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TO STUDY THE EFFICACY OF COLCHICINE IN REDUCING INSTENT RESTENOSIS IN INDIAN PATIENTS WITH BARE METAL STENTS

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Abstract

1. Background

Various drugs and modalities has been evaluated to address the In-stent restenosis in stents deployed for obstructive coronary artery disease. In this study we evaluated the efficacy of Colchicine in reducing Instent Restenosis in Indian patients with Bare Metal Stents in terms of binary restenosis, target lesion revascularization (TLR) and late lumen loss (LLL).

2. Methods.

The study was conducted at tertiary care hospital over a period of one year. The patients who presented with acute coronary syndrome or chronic stable angina requiring revascularization were included in the study.

3. Results

A total of 41 patients who fulfilled the inclusion criteria were randomized to two groups and followed up with a check CAG at 12 months. Out of 41 patients enrolled, 21 were randomly assigned to receive colchicine (colchicine

group) and 20 to receive placebo (placebo group). The late lumen loss was calculated for each patient by subtracting the MLD at 12 months from after procedure MLD and the mean late lumen loss in the two groups was 0.48±0.60 and 0.55±0.52 mm respectively which was not significant statistically (*p=0.67).*

4. Conclusion

In our study we found equivocal results in as much the efficacy of colchicine in preventing restenosis in all comers of an Indian population albeit this study confirmed the safety and compliance of colchicine in the study population.

1. Introduction

The use of percutaneous balloon angioplasty to recanalize narrowed coronary arteries and endovascular vessels revolutionized revascularization [(1)]. Balloon angioplasty (BA), however, was associated with subintimal dissection, abrupt vessel closure, and restenosis. The introduction of a metallic spring into the popliteal artery of an experimental animal by Charles Dotter [(2)] signaled the beginning of the stent era. However, the first human stent implantation, by Sigwart et al [(3)], did not occur until 1986. And it was only in 1994 that the US Food and Drug Administration approved the use of stents following two studies [(4,5)] that conclusively proved the superiority of stents over balloon angioplasty with regards to their long-term prognosis. Intracoronary bare metal stents (BMS), which could tackle dissections and eliminate elastic recoil, became the next mode of intervention [(4)] but their use was limited by increased inflammation and increased neointimal hyperplasia, leading to in-stent restenosis (ISR) [(6,7,8)]. Drug-eluting stents (DES) are another breakthrough in

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stent technology because of their ability to minimize cellular proliferation and to reduce restenosis rates to single-digit levels [9,10] and have become the interventional treatment of coronary atherosclerotic disease [11]. However, the demonstrated efficacy of DES is balanced by the small but unpredictable risk of very late stent thrombosis thought to be due to delayed vascular healing resulting from either the initial antiproliferative effect (and associated late acquired incomplete stent apposition) or a hypersensitivity reaction to the drug, polymer coating, or their combination [12,13]. Restenosis is also reported with DES, especially in complex subsets of patients and lesions [14].

In-stent restenosis occurs in up to one-half of patients treated with BMS [15]. Although it was initially considered to be a benign process, but later on the evidence showed that it presented with acute myocardial infarction or unstable angina in more than one-third of cases [16]. In addition, there is evidence that in-stent restenosis has a negative impact on the long-term survival of patients treated with BMS [17]. It has been estimated that about 60% of restenotic lesions require treatment with a repeat revascularization procedure [15], and this highlights the importance of finding effective preventive and therapeutic solutions for in-stent restenosis. Several treatment modalities have been proposed and used for bare-metal in-stent restenosis: plain/cutting BA, repeat stenting, vascular brachytherapy, rotational directional atherectomy and excimer laser-based angioplasty [18]. Previously plain BA with or without brachytherapy had been the most frequently used treatment for patients with in-stent restenosis but now a number of studies [19] showed superiority of DES over conventional treatment modalities for restenosis in BMS in terms of larger post-procedural lumen volume as well as a significant reduction in the volume of neointimal proliferation with DES than with plain BA at follow-up angiography

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[23]. However, they require dual antiplatelet therapy (DAPT) thereby increasing the risk of bleeding in high risk surgeries [20]. Hence, there is a considerable impetus for the development of new therapies to reduce the rate of restenosis after coronary stenting, especially with bare metal stents. Although coronary stenting has reduced the rates of angiographic and clinical restenosis caused by acute vessel recoil and chronic vessel remodeling, inflammation and neo-intimal proliferation continue to be associated with the pathophysiology of ISR [21]. Prevention of this neo-intimal proliferation with various immunosuppressive and anti-smooth muscle cell proliferation drugs (e.g.: Prednisolone, Rapamycin, and Sirolimus) has been hypothesized and demonstrated to reduce ISR [22].

Colchicine is a potent anti-inflammatory drug which inhibits the mitotic spindle by disrupting the self-assembly of microtubules in neutrophils, macrophages and smooth muscle cells [23]. Moreover, it shows a preferential concentration in leucocytes more than 16 times the peak concentration in plasma, thereby decreasing the systemic detrimental effects of the drug [24].

