 (45.7%) were diabetic while in Colchicine +standard group, 25 (54.3%) were diabetic. In standard group, 13 (28.3%) were smoker while in Colchicine+standard group, 15 (32.6%) were smoker. In standard group, 18 (39.1%) had family history of IHD while in Colchicine+standard group, 12 (26.1%) had family history of IHD. In standard group, 16 (34.8%) patients had stage 1 CKD and 30 (65.2%) patients ad stage 2 CKD. In Colchicine+standard group, 14 (30.4%) patients had stage 1 CKD and 32 (69.6%) patients ad stage 2 CKD. In standard group, mean BMI of patient was 31.50 ± 3.97 kg/m^2. In Colchicine+standard group, mean BMI of patient was 31.11 ± 4.08 kg/m2. In standard group, mean hemoglobin level of patient was 10.88 ± 0.59 g/dl. In Colchicine+standard group, mean hemoglobin level of patient was 10.71 ± 0.54 g/dl. In standard group, mean TLC was 8015.83 ± 1522.23. In Colchicine+standard group, mean TLC was 8516.70 ± 1486.73. In standard group, mean bilirubin level was 3.41 ± 1.30. In Colchicine+standard group, mean bilirubin level was 3.38 ± 1.23. In standard group, mean LDL level was 230.20 ± 37.26 mg/dl. In Colchicine+standard group, mean LDL level was 221.28 ± 41.22 mg/dl. In standard group, mean uric acid was 6.25 ± 0.60 mg/dl. In Colchicine+standard group, mean uric acid level was 6.18 ± 0.70 mg/dl. In standard group, mean ALT was 399.83 ± 213.37 mg/dl. In Colchicine+standard group, mean ALT level was 453.67 ± 203.71 mg/dl. In standard group, mean troponin I was 2065.07 ± 598.66 IU. In Colchicine+standard group, mean troponin I was 2181.83 ± 525.78 IU Table 1.

	Group	
	Standard treatment plus placebo	**Standard treatment plus Colchicine**
N	46	46
Age (years)	54.67 ± 13.41	48.83 ± 14.42
Gender		
Male	22 (47.8%)	26 (56.5%)
Female	24 (52.2%)	20 (43.5%)
Hypertension	21 (45.7%)	26 (56.5%)
Diabetes mellitus	21 (45.7%)	25 (54.3%)
Smoker	13 (28.3%)	15 (32.6%)
Family history of IHD	18 (39.1%)	12 (26.1%)
Stage of CKD		
1	16 (34.8%)	14 (30.4%)
2	30 (65.2%)	32 (69.6%)
BMI	31.50 ± 3.97	31.11 ± 4.08
Hemoglobin level	10.88 ± 0.59	10.71 ± 0.54
Total leukocyte count	8015.83 ± 1522.23	8516.70 ± 1486.73
Bilirubin	3.41 ± 1.30	3.38 ± 1.23
LDL	230.20 ± 37.26	221.28 ± 41.22
Uric acid	6.25 ± 0.60	6.18 ± 0.70
ALT	399.83 ± 213.37	453.67 ± 203.71
Troponin I level	2065.07 ± 598.66	2181.83 ± 525.78

Table 1: Demographics and laboratory finding of patients at presentation.

In standard treatment group, cardiovascular deaths were noted as 9 (19.6%) within 1st month while just 2 (4.3%) cases in Colchicine +standard treatment group and difference was statistically significant (P<0.05). In standard treatment group, cardiovascular deaths were noted as 10 (21.7%) within 3 months while just 3 (6.5%) cases in Colchicine+standard treatment group and difference was statistically significant (P<0.05). In standard treatment group, hospitalization was noted as 13 (28.3%) within 1st month while just 3 (6.5%) cases in Colchicine+standard treatment group and difference was statistically significant (P<0.05). In standard treatment group, hospitalization was noted as 15 (32.6%) within 3 months while just 4 (8.7%) cases in Colchicine+standard treatment group and difference was statistically significant (P<0.05). In standard treatment group, ischemic stroke was noted as 8 (17.4%) within 1st month while just 2 (4.3%) cases in Colchicine+standard treatment group and difference was statistically significant (P<0.05). In standard treatment group, ischemic stroke was noted as 12 (26.1%) within 3 months while just 2 (4.3%) cases in Colchicine+standard treatment group and difference was statistically significant (P<0.05). In standard treatment group, diarrhea was reported as 3 (6.5%) within 1st month while 4 (8.7%) cases in Colchicine+standard treatment group and difference was insignificant (P>0.05). In standard treatment group, ischemic stroke was noted as 8 (17.4%) within 3 months while just 5 (10.9%) cases in Colchicine +standard treatment group and difference was insignificant (P>0.05) Table 2.

