



Research Article

# Colchicine for the Prevention of Myocardial Injury Following Elective PCI: A Randomized Clinical Trial

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## Abstract

**Background:** Considering the potential benefits of colchicine in coronary artery diseases, we aimed to carry out the present study to assess the impact of colchicine in the prevention of myocardial injury following elective percutaneous coronary intervention (PCI).

**Methods:** A randomized, single-blinded, clinical trial was carried out on 102 patients undergoing elective PCI. All patients received the standard treatment prior to performing PCI. Moreover, the intervention group received 1, 0.5, 0.5 mg colchicine 12 to 18 hours before, 30-60 min before, and 12 hours after PCI, respectively. Serum concentrations of cardiac troponin I (cTnI) were measured before, 8, and 24 hours after the procedure to assess myocardial damage during PCI.

**Results:** There were no significant differences in cTnI levels at baseline ( $P = 0.839$ ), 8 ( $P = 0.729$ ), and 24 hours ( $P = 0.398$ ) after PCI between the intervention and the control groups. Likewise, no significant differences were seen regarding the mean differences of cTnI at baseline and 8 hours ( $P = 0.190$ ), at baseline and 24 hours ( $P = 0.780$ ), and 8 and 24 hours after PCI ( $P = 0.680$ ) in both groups.

**Conclusion:** The study did not support the potential benefit of colchicine in the prevention of myocardial injury following elective PCI. Conducting well-designed randomized clinical trials with adequate sample size is recommended.

## Introduction

Currently, percutaneous coronary intervention (PCI) plays a critical role in the management of occlusive coronary artery disease (CAD). After the introduction of PCI, the number of procedures has increased in an impressive manner worldwide. Coronary revascularization with PCI is a slightly invasive non-surgical procedure involving the utilization of balloon angioplasty and intracoronary stenting.<sup>1,2</sup>

PCI is associated with procedure-related complications such as stroke and life-threatening bleeding; however, the periprocedural myocardial necrosis is the most common complication, which can range from a periprocedural myocardial injury (PMI) to a massive myocardial infarction (MI).<sup>3</sup>

The patient-related risk factors of PMI following PCI include the extent of a preprocedural acute coronary syndrome (ACS), preprocedural elevation of cardiac biomarkers, a history of prior coronary artery bypass graft (CABG), previous MI, low ejection fraction (EF), smoking, diabetes, and older age. Importantly, a preprocedural elevation of C-reactive protein (CRP) leads to a higher incidence of periprocedural MI. Besides, procedural risk factors such as the number and length of the stents have

been reported to affect the incidence of PMI.<sup>4,5</sup>

PMI occurs approximately in up to one-third of elective PCIs and impacts the outcomes of patients.<sup>6</sup> Based on a meta-analysis of 20 randomized clinical trials (RCTs) with 15,581 cases, there is a significant link between the raise of cardiac troponins following PCI and mortality rate.<sup>7</sup>

PMI commonly takes place due to many factors such as platelet aggregation, embolization of atheroma or thrombus, epicardial or microvascular spasm, oxidative stress, and inflammation.<sup>8</sup> It has been shown that PCI could evoke an inflammatory response through different pathways. For example, Bagheri *et al.*<sup>9,10</sup> showed that the PCI procedure could increase the monocyte expression of human toll-like receptor-4 (hTLR-4) and the serum levels of interleukin-1 $\beta$  (IL-1 $\beta$ ) and tumor necrosis factor-alpha (TNF- $\alpha$ ) in individuals with stable angina. In another study, they showed that hydrocortisone could reduce inflammatory responses following PCI through decreasing monocyte expression of hTLR4 and serum levels of IL-1 $\beta$  and TNF- $\alpha$  in 71 patients with chronic stable angina. Despite advances in recognizing molecular and cellular mechanisms involved in the pathophysiology of reperfusion injury and performing successful animal studies, translation to the clinical setting has often proven

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unsatisfactory in practice.<sup>11</sup>

