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Effect of Colchicine on Neutrophil to Lymphocyte Ratio and Cardiac Function in Non-Diabetic Patients Post STEMI Using Speckle Tracking Imaging

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ABSTRACT

Background: Acute myocardial ischemia is accompanied by myocardial necrosis and endogenous inflammation, resulting in myocardial injury, ventricular dilation, and dysfunction. Colchicine is a low cost, orally given and potent anti-inflammatory drug.

Objective: To examine the effect of colchicine on inflammatory markers, such as neutrophil/lymphocyte ratio (NLR) and cardiac function in non-diabetic ST segment elevation myocardial infarction (STEMI) cases.

Patients and Methods: Our research was done in the Cardiology Department, Aswan University Hospital through the period from December 2020 to December 2021 on 40 non-diabetic cases who presented with STEMI and underwent primary percutaneous intervention (PCI). Cases were then randomized into 2 groups: After reperfusion group (A) that consisted of 20 patients who were given anti-ischemic medication plus colchicine 0.5 mg once/day, while group (B) consisted of 20 participants who were given anti-ischemic treatment alone. Each participant had tests like NLR and CRP and an echocardiogram of their hearts performed at the beginning and at the end of the research.

Results: Baseline NLR (P value > 0.05) and 1-month NLR (P value > 0.05) showed no statistically significant variance among groups. Also, did LVEF (p = 0.5), LVEDD (p = 0.63), LVESD (p = 0.29) and GLS (p = 0.91). Additionally, there was no statistical noteworthy change among groups in terms of LVEF, LVEDD and LVESD or global longitudinal strain (GLS) at follow-up.

Conclusion: Adding colchicine to standard anti-ischemic treatment did not significantly enhance inflammatory indicators (NLR, CRP, and cardiac function) in non-diabetic individuals suffering from STEMI.

Keywords: STEMI, NLR, Colchicine.

INTRODUCTION

Worldwide, coronary artery disease is responsible for the most deaths [(1)]. The 1-year mortality rate for patients presenting with STEMI is roughly 10%, with the in-hospital mortality rate ranging from 4% to 12% [(2)]. Myocardial necrosis and subsequent endogenous inflammation are the results of acute ischemia in acute myocardial infarction (AMI), which also causes ventricular dilatation and dysfunction and myocardial damage [(3)]. A non-Doppler method known as 2D speckle tracking echocardiography (STE) assists in the quantitative evaluation of systolic heart function by estimating deformation parameters such as strain and strain rate [(4)].

Colchicine use in gouty patients has been linked to a lower incidence of MI [(5)]. Colchicine is a cheap, effective anti-inflammatory drug that is administered orally. It may have an impact on the inflammasome, inflammatory chemokines, and cellular adhesion molecules. It inhibits tubulin polymerization and microtubule formation as reported by various researchers [(6)].

The goal of this research was to investigate the influence of colchicine on inflammatory markers like NLR and systolic function in non-diabetic instances of STEMI that had primary PCI (PPCI).

PATIENTS AND METHODS

Cases that did not have diabetes and had ST-elevation myocardial infarction (STEMI) and underwent PPCI to IRA at the Cardiology Department, Aswan University Hospital between December 2020 and December 2021 participated in a simple double-blind randomized control experiment. The experiment was designed to be as objective as possible. Group (A) consisted of twenty patients who were given colchicine (0.5 mg once/day) in addition to the typical anti-ischemic medicine, whereas group (B) consisted of twenty cases that were not given colchicine. Both groups received the normal anti-ischemic medication. The typical medicine for treating ischaemic conditions was given to both groups. Twenty individuals who were treated with the conventional anti-ischemic drug alone served as a control group for this study.

The eligible subjects included in this research were subjected to the following:

- **Full history including:**

- Personal data (age, gender), CV risk factors such as smoking, hypertension, dyslipidemia, and Family history of CAD. Character and onset of the chest pain.

- **Physical examination including:**

- Vital signs (temperature, pulse, blood pressure). Local cardiac examination and chest auscultation. Anthropometric evaluation included weight (Kg), height (cm) and BMI.

- **Standard 12-lead electrocardiogram (ECG):** before & after medication to look for ischemic changes.
- As part of the laboratory research, a sample of venous blood was obtained from each patient at admission, prior to the initial PCI procedure. In

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addition to the overall white blood cell count, the automated blood cell counter also calculated the amount of neutrophils, lymphocytes, and monocytes. NLR was calculated by dividing the absolute levels of neutrophils and lymphocytes from the same blood sample collected upon entry.