In this study we evaluated the efficacy of Colchicine in reducing Instent Restenosis in Indian patients with Bare Metal Stents in terms of binary restenosis, target lesion revascularization (TLR) and late lumen loss (LLL).

3. Aims and Objectives:

To study the Efficacy of Colchicine in reducing Instent Restenosis in Indian patients with Bare Metal Stents in terms of binary restenosis, target lesion revascularization (TLR) and late lumen loss (LLL) by Coronary Angiography at 12 months.

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4. Materials and Methods.

The study was conducted at tertiary care hospital from April 2015 to May 2016. The patients who presented with acute coronary syndrome or chronic stable angina requiring revascularization were included in the study.

Inclusion criteria

- Age >18 years
- Clinical evidence of stable or unstable angina or abnormal functional study
- CAD patients requiring PCI but having contraindications to DES deployment (e.g. planned necessary surgery within 1 year).
- Those who need anticoagulation treatment, in whom triple antithrombotic therapy (double antiplatelet and 1 anticoagulant) is associated with a high risk of bleeding and should be as short term as possible
- Patients with disorders who may require discontinuation of DAPT within 1 year

Only 1 lesion per patient was included in the study. (If PCI was performed in **>** 1 coronary site in a patient, the site with the greater artery diameter was included).

Baseline clinical characteristics studied were age, sex, the presence of acute coronary syndrome (ACS), diabetes mellitus (DM), smoking, hyperlipidemia and hypertension.

Exclusion criteria

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- An acute myocardial infarction within the previous 48 hours
- Severe renal insufficiency (GFR <30mL/min)
- Known hypersensitivity or contraindication to the required medication
- Malignancies causing life expectancy of < 2 years
- Angiographic exclusion criteria consisting of
    - Vessel diameters of <2.5 mm
    - Unprotected left main stenosis
    - Stents covering a major side branch (> 2 mm)

A total of 41 who patients fulfilled the inclusion and exclusion criteria and were enrolled in the study. Patients underwent baseline coronary angiography and PCI with a BMS. All stents were post-dilated with an appropriately sized noncompliant balloon. The patients were then randomized to the two arms of the study wherein the control group was given placebo by and the study group was given Colchicine 0.5mg BD. The study was designed as a prospective randomized single-blind study, and the patients were blinded to the treatment assignment during the study. Procedural success was assessed by the performance characteristics in terms of tracking ability, deliverability and acute luminal gain on QCA. All patients were prescribed the standard doses of dual antiplatelet therapy (DAPT) with aspirin 150 mg once a day and Clopidogrel 75 mg bid for one year. Late lumen loss and any ISR (the difference between the in-segment minimal lumen diameter after the procedure and at 12 months, as evaluated by quantitative coronary angiography) was the primary end point. Secondary end points included the rate of restenosis and the rate of the combined clinical events up to 12 months, including stent thrombosis, target-lesion revascularization, myocardial infarction, and death. A written informed consent was obtained from all patients before randomization.

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Statistical Methods

Continuous variables were expressed as mean ± SD. Values were reported as numbers with relative percentage or SD. For continuous data, groups were compared with a parametric Student *t* test or a Fischer exact t test according to the distribution of the data. Categorical variables were compared with a chi-square test. A p value of <0.05 was considered statistically significant. The SPSS statistical software (version 20.0, SPSS, Inc., Chicago, Illinois) was used for all statistical calculations.

5. Results

A total of 41 patients who fulfilled the inclusion criteria were enrolled in the study and followed up with a check CAG at 12 months. Out of 41 patients enrolled, 21 were randomly assigned to receive colchicine (colchicine group) and 20 to receive placebo (placebo group). **16(39.02%) patients out of 41 had LAD as affected artery, 20 (48.78%) had RCA and 5(12.19%) had LCX as affected artery.** The mean % diameter stenosis in the coronaries in the colchicine group was 85.19±11.17% with a minimal lumen diameter of 0.43±0.32mm before procedure and 10.71±6.67 and 2.74±0.36 mm immediately after revascularisation respectively. Whereas the mean % diameter stenosis and MLD in the placebo group was 83.00±12.18% and 0.47±0.36 mm before procedure and 11.55±6.59% and MLD increased to 2.58±0.44mm. There was statistically no significant difference between colchicine and placebo treatment groups in

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the immediate post procedure outcome in terms of minimal lumen diameter (*p =0.22)*. Follow up CAG at 12 months revealed a mean MLD of 2.26±0.64 mm in colchicine treated patients and 2.00±0.57 mm in patients who were given placebo (p=0.189). The late lumen loss was calculated for each patient by subtracting the MLD at 12 months from after procedure MLD and the mean late lumen loss in the two groups was 0.48±0.60 and 0.55±0.52 mm respectively which was not significant statistically (*p=0.67).* MACE was 19.04% in colchicine group and 20% in placebo group (p= 1.00) that was all due to the need for TLR. 4 patients in colchicine group and 4 patients in placebo group developed significant restenosis needing revascularization.