Colchicine, an inexpensive anti-inflammatory medicine with proven safety and efficacy for numerous inflammatory diseases, was initially extracted from the autumn crocus plant and has been administered for gout treatment for hundreds of years.<sup>12</sup> Currently, colchicine has also emerged with promising results in the management of a broad range of cardiovascular disorders. In a Cochrane review and meta-analysis of 39 RCTs involving 4992 individuals with follow-up as long as 14 years, colchicine was found to have no effect on all-cause mortality; however, a significant reduction in the risk of MI was demonstrated.<sup>13</sup> Furthermore, in Tardif *et al.*<sup>14</sup> double-blinded RCT, a total of 4745 cases with a history of MI within one month were randomly assigned to receive colchicine 0.5 mg daily or placebo. Data analysis revealed that death from atherosclerotic cardiovascular diseases was significantly lower in the colchicine group (5.5%) than those who received placebo (7.1%).

Given these facts, the present RCT was performed to assess the potential effects of colchicine on preventing myocardial injury in individuals undergoing elective PCI.

## Methods

### Study design and setting

This study was a pilot, randomized, single-blinded clinical trial that was carried out in the Shahid Madani Heart Center, one of the largest referral hospitals for cardiovascular in Iran, from March 2019 to December 2019. Our study was the first RCT evaluated the effects of colchicine for the prevention of myocardial injury following elective PCI in patients with ischemic heart disease.

### Study population

All the consented individuals with ischemic heart disease (IHD), with ages from 18 to 80 years old who were candidates for elective PCI (balloon angioplasty and stent insertion) were enrolled.

Patients with an elevated cardiac biomarker (cTnI > 1 ng/mL), a history of MI or CABG in last three months, unsuccessful PCI, renal dysfunction (GFR <30 ml/min), liver dysfunction (Child-Pugh classes B and C), severe infection, cardiogenic shock, cancer, uncontrolled autoimmune diseases, or any contraindications to the prescribed drugs were excluded. Besides, pregnant or breastfeeding women and patients who required to discontinue the trial were ruled out.

### Study process

Totally, 102 individuals were randomly divided into intervention (n=51) and control groups (n=51) using online Graphpad prism randomization (<https://www.graphpad.com/quickcalcs/randMenu/>) by a person who was not involved in the study. Individuals were admitted to the hospital just one day before undergoing elective PCI. Patients in the intervention group received a total dose of 2 mg colchicine as follows: 1 mg oral colchicine (one tablet of colchicine generic form) was administered one day before

the procedure (12 to 18 hours before depending on the time of performing PCI), 0.5 mg just 30-60 min before, and then 0.5 mg 12 hours after PCI, respectively. In the control group, elective PCI was run out with no colchicine administration.

Patients in the intervention and control groups received weight-adjusted heparin (activated clotting time of 250–350 seconds), and dual antiplatelet (aspirin 325 mg and clopidogrel 300 mg). Besides, they were given 100±20 mL contrast agent visipaque™ (iodixanol) during PCI procedure. All PCIs were performed by interventional cardiologists who were blinded to the allocation of participants.

Demographic and clinical data of individuals, such as sex, age, body mass index, serum creatinine, fasting blood sugar, hemoglobin, ejection fraction, past medical history, positive family history for cardiovascular diseases, drug history, and the number of used stents were recorded in data collecting forms.

### Blood sampling

Blood samples were collected at the hospital lab from all patients to measure cTnI values at the baseline, 8, and 24 hours after PCI. Detection limits for measuring cTnI level in blood was 0.1 ng/ml.

### Outcomes

Our primary outcome measure was mean cTnI change from baseline between the intervention and control groups at 8- and 24- hours after PCI.