- Renal function tests, serum uric acid, Lipid profile (serum cholesterol, LDL, HDL, and Triglycerides), hemoglobin, and C-reactive protein were assessed before therapy.

- **Two-dimensional echocardiography:** All cases underwent two-dimensional echocardiography within twenty-four hours of undergoing PPCI using a Phillips IE 33 that was outfitted with a harmonic X5 variable frequency phase array transducer. In accordance with guidelines from the American Society of Echocardiography, pictures were taken with the patient lying on their side at the end of their exhalation. Standard measurements (LVEF, LVESD, LVEDD, E/a, GLS), as well as parasternal long- and short-axis views, apical 4-chamber and 2-chamber and apical long-axis views, were obtained.

- **Speckle tracking 2D echocardiography:** Within twenty-four hours following the revascularization procedure, a speckle tracking 2D echocardiogram with global longitudinal strain was performed. We used a model with 16 segments to investigate regional anomalies in the motion of the ventricular wall. Following the completion of an examination, an experienced cardiologist assigned the grades 1, 2, 3, and 4 respectively to each of the four patients.
- Apical 4-chamber, 2-chamber, and 3-chamber views from high-quality electrocardiogram-gated images were utilized for longitudinal strain imaging using 2D-speckle tracking echocardiography.
- The Wall Motion Score Index (WMSI) is a weighted mean of the ratings for each individual wall section.
- The volume settings had been adjusted to the point where they were just right. We lowered the contrast in the photograph so that the LV would be more noticeable. A minimum of three cardiac cycles were gathered for each loop to avoid foreshortening of the LV, and the frame rate was kept between 50 and 90 frames per second throughout. In addition, the subjects in all of the photographs were instructed to hold their breath so that breathing would not create blurring in the images. A cine-loop format was used for the storage of the photos. In order to create a timeline for cardiac events, radial pulse Doppler was used to capture the velocities of the mitral and aortic valves leading into and away from the LV.

- **Follow up after 1 month:** Clinical follow-up included chest symptoms and shortness of breath. Follow-up of laboratory evaluations included CRP, NLR and renal function. Imaging follow-up included GLS, LVESD, LVEDD and LVEF.

Ethical consideration: Medical Ethics Committee of Aswan Faculty of Medicine gave its approval to this study. All participants gave written consents after receiving all information. The Helsinki Declaration was followed throughout the study's conduction.

Statistical analysis

The IBM SPSS software, version 20.0, was used to analyse the data that were entered into the computer. For qualitative data, percentage and numerical descriptions were given. The distribution's normality was assessed using the Kolmogorov-Smirnov test. Quantitative data were described using the range (minimum and maximum), mean ± SD, median, and IQR. The generated results were judged significant at the 5% level of significance. Using the chi-square test, categorical variables may be compared between several groups. Student t-test for comparing two groups under study using normally distributed quantitative variables. $P \leq 0.05$ for statistical significance and ≤ 0.001 for high significant result.

RESULTS

From December 2020 and December 2021, we conducted our research at Aswan University Hospital's Cardiology Department. All of the individuals in our research who suffered from STEMI and were treated with PPCI were free of diabetes. Cases were then randomly assigned to either group A (receiving colchicine in addition to standard anti-ischemic medicine) or group B (receiving standard anti-ischemic treatment alone). There are 80% men and 20% females in group A, with a mean age of 41.4 ± 5.48. The average age of those in group B was 44.1 ± 8.39 years. There was no statistically significant difference between the two groups regarding demographics (p value > 0.05), and the subtype of MI (p value >0.05) (Table 1).

Table (1): Comparison between the studied groups as regard demographic data

	Group A (n=20)		Group B (n=20)		p
Age (years)					
Range	35 – 58		34 – 60		0.2
Mean ± SD	41.4 ± 5.48		44.15 ± 8.39		
BMI (kg/m^2)					
Range	26.4 – 32.2		26.8-31.8		0.8
Mean ± SD	29.08 ± 1.59		29.16 ±1.61		
Gender	No.	%		%	
Female	4	20.0	11	20.0	1.0
Male	16	80.0	9	80.0	
Hypertension					
No	7	35.0	8	30.0	0.7
Yes	12	65.0	3	70.0	
Dyslipidemia			9		
No	11	55.0	8	55.0	1.0
Yes	9	45.0	3	45.0	
Smoking			9		
Never	13	65.0	8	40.0	0.2
Ex-smoker	2	10.0	3	15.0	
Current	5	25.0	9	45.0	

Anterior MI was the most prevalent kind in both groups **(Table 2).**

Table (2): Comparison between both groups as regard type of myocardial infarction

	Group A	Group B	p-value
Anterior	14	13	0.6
Inferior	3	2	
Lateral	3	5	

Table (3) showed that NLR at baseline (P > 0.05) and after 1 month (P > 0.05) as well as CRP at baseline (P > 0.05) showed no significant differences among the studied groups.