Adverse Effects

Adverse effects occurred more commonly in colchicine group than in the placebo group. Gastrointestinal symptoms (diarrhea and nausea) were the most common adverse events in the colchicine group. None of the patients in the colchicine group had bleeding. Myalgias and muscle cramps comprised second most frequent side effects. None of the patients had hepatic or nephro-toxicity or rash in the colchicine group. Whereas dyspepsia, nausea and gastric irritation was the most commonly reported complaints in the placebo group.

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7. Conclusion

a) In our study we found equivocal results in as much the efficacy of colchicine in preventing restenosis in all comers of an Indian population albeit this study confirmed the safety and compliance of colchicine in the study population.

b) Although the restenosis rate of 19.04% seen in our study suggests a lack of efficacy, since only cut off values of >50% stenosis were used. But a smaller beneficial effect may be present as since the average late lumen loss was less in the colchicine group.

We recommend that a multicenter study should be conducted with a larger sample size and diabetic patients.

Tables and Charts

Fig. 1: Treatment Assigned

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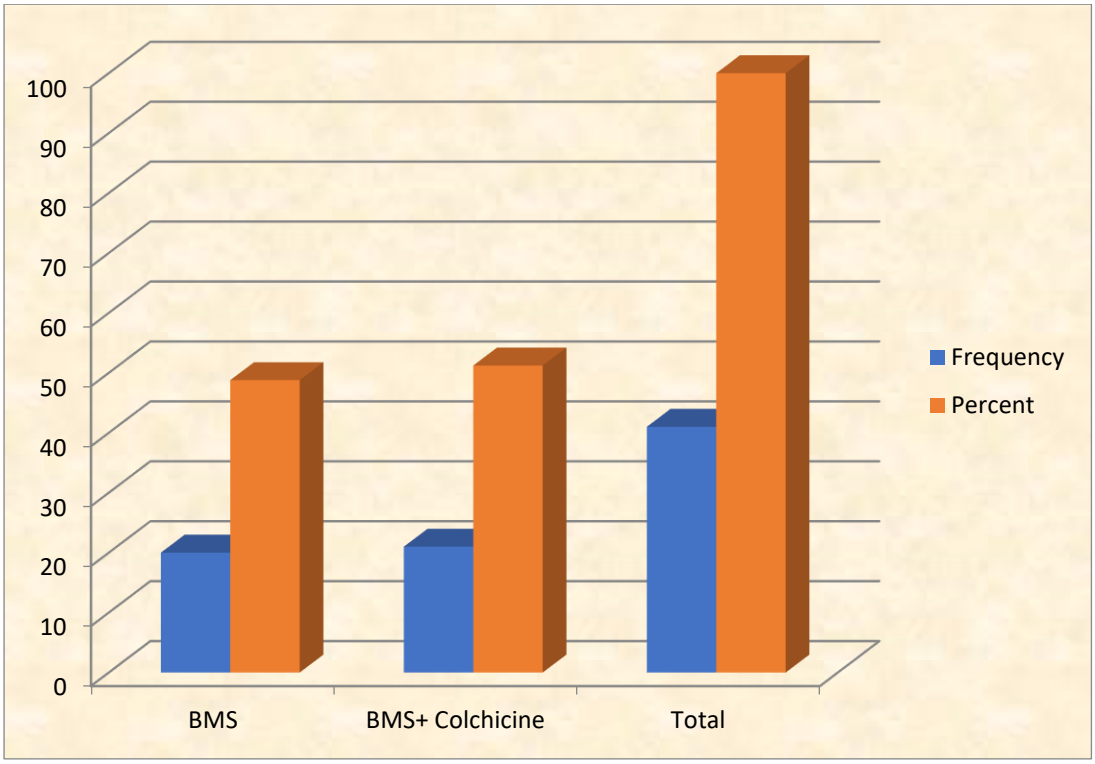

Table 1: Distribution of patients according to the treatment assigned

Treatment assigned	Frequency	Percent
BMS	20	48.78
BMS+ Colchicine	21	51.22
Total	**41**	**100**

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Fig. 2: Age wise distribution in 2 groups