	Group		p-value
	Standard treatment plus placebo	**Standard treatment plus Colchicine**	
N	46	46	
CV death at 1 month	9 (19.6%)	2 (4.3%)	0.024
CV death at 3 months	10 (21.7%)	3 (6.5%)	0.036

Hospitalization at 1 month	13 (28.3%)	3 (6.5%)	0.006
Hospitalization at 3 months	15 (32.6%)	4 (8.7%)	0.005
Ischemic CVA at 1 month	8 (17.4%)	2 (4.3%)	0.044
Ischemic CVA at 3 months	12 (26.1%)	2 (4.3%)	0.004
Diarrhea at 1 month	3 (6.5%)	4 (8.7%)	0.694
Diarrhea at 3 months	8 (17.4%)	5 (10.9%)	0.369

Table 2: Comparison of outcome in both groups.

Discussion

The involvement of inflammation in the clinical symptoms and consequences of ACS is essential [13]. Cardiovascular disease, particularly ACS, continues to be one of the leading causes of morbidity and mortality on an annual basis. Colchicine, an anti-inflammatory medicine, is introduced to be effective in the pathophysiology, prognosis, and death rate of these individuals, based on the inflammatory pathway of atherosclerosis [14].

In our trial, we observed that cardiovascular deaths were noted as 9 (19.6%) *vs*. 2 (4.3%) cases within 1 month while 10 (21.7%) *vs*. 3 (6.5%) within 3 months. Hospitalization was noted as 13 (28.3%) *vs*. 3 (6.5%) after 1 months while 15 (32.6%) *vs*. 4 (8.7%) cases after 3 months. Ischemic stroke was 8 (17.4%) *vs*. 2 (4.3%) after 1 months while 12 (26.1%) *vs*. 2 (4.3%) after 3 months and difference was significant.

Tong et al., conducted a trial on 795 patients with mean age of 59.8 ± 10.3 years; 21% female. Over the 12-month follow-up, there were 24 events with colchicine versus 38 events with placebo. Death rate was higher (8 versus 1; P=0.017) and, especially, non-cardiovascular death with colchicine (5 versus 0; P=0.024). The rates of reported adverse effects were insignificant (colchicine=23.0% versus placebo=24.3%), and they were mainly gastrointestinal symptoms (colchicine=23.0% versus placebo=20.8%).

Patients with stable coronary disease who received colchicine at a dose of 0.5 mg once day had fewer Major Adverse Cardiovascular Events (MACE) than those who received placebo in the Low-Dose Colchicine (LDC) trial [15]. The Colchicine Cardiovascular Outcomes Trial (COLCOT), which included patients with acute myocardial infarction and stable CAD, found that individuals who took colchicine 0.5 mg/day 12 had a significantly lower MACE than those who got placebo (5.5 percent *vs* 7.1 percent HR: 0.77 CI 0.61-0.96). In patients with chronic coronary syndrome, the Low Dose Colchicine Trial-2 (LoDoCo-2) revealed a 31% reduction in MACE [16]. These findings support earlier research showing that short-term colchicine medication lowers inflammatory cytokine levels in ACS patients and reduces infarct size in STEMI patients treated with primary PCI [17].

