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Effect of Vitamin D in the Prevention of Myocardial Injury Following Elective Percutaneous Coronary Intervention: A Pilot Randomized Clinical Trial

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Abstract

Myocardial injury following elective percutaneous coronary intervention (PCI) occurs in about one-third of patients and is associated with mortality. Platelet aggregation, thrombosis formation, and inflammation are the main causes of cardiac injury during PCI. Vitamin D plays a key role in the cardiovascular system by exerting antiplatelet, anticoagulant, and anti-inflammatory properties. There is no published study that investigated the effect of vitamin D in the prevention of cardiac injury following elective PCI. In a randomized clinical trial, 99 patients admitted for elective PCI were randomized into vitamin D (n = 52) and control (n = 47) groups. The intervention group received 300 000 IU vitamin D orally 12 hours before PCI. The cardiac biomarkers were checked at baseline, 8 and 24 hours after PCI. hs-CRP was also measured at baseline and after 24 hours. The increase in CK-MB was documented in 20 patients (42%) in the control group and 18 patients (34.6%) in the intervention group ($P = .417$). Furthermore, the increase in cTnI occurred in 4 patients (8%) and 2 patients (3.3%) in the control and intervention groups, respectively ($P = .419$). No significant changes were noted in the level of cardiac biomarkers. In the vitamin D group, the mean difference in CK-MB between 8 and 24 hours was significantly lower ($P = .048$). The mean difference in hs-CRP was significantly lower in the vitamin D group ($P = .045$). This study could not show a clear effect of vitamin D in the prevention of cardiac injury during elective PCI. Further outcome-based studies are needed to describe the role of vitamin D in the prevention of periprocedural myocardial injury.

Keywords

vitamin D, percutaneous coronary intervention, periprocedural myocardial injury, CK-MB, cTnI, hs-CRP

Percutaneous coronary intervention (PCI) is an important procedure in the management of occlusive coronary artery disease.[1,2] Despite the known safety and minimally invasive nature of the procedure, it may result in cardiac injury in about one-third of patients undergoing elective PCI and influence patients' outcomes.[3–5]

American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines have also focused on periprocedural myocardial injury (PMI) and recommended the check of cardiac biomarkers following PCI for outcome assessment.[6]

Based on the 2012 Joint ESC/ACCF/AHA/WHF Task Force on the third universal definition of myocardial infarction (MI), the rising cardiac biomarkers above the 99th percentile upper limit of normal (ULN) following elective PCI was defined as PCI-related myocardial injury. Furthermore, the raising of cardiac troponins above 5 times the 99th percentile ULN along with ischemic, radiographic, or imaging findings was defined as PCI-related MI or type 4a MI.[6]

Commonly, PMI occurs because of embolization of thrombotic plaque, platelet aggregation, thrombosis formation, coronary artery vasospasm, oxidative stress, and inflammation.[5]

Based on recent data, a low level of vitamin D is associated with increased risk of cardiovascular diseases and mortality.[7–11] It was suggested that vitamin D may be involved in the pathogenesis of cardiovascular disease by exerting anti-inflammatory and antithrombotic

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properties. It may also inhibit the renin-angiotensin-aldosterone system (RAAS), vascular calcification, and progression of the atherosclerosis process.[7–11]

Given the possible mechanisms of PMI and the pivotal role of vitamin D in cardiovascular disease, this study was performed to evaluate the effect of vitamin D in the prevention of myocardial injury in patients undergoing elective PCI.

To the best of our knowledge, there is no published study that investigated the effect of vitamin D in the prevention of cardiac injury following elective PCI.

Methods

Ethics

The study was approved by the institutional review board of the university and was recorded in the World Health Organization clinical trial registry platform (ID: IRCT201402078307N6). All patients completed a written informed consent form before entering the study. The study was done according to the Declaration of Helsinki and later revisions as a statement of ethical principles for medical research involving human subjects.[12]

Study Design and Setting

This is a pilot prospective randomized, single-blind, controlled trial that was conducted in the Shahid Madani Heart Center, the largest referral hospital for cardiovascular disorders in the northwest of Iran from September 2014 to February 2015.

Study Population

All patients aged 18–80 years who signed the consent form and were planned to have elective PCI with balloon angioplasty and stent placement were enrolled in the study.