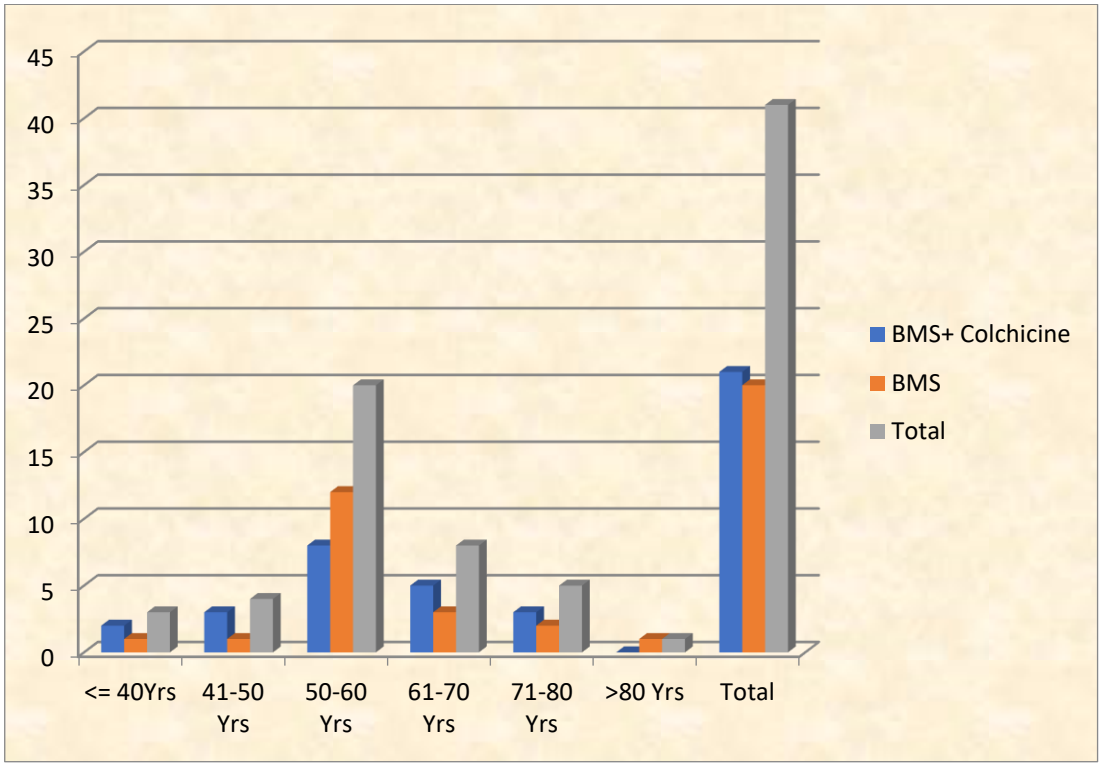

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Table 2: Age wise distribution of patients in 2 study groups

Age group	Study groups		Total	Pearson Chi-Square	p-value
	BMS+ Colchicine	BMS			
<= 40Yrs	2	1	3	3.811	0.577
41-50 Yrs	3	1	4		
50-60 Yrs	8	12	20		
61-70 Yrs	5	3	8		
71-80 Yrs	3	2	5		
>80 Yrs	0	1	1		
Total	**21**	**20**	**41**		

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Fig. 3: Sex wise distribution in 2 groups

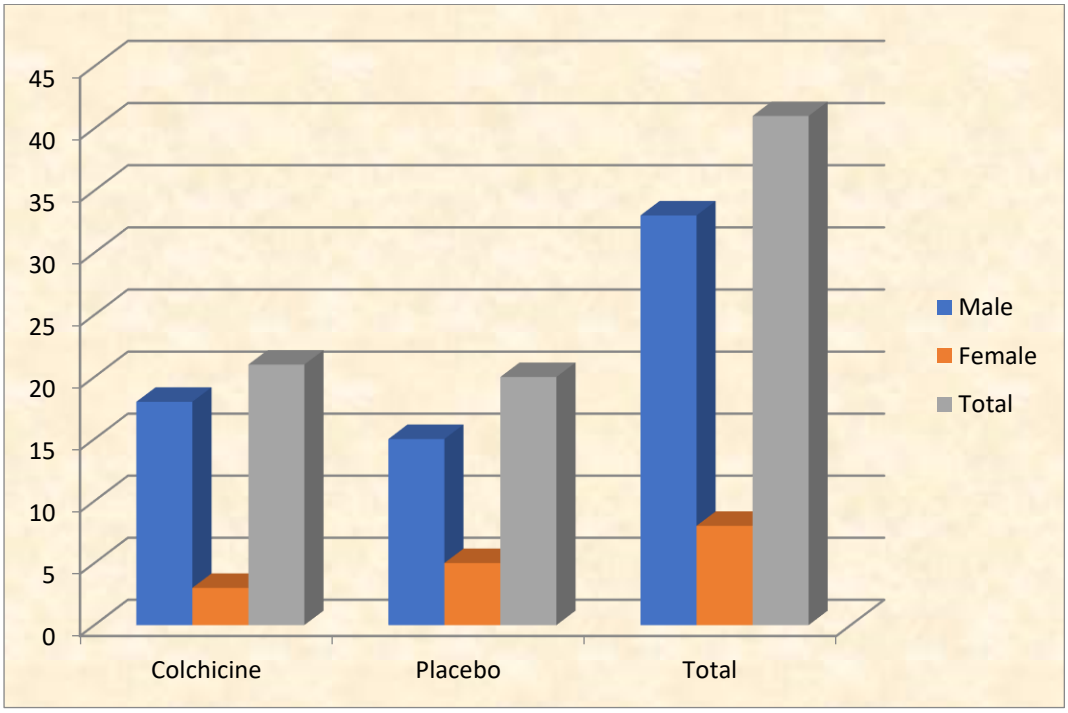

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Table 3: Sex wise distribution of patients in two study groups