### Statistical analysis

Data analysis was carried out in IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). First, the Kolmogorov-Smirnov test was conducted to evaluate whether sample data is normally distributed. For assessing between and within-subject interactions, repeated measures analysis of variance (ANOVA) or Friedman and Kruskal-Wallis tests were performed. Bonferroni adjustment was conducted for pairwise comparisons. Mann-Whitney and/or independent t-test were used to compare means between the groups. Chi-square and/or Fisher's exact tests were applied to sets of categorical data. Continuous data were presented as mean ± standard deviation (SD). The p-values < 0.05 were considered statistically significant.

## Results

Totally, 110 patients were evaluated for eligibility. Among them, eight patients were excluded because of baseline elevation of cTnI before PCI (n=4) and lack of the indication of stent insertion (n=4); therefore, 102 patients were randomized equally to the intervention (n=51) and control (n=51) groups (Figure 1).

No statistically significant differences were observed regarding demographic and clinical data between the study groups (all P > 0.05) (Table 1). Most of the patients

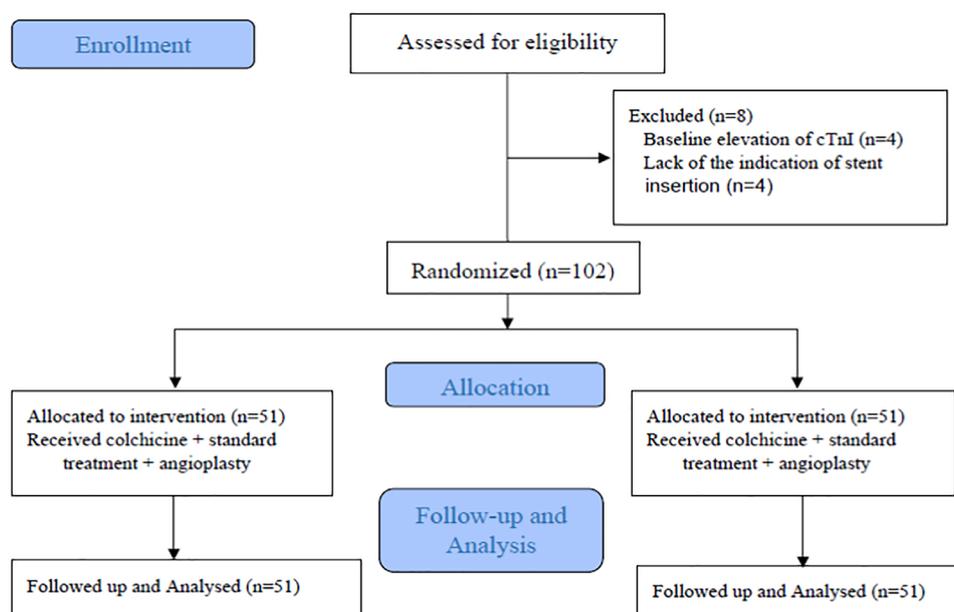


Figure 1. CONSORT Flow diagram of the study.

were male (64.8% in the intervention and 55% in the control groups). The participants' age was  $60.8 \pm 10.2$  in the intervention and  $58.3 \pm 9.0$  in the control groups. The stented target vessels of the patients are shown in Table 2. Performing within-group analysis indicated that there was no significant difference in the intervention group regarding the cTnI levels between baseline with 8 hours ( $P=0.589$ ), baseline with 24 hours ( $P=0.933$ ), and 8 hours with and 24 hours ( $P=0.916$ ). Similarly, no significant difference was observed in the cTnI level of patients in the control group between baseline with 8 hours ( $P=0.992$ ), baseline with 24 hours ( $P=1.00$ ), and 8 hours with and 24 hours

( $P=0.897$ ). Besides, performing between-group analysis showed that the cTnI level did not differ between the intervention and control groups ( $P=0.839$ ). No statistically significant differences were noted in cTnI level 8 hours ( $P=0.729$ ) and 24 hours ( $P=0.398$ ) after performing PCI. Besides, no significant changes were observed in the mean differences of cTnI in the intervention and control groups at baseline and 8 hours ( $P=0.190$ ), at baseline and 24 hours ( $P=0.780$ ), and 8 and 24 hours after PCI ( $P=0.680$ ) (Table 3 and Figure 2). No obvious adverse drug reactions were seen at the tested doses of colchicine.