The exclusion criteria of the study were: patients with cardiac biomarkers elevated above the upper limit of normal before PCI; patients with acute MI or recent history (within 3 months) of MI or coronary artery bypass grafting (CABG) or vitamin D supplementation; patients with unsuccessful PCI; patients with hypercalcemia, nephrolithiasis, sarcoidosis, malabsorption syndrome, severe infection, cancer, renal or hepatic dysfunction, or uncontrolled autoimmune or inflammatory diseases; breastfeeding or pregnant women; patients with the inability to fill out or understand the consent form; those who were unconsented; and those who wanted to discontinue the study at any time.

Study Process

All patients who were admitted 1 day before elective PCI and met the inclusion criteria were randomized 1:1 into the vitamin D–treated group (n = 53) and the control group (n = 53) by the systematic randomization method using computer-generated random numbers by an independent person.

The intervention group received a 300 000-IU dose of vitamin D orally (6 softgels, 50 000 IU) 12 hours before PCI (based on the 11-hour time to peak of oral vitamin D in plasma).[13]

We used 300 000 IU vitamin D, the maximum effective dose that significantly increases the level of 25-hydroxy vitamin D with no apparent adverse reaction and toxicity.[14,15]

Both groups received the standard PCI pretreatment protocol of aspirin 325 mg, clopidogrel 300 mg, and weight-adjusted intravenous heparin with a target activated clotting time of 250–350 seconds.[6] All patients in both groups received 100 ± 20 cc of the contrast agent visipaque (iodixanol) during PCI with the standard protocol for prevention of contrast-induced nephropathy including 1200 mg acetyl cysteine twice daily plus normal saline. All PCIs were done according to the standard practice guidelines by certain interventional cardiologists who were blinded to the allocation. All patients were followed up for a 1-month period for the major adverse cardiac effects (MACE) including death, Q-wave MI, target vessel revascularization, and ischemic stroke.

Patients' demographic data including sex, age, weight, height, body mass index, drug history, medical history, laboratory data, and positive family history of cardiovascular disease were recorded in a data-collecting form.

Study Sample Size and Power Calculation

The power of the study was calculated using G-Power (version 3.1.9.2) assuming type I error probability $\alpha = 0.05$, n = 99, groups = 2, and 3 times the serial measurements of enzymes. The power (1 - β_{error}) for the CK-MB test with partial $\eta^2 = 0.02$ and estimated effect size (F) = 0.14 was calculated as 86%. Accordingly, the power of troponin-I (cTnI) with partial $\eta^2 = 0.022$ and F = 0.15 was calculated as 91%.

Blood Sampling

The CK-MB and cTnI levels were measured at baseline (before giving vitamin D) and 8 and 24 hours after PCI based on the AHA/ACCF guidelines.[6] The hs-CRP was also measured at baseline and after 24 hours for assessment of inflammation. The detection limits for measuring CK-MB and cTnI levels in blood were 1 U/L and 0.1 ng/mL, respectively.

End-Point Outcomes

The primary outcome included comparison of CK-MB and cTnI levels at baseline and 8 and 24 hours after PCI for assessing PMI as well as comparison of hs-CRP before and after PCI to assess the anti-inflammatory

