Impact of Short-Term Treatment with Colchicine on Endothelial Function in Non-ST Elevation- Acute Coronary Syndrome Patients

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Abstract

Background: NSTE-ACS are associated with a systemic inflammatory response that may accelerate coronary atherosclerotic processes. **This study aimed to** evaluate the impact of short-term treatment with colchicine on endothelial function in NSTE-ACS patients. **Methods:** All patients were subjected to history taking & physical examination. ECG & Echocardiography using conventional & tissue Doppler parameters were done to all patients, ESR & CRP were done at admission & 1 week after. All patients undergo baseline testing of endothelial function by using endothelium-dependent flow-mediated dilatation technique (FMD). **Results**: Both groups had similar ranges of relative FMD on admission. Group (A) had a range of 2.1-6.6 with a mean value of 4.42±1.07, while Group (B) had a range of 2.2-6.7 with a mean value of 4.54±1.18. After one week, both groups showed a slight increase in FMD values compared to admission. Group A had a range of 2.2-6.7 with a mean value of 4.54±1.18, and Group (B) had a range of 2.5-6.9 with a mean value of 4.36±1.14. After 3 months, Group A had a slight increase in FMD values compared to the one-week value, ranging from 2.3-6.8 with a mean value of 4.36±1.14. Group (B) also showed a slight increase in FMD values, ranging from 2.7-7.2 with a mean value of 4.86±1.55. **Conclusion:** Colchicine seems to slightly improve endothelial function in patients with NSTE-ACS assessed by flow meditated dilatation but this effect was non-statistically significant.

Keywords: Short-Term; Colchicine; Endothelial Function; Non-ST Elevation; Acute Coronary Syndrome.

Introduction

Non-ST elevation - acute coronary syndromes are associated with a systemic inflammatory response that may accelerate coronary atherosclerotic processes, leading to plaque destabilization and increased risk of further cardiovascular events (1).

Coronary artery disease patients are at continued risk of major atherosclerotic events despite effective secondary prevention strategies, there is a need to continue to develop

additional safe, effective and well-tolerated therapies for secondary prevention of cardiovascular disease (2).

Inflammation play a major role in precipitating a cascade of events from formation of the athermanous lesion in response to vascular injury through lipid ingestion by macrophages, to subsequent rupture of the lesion, and myocardial infarction, C-reactive protein (CRP) an inflammatory marker may play a pro-inflammatory role in activating monocyte chemotactic protein (3).

Colchicine is an established anti-inflammatory drug which attenuates NLRP3 (nucleotide-binding oligomerization domain-, leucine-rich repeat-, and pyrin domain-containing protein 3) inflammasome–mediated crystal-induced inflammation & inhibit phagocytosis and neutrophil activity (4).

This study aimed to evaluate the impact of short-term treatment with colchicine on endothelial function in non-ST elevation - acute coronary syndrome patients.

Patients and methods

This study included 200 patients who were admitted to cardiac care unit of Benha University Hospital with non-ST elevation-acute coronary syndrome during the period from January 2022 to January 2023.

The patients were classified into 2 groups: Group A: included 100 patients who received appropriate optimal medical treatment of non-ST elevation-acute coronary syndrome according to their clinical situation (control group). **Group B:** included 100 patients who received appropriate optimal medical treatment of non-ST elevation-acute coronary syndrome in addition to low dose colchicine 0.5mg / daily for 3 months.

Patients were randomized according to numbers as odd number 1,3, 5,etc received optimal medical treatment (Group A) and even 2,4,6…..etc received optimal medical treatment in addition to low dose colchicine 0.5mg / daily (Group B).

The study was done after being approved by the research ethics committee, faculty of medicine, Benha University and informed consent was obtained from all participants included.

Inclusion Criteria were patients who were diagnosed as non-ST elevation-acute coronary syndrome, their age was more than 30 years, and did not have contraindication to colchicine.

The exclusion criteria were individuals who are aged 75 years or older, those with malignant arrhythmia, individuals in cardiogenic shock, individuals experiencing rest angina with dynamic ST changes of at least 0.5mm, and those with contraindications to colchicine such as pregnancy or end-stage renal disease.