Table 1. Demographic and clinical data of the study groups.

Demographic/Clinical Data	Intervention (n=51)	Control (n= 51)	P
Age (years), mean $\pm$ SD	60.8 $\pm$ 10.2	58.3 $\pm$ 9.0	0.196
Sex, male, n (%)	33 (64.8)	28 (55.0)	0.313
body mass index; (kg/m <sup>2</sup> ), mean $\pm$ SD	27.7 $\pm$ 3.8	28.7 $\pm$ 5.2	0.287
Serum creatinine (mg/dL), mean $\pm$ SD	1.1 $\pm$ 0.2	1.0 $\pm$ 0.17	0.057
Blood urea nitrogen (mg/dL), mean $\pm$ SD	16.8 $\pm$ 4.7	15.1 $\pm$ 4.0	0.057
Hemoglobin (g/dL), mean $\pm$ SD	14.1 $\pm$ 1.8	13.9 $\pm$ 1.3	0.703
Fasting blood sugar (mg/dL), mean $\pm$ SD	110.6 $\pm$ 31.5	104.6 $\pm$ 29.8	0.310
Ejection fraction (%), mean $\pm$ SD	47.4 $\pm$ 8.6	48.4 $\pm$ 5.5	0.496
Diabetes mellitus, n (%)	14 (27.5)	19 (37.3)	0.290
Hypertension, n (%)	36 (65.5)	36 (65.5)	1.00
Positive family history of cardiovascular diseases, n (%)	34 (66.7)	37 (72.5)	0.518
ACEIs/ARBs history, n (%)	30 (58.8)	34 (66.7)	0.413
Beta blockers history, n (%)	26 (50.9)	26 (50.9)	1.00
Hydrochlorothiazide history, n (%)	15 (29.4)	13 (25.4)	0.657
Calcium channel blockers history, n (%)	15 (29.4)	9 (17.6)	0.178
Nitrate history, n (%)	14 (27.5)	23 (45)	0.064
Anti-lipid drug history, n (%)	35 (68.6)	31 (60.7)	0.407
Anti-diabetic drug history, n (%)	14 (27.5)	19 (37.2)	0.290
Aspirin history, n (%)	38 (74.5)	31 (60.7)	0.138
Other drug history, n (%)	19 (37.2)	18 (35.2)	0.837

SD, standard deviation; ACEI, Angiotensin-converting-enzyme inhibitors; ARB, Angiotensin II receptor blockers

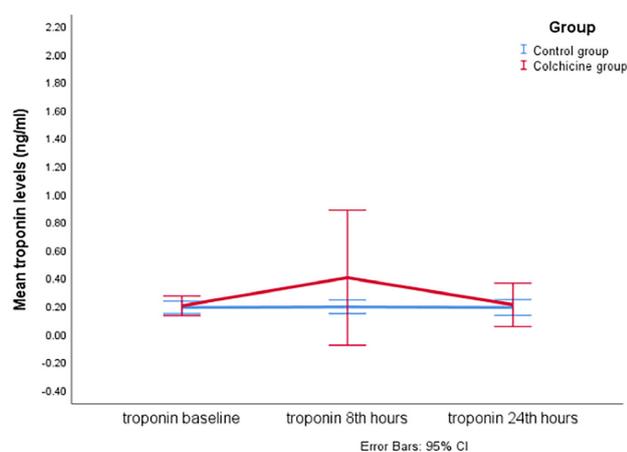
**Table 2.** Target vessel(s), size, and number of stents in the study groups.