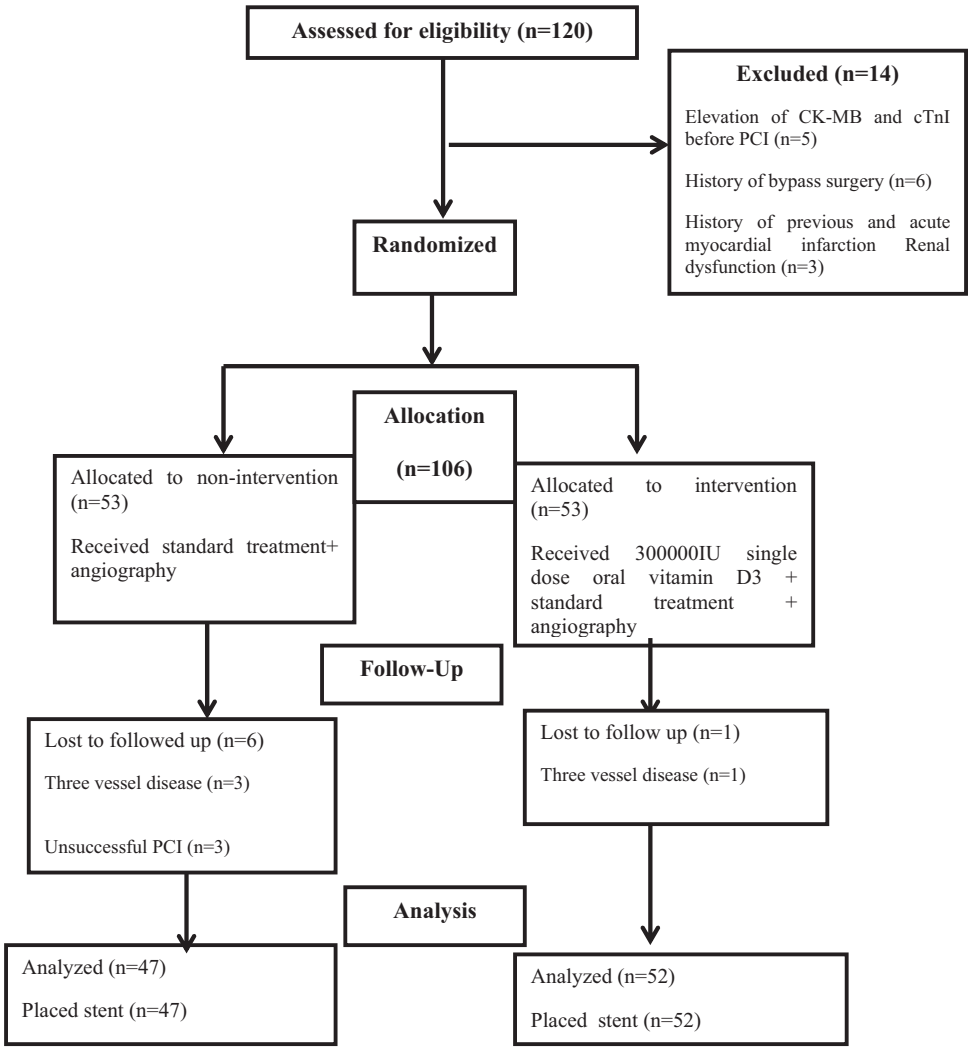

Figure 1. CONSORT flow diagram of the study.

effect of vitamin D. The secondary outcome was the incidence of MACE (death, Q wave MI, target vessel revascularization, ischemic stroke) during a 1-month follow-up.

Statistical Analysis

Data were analyzed in SPSS 16.0 (Chicago, Illinois, SPSS Inc., 2007). The normality distribution of data was assessed by the Kolmogorov–Smirnov test. Repeated-measures analysis of variance was performed to assess the effect of groups and times of sampling on cardiac biomarkers. Bonferroni adjustment was conducted for pairwise comparisons. For more details, the paired *t* test and/or the Wilcoxon test were used to compare the means in the same groups. Mann–Whitney and independent-sample *t* tests were used to compare means between the different groups. Chi-square and Fisher's exact tests were applied to perform the frequency analysis. Continuous data were shown as mean ± standard deviation (SD). $P < .05$ was assumed to be statistically significant.

Results

A total number of 120 patients were assessed for eligibility, of whom 14 were excluded from the study because of elevation of cardiac biomarkers before PCI (n = 5), recent 3-month history of CABG or MI (n = 6), and renal dysfunction (n = 3). Next, 106 patients were allocated 1:1 to the intervention and control groups. After PCI, 6 patients in the control group and 1 patient in the intervention group were excluded, and finally, 99 patients (vitamin D group = 52, control group = 47) were entered in the analysis (Figure 1).

Mean ± SD for age of patients was 58.9 ± 8 and 61.5 ± 8 years in the control and intervention groups, respectively. Demographic and clinical data of the study groups are presented in Table 1. The stented target vessels are presented in Table 2.

Table 1. Demographic and Clinical Data of the Study Groups

Demographic/Clinical Data	Intervention (n = 52)	Control (n = 47)	*P*
Age (years), mean ± SD	61.5 ± 8	58.9 ± 8	.104
Sex, male, n (%)	20 (38.5)	25 (53.2)	.142
Weight (kg), mean ± SD	75.3 ± 12.7	72.8 ± 14.4	.471
Height (cm), mean ± SD	164.8 ± 10.7	163.5 ± 10.3	.825
BMI (kg/m^2), mean ± SD	27.8 ± 3.7	27.2 ± 4.2	.579
Serum creatinine (mg/dL), mean ± SD	1.1 ± 0.1	1 ± 0.1	.005
Blood urea nitrogen (mg/dL), mean ± SD	17.8 ± 4.5	17 ± 3.8	.359
Fasting blood sugar (mg/dL), mean ± SD	141.3 ± 22.6	150.3 ± 95.4	.797
Hemoglobin (g/dL), mean ± SD	13.6 ± 1.1	13.3 ± 1	.323
Ejection fraction (%), mean ± SD	47.1 ± 10.7	49.5 ± 7.9	.498
Smoking, n (%)	21 (40.4)	14 (29.8)	.271
Diabetes mellitus, n (%)	26 (50)	21 (44.7)	.597
Hypertension, n (%)	24 (46.2)	25 (53.2)	.484
Dyslipidemia, n (%)	17 (32.7)	22 (46.8)	.151
History of other disease, n (%)	8 (15.4)	6 (12.7)	.709
Positive family history of cardiovascular diseases, n (%)	22 (42.3)	20 (42.6)	.980
Previous bypass surgery, n (%)	1 (1.9)	2 (4.2)	.929
Previous coronary intervention, n (%)	5 (9.6)	1 (1.9)	.225
Cardiovascular drug history, n (%)	31 (59.6)	28 (59.5)	.997
Antidiabetic drug history, n (%)	26 (50)	21 (44.7)	.597
Antilipid drug, n (%)	17 (32.7)	22 (46.8)	.151
Other drug history, n (%)	7 (13.4)	5 (10.6)	.667

