Colchicine for Prevention of in Stent Restenosis in Patients with Bare Metal Stents (Colisr-BMS Trial)

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Abstract

Background: In stent restenosis has been a considerable major problem with bare-metal stents (BMS). Pharmacological interventions to decrease Instent restenosis (ISR) could be of clinical relevance. Colchicine is associated with reduced inflammation and can be a reduced ISR rate when administered to patients after BMS implantation. The current study aimed to evaluate the efficacy of colchicine additional to BMS in the prevention of BMS restenosis in patients who underwent percutaneous coronary intervention (PCI).

Methods: The current clinical study was conducted at Gaza city. It involved 90 patients who were scheduled for coronary angioplasty procedure. The patients were divided into three groups: The first group, underwent BMS implantation and received colchicine 0.5 mg twice daily for six months. The second group, underwent BMS implantation alone. The third group, underwent DES implantation. All the patients were followed up for six months. The primary endpoint was clinical ISR at 6months. Secondary endpoints included target vessel revascularization (TVR) and stent thrombosis (ST).

Results: The mean age of the patients was 60.03 ± 7.8 years. After 6 months follow-up, significant differences were found in clinical ISR rate among the three groups (3% for the colchicine group, 23% for BMS alone and 0% for DES group, P=0.005). In addition, There were significant differences in TVR rate (3% for the colchicine group, 27% for BMS alone and 0% for DES group, P=0.002). However, there were no significant differences in the rate of stent thrombosis (0% for the colchicine group, 3% for BMS alone and 0% for DES group, P= 1).

Conclusion: Colchicine is associated with reduced ISR and TVR rate when administered to patients who underwent PCI with BMS as compared to BMS alone.

Keywords: Instent restenosis (ISR) • Colchicine • Thrombosis • Myocardial Infarction • Revascularization

Introduction

Inflammation plays an important role in coronary artery disease development and several processes involved in the sequence of events that follow the obstruction of an epicardial coronary artery in the context of STEMI, including thrombus composition, endothelial function, post-infarction myocardial function [1-3]. Colchicine is a drug with well-known anti-inflammatory properties, shown to be safe in various settings of cardiovascular disease [4,5]. The results of previous randomized trial suggested that treatment with colchicine in patients with STEMI undergoing primary percutaneous coronary intervention is associated with smaller infarct size. This effect was accompanied by a substantial treatment-related difference in markers of post–myocardial infarction inflammatory response, namely neutrophil count and C-reactive protein [6,7]. Our aim of study aimed to evaluate the efficacy of colchicine in the prevention of bare-metal stent restenosis and target vessel revascularization in patients with BMS plus colchicine compared to BMS alone and DES.

Methods

Study design

90 patients who underwent coronary angiography and PCI were randomize into 3 groups according to type of stent and uses of colchicine.

Group1: Bare-metal stent and 0.5 mg tablet colchicine twice daily for 6 months

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Group 2: bare-metal stent alone

Group 3: Drug eluting stent

Study population

The study population was single Center trial derived from Al-shifa Hospital between June 2014 to August 2015. We identified 90 patients (≥ 40 years) with Acute coronary syndrome (ACS) or Stable coronary artery disease.

All subjects received aspirin 75 mg+clopidogrel 300-600 mg just before the procedure. Unfractionated heparin bolus at least 5,000 IU during PCI followed by enoxaparin 1 mg/kg twice daily subcutaneous for 24-48 hours, beta blocker, Angiotensin converting enzyme inhibitors and high dose statin (Atorvastatin 40-80 mg) and patients with first group additionally colchicine 0.5 mg twice daily after BMS implantation.

Eligibility criteria

• **Inclusion criteria for patients**

Patients 40 years of age or older who were capable of providing an informed consent

and underwent a PCI with BMS or DES implantation for the treatment of stable IHD

or ACS.

• **Exclusion criteria**

➢ Patients with end stage renal failure (estimated glomerular filtration rate ≤ 20

➢ ml/min/1.73 m2).

➢ Patients with history of intolerance to colchicine, myopathy, and statin

➢ hepatotoxicity or myotoxicity.

➢ Women with child-bearing potential.

➢ Unwillingness or inability to comply with protocol procedures.