Methods: All patients were subjected to the following, medical history taking involving age, sex and presence of risk factors, prior history of coronary artery disease, risk factors

(DM , HTN , smoking and dyslipidemia), prior history of intervention, clinical examination (pulse, blood pressure, auscultation of back), baseline ECG findings involving rhythm & ST segment and T wave changes and baseline Transthoracic Echocardiography: all examinations were performed by using Vivivd 7 (G E Healthcare, Milaukee, MI, USA) echocardiography machine equipped with multi-frequency transducer and programmed with Doppler (color and spectral) and tissue Doppler options with assessment of the following:

A) Left ventricular function with special emphasis on the "ejection fraction" which was measured by Modified Simpson method. (B) Left ventricular diastolic function was measured by echo-Doppler through estimating E/A, E/e', Lateral e' velocity, septal e' velocity. (5) **.**

Lab investigation including fasting blood sugar, CBC including Patient HB%, Serum creatinine and urea, Liver function tests, and Lipid profile. Level of hs-CRP was done on admission and after 7days. Also measurement of level of ESR was done on admission and after 7days.

Flow Mediated Dilatation (FMD was done at time of admission then after 1week and repeated again after 3months**:** All patients undergone baseline testing of endothelial function by using endothelium-dependent flow-mediated dilatation technique (FMD) with high-resolution ultrasound according to recommended guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery (6).

All examinations performed between 8:00 am and 12:00 pm at temperature-controlled room between 22°C–24°C, in a semi-dark and quietness circumference. All patients were requested to lie in the supine position, and electrocardiographic monitoring was done. The cuff of the sphygmomanometer was putted in the middle of the right forearm approximately 1 cm distal to the ante-cubital fossa. Using a 10 MHz resolution linear array vascular ultrasound transducer with Philips iE33, the brachial artery located above the elbow and scanned in longitudinal sections. After recording baseline B-mode digital images of the brachial artery and spectral Doppler images of flow, the blood pressure cuff inflated to 250 mmHg for 5 min to motivate reactive hyperemia. Immediately after deflation, spectral Doppler images are acquired to confirm hyperemia **(7).**

FMD was done using a 10 MHz resolution linear array vascular ultrasound transducer with Philips iE33

Measurement of vessel diameter was done from the anterior vessel wall intima to the posterior vessel wall intima. Three successive measurements on the same image were averaged **.** FMD %= (peak arterial diameter at hyperemia-basal arterial diameter) / basal arterial diameter) × 100 **(8)**.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The used tests were 1 - Chi-square test for categorical variables, to compare between

different groups, 2 - Student t-test, for normally quantitative variables, to compare between two studied groups, 4 - Mann Whitney test for abnormally quantitative variables, to compare between two studied groups.

Results

This study included 200 patients who presented with NSTE-ACS that were divided into 2 groups: Group A: Age ranged between 30-79 years old & Group B: Age ranged between 30-68 years old, with no statistically significant differences between the two groups with P=0.4122.

Demographic criteria & risk factors and patient's presentation were shown in **Table 1**.

EF% in Group (A) ranged between 50-70 % with mean ±S.D. 59.44±6.679 % while in Group (B) ranged between 50-72 % with mean ±S.D. 58.12±4.717 %. There was no statistically significant difference between groups where P=0.179. **Figure 1**

Systolic blood pressure in Group (A) ranged between 100-210 with mean±S.D. 144.20±34.544 while in Group (B) ranged between 80-230 with mean±S.D. 142.60±34.322, with no statistically significant difference between groups where P=0.984. Diastolic blood pressure in Group (A) ranged between 70-120 with mean±S.D. 90.40±16.753 while in Group (B) ranged between 60-130 with mean±S.D. 94.00±25.386, P=0.429. Pulse in Group (A) ranged between 60-120 with mean±S.D. 91.24±15.754 while in Group (B) ranged between 60-135 with mean±S.D. 94.28±20.351, P=0.543. **Table 2**

ESR on admission in Group (A) at 1st hour ranged between 40-70 with a mean value of 57.22±8.00 while at 2nd hour ranged between 70-110 with a mean value of 90.48±11.73 then it decreased to be after 1 week at 1st hour ranged between 32-59 with a mean value of 46.36±8.51 and at 2nd hour ranged between 61-96 with a mean value of 78.38±9.81 while in Group (B) ESR at 1st hour ranged between 44-73 with a mean value of 57.08±8.04 and ESR at 2nd hour ranged between 75-115 with a mean value of 94.06±11.88 then it decreased highly significantly after 1 week at 1st hour and ranged between 6-10 with a mean value of 8.06±1.48 also at 2nd hour and ranged between 12-16 with a mean value of 14.10±1.46. There were highly statistically significant differences between the two groups. **Table 3**