BMI, body mass index; SD, standard deviation.

Table 2. Target Vessel(s), Size, and Number of Stents in the Study Groups

Target Vessel(s), Size, and Number of Stents	Intervention (n = 52)	Control (n = 47)	*P*
LAD, n (%)	14 (26.9)	12 (25.5)	.875
LCX, n (%)	10 (19.2)	9 (19.1)	.992
RCA, n (%)	8 (15.4)	7 (14.9)	.946
OM, n (%)	2 (3.8)	4 (8.5)	.419
LAD + RCA, n (%)	3 (5.7)	3 (6.3)	1.00
LAD + LCX, n (%)	4 (7.7)	2 (4.2)	.680
RCA + LCX, n (%)	2 (3.8)	1 (2.1)	1.00
LAD + OM, n (%)	1 (1.9)	1 (2.1)	1.00
LCX + OM, n (%)	2 (8)	1 (2.1)	1.00
RCA + LAD + LCX, n (%)	2 (3.8)	4 (8.5)	.419
LAD + RCA + PDA, n (%)	1 (1.9)	1 (2.1)	1.00
Other positions, n (%)	3 (5.7)	2 (4.2)	1.00
Bare-metal stent, n (%)	9 (12.7)	8 (11.9)	.895
Drug-eluting stent, n (%)	62 (87.3)	59 (88.1)	.895
Deployed stents, mean ± SD	1.3 ± 0.6	1.4 ± 0.7	.641
Total number of stents, n	71	67	.733

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

The rise of CK-MB was documented in 20 patients (42%) in the control group and 18 patients (34.6%) in the vitamin D group ($P = .417$); in addition, an increase of cTnI occurred in 4 patients (8%) and 2 patients (3.3%) in the control and vitamin D groups, respectively ($P = .419$).

At baseline, CK-MB level did not differ between the groups ($P = .074$). No significant differences were observed in CK-MB level 8 hours ($P = .103$) and 24 hours ($P = .509$) after PCI. Also, no significant changes were noted in the mean differences of CK-MB in both groups at baseline and 8 hours ($P = .075$), at baseline and 24 hours ($P = .194$), and 8 and 24 hours after PCI ($P = .424$); see Table 3 and Figure 2.

cTnI level was not statistically different between baseline ($P = .103$) and 8 hours ($P = .187$) and 24 hours ($P = .122$) after PCI in both groups; in addition, the mean differences in cTnI at baseline and 8 hours ($P = .251$) and baseline and 24 hours after PCI ($P = .153$) were not significant in both groups. The mean differences in cTnI at 8 and 24 hours after PCI were significant between the groups ($P = .048$); see Table 4 and Figure 3).

Table 3. Mean CK-MB Level at Baseline and 8 and 24 Hous After PCI in the Study Groups

CK-MB Level	Intervention (n = 52)	Control (n = 47)	*P*
Baseline	21.8 ± 5	20 ± 5.4	.074
At 8 hours	27 ± 9.3	29.7 ± 16.8	.103
At 24 hours	29.6 ± 11.6	31.5 ± 18.2	.509
Mean difference of baseline to 8 hours	−5.2 ± 8.9	−9.7 ± 17.8	.075
Mean difference of baseline to 24 hours	−7.8 ± 11.4	−11.5 ± 18	.194
Mean difference of 8 to 24 hours	−2.5 ± 6.1	−1.7 ± 4.3	.424