Data collection

Data sheet was designed for each patient and was numbered by the researcher. This sheet included all information about the patient: sex, age, medical history (hypertension, diabetes and hyperlipidemia), smoking, family history, clinical presentation (stable IHD, ACS), Procedure-related parameters (Lesion site, number of stents, total stent length, mm, stent diameter, mm) and outcome (clinical ISR, target vessel revascularization and stent thrombosis). Data were collected by the researcher using face to face questionnaire with the patients and from medical file of patients during the period from June 2014 to August 2015.

End points

Primary end point: Clinical ISR at 6 months; which is defined as the recurrence of angina pectoris or objective evidence of myocardial ischemia and Objective evidence of myocardial ischemia is a condition characterized by >50% instent restenosis.

Secondary end points: Target-vessel revascularization and stent thrombosis within sixth months.

Target-vessel revascularization is defined as any percutaneous intervention performed on the index target vessel any time after the index procedure.

Stent thrombosis is defined as an acute coronary syndrome with angiographic documentation of vessel occlusion by thrombus within stented segment

Statistical analysis

Continuous variables (age, ejection fraction, stent diameter and stent length) were expressed as mean ± SD and compared using ANOVA test. Categorical data (sex, diabetes, hypertension, family history, smoking, hyperlipidemia, clinical diagnosis, lesion site, TVR, stent thrombosis and clinical ISR) were expressed as absolute values and percentages and compared using chi-square test or Fisher exact tests if the produced matrices contained cells with an expected value <5. Factors tested for possible association with clinical ISR (diabetes, hypertension, family history, smoking, hyperlipidemia , number of stents, stent diameter and length of stent) were analyzed with univariate analysis. Multivariate predictors were calculated using stepwise logistic regression. Variables selected for the multivariate analysis were those with a P value < 0.05. Values of P < 0.05 (2 sided) were considered indicative of statistical significance.

Results

A 90 patients (30 patient in the colchicine group, 30 patient in the BMS alone group, and 30 patient in DES group) completed the study and were available for analysis.

Baseline characteristics of the patients in the three study groups are presented in (Table 1). Women composed 16.7%; while men composed 83.3% of the study sample. There were more men than women in the three groups. The mean age of the patients was 60.03 ± 7.8 yrs. A total of 39 (43%) patients were diabetic, 43 (47.8%) were hypertensive, 32 (35.6%) were hyperlipidemic, 28 (31.3%) had family history of IHD and 32 (35.6%) were smokers. Most patients (45.6%) presented with MI, 20% with unstable angina, and 34.4% with stable angina pectoris. The mean ejection fraction of patients was 61.33% ± 4.5. There were no statistically significant differences among the three study groups regarding age, diabetes, hypertension, hyperlipidemia, family history, mean ejection fraction and clinical presentation. However, there were statistically significant differences among the three study groups with regard to sex (Table 1).

Lesion site

A total of 52 (58%) patients had stenosis in LAD artery, 15 (17%) had stenosis in LCX artery, 9 (10%) had stenosis in RCA artery, 4 (4%) had stenosis in two arteries (LAD and RCA; LAD and obtuse marginal branch; RCA and LCX) and 10 (11%) had stenosis in other arteries such as obtuse marginal branch, and ramus branch. No significant differences were found among the three study groups with respect to the lesion site (P value= 0.212).

Number of stents

A total of 72 (80%) patients have implanted one stent, 14 (16 %) have implanted two stents, and 4 (4%) have implanted three stents. Significant differences were found in the number of implanted stents among the three groups (P value= 0.015).

Stent length: The mean stent length was 20.54 ± 5.08 mm. No significant differences were found in

the mean stent length among the three groups (P value= 0.195) (Figure 1).

Stent diameter: The mean stent diameter was 2.9 ±. 31mm. Significant differences were found in the

mean stent diameter among the three groups (P value=0.034). The mean stent diameter in group B (bare metal stent group) was significantly higher than that of group A (colchicine group) and group C (drug eluting stent group) (P=0.013) (Figure 2).

Maintenance drug therapy after PCI: Almost all patients in the three groups were on dual antiplatelet therapy and statin therapy. Of the 90 patients 10

Table 1. Baseline characteristics of the patients.

