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ORIGINAL ARTICLE

Effect of Poststenting Intracoronary Verapamil on Coronary Microcirculation in Primary Percutaneous Coronary Intervention

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Abstract

Background: **Primary percutaneous coronary intervention (PCI), also known as primary angioplasty, is considered to be the standard of care for cases with ST-segment elevation myocardial infarction (STEMI). Verapamil enhances microvascular circulation and reduces the no-reflow phenomena.**

Aim: **To assess the impact of intracoronary (IC) verapamil on coronary microcirculation following implantation of a stent in infraction-related vessels during primary PCI.**

Patients and methods: **Sixty patients (Pts) with STEMI were given verapamil 100−300 μg IC following primary PCI to the culprit vessel. The following parameters were compared before and after giving verapamil IC: TIMI flow grads (TFGs) 0−3, TIMI myocardial perfusion grade (TMPG) 0−3 and corrected TIMI frame count (cTFC) which measures the numbers of cine frames necessary to fill the culprit vessel.**

Results: **The mean age of the 60 pts was 54.7 ± 10.6 years, and 44 (73.3%) were males. TFG, TMPG, and cTFC were significantly better following verapamil than before its administration IC ($P < 0.001$, $P < 0.003$, and $P < 0.001$, respectively). Bradycardia was observed in 3.3% of pts. Our pts did not have any cases of cardiac failure. or died before hospital discharge.**

Conclusion: **Verapamil administration after PCI had a statistically significant positive influence on coronary blood flow and myocardial perfusion.**

Keywords: Coronary microcirculation, Post stenting intracoronary verapamil, Primary percutaneous coronary intervention

1. Introduction

Primary percutaneous coronary intervention (PCI), also known as primary angioplasty, is the gold standard treatment for patients (Pts) with ST-segment elevation myocardial infarction (STEMI).[1] Prompt restoration of blood flow in the occluded coronary artery is crucial to salvage the ischemic myocardium and improve pt outcomes. However, despite successful stent placement and resolution of epicardial coronary obstruction, some pts may experience impaired microvascular perfusion, a condition known as microvascular dysfunction or no-reflow phenomenon.[2]

The no-reflow phenomenon occurs due to various factors, including distal embolization, microvascular spasm, and inflammation, which can lead to impaired coronary microcirculation. This phenomenon has been related to worse clinical results, larger infarct size, and increased mortality in STEMI pts despite successful primary PCI.[3]

Intracoronary (IC) verapamil, a calcium channel blocker, has been proposed as a potential therapeutic agent to improve coronary microcirculation in pts undergoing primary PCI. Verapamil has vasodilatory properties and can potentially reduce microvascular spasms, enhance microvascular perfusion, and reduce the no-reflow phenomenon.[4]

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Several researchers have studied the effects of poststenting IC verapamil on coronary microcirculation in Pts having primary PCI for STEMI.[5] While some studies have shown promising results in light of improved microvascular perfusion and clinical results, others have reported conflicting findings.[6]

To assess the impact of IC verapamil on coronary microcirculation following implantation of stent in infraction-related vessels during primary PCI.

2. Patients and methods

Our university's research and development committee, the local research ethics committee, and the radiation protection consultant all gave their stamps of approval to the study plan. All of the pts who participated in the trial were given a pt information leaflet that detailed the research, in addition to the advantages and potential hazards of cardiac catheterization and angioplasty. Every participant in the research project was given a thorough explanation of both the possible benefits and drawbacks of the medications that were utilized in the study. It was possible to get participants' written agreement to take part in the research.

2.1. Patient selection and exclusion

This study includes 60 pts with STEMI who attended the National Heart Institute, Cairo in the period between April 2021 to June 2023. Primary PCI was done to the infarction related vessel. Excluded Pts those who were not indicated for stent implantation, culprit lesion in the left main coronary artery or a by-pass graft, reduced ejection fraction, severe renal insufficiency on hemodialysis and cardiogenic shock and/or bradycardia [heart rate (HR) < 60 beats/min].