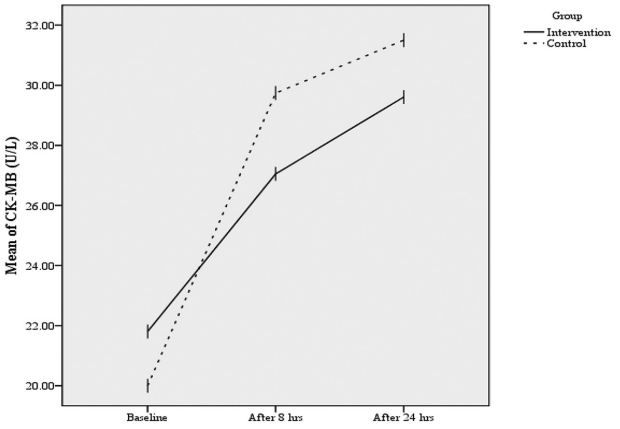

Figure 2. Changes in CK-MB after PCI.

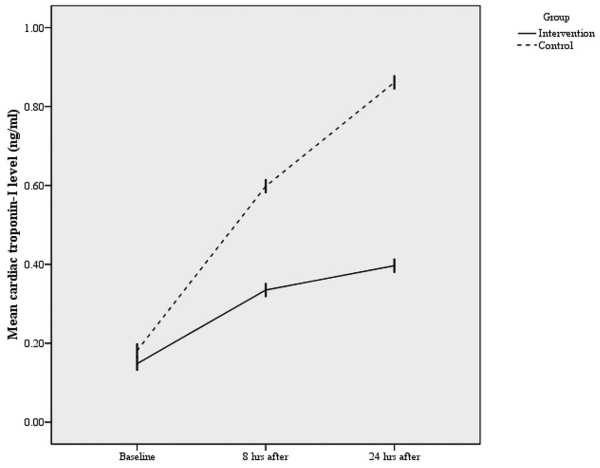

Figure 3. Changes in troponin I after PCI.

The baseline hs-CRP level in both groups was not statistically significant ($P = .806$). Also, no significant difference was observed in hs-CRP levels 24 hours after PCI in both groups ($P = .499$). The mean differences in hs-CRP at baseline and 24 hours after PCI was significant between the groups ($P = .045$; Table 5). No significant case of MACE was observed during the 1-month follow-up.

Discussion

This randomized, controlled trial was the first study that evaluated the effect of vitamin D in the prevention of cardiac injury in patients undergoing elective PCI and balloon angioplasty and stenting. The results showed a nonsignificant effect of vitamin D on cardiac biomarkers; however, the mean difference in CK-MB between 8 and 24 hours and mean difference in hs-CRP were significantly in favor of the vitamin D group.

Myocardial Injury Following PCI: Mechanisms, Incidence, and Clinical Significance

As mentioned above, embolization of thrombotic plaque, platelet aggregation, thrombosis formation, coronary artery vasospasm, oxidative stress, and inflammation during PCI are the main causes of myocardial injury during PCI, which is detected by rising cardiac biomarkers above their upper limit of normal, reported in about one-third of patients.[5,6,16,17]

The clinical significance of elevation of cardiac biomarkers following PCI has been described by large studies.[16,17] A meta-analysis of 11 randomized, control trials (RCTs) containing 23 230 patients showed that 1- to 3, 3- to 5, and >5-fold increases in CK-MB level

Table 4. Mean Troponin I Level at Baseline and 8 and 24 Hours After PCI in the Study Groups

Troponin-I Level	Intervention (n = 52)	Control (n = 47)	*P*
Baseline	0.14 ± 0.1	0.18 ± 0.9	.103
At 8 hours	0.33 ± 0.4	0.59 ± 1.3	.187
At 24 hours	0.39 ± 0.6	0.86 ± 1.9	.122
Mean difference of baseline to 8 hours	− 0.18 ± 0.4	− 0.4 ± 1.3	.251
Mean difference of baseline to 24 hours	− 0.24 ± 0.6	− 0.66 ± 1.9	.153
Mean difference of 8 to 24 hours	− 0.06 ± 0.2	− 0.25 ± 0.6	.048

Table 5. Mean Hs-CRP Level at Baseline and 24 Hours After PCI in the Study Groups

hs-CRP Level	Intervention (n = 52)	Control (n = 47)	*P*
Baseline	3.6 ± 1.8	3.9 ± 2.4	.806
At 24 hours	5.9 ± 2.5	6.8 ± 3.7	.499
Mean difference of baseline to 24 hours	−2.1 ± 2.4	−3 ± 1.8	.045

following elective PCI were correlated with 1.5, 1.8, and 3.1-fold increases in the risk of mortality.[16] Another meta-analysis of 20 RCTs with 15 581 patients showed a significant link between the elevation of cardiac troponins and rate of mortality following PCI (4.4 vs 3.3%, $P = .001$; OR, 1.35).[17]