Table (3): Comparison between the studied groups as regard lab investigation

	At baseline			After one month		
	Group A (n=20)	Group B (n=20)	p	Group A (n=20)	Group B (n=20)	p
NLR						
Mean ± SD	3.9 ± 0.7	3.77 ± 0.75	0.5	2.28 ± 0.53	1.99 ± 0.48	0.1
CRP (mg/L)						
Mean ± SD	8.04 ± 1.90	7.09 ± 1.67	0.6	7.0 ± 1.64	2.1 ±0.48	0.6

Table (4) showed that there was no significant difference among the groups at baseline with respect to ejection fraction (p = 0.4), LVESD (p = 0.8) and LVEDD (p = 0.9), or GLS (p = 0.6). Besides, there were no statistically significant differences in follow-up after one month after revascularization concerning ejection fraction (p = 0.5), LVEDD (p = 0.63) and LVESD (p = 0.29), or GLS (p = 0.91).

Table (4): Comparison between the studied groups as regards echocardiographic parameters

	Baseline			Follow up		
	Group A (n=20)	Group B (n=20)	p	Group A (n=20)	Group B (n=20)	p
Ejection fraction						
Range	37–41.5	37–41.8	0.4	38– 43	37 – 42.5	<0.5
Mean ± SD	38.8± 1.5	39.2± 1.5		38.76 ± 1.7	42.9± 2.6	
LVEDD						
Range	44- 69	44- 69	0.9	39.4-67.4	39.3-68.3	0.6
Mean ± SD	59.1± 8.5	58.7± 8.32		52.4± 8.5	53.7± 8.5	
LVESD						
Range	40- 57	40- 57	0.8	26-60.6	25.6-58.3	0.2
Mean ± SD	53.6± 5.8	53.7± 10.1		42.1± 11.4	38.5± 9.7	
GLS						
Range	-9 – -20	-9 – -19	0.6	-22--12.1	-21.9--12	0.9
Mean ± SD	-13.5± 3.4	-13± 3		-16.9 ± 32	-16.7± 3.5	

Regarding MACE (MI, stroke, and death) and adverse events through the follow-up, there was no significant difference among the studied groups (P value > 0.5) (Tables 5 & 6)**.**

Table (5): Comparison between the studied groups as regard primary end point

	Group A (n=20)		Group B (n=20)		p
Components of primary end point	No	%	No	%	
MI	2	10.0	2	10	0.5
Stroke	1	5.0	3	15	0.5
Urgent hospitalization for angina leading to revascularization	2	10.0	4	20	0.6

Table (6): Comparison between the studied groups as regard adverse events

Adverse events	Group A (n=20)		Group B (n=20)		p
	No.	%	No.	%	
Gastrointestinal event	8	40.0	7	35.0	0.744
Diarrhea	5	25.0	4	20.0	0.705
Nausea	2	10.0	1	5.0	0.548
Flatulence	2	10.0	0	0.0	0.147
Gastrointestinal hemorrhage	1	5.0	0	0.0	0.311
Anemia	2	10.0	0	0.0	0.147
Infection	8	40.0	9	45.0	0.749
Pneumonia	2	10.0	1	5.0	0.548

DISCUSSION

Atherosclerosis appears to be significantly influenced by inflammation. The Canakinumab Anti-inflammatory Thrombosis Outcomes research (CANTOS) found a 15% reduction in the incidence of cardiovascular events compared to placebo among those who received the injectable monoclonal antibody canakinumab, but an increase in fatal infections among those who received the placebo. In the Cardiovascular Inflammation Reduction Trial (CIRT), it was determined that methotrexate had no impact on cardiovascular outcomes or plasma inflammatory markers. In view of these inconsistent results and the fact that canakinumab has not been validated for cardiovascular protection, the quest for a popular alternative anti-inflammatory drug that may lower the risk of atherosclerotic events in patients with ischemic heart disease continues [(7)].

