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Original Article

Efficacy of Verapamil Injection into the Saphenous Vein Graft Before Percutaneous Coronary Intervention in Preventing Slow-Flow and No-Reflow

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ABSTRACT

Background: Degenerative plaques in the saphenous vein graft (SVG) are prone to embolization during percutaneous coronary intervention (PCI), resulting in the slow-flow or no-reflow phenomenon and unfavorable PCI outcomes.

Methods: This prospective cohort study was conducted on 63 patients who underwent PCI on the SVG divided into 2 groups. The case group (n=32) received 200 μg of verapamil injection into the SVG before PCI, and the control group (n=31) did not receive verapamil. The primary endpoints comprised slow-flow or no-reflow, the thrombolysis in myocardial infarction (TIMI) flow grade, the TIMI frame count, and the TIMI myocardial perfusion grade after PCI. The secondary endpoints consisted of unstable angina and major adverse cardiac events, defined as a composite of total death, ST-segment or non–ST-segment elevation myocardial infarction, cerebrovascular accident, hospitalization due to heart failure, and revascularization (PCI and coronary artery bypass grafting) during hospitalization and a 3-month follow-up.

Results: The patients who received verapamil injection, compared with the control group, had significantly low rates of slow-flow and no-reflow (4.8% vs 17.5%; *P*=0.01) and favorable TIMI frame counts (46% vs 12%; *P*<0.01), TIMI flow grades (31.7% vs 14.3%; *P*=0.015), and TIMI myocardial perfusion grades (34.9% vs 9.5%; *P*=0.001). There were no differences in the secondary outcomes during both hospital stay and the 3-month follow-up.

Conclusions: Our study demonstrated that verapamil injection into the SVG before PCI significantly decreased the rate of postprocedural slow-flow and no-reflow and conferred favorable TIMI flow grades, TIMI frame counts, and TIMI myocardial perfusion grades.
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KEYWORDS: Percutaneous coronary intervention, Saphenous vein graft, Calcium-channel blocker

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The saphenous vein graft (SVG), which is usually used for coronary artery bypass graft surgery (CABG), has no long-term optimal patency. [1] Approximately, 50% of venous grafts are occluded or disrupted after 10 years. [2] Neo-intimal hyperplasia, thrombosis, and atherosclerosis in the venous graft can affect the durability of the graft, leading to repeated chest pain and myocardial infarction. [3] Aspirin and lipid-lowering agents can improve the midterm patency rate in venous grafts [4]; nonetheless, the long-term effects have yet to be elucidated. [3] Percutaneous coronary intervention (PCI) on venous grafts is associated with worse clinical outcomes than on native vessels, with the undesirable outcomes including higher in-stent restenosis, need for repeat vascularization, myocardial infarction, and mortality. [1]

During PCI on venous grafts, plaque embolization and platelet aggregation may lead to unique and significant procedural problems. [5, 6] Indeed, plaques in the SVG are fragile and large, and they can create technical PCI problems. Since there is no collateral branch, plaque embolization may result in the slow-flow or no-reflow phenomenon, which is the decreased or absence of the antegrade distal flow without occlusion. The background mechanism is not clear; nevertheless, endothelial swelling, neutrophil penetration, and platelet aggregation may cause spasm in the distal microvasculature. [7, 8]

The slow-flow or no-reflow phenomenon occurs in between 10% and 40% of PCI procedures on the SVG. [7-9] Different pharmacological and mechanical strategies have been proposed for the reduction of adverse effects in PCI on the SVG including glycoprotein IIb/IIIa inhibitors, vasodilators, and distal embolization protective devices such as the FilterWire EZ Embolic Protection System. [9] The intracoronary injection of adenosine before elective PCI can reduce postprocedural myocardial infarction. [10, 11] Furthermore, the usefulness of calcium-channel blockers for no-flow improvement has been previously demonstrated in animal models [12, 13] and clinical trials. [14-16]