CRP on admission in Group (A) ranged between 48-82 with mean±S.D. 63.66±9.37 and it decreased after 1 week with a mean value of 56.02±9.79 while in Group (B) on admission ranged between 52-89 with mean ±S.D. 70. 20±11.67 and it decreased highly significantly after 1 week with a mean value of 11.26±2.89. There were highly statistically significant differences between the two groups. **Table 4**

Both groups show similar ranges of relative flow-mediated dilation (FMD) on admission, Group (A) ranging between 2.1-6.6 with a mean value of 4.42±1.07 and Group (B) ranging between 2.2-6.7with a mean value of 4.54±1.18. After one week, group A show slight increase in relative flow-mediated dilation value compared to admission value ranging between 2.2-6.7 with a mean value of 4.54±1.18. Also, group (B) show slight increase in relative flow-mediated dilation value compared to admission value ranging between 2.5-6.9 with a mean value of 4.36±1.14. There was no statistically significant difference

between the two groups (P=0.8630). After 3 months, group A show slight increase in relative flow-mediated dilation value compared to one week value ranging between 2.3-6.8with a mean value of 4.36±1.14. Also, group (B) show slight increase in relative flow-mediated dilation value compared to one week value ranging between 2.7-7.2with a mean value of 4.86±1.55. There is no statistically significant difference between the two groups (P=0.0693). **Table 5**

Discussion

Non-STE ACS remains the main reason of morbidity and mortality globally (9). researches has pointed to the role of inflammation which seems to play a critical part in the atherosclerosis progression and frequent attack of non ST-elevation acute coronary syndrome (10).

The purpose of the present study was to evaluate short-term treatment with colchicine on endothelial function in a group of Egyptian patients who were admitted to cardiac care unit of Benha University Hospital with NSTE-ACS. The patients were classified into 2 equal groups: Group A: patients who received appropriate optimal medical treatment of NSTE-ACS according to their clinical situation (control group). Group B: patients who received appropriate optimal medical treatment of non-ST elevation-acute coronary syndrome in addition to low dose colchicine 0.5mg / daily for 3 months.

In the current study, the mean age of patients was 49.48 years.

Tong & his colleagues (11), who studied 795 patients and aimed to determine the potential usefulness of colchicine treatment in patients with ACS, diabetic patients were 19% compared with diabetic patients in our study were 52%,smokers were 32% compared with smoker patients in our study were 40%. While dyslipidemic patients were 46% compared while in our study were 48%. this risk factors discrepancy may explain early onset of ACS in our study.

Another study by Martinez et al, (12) ,who included 43 patients, 33 patients with stable coronary artery disease and 10 patients as controls and aimed to assess the local cardiac production of inflammatory cytokines in patients with acute coronary syndromes, mean age of patients was 64.5 years. Diabetic patients were 33%.smokers were 33%.

Vaidya et al, (13), aimed to evaluate the plaque-modifying effects of low-dose colchicine therapy plus optimal medical therapy in patient's post-acute coronary syndrome, as assessed by coronary computed tomography angiography. They included 80 patients; their mean age was 57.4 years. 22.5% of them were diabetics.

Another study performed by Akrami & his colleagues (14) who studied 249 patients and aimed to evaluate the effect of short-term, low-dose colchicine therapy, along with the standard medical therapy in approved ACS patients within a period of six months after a cardiac event. Mean age was 59.7 years. 22% were diabetics, 33.3% smokers while dyslipidemia was found in 30.8% of patients.

The younger age of ACS patients noted in our study in comparison with other studies may be attributable to more incidences of risk factors for ischemic heart disease in our patients.

In the current study, ejection fraction was comparable between the two groups with no statistically significant difference with mean EF% (59.44% & 58.12% in group I & II respectively), P=0.179.

This was in agreement with McKnight, et al, (15) who aimed to evaluate the efficacy and safety of colchicine after acute coronary syndrome, and reported that there was no significant statistical difference in ejection fraction EF between patients who take colchicine versus others (mean56%vs50.6%. p=0.15) .