Characteristics	Group A[a]	Groups B[b]	Groups C[c]	Total	P[d] value
Total no	n[e]=30	n[e]=30	n[e]=30	n[e]=90	
Mean age in year	57.5 ± 6.7	62.2 ± 3	61.8 ± 7	60.03±7.8	.099[f]
Sex					.044[j]
Male	28 (93.3%)	21 (70%)	26 (86.7%)	75 (83.3%)	
Female	2 (6.7%)	9 (30%)	4 (13.3%)	15 (16.7%)	
Present medical history Diabetes mellitus	15 (50%)	10 (33.3%)	14 (46.7%)	39 (43.3%)	.387[j]
Hypertension	18 (60%)	11 (36.7%)	14 (46.7%)	43 (47.8%)	.192[j]
Hperlipidemia	8 (26.6%)	12 (40%)	13 (43.3%)	33 (36.6 %)	.366[j]
Family history	14 (63.3%)	8 (26.7%)	7 (23.7%)	28 (31.3%)	.373[j]
Smoking	9 (30%)	12 (40%)	10 (33.3%)	32 (35.6%)	.257[j]
Mean ejection fraction	62.2 % ± 3	61.8 % ± 5.8	60.6 % ± 6	61.33 % ± 4.5	.169[f]
Clinical presentation Myocardial infraction	15 (50%)	17 (56.7%)	9 (30%)	41 (45.6%)	
					.297[j]
Unstable angina pectoris	6 (20%)	4 (13.3%)	8 (26.7%)	18 (20%)	
Stable angina pectoris	9 (30%)	9 (30%)	13 (43.3%)	31 (34.4%)	

A: colchicine group; b: bare metal stent group; c: drug eluting stent group ;d: P value ≤0.05 were considered significant; e: Number of patients; f: ANOVA test; j: Chi-square test
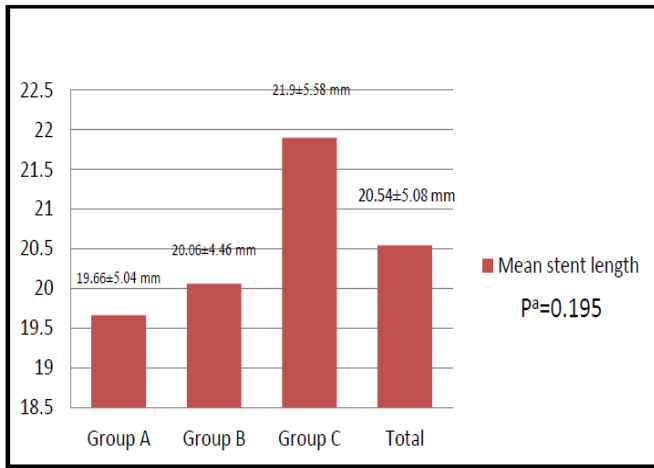
Figure 1. The mean stent length of implanted stents in the three groups.
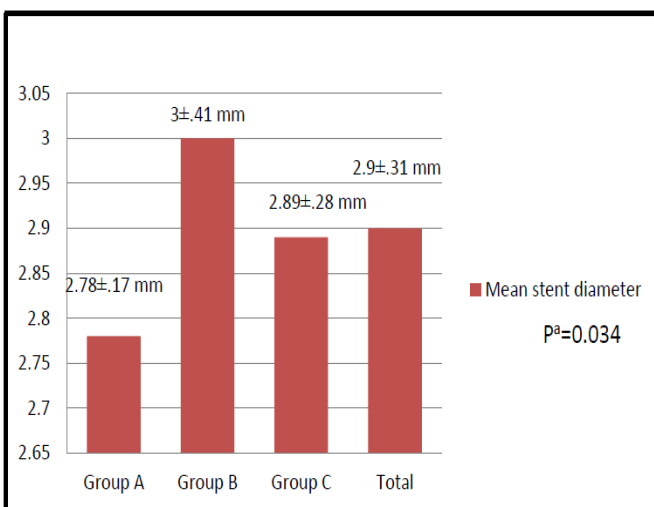

Figure 2. The mean stent diameter of implanted stents in the three groups.