Sex	Study Group		Total	p-value (Fisher's Exact Test)
	Colchicine	Placebo		
Male	18	15	33	0.454
Female	3	5	8	
Total	**21**	**20**	**41**	

Fig. 4: LV function in 2 groups

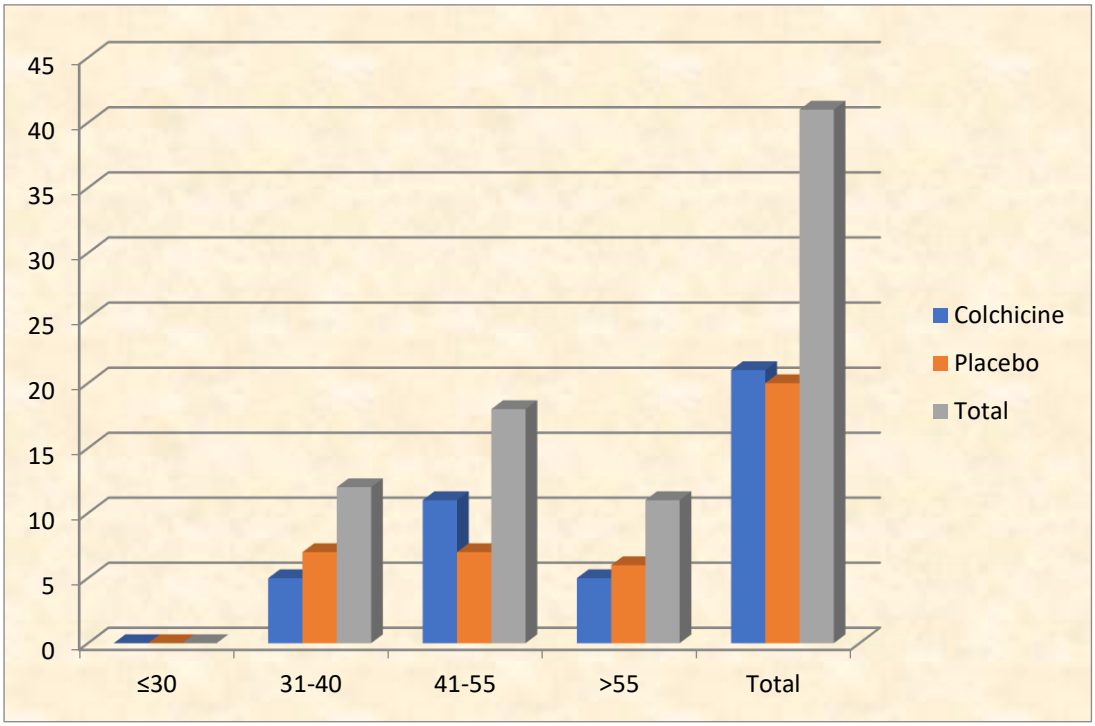

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Table 4: Distribution of patients according to the LV function in 2 groups

LVEF	Study Group		Total
	Colchicine	Placebo	
≤30	0	0	0
31-40	5	7	12
41-55	11	7	18
>55	5	6	11
Total	**21**	**20**	**41**

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Fig. 5: Affected coronaries in 2 groups