In the current study, blood pressure showed no significant difference between both groups with the mean blood pressure in control group was 144.2 mmHg, while in colchicine group was 142.60 mmHg, also heart rate in groups showed no statistically significant difference (91.24 BPM in control group versus 94.28 BPM in colchicine group), with P=0.543.

This was in agreement with Kajikawa & his colleagues (16) , who found no significant difference with the mean blood pressure in the colchicine group versus control group (128 mmHg & 142 mmHg in colchicine & control groups respectively). The mean heart rate in the colchicine group was 67 BPM while in control group was 67 BPM.

In the current study, the mean serum level of hs-CRP in control group was 63.66 & 56.02 at admission & 1 week after. While in colchicine group, CRP was 70.20 at admission & decreased to 11.26 after 1 week with highly statistically significant difference.

Raju et al, (17) ,who studied 80 patients and aimed to determine whether colchicine compared with placebo could suppress hs-CRP in patients admitted to hospital with an acute coronary syndrome or acute ischemic stroke. They found that no evidence that colchicine 1 mg daily for 30 days compared with placebo suppresses inflammation in patients with acute coronary syndrome or acute ischemic stroke with median 1.0 mg/l in colchicine group versus 1.5 mg/l in control group, P = 0.22 ,In this cohort patients received 1mg daily colchicine compared with our study patients received 0.5mg , Also in this cohort hs-CRP evaluated after 30 days while in our study hs-CRP evaluated after 7 days and patients number in this cohort were 80 patients compared with our study which included 200 patients & these differences could explain the difference in outcome.

A study by Fiolet et al (18) , which included 138 patients and aimed to investigate whether short-term exposure to colchicine reduces inflammatory markers and whether additional laboratory changes occur in patients with chronic coronary artery disease. They found that patients with chronic coronary artery disease and a pro-inflammatory state defined by hs-CRP $\geq$ 2 mg/L, had a significant decrease in both hs-CRP and IL-6 after one month of colchicine exposure, median of the differences was (1.66 mg/L vs 1.22 mg/L, p-value <0.01 in cholchicine versus control group respectively), In this cohort, hs-CRP evaluated after 30 days compared with our study hs-CRP evaluated after 7 days, Also in this cohort patients were CCS with proinflammatory state compared with our study patients were NSTE-ACS .

Our study can be supported by Aimo et al., (19) who aimed to evaluate the pooled effect of colchicine on high-sensitivity C-reactive protein (hs-CRP) levels in the same setting. This study included 80 patients with acute coronary syndrome or acute ischemic stroke .They found that Colchicine tended to reduce the hs-CRP level.

In the current study the mean of FMD after one week was 4.36, while after 3 months the mean was 4.86 with no statistically significant difference, P value=0.0693.

This was in agreement with Kajikawa et al., (16) which included 28 patients with CAD and aimed to assess effect of short-term colchicine treatment on endothelial function in patients with coronary artery disease. They reported that FMD after administration of colchicine was not significantly different from that after administration of the placebo. Changes in FMD after administration of colchicine did not correlate with changes in hs-CRP.

Conclusion

Colchicine revealed considerable efficacy for lowering CRP, ESR level, which is a prognostic factor for cardiovascular complications. Colchicine, especially in low doses, seems to be relatively safe in the clinical setting. Colchicine seems to improve endothelial function in patients with NSTE-ACS assessed by flow meditated dilatation but this improvement was non statistically significant. Further studies are needed to assess the long-term effects of colchicine on vascular function and cardiovascular events in CAD patients.

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Author contribution

Authors contributed equally in the study.

Conflicts of interest

No conflicts of interest

References

1. Aimo A, Pascual-Figal DA, Barison A, Cediel G, Vicente Á H, Saccaro LF, et al. Colchicine for the treatment of coronary artery disease. Trends Cardiovasc Med. 2021;31:497-504.
2. Nidorf SM, Thompson PL. Why Colchicine Should Be Considered for Secondary Prevention of Atherosclerosis: An Overview. Clin Ther. 2019;41:41-8.
3. Yeh ET. CRP as a mediator of disease. Circulation. 2004;109:Ii11-4.
4. Hemenway G, Frishman WH. Therapeutic Implications of NLRP3-Mediated Inflammation in Coronary Artery Disease. Cardiol Rev. 2022;30:90-9.
5. Lang, R. M., Badano, L. P., Mor-Avi, V., Afilalo, J., Armstrong, A., Ernande, L.,et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the

European Association of Cardiovascular Imaging. European Heart Journal-Cardiovascular Imaging 2015, 16(3), 233-271.