Target Vessel(s)	Intervention (n = 51)	Control (n = 51)	P
LAD, n (%)	33 (64.7)	25 (49)	0.110
RCA, n (%)	15 (29.4)	17 (33.3)	0.670
LCX, n (%)	9 (17.6)	7 (13.7)	0.586
OM, n (%)	6 (11.8)	7 (13.7)	0.767
RAMUS, n (%)	0 (0)	2 (3.9)	0.495
PDA, n (%)	2 (3.9)	4 (7.8)	0.675
DIAG, n (%)	3 (5.9)	2 (3.2)	1.00
LAD + OM, n (%)	1 (2)	2 (3.9)	1.00
LAD + RCA, n (%)	6 (11.8)	2 (3.9)	0.269
LAD + DIAG, n (%)	2 (3.9)	1 (2)	1.00
RCA + OM, n (%)	0 (0)	2 (3.9)	0.495
Other positions, n (%)	4 (7.8)	4 (7.8)	1.00
Number of stents per patient, mean ± SD	1.33 ± 0.58	1.54 ± 0.72	0.104
Total stents diameter (mm), mean ± SD	2.95 ± 0.39	2.81 ± 0.44	0.122
Total stents length (mm), mean ± SD	19.38 ± 5.39	20.90 ± 6.53	0.199

LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery; OM, obtuse marginal artery; PDA, posterior descending artery; DIAG, diagonal artery; RAMUS, ramus artery; SD, standard deviation.

**Table 3.** Mean troponin I level at baseline and 8 and 24 hours after PCI in the study groups.

Troponin-I Level	Intervention (n = 51)	Control (n = 51)	P
Baseline	0.188 ± 0.208	0.188 ± 0.158	0.839
At 8 hours	0.364 ± 1.405	0.192 ± 0.171	0.729
At 24 hours	0.204 ± 0.472	0.188 ± 0.196	0.398
Mean difference of baseline to 8 hours	0.176 ± 1.197	0.004 ± 0.013	0.190
Mean difference of baseline to 24 hours	0.016 ± 0.264	0.0 ± 0.038	0.780
Mean difference of 8 to 24 hours	0.160 ± 0.933	0.004 ± 0.025	0.680

**Figure 2.** The mean troponin I level during the study.

## Discussion

The present randomized, single-blinded clinical trial did not show the beneficial effects of colchicine in preventing PMI in the setting of elective PCI, and no significant difference was observed in the within-group analysis, between-groups, and mean differences analyses.

### Colchicine's evidence in cardiovascular diseases

Colchicine has been used widely in patients with calcium pyrophosphate crystal arthritis, gout, Behcet's syndrome, familial Mediterranean fever, sweet syndrome, vasculitis, cutaneous small vessel (idiopathic), pericarditis, and postpericardiotomy syndrome. Besides, colchicine's ability

to modify cardiovascular diseases induced inflammatory responses has been the subject of the recent research area.<sup>15</sup> The decades-old drug colchicine inhibits  $\beta$ -tubulin polymerization into microtubules. It inhibits activation, degranulation, and migration of neutrophils. Colchicine also interferes with the intracellular assembly of the inflammasome complex in monocytes and neutrophils, and mediates activation of Interleukin 1 beta. Besides, it could inhibit chemotaxis, platelet aggregation, muscle cell proliferation, and collagen formation. Based on experimental animal models, the medication could prevent or decrease the formation of the atherosclerotic plaque.<sup>15-19</sup> It has been shown that colchicine inhibits endothelial function and ameliorating inflammation in rats. According to an animal study, adding colchicine into atorvastatin was associated with a further increase in nitric oxide (NO) production as well as a decrease in (lipoprotein-associated phospholipase A2) Lp-PLA2 and CRP levels.<sup>20</sup>

Numerous RCTs have indicated the beneficial effects of colchicine in decreasing inflammatory markers in individuals with heart failure and atrial fibrillation.<sup>21-23</sup> Furthermore, in Nidorf *et al.*<sup>24</sup> RCT, a total of 532 individuals with clinically stable coronary disease were randomly assigned to two groups to receive either colchicine 0.5 mg/day or not. They were followed up for approximately three years. Data analysis revealed that co-administration of colchicine with statins and other standard secondary prevention therapies is correlated with a significant decrease in cardiovascular events (out-

of-hospital cardiac arrest, or non-cardioembolic ischemic stroke, ACS) (Hazard Ratio (HR): 0.33; 95% confidence interval [CI] 0.18 to 0.59;  $p < 0.001$ ).<sup>24</sup>