Time and Dosing of Vitamin D for Prevention of PMI

Based on data, several mechanisms have been suggested for potential benefits of vitamin D in the cardiovascular system.[7–11] Vitamin D exerts its antithrombotic effect mainly by upregulation of the anticoagulant factor thrombomodulin and downregulation of tissue factor and inhibition of inflammatory cytokines such as tumor necrosis factor α and interleukin 6. Vitamin D also inhibits the RAAS and suppresses rennin production and nuclear factor kappa-B, which could result in vasodilatation and reduced blood pressure, vascular calcification, and an atherosclerosis process.[7–11]

Recently, the effect of large single doses of oral vitamin D on blood 25-hydroxy vitamin D_3 level has been reviewed by Kearns et al.[14] Based on this review, oral doses of vitamin D_2 and D_3 (100 000 to 600 000 IU) significantly increased serum 25-hydroxy vitamin D concentrations from baseline. The greatest increases have been achieved 1 to 30 days after supplementation. They concluded that single doses ≥ 300 000 IU of vitamin D_3 are the most effective at improving vitamin D status and suppressing parathyroid hormone (PTH) concentrations for up to 3 months. They recommended that vitamin D doses > 500 000 IU should be used with caution to reduce adverse events.[14] Furthermore, 300 000 IU of vitamin D_3 is a safe physiologic dose with no adverse reaction regardless of plasma level of vitamin D.[15]

Comparison With Other Trials

Cardioprotection for the prevention of cardiac injury plays an important role in the process of PCI; several large trials have evaluated the effect of numerous potential medications for the prevention of cardiac injury following elective PCI. For example, the cardioprotective role of atorvastatin following PCI was shown in the ARMYDA and NAPLES trials.[18,19] Moreover, the meta-analysis of 9 trials including 4751 patients showed a significantly lower rate of PMI in statin-treated group (9% vs 17.5%).[20] In another randomized trial, a 50-mg intracoronary bolus of adenosine before elective PCI among 62 patients showed a lower rate of PMI (13 vs 39%; OR, 0.23; 95%CI, 0.05–0.95; $P = .020$).[21]

Intracoronary trial of 15 μg/kg propranolol following elective PCI in 150 patients showed a lower rate of CK-MB (17% versus 36%; $P = .01$) and troponin-T elevation (13% versus 33%; $P = .005$) in the propranolol group.[22] Pelliccia et al in a pilot randomized trial among 70 patients who underwent elective PCI showed that 1000 mg ranolazine twice daily for 7 days before procedure could reduce both CK-MB (23% vs 40%, $P = .010$) and cTnI elevation (31% vs 48%, $P = .011$).[23]

Moreover, in 1 randomized trial, infusion of 3 g of vitamin C within 6 hours before elective PCI significantly reduced PMI in the vitamin C group (CK-MB, 4.2% versus 8.6%; $P = .035$; cTnI, 10.9% versus 18.4%; $P = .016$).[24]

Recently in 2 randomized trials, we evaluated the effect of 1200 mg pentoxifylline and 300 mg coenzyme Q10 for the prevention of myocardial injury following elective PCI.[25,26] In the first trial, a loading dose of 1200 mg pentoxifylline before elective PCI in 85 patients could not lead to a significant result.[25] The second trial among 100 patients showed that 300 mg coenzyme Q10 12 hours before elective PCI could not reduce PMI. However, it significantly decreased hs-CRP.[26]

Study Limitations and Strengths

The results of the present study should be interpreted with caution because the present study includes some limitations. First, we had cost limitations to measure the level of 25-hydroxy vitamin D and PTH at baseline and after intervention. However, based on Kearns et al's review, a single large dose of vitamin D3 ≥ 300 000 IU could significantly increase the level of 25-hydroxy vitamin D and suppress PTH after 1 to 30 days of supplementation.[16] Therefore, we used 300 000 IU of vitamin D to obtain the maximum effect of vitamin D. Second, we could not extend the time of vitamin D supplementation before the procedure. Of note, based on time to peak oral vitamin D in plasma (11 hours),[13] we tried to administer vitamin D 12 hours before the procedure to obtain the maximum levels of vitamin D during PCI to protect the heart from injury. However, correction of vitamin D levels to 30 ng/mL and greater before the procedure may show a positive result.