6. Thijssen DH, Black MA, Pyke KE, Padilla J, Atkinson G, Harris RA, et al. Assessment of flow-mediated dilation in humans: a methodological and physiological guideline. Am J Physiol Heart Circ Physiol. 2011;300:H2-12.
7. Higgins JP, Yang B, Herrin NE, Yarlagadda S, Le GT, Ortiz BL, et al. Consumption of energy beverage is associated with attenuation of arterial endothelial flow-mediated dilatation. World J Cardiol. 2017;9:162-6.
8. Akhundova J, Kaya CT, Gerede Uludağ DM. Acute effects of consumption of low-caffeine energy drinks on endothelial functions in healthy volunteers. Anatol J Cardiol. 2021;25:678-83.
9. Lee, Reyes, Mieszczanska etal., (2018). Non-ST-Segment Elevation Acute Coronary Syndromes (NSTE-ACS). Springer.
10. Nus , Mallat. (2016). Immune-mediated mechanisms of atherosclerosis and implications for the clinic. Expert Review of Clinical Immunology, 12(11), 1217–1237.
11. Tong DC, Quinn S, Nasis A, Hiew C, Lee N ,Roberts-Thomson P, Adams H, et al. Colchicine in Patients With Acute Coronary Syndrome: The Australian COPS Randomized Clinical Trial. Circulation. 2020;142:1890-900.
12. Martínez GJ, Robertson S, Barraclough J, Xia Q, Mallat Z, Bursill C, et al. Colchicine Acutely Suppresses Local Cardiac Production of Inflammatory Cytokines in Patients With an Acute Coronary Syndrome. J Am Heart Assoc. 2015;4:e002128.
13. Vaidya K, Arnott C, Martínez GJ, Ng B, McCormack S, Sullivan DR, et al. Colchicine Therapy and Plaque Stabilization in Patients With Acute Coronary Syndrome: A CT Coronary Angiography Study. JACC Cardiovasc Imaging. 2018;11:305-16.
14. Akrami M, Izadpanah P, Bazrafshan M, Hatamipour U, Nouraein N, Drissi HB, et al. 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. 2021;21:583.
15. McKnight AH, Katzenberger DR, Britnell SR. Colchicine in Acute Coronary Syndrome: A Systematic Review. Ann Pharmacother. 2021;55:187-97.
16. Kajikawa M, Higashi Y, Tomiyama H, Maruhashi T, Kurisu S, Kihara Y, et al. Effect of short-term colchicine treatment on endothelial function in patients with coronary artery disease. Int J Cardiol. 2019;281:35-9.
17. Raju NC, Yi Q, Nidorf M, Fagel ND, Hiralal R, Eikelboom JW. Effect of colchicine compared with placebo on high sensitivity C-reactive protein in patients with acute coronary syndrome or acute stroke: a pilot randomized controlled trial. J Thromb Thrombolysis. 2012;33:88-94.
18. Fiolet ATL, Silvis MJM, Opstal TSJ, Bax WA, van der Horst FAL, Mosterd A, et al. Short-term effect of low-dose colchicine on inflammatory biomarkers, lipids, blood count and renal function in chronic coronary artery disease and elevated high-sensitivity C-reactive protein. PLoS One. 2020;15:e0237665.
19. Aimo, Pascual-Figal, Barton etal., (2021). Colchicine for the treatment of coronary artery disease. Trends in Cardiovascular Medicine, 31(8), 497–504.

Table 1: Comparison between the two groups as regard to demographic criteria & risk factors and patient's presentation

Demographic criteria & risk factors	Group (A) (n = 100)		Group (B) (n = 100)		P Value
	No.	%	No.	%	
Male	60	60.0	56	56.0	0.5665
Female	40	40.0	44	44.0	
Smoking	44	44.0	40	40.0	0.5665
HTN	40	40.0	36	36.0	0.56008
DM	56	56.0	52	52.0	0.5704
Dyslipidemia	44	44.0	48	48.0	0.5704
Presentation					
NSTEMI	44	44.0	49	49.0	0.47842
UA	56	56.0	51	51.0	

U: Mann- Whitney test, p: p value for comparing between the two studied groups, *: Statistically significant at P <0.05