Furthermore, in a meta-analysis of five RCTs involving 1301 patients with cardiovascular disease, administration of colchicine led to decrease in composite cardiovascular outcomes by approximately 60% (Risk Ratio (RR) 0.44, 95% CI 0.28-0.69,  $p = 0.0004$ ;  $I^2 = 0\%$ ).<sup>25</sup>

#### Colchicine timing and dosing in cardiovascular diseases

In Tabbalat *et al.*<sup>26</sup> multi-center RCT, 360 cases who planned to undergo elective cardiac surgery were randomly assigned to two groups to receive either colchicine or not. In the colchicine group, 179 individuals received colchicine 2 mg, 12 to 24 hours before surgery followed by 1 mg, 4 hours before or immediately after surgery, and then 0.5 mg BID until hospital discharge. Data analysis revealed that colchicine had no statically significant decrease in the incidence of early postoperative atrial fibrillation (17.5% vs. 14.5%; relative risk reduction 29.3%;  $P = 0.14$ ).

In Deftereos *et al.*<sup>27</sup> randomized placebo-controlled trial, 151 individuals with a diagnosis of ST-segment-elevation MI were randomized to receive colchicine with a loading dose of 2 mg followed by 0.5 mg twice daily for five days, or placebo. The area under the creatine kinase MB (CK-MB) fraction curve was significantly lower in the colchicine group than the control group (3144 ng. h/ml (interquartile range, 1754–6940) vs. 6184 (interquartile range, 4456–6980);  $P < 0.001$ ).

Another RCT was carried out to evaluate colchicine perioperative course on myocardial injury biomarker levels within 48 hours after surgery in 59 patients who underwent CABG. Patients were randomized to receive colchicine starting 48 hours before CABG followed by .5 mg twice daily for eight days. Data showed that the maximal hsTnT (616 pg/ml vs. 1,613 pg/ml;  $p = 0.002$ ) and CK-MB (44.6 ng/ml vs. 93.0 ng/ml;  $p = 0.002$ ) were significantly lower in the colchicine group than the control group. Similarly, the median AUC for hsTnT (20,363 pg h/ml vs. 40,755 pg h/ml;  $p = 0.002$ ) and CK-MB (1,586 ng h/ml vs. 2,552 ng h/ml;  $p = 0.003$ ) were lower in the patients treated with colchicine compared with those received placebo. Finally, five patients experienced gastrointestinal complications in the colchicine group, and only one patient in the control group ( $p = 0.195$ ).<sup>28</sup>

In agreement with our trial, in a single-site prospective randomized, double-blind study, Shah *et al.*<sup>29</sup> showed that pre-procedural oral administration of 1.8 mg of colchicine within one hour before PCI could not decrease the risk of PMI. In this trial, among 400 patients who underwent PCI, there was no statistically significant regarding PCI-related myocardial injury (57.3% versus 64.2%,  $P = 0.19$ ), composite outcome of target vessel revascularization, death from any cause, and nonfatal MI at 30 days (11.7% versus 12.9%,  $P = 0.82$ ), and outcome of PCI-related MI (2.9% versus 4.7%,  $P = 0.49$ ) between the study groups. Notably, inflammatory biomarkers were not evaluated in

our study; whereas, in the Shah *et al.*<sup>29</sup> trial, colchicine administration attenuated the increase in concentrations of high-sensitivity CRP (11% [–14 to 80] versus 66% [1 to 172],  $P = 0.001$ ) and interleukin-6 (76% [–6 to 898] versus 338% [27 to 1264],  $P = 0.02$ ).