Third, some variables such as race, genetic, geographical, and seasonal conditions, and different baseline levels of vitamin D may influence the response to vitamin D supplementation.[7–10] In our study all participants had the same ethnic and geographical origin. Furthermore, based on our previous studies, in our center the rate of vitamin D deficiency was reported as about 60%–65%. Therefore, we can assume a homogeneous level of vitamin D in our population.[27–31]

Fourth, despite the excellent calculated power of the study (86% for CK-MB and 91% for cTnI), the sample size of the study may not have been enough to show the exact effect of vitamin D for the prevention of myocardial injury following PCI. Nevertheless, as mentioned above, our study had the nature of a pilot, which was conducted for first time; therefore, this sample size (n = 99) was acceptable for a novel pilot study. Fifth, given the cost and time limitations, the follow-up period in our study was relatively short. Application of a longer follow-up period might show an accurate outcome.

Sixth, the obtained *P* values for the mean difference of hs-CRP and CK-MB between 8 and 24 hours were borderline statistically significant ($P = .048$ for CK-MB and $P = .045$ for hs-CRP); importantly, the clinical significance of these findings should be confirmed by further outcome-based studies. Last, because of accessibility problems, we could not use placebo softgels of vitamin D to minimize the potential treatment bias. Therefore, double-blind, placebo-controlled studies are recommended for future studies.

The strengths of the study should also be noted. First, based on a key role of vitamin D in cardiovascular disease, the current study is the first clinical randomized trial that investigated the effect of vitamin D in the prevention of cardiac injury following elective PCI. The significant lower mean differences of CK-MB between 8 and 24 hours and hs-CRP in the vitamin D group may be the positive findings of the study that might amplify the role of vitamin D in the prevention of myocardial injury. Future studies can investigate the effect of vitamin D in the protection of the heart from injury.

Future Recommendations

Based on the results of the present study, larger outcome-based, double-blind, placebo-controlled trials with a longer duration of vitamin D administration to correct the level of vitamin D above 30 ng/mL are recommended to demonstrate a clear effect of vitamin D supplementation in the prevention of cardiac injury following elective PCI. Of note, given the high prevalence rate of vitamin D deficiency in the community and its important role in the pathophysiology of cardiovascular disease, the supplementation of vitamin D in vitamin D–deficient people can be reasonable regardless of the results of future studies.

Conclusion

Our study could not show a clear effect of vitamin D in the prevention of cardiac injury during elective PCI. Further outcome-based studies are needed to describe the role of vitamin D in the prevention of PMI.

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Declaration of Conflicting Interests

The authors declare that they do not have any conflicts of interest about this work.

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References

1. Moschovitis A, Cook S, Meier B. Percutaneous coronary interventions in Europe in 2006. *EuroIntervention.* 2010;6:189–194.
2. Cook S, Walker A, Hugli O, et al. Percutaneous coronary interventions in Europe: prevalence, numerical estimates, and projections based on data up to 2004. *Clin Res Cardiol.* 2007;96:375–382.
3. Popma JJ, Kuntz RE, Baim DS. A decade of improvement in the clinical outcomes of percutaneous coronary intervention for multivessel coronary artery disease. *Circulation.* 2002;106:1592–1594.
4. Bhatt DL, Topol EJ. Does creatine kinase-MB elevation after percutaneous coronary intervention predict outcomes in 2005? Periprocedural cardiac enzyme elevation predicts adverse outcomes. *Circulation.* 2005;112:906–915.
5. Babu GG, Walker JM, Yellon DM, et al. Peri-procedural myocardial injury during percutaneous coronary intervention: an important target for cardioprotection. *Eur Heart J*. 2011;32:23–31.
6. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation.* 2012;126:2020-35.
7. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357:266–281.
8. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation.* 2008;117:503–511.
9. Anderson JL, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, Lappé DL, Muhlestein JB. Intermountain Heart Collaborative (IHC) Study Group. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. *Am J Cardiol*. 2010;106:963–968.
10. McGreevy C, Williams D. New insights about vitamin D and cardiovascular disease: a narrative review. *Ann Intern Med*. 2011;155:820–826.