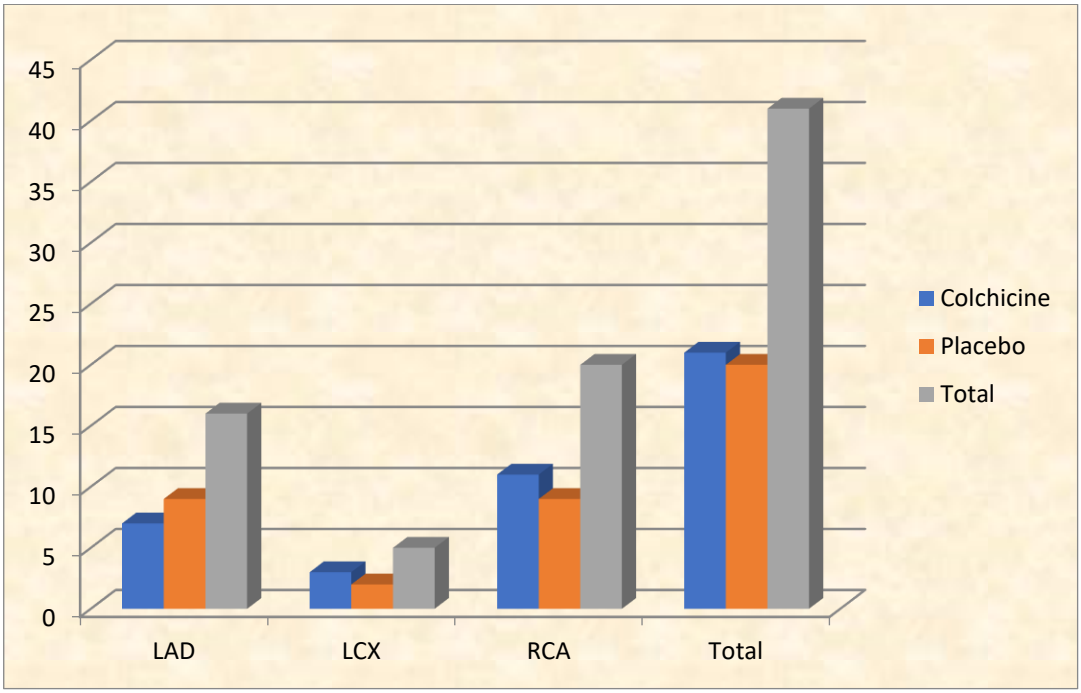

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Table 5: Affected coronary in 2 study groups

Affected Coronary	Study Group		Total	Pearson Chi-Square	p-value
	Colchicine	Placebo			
LAD	7	9	16	0.626	0.73
LCX	3	2	5		
RCA	11	9	20		
Total	**21**	**20**	**41**		

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Fig. 6a: % Diameter Stenosis

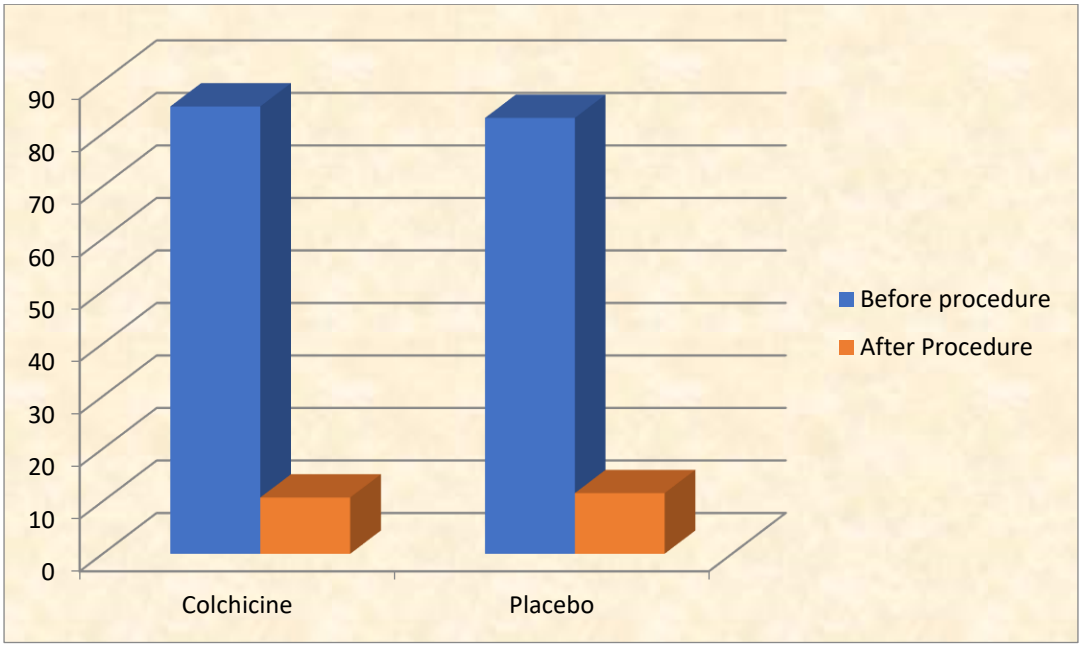

Fig.6b: Minimal Lumen Diameter (MLD)