The VAPOR study revealed that intragraft verapamil injection reduced no-reflow significantly and improved the thrombolysis in myocardial infarction (TIMI) flow. [17] The major limitation of that study, however, was its small sample volume. [22] Two other studies have shown that intragraft verapamil injection lessens the no-reflow phenomenon in PCI on venous grafts. [18, 19] A retrospective study on 163 patients reported that the injection of verapamil plus abciximab before PCI on the SVG, besides direct stenting, in patients without obvious SVG thrombosis significantly lowered the risk of slow-flow and no-reflow. [20] Further investigations on this issue are warranted since similar studies on calcium-channel blockers have either small sample populations or retrospective designs. [21-23] The literature also contains few investigations on the effects of the pre-PCI intragraft injection of verapamil on major adverse cardiac events (MACE), defined as a composite of total death, ST-segment-elevation myocardial infarction (STEMI) or non–STEMI, cerebrovascular accident, hospitalization due to heart failure, and revascularization including PCI and CABG. Since protective devices are used in patients with obvious thrombosis in the SVG or the severely degenerated SVG, it is necessary to determine the effects of intragraft verapamil injection before PCI on the SVG in several conditions.

METHODS

The present prospective cohort study was conducted on 63 patients who underwent PCI on the SVG between January 2019 and December 2019 in the Catheterization Laboratory of Rajaie Cardiovascular Medical and Research Center, affiliated with

Iran University of Medical Sciences. The study population was divided into a case group (n=32), who received a pre-PCI intragraft injection of verapamil, and a control group (n=31), who received no verapamil. All the study participants signed informed consent forms.

Age, sex, diabetes mellitus, hypertension, stroke history, cardiovascular disease history, peripheral vascular disease, heart failure, chronic lung disease, the time elapsed from CABG, the reason for angiography, the SVG location (right coronary artery, obtuse marginal, diagonal, or left anterior descending), the stent size, inflation times, the procedure type (pre-dilation, direct stenting, or post-dilation), the protective device use, glycoprotein IIb/IIIa inhibitor injection, rotational atherectomy, and the injection of another vasodilator were assessed across the groups. Additionally, the TIMI flow grade, the TIMI myocardial perfusion grade, and the TIMI frame count were assessed before and immediately after PCI on the SVG.

The intragraft injection of 200 µg of verapamil was done via a guiding catheter before the wiring of the SVG. Coronary angiography was performed before and after PCI on the SVG. Cardiac enzymes (CK-MB and troponin I) were assessed 6 and 12 hours after PCI. STEMI was defined as typical chest pain, ST-elevation, and increased cardiac enzymes over fivefold the baseline values; and non-STEMI was defined as typical chest pain, electrocardiographic alterations, and increased cardiac enzymes over fivefold the baseline values. The patients with reduced TIMI flow grades (from 2 and 3 to 1 and 0) were considered to have the slow-flow or no-reflow phenomenon. In-hospital assessments and 3-month follow-ups were carried out with respect to MACE (ie, death, stroke, target vessel revascularization, and myocardial infarction).

Data analysis was done using IBM SPSS Statistics, version 22 (IBM Inc, Armonk, NY). The parametric distribution of the numerical data was assessed using the one-sample Kolmogorov–Smirnov test. Comparisons were also made using the independent-sample *t*-test, the Mann–Whitney *U* test, the Fisher exact test, and the Pearson test. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

The mean age was 60.5±5.7 years in the verapamil group and 64.0±3.8 years in the control group (*P*=0.3). There were 23 men in the verapamil group and 21 men in the control group (*P*=0.4). The mean duration of CABG history was 11.5±3.5 years in the verapamil group and 9.5±1.6 years in the control group (*P*=0.4). As is shown in Table 1, the frequency of cardiovascular risk factors was the same between the 2 groups (*P*>0.05).

Table 1: Frequency of cardiovascular risk factors in the groups

Risk Factor	Group		*P* value
	Verapamil n (%)	Control n (%)	
Diabetes mellitus	12 (37.5%)	13 (41.9%)	0.4
Hypertension	17 (53.1%)	16 (51.6%)	0.5
Stroke	1 (3.1%)	2 (6.4%)	0.4
Chronic kidney disease	3(9.3%)	2 (6.4%)	0.4
Peripheral vascular disease	1 (3.1%)	1 (3.2%)	0.2
COPD	2 (6.2%)	3 (9.6%)	0.3
Dyslipidemia	10 (31.2%)	14 (45.1%)	0.1
Family history	8 (25%)	13 (41.9%)	0.1

COPD, Chronic obstructive pulmonary disease

Table 2: Reasons for angiography in the groups

Reason for Angiography	Group		*P* value
	Verapamil n (%)	Control n (%)	
Unstable angina	12 (37.5%)	12 (38.7%)	0.5
NSTEMI	11 (34.3%)	10 (32.2%)	0.3
STEMI	2 (6.2%)	3 (9.6%)	0.4
Positive noninvasive tests	7 (21.8%)	6 (19.3%)	0.5
Total	32 (100%)	31 (100%)	