In our trial, diarrhea was reported as 3 (6.5%) *vs.* 4 (8.7%) after 1 month while 8 (17.4%) *vs*. 5 (10.9%) after 3 months. Tardif et al., also found that the most common adverse events observed were related gastrointestinal tract. Diarrhea was recorded in 9.7% of colchicine patients and 8.9% of placebo patients, whereas nausea was reported in 1.8 percent and 1.0 percent, respectively. These disparities in infection rates could be due to chance, or they could indicate different immune responses. Infections have been reported in patients who attempted suicide by ingesting an excessive amount of colchicine [18].

Conclusion

Thus, addition of Colchicine in standard treatment for primary STEMI is more effective in reducing MACE, while having no significant adverse effects were noted. In future, we will implement addition of Colchicine in standard treatment of patients presenting with primary STEMI. But further trials show also is done to confirm this evidence with larger sample size and at different centers.

References

1. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, et al. (2017) Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol 70:1-25.
2. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, et al. (2015) Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation 132:1667-1678.
3. Alfaddagh A, Khraishah H, Rashed W, Sharma G, Blumenthal RS, et al. (2020) Clinical characteristics and outcomes of young adults with first myocardial infarction: Results from Gulf COAST. Int J Cardiol Heart Vasc 31:100680.
4. Lawler PR, Bhatt DL, Godoy LC, Lüscher TF, Bonow RO, Verma S, et al. (2020) Targeting cardiovascular inflammation: next steps in clinical translation. Eur Heart J 42:113-131.
5. Tong DC, Wilson AM, Layland J (2016) Colchicine in cardiovascular disease: an ancient drug with modern tricks. Heart 102:995-1002.
6. Aimo A, Pascual-Figal DA, Barison A, Cediel G, Vicente Á H, et al. (2020) Colchicine for the Treatment of Coronary Artery Disease. Trends Cardiovasc Med 31:497-504.
7. Yan Z, Qi Z, Yang X, Ji N, Wang Y, et al. (2021) The NLRP3 inflammasome: Multiple activation pathways and its role in primary cells during ventricular remodeling. J Cell Physiol. 236:5547-5563.
8. Buckley LF, Libby P (2019) Inhibiting NLRP3 Inflammasome Activity in Acute Myocardial Infarction: A Review of Pharmacologic Agents and Clinical Outcomes. J Cardiovasc Pharmacol 74:297-305.
9. Leung YY, Yao Hui LL, Kraus VB (2015) Colchicine-Update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum 45:341-50.
10. Martínez GJ, Celermajer DS, Patel S (2018) The NLRP3 inflammasome and the emerging role of colchicine to inhibit

atherosclerosis-associated inflammation. Atherosclerosis 269:262-71.

11. Spartalis M, Spartalis E, Tzatzaki E, Tsilimigras DI, Moris D, et al. (2018) The Beneficial Therapy with Colchicine for Atherosclerosis *via* Anti-inflammation and Decrease in Hypertriglyceridemia. Cardiovasc Hematol Agents Med Chem 16:74-80.
12. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, et al. (2019) Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. N Engl J Med 381:2497-2505.
13. Tong DC, Quinn S, Nasis A, Hiew C, Roberts-Thomson P, Adams H, et al. (2020) Colchicine in patients with acute coronary syndrome: the Australian COPS randomized clinical trial. Circulation 142:1890-1900.
14. Akrami M, Izadpanah P, Bazrafshan M, Hatamipour U, Nouraein N, et al. (2021) Effects of colchicine on major adverse cardiac events in next 6-month period after acute coronary syndrome occurrence; a randomized placebo-control trial. BMC Cardiovasc Disord 21:583.
15. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL (2013) Low-dose colchicine for secondary prevention of cardiovascular disease. J Am Coll Cardiol 61:404-410.
16. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, et al. (2020) Colchicine in Patients with Chronic Coronary Disease. N Engl J Med 383:1838-1847.
17. Deftereos S, Giannopoulos G, Angelidis C, Alexopoulos N, Filippatos G, et al. (2015) Anti-Inflammatory Treatment With Colchicine in Acute Myocardial Infarction: A Pilot Study. Circulation 132:1395-403.
18. Jahn-Eimermacher (2008) A Comparison of the Andersen–Gill model with Poisson and negative binomial regression on recurrent event data. Comput Stat Data Anal 52:4989-4997.