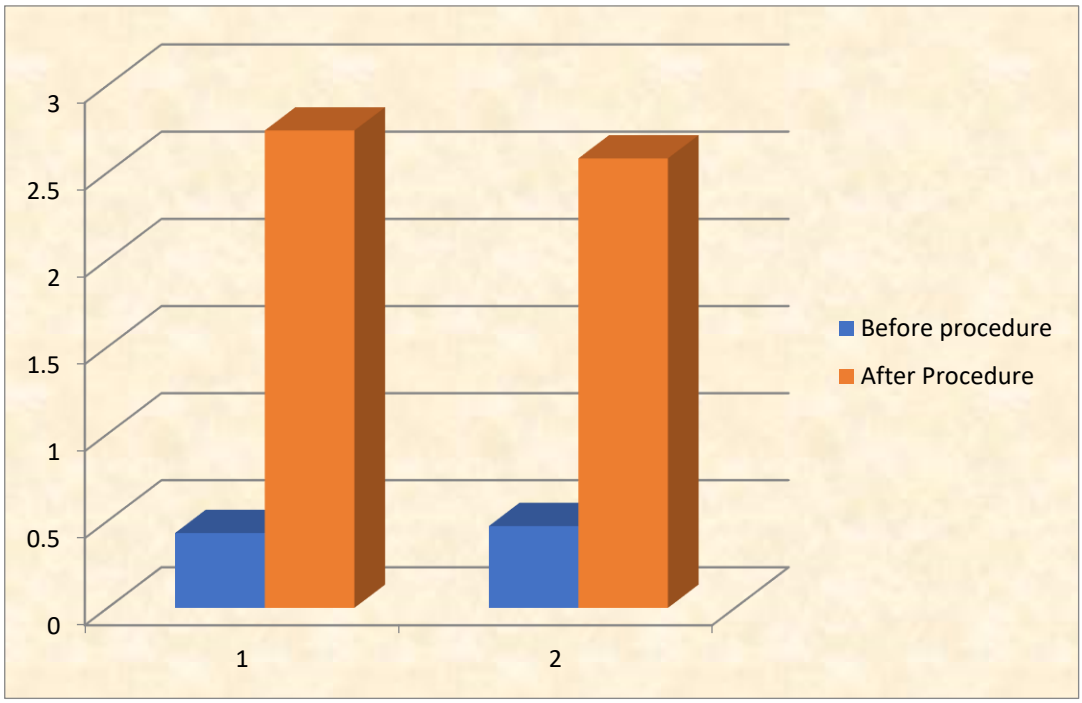

Table 6: Angiographic Data before and after procedure (mean ± sd)

	% Diameter stenosis			Minimal lumen diameter (MLD) (mm)		
	Colchicine	**Placebo**	**p value**	**Colchicine**	**Placebo**	**p value**
Before procedure	85.19±11.17	83.00±12.18	0.55	0.43±0.32	0.47±0.36	0.65
After Procedure	10.71±6.67	11.55±6.59	0.68	2.74±0.36	2.58±0.44	0.22

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Fig. 7: TIMI Flow

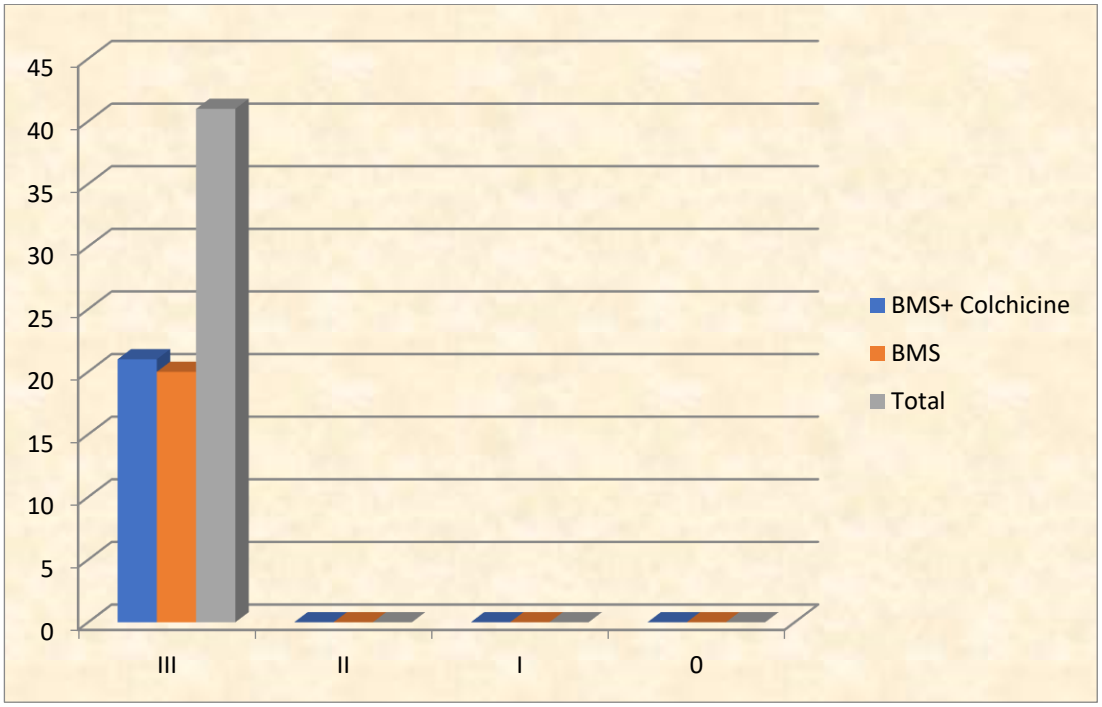

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Table 7: Procedural success (in terms of TIMI flow) after revascularization in 2 study groups

TIMI flow	Study Group		Total
	BMS+ Colchicine	BMS	
III	21	20	41
II	0	0	0
I	0	0	0
0	0	0	0
Total	**21**	**20**	**41**

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Fig. 8: Late lumen loss at 12 months