Colchicine is a medication with well-known anti-inflammatory characteristics that has been shown to be safe in several cardiovascular disease scenarios. Because of its capacity to obstruct microtubule polymerization, it has peculiar effects. Each hollow microtubule is made up of 13 parallel protofilaments, which are themselves made up of alternating, extremely tightly coupled pairs of alpha- and beta-tubulin subunits arranged along a longitudinal axis. Colchicine treatment has also been linked to decreased levels of inflammatory cytokines and smaller infarct sizes in patients who had PCI following an incident of STEMI [(8)]. In order to determine how colchicine affects L/N ratio and cardiac function in non-diabetic STEMI patients, our study was carried out. We showed that there was no statistically significant difference between the analysed groups in terms of demographic information. This is in line with the findings of **Deftereos *et al.*** [(9)] who discovered comparable demographic traits in their investigation on the comparative effectiveness of colchicine and standard therapy in terms of cardiac and inflammatory biomarkers and clinical outcomes.

In our investigation, we demonstrated that there was no statistically significant difference in BMI between the analysed groups (p = 0.883). This is in agreement with **Tardif *et al.*** [(10)] who found in a study to evaluate the efficiency and safety of low-dose of colchicine after a MI, that there was insignificant difference between placebo group and colchicine group as regards BMI (p > 0.05).

In our study, we found no statistically significant difference between the analysed groups for lab tests like NLR and CRP. This is in agreement with **Akodad *et al.*** [(8)] who found no significant difference between the studied groups as regards CRP, it was 29.03 ± 25.56 mg/L in the colchicine group vs 21.86 ± 25.39 mg/L in the control group (P = 0.36). Also, the leukocyte peak was 13.1 g/L in the colchicine group vs 11.5 g/L in the control group (P = 0.16). Also, **Mewton *et al.*** [(11)] inflammatory indicators as WBC count, neutrophil count, and fibrinogen at admission, 24 hours, and 48 hours did not show any significant changes between groups.

Fujisue *et al.* [(12)] found that, at 24 hours after MI, TTE did not detect a significant difference between the colchicine group and the control group in the LVEF, LVDD, and LVSD measurements. **Mewton *et al.*** [(11)] found that other predetermined secondary outcomes such as LV remodeling and LV ejection fraction did not change significantly between the colchicine and placebo groups.

Hennessy *et al.* [(13)] discovered that the LVEF, LV strain values, and LVDD & LVSD did not significantly change between the colchicine group and the control group. All these previous findings are in agreement with our study that revealed no statistically significant difference between the studied groups regarding LVEF, LVEDD, LVESSD, LVEF and GLS at baseline and at follow up after one month (P > 0.05).

Zarpelon *et al.* [(14)] found that both the mortality from any cause rate (5.6% compared to 10.1%, respectively; p = 0.363) and the length of hospital stay (14.5 versus 11.5 versus 13.3 versus 9.4 days, respectively; p = 0,490) did not differ statistically significantly between the colchicine and control groups.

Akodad *et al.* [(8)] found that, with one recurrence of MI in the control group and one case of acute heart failure in a patient treated with colchicine at one month post-treatment, there was no statistically significant difference between the two study groups regarding the risk of severe adverse cardiac events (P = 1). No patients passed away while they were being treated in the hospital or a month later. **Diaz *et al.*** [(15)] found that, colchicine did not substantially lower the risk of cardiovascular mortality (0.79 vs. 0.86%, p = 0.64) or recurrent MI (3.31 vs. 3.84%, p = 0.28 in comparison with control group) in four RCTs involving 5,821 participants. This is in agreement with our study that revealed no statistically significant difference between

patients that received colchicine than patients that received anti-ischemic treatment only (P value > 0.05).

Our study results showed that there was no statistically noteworthy distinction among those who received colchicine and those who received anti-ischemic medication alone as regards adverse events, (p = 0.705). This was in agreement with **Tardif *et al.*** [10] who found no significant difference in adverse events between the colchicine and placebo groups, and the total incidence of major adverse events was 16.4% and 17.2%, respectively.

CONCLUSIONS

Addition of colchicine to conventional anti-ischemic treatment post STEMI did not lead to significant effects on inflammatory marker, cardiac function and MACE in non-diabetic patients.

LIMITATIONS

Our study had a number of limitations, including a limited sample size, a single centre investigation, and an unbalanced group, particularly in terms of clinical aspects. With varying infarct sizes, the STEMI populations notably varied. Additionally, the follow-up period was not very long. Finally, only non-diabetic individuals who recently survived with AMI can use our data.

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Competing interests: Nil.

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