11. Modarresi-Ghazani F, Hejazi ME, Gharekhani A, Entezari-Maleki T. Role of vitamin D in cardiovascular disease. *Arch Iran Med*. 2016;19(5):359–362.
12. World Medical Association. www.wma.net/en/20activities/10ethics/10helsinki/DoH-Oct2013-JAMA.pdf.
13. Vitamin D (Cholecalciferol): drug information; Post TW, ed. *UpToDate* (version 21.2). Waltham, MA.
14. Kearns MD, Alvarez JA, Tangpricha V. Large, single-dose, oral vitamin D supplementation in adult populations: a systematic review. *Endocr Pract*. 2014 20(4):341–351.
15. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr*. 1999;69(5):842–856.
16. Ioannidis JP, Karvouni E, Katritsis DG. Mortality risk conferred by small elevations of creatine kinase-MB isoenzyme after percutaneous coronary intervention. *J Am Coll Cardiol.* 2003;42:1406–1411.
17. Nienhuis MB, Ottervanger JP, Bilo HJ, et al. Prognostic value of troponin after elective percutaneous coronary intervention: a meta-analysis. *Catheter Cardiovasc Interv.* 2008;71:318–324.
18. Pasceri V, Patti G, Nusca A, et al. Randomized trial of atorvastatin for reduction of myocardial injury during coronary intervention: results from the ARMYDA (Atorvastatin for Reduction of Myocardial Injury during Angioplasty) study. *Circulation.* 2004;110:674–678.
19. Briguori C, Visconti G, Focaccio A, et al. Novel approaches for preventing or limiting events (Naples) II: trial impact of a single high loading dose of atorvastatin on periprocedural myocardial infarction. *J Am Coll Cardiol.* 2009;54:2157–2163.
20. Merla R, Reddy NK, Wang FW, et al. Meta-analysis of published reports on the effect of statin treatment before percutaneous coronary intervention on periprocedural myonecrosis. *Am J Cardiol.* 2007;100:770–776.
21. Lee CH, Low A, Tai BC, et al. Pretreatment with intracoronary adenosine reduces the incidence of myonecrosis after nonurgent percutaneous coronary intervention: a prospective randomized study. *Eur Heart J.* 2007;28:19–25.
22. Wang FW, Osman A, Otero J, et al. Distal myocardial protection during percutaneous coronary intervention with an intracoronary betablocker. *Circulation.* 2003;107:2914–2919.
23. Pelliccia F, Pasceri V, Marazzi G, et al. A pilot randomized study of ranolazine for reduction of myocardial injury during elective percutaneous coronary intervention. *Am Heart J*. 2012;163:1019–1023.
24. Wang ZJ, Hu WK, Liu YY, et al. The effect of intravenous vitamin C infusion on periprocedural myocardial injury for patients undergoing elective percutaneous coronary intervention. *Can J Cardiol.* 2014;30:96–101.
25. Aslanabadi N, Shirzadi HR, Asghari-Soufi H, et al. A pilot randomized trial of pentoxifylline for the reduction of periprocedural myocardial injury in patients undergoing elective percutaneous coronary intervention. *Eur J Clin Pharmacol.* 2015;71:143–149.
26. Aslanabadi N, Safaie N, Asgharzadeh Y, et al. The randomized clinical trial of coenzyme Q10 for the prevention of periprocedural myocardial injury following elective percutaneous coronary intervention. *Cardiovasc Ther*. 2016;34(4):254–260.
27. Hejazi ME, Modarresi-Ghazani F, Hamishehkar H, et al. The effect of treatment of vitamin D deficiency on the level of P-selectin and hs-CRP in patients with thromboembolism: a pilot randomized clinical trial. *J Clin Pharmacol*. 2017;57(1):40–47.
28. Gholami K, Talasaz AH, Entezari-Maleki T, et al. The effect of high-dose vitamin D3 on soluble P-selectin and hs-CRP level in patients with venous thromboembolism: a randomized clinical trial. *Clin Appl Thromb Hemost*. 2016;22(5):483–489.
29. Entezari-Maleki T, Hajhossein Talasaz A, Salarifar M, et al. Plasma vitamin D status and its correlation with risk factors of thrombosis, P-selectin and hs-CRP level in patients with venous thromboembolism; the first study of Iranian population. *Iran J Pharm Res*. 2014;13(1):319–327.
30. Shadvar K, Ramezani F, Sanaie S, et al. Relationship between plasma level of vitamin D and post operative atrial fibrillation in patients undergoing CABG. *Pak J Med Sci*. 2016;32(4):900–904.
31. Safaie N, Rezaee H, Seif Dvati B, Entezari-Maleki T. Vitamin D deficiency predicts the ST elevation type of myocardial infarction in patients with acute coronary syndrome. *Iran J Pharm Res*. 2017 (accepted).