Table 2: Comparison between two groups as regard to patient's hemodynamic

Hemodynamic	Blood Pressure				Pulse	
	Systolic		Diastolic			
	Min.-Max.	Mean± S.D	Min.-Max.	Mean± S.D	Min.-Max.	Mean± S.D
Group (A)	100-210	144.20±34.544	70-120	90.40±16.753	60-120	91.24±15.754
Group (B)	80-230	142.60±34.322	60-130	4.00±25.386	60-135	94.00±20.351
P value	0.984		0.429		0.543	

U: Mann- Whitney test p: p value for comparing between the two studied groups, *: Statistically significant at P <0.05

Table 3: Comparison between two groups as regard to patient's ESR

ESR		Group (A)		Group (B)	
		Min.-Max.	Mean± S.D	Min.-Max.	Mean± S.D
On admission	1st hour	40-70	57.22±8.00	44-73	57.8±8.04
	2nd hour	70-110	90.48±11.73	75-115	94.06±11.88
After 1 week	1st hour	32-59	46.36±8.51	6-10	8.06± 1.48
	2nd hour	61-96	78.38±9.81	12-16	14.10±1.46
P value (1st hour)		0.0001		0.0001	
P value (2nd hour)		0.0001		0.0001	

U: Mann- Whitney test, p: p value for comparing between the two studied groups, *: Statistically significant at P <0.05

Table 4: Comparison between two groups as regard to patient's CRP

CRP	Group (A)		Group (B)	
	Min.-Max.	Mean± S.D	Min.-Max.	Mean± S.D
On admission	48-82	63.66±9.37	52-89	70. 20±11.67
After 1 week	40-71	56.02±9.79	7-16	11.26±2.89
P value	0.0026		0.0001	

U: Mann- Whitney test, p: p value for comparing between the two studied groups, *: Statistically significant at P <0.05

Table 5: Comparison between two groups as regard to patient's FMD

Relative FMD%	Group (A)		Group (B)	P value	
	Min.-Max.	Mean± S.D	Min.-Max.	Mean± S.D	
On admission	2.1-6.6	4.42±1.07	2.2-6.7	4.54 ±1.18	00.5959
After 1 week	2.2-6.7	4.54±1.18	2.5-6.9	4.36±1.14	00.8630
After3 months	2.3-6.8	4.36±1.14	2.7-7.2	4.86±1.55	0.0693

U: Mann- Whitney test, p: p value for comparing between the two studied groups, *: Statistically significant at P <0.05

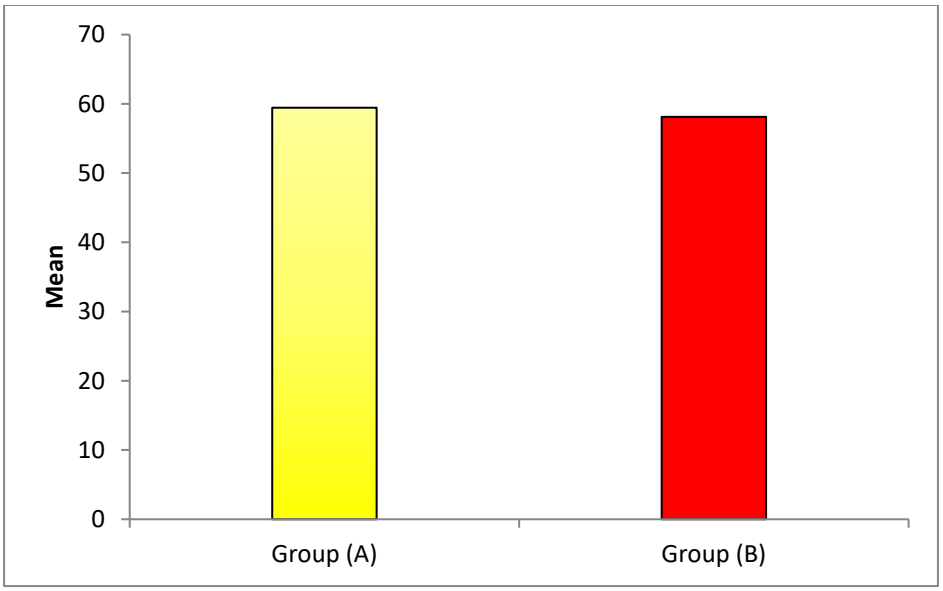

Figure 1: Comparison between two groups as regard to patient's EF