STEMI, ST-segment-elevation myocardial infarction; NSTEMI, non–ST-segment-elevation myocardial infarction

Table 3: Targeted vessels for the SVG in the groups

SVG on	Group		*P* value
	Verapamil n (%)	Control n (%)	
Diagonal	2 (6.2%)	5 (16.1%)	0.1
OM	18 (56.2%)	16 (51.6%)	0.4
RCA	11 (34.3%)	10 (32.2%)	0.5
LAD	1 (3.1%)	0 (0%)	0.5
Total	32 (100%)	31 (100%)	

SVG, Saphenous vein graft; OM, Obtuse marginal; RCA, right coronary artery; LAD, Left anterior descending artery

Table 4: Stent diameter and length in the groups

Stent	Group	mean ± SD	Range	50th Percentile (25–75)	*P* value
Diameter	Verapamil	3.1 ± 0.7	2-5	3 (2.5-4)	0.4
	Control	3.02 ±0.5	2-4	3 (2.75-3.5)	
Length	Verapamil	23.6 ± 8.4	12-38	23 (16-29)	0.5
	Control	25.08±6.7	12-38	24 (23-29)	

Table 5: Number of inflations in the groups

Number of Inflations	Group		*P* value
	Verapamil n (%)	Control n (%)	
1	13 (40.6%)	13 (41.9%)	0.6
2	8 (25%)	5 (16.1%)	0.1
≥ 3	11 (34.3%)	13 (41.9%)	0.2
Total	32 (100%)	31 (100%)	

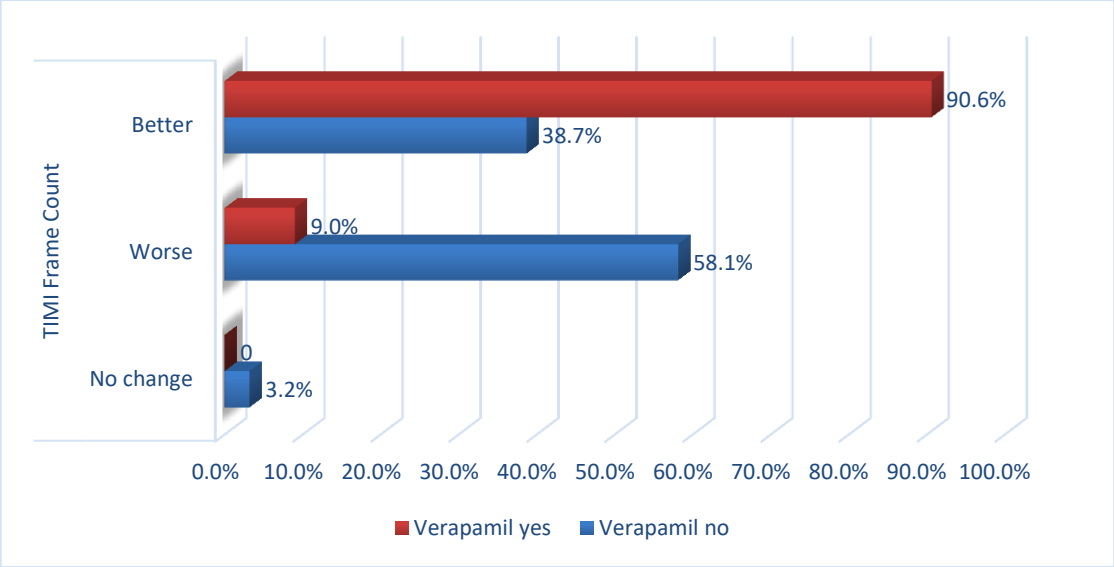

Figure 1: The image depicts comparisons of the TIMI frame count between the 2 groups.