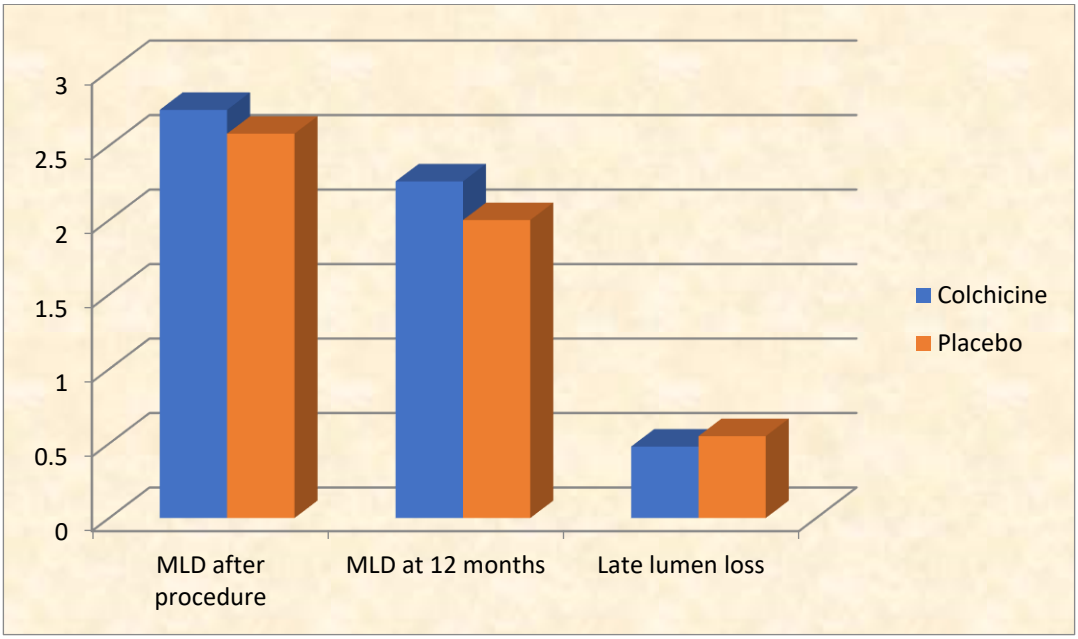

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Table 8: Results of check CAG at 12 months in 2 study groups (mean±sd)

	Colchicine	Placebo	p value
MLD after procedure	2.74±0.36	2.58±0.44	0.22
MLD at 12 months	2.26±0.64	2.00±0.57	0.189
Late lumen loss	0.48±0.60	0.55±0.52	0.67

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Fig. 9: MACE

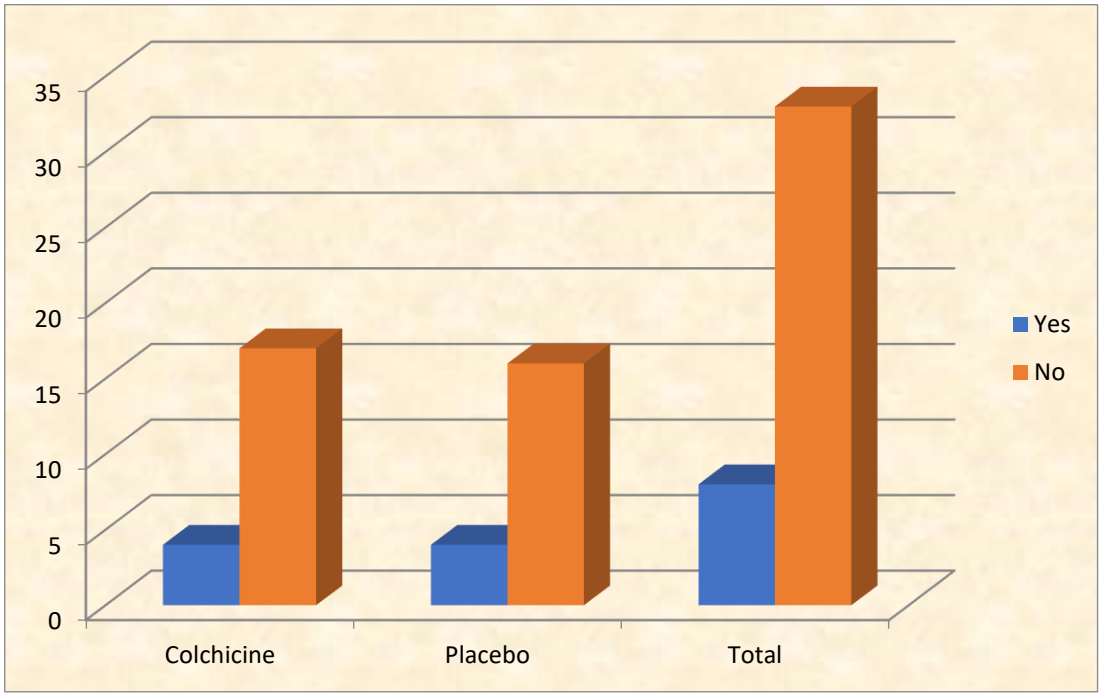

Table 9: Incidence of MACE in 2 groups

MACE			Total	p-value (Fisher's Exact Test)
	Colchicine	Placebo		
Yes	4	4	8	1.000
No	17	16	33	
Total	**21**	**20**	**41**	

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