(11%) patients had an increase in the level of total cholesterol that returned to normal after increasing the dose of statin (rosuvastatin or atorvastatin) (Table 2).

Primary outcome

Incidence of ISR: ISR was found in 8 (9%) patients. Significant differences were found in clinical ISR among the three groups (P=0.005). One patient (3%) in group A(colchicine group) had recurrent chest pain (angina pectoris) compared to seven patients (23%) in group B (BMS group) had recurrent chest pain. On the other hand, there were no reported cases of in stent restenosis in group C (drug eluting stent) (Figure 3).

Stent thrombosis: During 6 months follow up, only one patient (3%) in group B (BMS group) had MI.No significant differences were found in stent thrombosis among the three groups (P=1) (Figure 4).

Target vessel revascularization: Of the 90 patients; 9 patients (10%) underwent TVR. Significant differences were found in TVR among the three groups (P=0.002). One patient (3%) in group A (colchicine group) underwent TVR after three months compared to 8 (27%) patients in group B (bare metal stent group) underwent TVR after four months. While no one underwent TVR in group C (drug eluting stent group) (Figure 5).

Discussion

The present clinical trial is the first study conducted in the Gaza strip to evaluate the efficacy of colchicine in the prevention of in-stent restenosis in patients with IHD who undergo PCI with BMS compared with BMS alone or

Table 2. Drug therapy at six months follow up.

Drug	Group A[a] (n[e]%)	Group B[b] (n[e]%)	Group C[c] (n[e]%)	[d]P value
Aspirin	30 (100%)	29* (97%)	30 (100%)	1[f]
Clopidogrel	28 (93%)	26 (87%)	29 (97%)	0.493[f]
Rosuvastatin	14 (47%)	17 (57%)	14 (47%)	
Atrovastatin	16 (53%)	13 (43%)	16 (53%)	0.670[j]
Ramipril	10 (33%)	15 (50%)	12 (40%)	0.418[j]
B blockers				
Carvedilol	7 (24%)	10 (33%)	8 (27%)	0.818[j]
Bisoprolol	10 (33%)	10 (33%)	8 (27%)	
Oral hypoglycemic				
Drugs				
Glimepiride	5 (17%)	5 (17%)	7 (24%)	0.721[f]
Glimepiride+ metformin	5(17%)	3 (10%)	6 (20%)	
Insluin therapy	5 (17%)	2 (7%)	1 (3%)	0.263[f]

a:Colchicine group; b:bare metal stent group; c:drug eluting stent group; d:P value ≤ 0.05 were considered significant; e:number of patients; f:Fisher exact test; j:Chi-square test.*One patient stopped aspirin due to bleeding
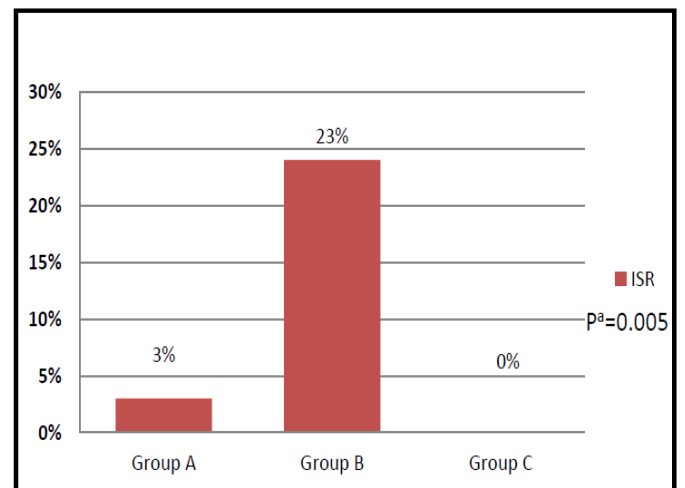