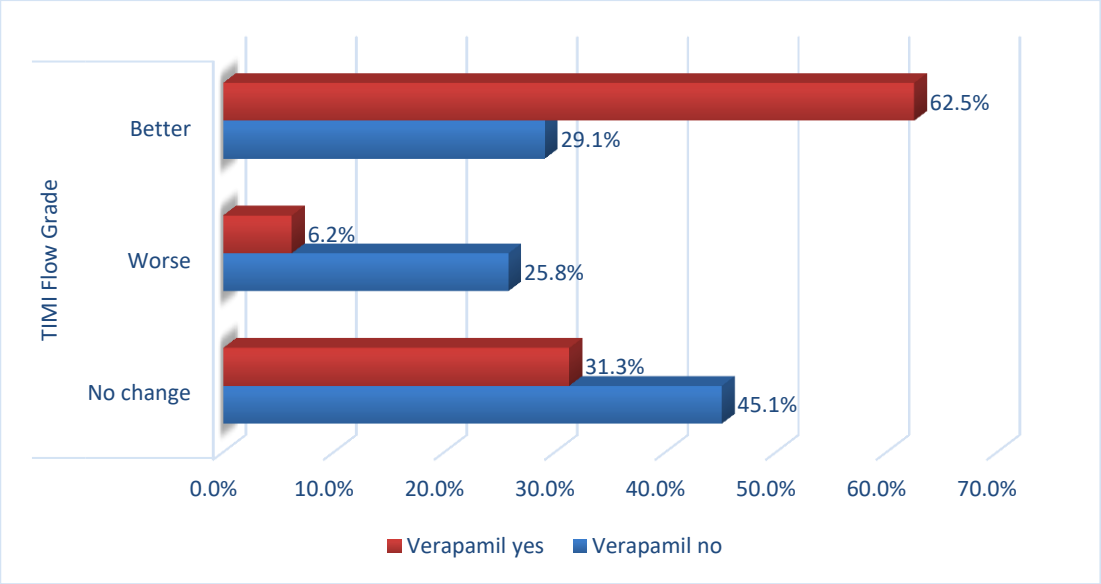

Figure 2: The image depicts comparisons of the TIMI flow grade between the 2 groups.

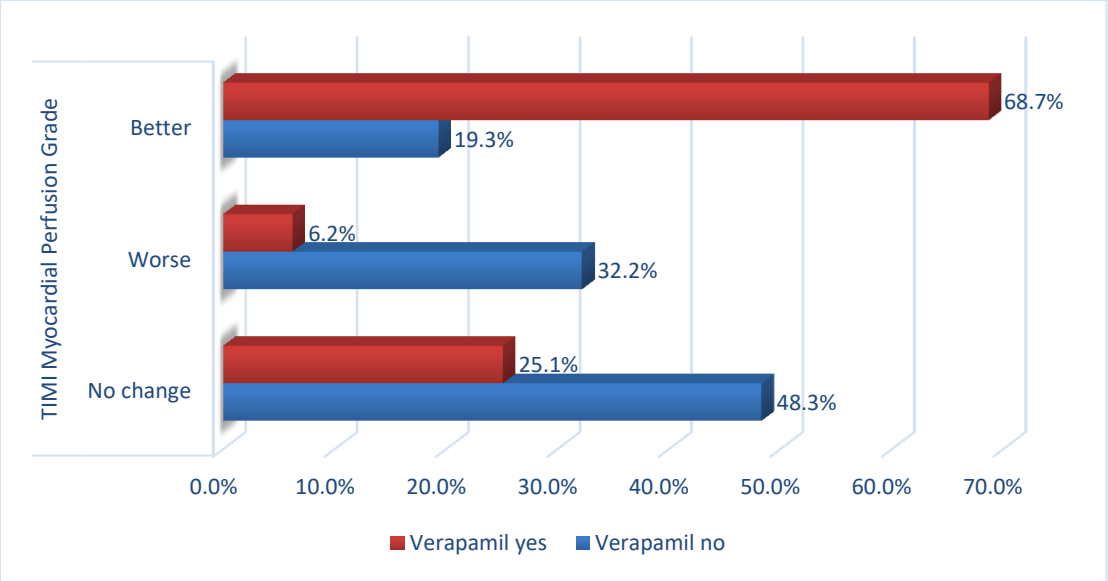

Figure 3: The image depicts comparisons of the TIMI myocardial perfusion grade between the 2 groups.

The mean ejection fraction was 40.6±6.8% in the case group and 40.0±5.1% in the control group (*P*=0.3). The different reasons for angiography are presented in Table 2. The targeted vessels for the SVG were similar in the 2 study groups (Table 3).