The standard regimens of colchicine for gout flares are 1.2 mg at the first sign of flare, followed by 0.6 mg after one hour. In our RCT, patients were given 1, 0.5, 0.5 mg colchicine 12 to 18 hours, 30-60 min before, and 12 hours after PCI, respectively. Whereas in the Shah trial, the patients received 1 and 0.5 mg of colchicine 1 hour and immediately before the procedure. Importantly, peak plasma concentration is reached following approximately half to three hours of oral dose administration of colchicine; however, its maximal anti-inflammatory effect occurs over one to two days, reflecting the time required for the medicine to achieve peak concentration in the leucocytes. Besides, the onset of action of colchicine pain relief and anti-inflammatory properties is about 18 to 24 hours. Consequently, it seems that the administration of the drug within one hour before PCI was not rational.<sup>29,30</sup> Notably, in the Giannopoulos *et al.*<sup>28</sup> study with a positive result with colchicine, individuals who underwent CABG received colchicine (two days before CABG) followed by 0.5 mg twice daily for eight days experienced lower cardiac surgery-related myocardial damage compared with placebo. Besides, in Cole *et al.*<sup>31</sup> RCT on 75 patients with NSTEMI ( $n = 44$ ) or stable angina ( $n = 31$ ), administration of colchicine (1 mg followed by 0.5 mg 1 hour later) 6 to 24 hours before the PCI could significantly reduce both major (31% vs. 54%;  $P = 0.04$ ) and minor (58% vs. 85%;  $P = 0.01$ ) PMI. Moreover, absolute change in high sensitive cTnI was significantly higher in the placebo group: compared with the colchicine group (166 (53–530) vs. 59 (1–221);  $P = 0.02$ ). These reports have highlighted the time of colchicine administration in preventing PMI in the setting of elective PCI.

#### Limitations

The result of the RCT should be interpreted with caution because of the following limitations. First of all, we did not measure the level of CK-MB and inflammatory biomarkers because of the cost limitation of the trial. However, it is important to mention that the definition of myocardial injury following PCI is according to the levels of cardiac troponins.<sup>32</sup> Second, as colchicine metabolism is influenced by genetic variations, genetic data were not collected to assess predisposition to colchicine resistance; however, the RCT nature of the study would neutralize this effect. Third, the present study has a relatively small sample size; consequently, the effect of colchicine on PMI may not be seen. Notably, in our study, no significant difference was observed in the within-group analysis, between-groups, and mean differences analyses. Fourth, certain timing and dosing of colchicine in the prevention of myocardial injury following PCI have not yet been identified and need to be elucidated by ongoing trials. Of note, in the Shah

*et al.*<sup>29</sup> trial in the setting of PCI, the colchicine regimen does not seem to be logical regarding its pharmacokinetic properties. Fifth, due to accessibility problems, we did not use a colchicine placebo to minimize the potential treatment bias.

### Conclusion

The present study showed that the colchicine starting 12 to 18 hours before scheduled PCI could not reduce myocardial injury following elective PCI. Performing well-designed RCTs with adequate sample size is recommended to evaluate the study hypothesis.

### Ethical Issues

The study protocol was approved by the Research Ethics Committee of Tabriz University of Medical Sciences (ID: IR.TBZMED.REC.1397.432) and then registered at [www.irct.ir](http://www.irct.ir) under the ID: IRCT20111206008307N33. All patients were informed about how the study would be carried out, and written informed consent was obtained from them before the study. They were free to withdraw from the study at any time. The patients' information will remain confidential to the researchers.

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### Data Sharing

Applicants can obtain data by contacting the corresponding author.

### Author Contributions

NA: Supervised the study, Conducted the PCIs, Wrote and edited the article, SK: Wrote, edited revised the manuscript, SJ: Conducted the PCIs, Collected the samples, Ordered the medication, edited the manuscript, MM: Wrote the proposal, Collected the samples, wrote and edited the manuscript, TEM: Conceptualized, designed, supervised the study, wrote and edited the manuscript.

### Conflict of Interest

The authors report no conflicts of interest.

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