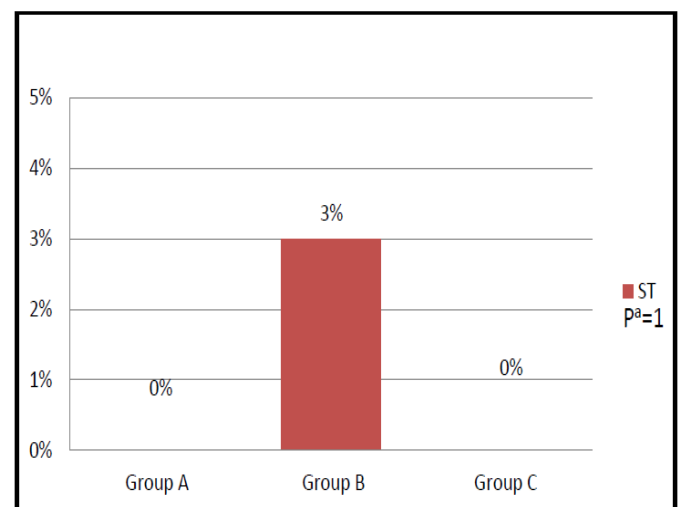**Figure 3.** Incidence of ISR in the three groups.

Figure 4. Incidence of ST in the three groups.

DES. the Clinical ISR, and TVR were significantly higher in patients with MBS and colchicine compared with BMS alone, and similar within patient with DES. No significant differences were found in stent thrombosis among the three groups.
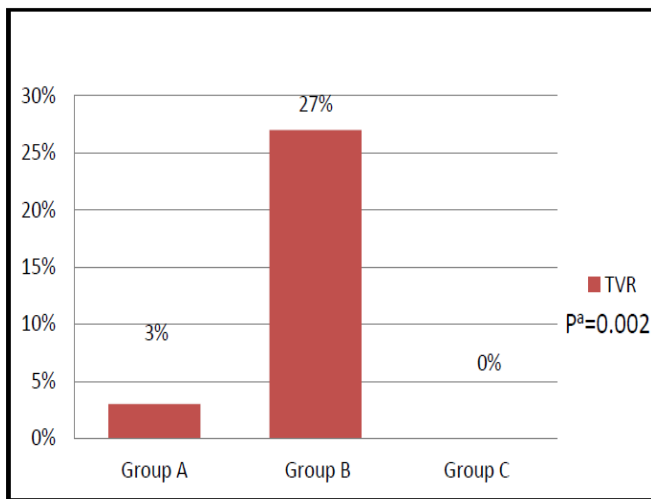
Figure 5. Incidence of ST in the three groups.

Our results were consistent with the results of the study by Deftereos et al. (2013). This study involved 196 diabetic patients who underwent PCI with BMS. The patients were divided randomly into placebo group (n=96) and colchicine group (n=100) in which colchicine was administrated at a dose of 0.5 mg twice daily. The patients were followed up for 6 months. Angiographic ISR rate was 16% in the colchicine group and 33% in the control group (P=0.007). Four patients (3.6%) in the colchicine group and 5 patients (4.5%) in the control group underwent reintervention. No stent thrombosis occurred. Our study determined angiographic ISR rate, while the present study determined clinically ISR rate and involved diabetic and non diabetics patients [7].

Limitations of our study include

- A relatively small sample size. The sample size in our study (n=90).
- Angiography not routine performed at six months, so that difficulty in calculation in the percentage of stent restenosis rate.
- Absence of intracoronary ultrasound evaluation in the angiographic analysis of ISR.

Conclusions

Colchicine has an antimitotic effect, obviously useful for preventing a process characterized by an anti-inflammatory effect, which should inhibit the very important contribution of inflammation to in-stent neointima formation. In addition, colchicine does not seem to share the undesirable properties of other classes of anti-inflammatory agents that render them unsafe for use in patients with cardiovascular disease. This study was carried out on ninety (three groups) patients to evaluate the efficacy of colchicine in the prevention of in -stent restenosis in patients with CAD who undergo PCI with BMS. At the end of the study and following data analysis, we concluded that:

- Colchicine is associated with reduced ISR rate when administered to patients with IHD who undergo PCI with BMS.
- Colchicine may prove to be an alternative for DES when administered at a daily dose of 1 mg for 6 months to IHD patients undergoing PCI with implantation of a BMS in patient who not tolerate to long term dual antiplatelet or high risk of bleeding. More powered studies with large patients' number and longer follow-up would be needed to demonstrate a clinical benefit for colchicine use in this setting.

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