The mean stent diameter and the mean stent length were alike in the 2 groups (Table 4). Post-dilatation was reported in 14 patients (22.2%) in the verapamil group and 10 (15.9%) patients in the control group (*P*=0.3). Direct stenting was done in 26 (41.3%) and 23 (36.5%) patients in the case and control groups, correspondingly (*P*=0.5). There was no rotational atherectomy in either group.

Glycoprotein IIb/IIIa inhibitors were used in 2 patients (3.2%) in the verapamil and 3 patients (4.8%) in the control group (*P*=0.6). Distal protective devices were utilized, respectively, in 2 (3.2%) and 2 (3.2%) patients in the verapamil and control groups (*P*=0.9). The number of inflations was the same in the 2 groups (Table 5).

The patients who received pre-PCI intragraft verapamil injection had a statistically significantly lower rate of slow-flow and no-reflow than did the control group (4.8% vs 17.5%; *P*=0.01). As is illustrated in Figures 1, 2, and 3, by comparison with the control group, the verapamil group also had favorable TIMI frame counts (90.6% vs 38.7%; *P*<0.01), TIMI flow grades (31.7% vs 14.3%; *P*=0.015), and TIMI myocardial perfusion grades (34.9% vs 9.5%; *P*=0.001). There was no difference in the secondary outcomes between the 2 groups (ie, unstable angina and MACE) during both hospital stay and the 3-month follow-up. MACE was reported in 1 patient (1.6%) in the verapamil group and 3 patients (4.8%) in the control group (*P*=0.2).

DISCUSSION

In the current study, we compared a group with a pre-PCI intragraft injection of verapamil and a control group concerning the postprocedural rate of slow-flow and no-reflow. The case group had not only significantly low rates of slow-flow and no-reflow but also favorable TIMI frame

counts, TIMI flow grades, and TIMI myocardial perfusion grades. There were, however, no statistically significant differences between the 2 groups regarding unstable angina and MACE. A study by Watts et al [12] revealed lower rates of the no-reflow phenomenon in an animal model with the injection of nisoldipine as a calcium-channel blocker. Likewise, Villart et al [13] reported good results in terms of reduced infarct size in ischemia for another calcium-channel blocker, gallopamil, in rabbits. These findings are consistent with the results of our human study.

Kaplan et al [18] similarly reported an 88% rate of improvement in TIMI flow grade III in degenerated venous grafts after intragraft verapamil injection; they, nonetheless, reported that nitroglycerin had no significant effect on the TIMI flow. Saito et al [23] demonstrated reduced ST-elevation and chest pain during balloon inflation before percutaneous transluminal coronary angioplasty with the injection of diltiazem. Taniyama et al [14] assessed 40 patients with acute myocardial infarction and found reduced microvascular dysfunction after PCI with intracoronary verapamil injection, leading to improved myocardial blood flow and functional status.

Jalinus et al [22] reported lower risks of non–Q-wave myocardial infarction with intracoronary verapamil injection before directional atherectomy. Neither of our study groups underwent rotational atherectomy. Chiming in with our investigation, Michaels et al [17] performed the VAPOR clinical trial and showed reduced no-reflow rates and better myocardial perfusion with the intragraft injection of verapamil before PCI. Vijayalakshmi et al [16] reported similar results between adenosine and verapamil among 150 patients with acute coronary syndromes. Their study, however, lacked a control group. Sharma et al [20] reported that among their subjects with occlusion but without obvious thrombosis, the injection of verapamil plus abciximab, accompanied by direct stenting and pre-dilation, significantly diminished the slow-flow and no-reflow rates. In our study, verapamil alone conferred favorable results. Abu Arab et al [21] reported the efficacy of epinephrine plus verapamil injection into the distal coronary artery in the treatment of patients with the no-reflow phenomenon.

To sum up, our results demonstrated that pre-PCI verapamil injection into the SVG significantly lowered the postprocedural rates of slow-flow and no-reflow and conferred improved TIMI flow grades, TIMI frame counts, and TIMI myocardial perfusion grades in the case group. Salient among the limitations of our study is its non-randomized design, followed by its limited follow-up duration. Further studies, especially randomized clinical trials, with longer follow-up durations are required to shed sufficient light on whether pre-PCI verapamil injection into the SVG can decrease the risk of postprocedural no-reflow and slow-flow. Moreover, long-term follow-ups may help to determine the effects of this interventional approach on unstable angina and MACE in this group of patients.

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