2.2. Sample size

These assumptions were utilized to determine the sample size for the present investigation, which was based on research conducted by Yassin *et al*. −80% power, and a 95% two-sided CI. A 5% margin of error and the maximum number of output samples that could be captured was 58. To account for potential individuals dropping out throughout follow-up, the sample size was expanded to 60.[7]

2.3. Clinical data include

Age, sex, history of DM, hypertension, IHD, CKD, stroke, smoking, dyslipidemia, and FH of ischemic heart disease. The history of 'Onset to door time' refers to the duration, in minutes, from the time symptoms first appear (such as chest pain or other signs of acute coronary syndrome) to the time the pt checks into the emergency room (door), as well as, the 'Door to balloon time' refers to the duration, in minutes, from the time the pt checks into the emergency room (door) to the initiation of PCI with balloon angioplasty to open the blocked coronary artery. Cardiac examination and chest auscultation were performed in our Pts.

2.4. Other investigations

12-lead ECG was taken at admission and right following the angioplasty. Cardiac enzymes were measured on arrival.

2.5. Cardiac catheterization

Pts were randomly allocated to receive either a placebo or an IC bolus of verapamil following the initial PCI operation. Verapamil (100 μg in 10 ml saline) and repeated three times maximum (maximum dose 300 μg).

All pts received aspirin, loaded with 600 mg of clopidogrel and 10 000 IU IV unfractionated heparin before PCI.

2.6. Quantitative coronary angiography and cTFC

To conduct coronary angiography, a Philips DCI-SX Integris Monoplane system was used. The radiologist in charge of the case utilized Philips Inturis Suite R2.2 commercial software to do quantitative coronary angiography. The frame rate for the angiograms was set at 15 frames/s. In order to count frames, we used the previously mentioned approach. One observer, who was not privy to the data, assessed cTFC. Following PCI and medication delivery, the angiograms were analyzed to determine cTFC, TIMI flow grade (TFG), and TMPG. In order to assess myocardial blush, a 16 s angiographic film sequence was collected.

2.7. TIMI flow grades

TFGs were previously described: grade 0, no perfusion (no antegrade flow beyond the point of occlusion); grade 1, penetration without perfusion, grade 2, partial perfusion and grade 3, complete perfusion.

No-reflow is considered when TIMI grade less than 3 at the end of PCI.[8]

2.8. The corrected TIMI frame count (cTFC)

It measures the number of cineangiography frames necessary for the contrast dye to traverse a specific segment of the coronary artery. A higher cTFC value indicates slower coronary blood flow, which may be indicative of distal embolization, microvascular spasm, or other factors that can result in impaired microvascular perfusion, known as the no-reflow phenomenon. Lower cTFC values afterward reperfusion treatment are associated with better clinical outcomes and reduced myocardial damage.

2.9. TIMI myocardial perfusion grade (TMPG)

The TMPG was utilized to evaluate contrast uptake and clearance in the myocardium. The absence of tissue-level perfusion along the path of the culprit artery was taken to be diagnostic of TMPG-0. Myocardial blush was present, however there was no clearing from the microvasculature, as measured by TMPG-1. The TMPG-2 results showed that the blush diminished gradually. According to TMPG-3, the blush cleared throughout the washing process.

2.10. Justification of cTFC categorization

A cTFC that was quicker than the 95% confidence interval (CI) for normal flow (also referred to as 0 to 13 frames, hyperemia, and TIMI grade 4 flow) was considered to have a cTFC that was more than 14. In the past, a cTFC of 40 was determined to represent the cutoff point among TIMI grade 3 flow and TIMI grade 2 flow.[9] The TFC was assigned the value of 100 in the event that the vessel in question was occluded, which is the value that corresponds to the 99th percentile of occluded vessels.[10]

2.11. Statistical analysis

The data collected were tabulated and analyzed by SPSS (statistical package for social science) version 26.0 on IBM compatible computer.

Two types of statistical analysis were done: Descriptive statistics e.g. g. Number (No), percentage (%), for qualitative data and mean ± SD or median (IQR) for quantitative data.

Analytic statistics: Chi-squared test (χ^2), McNemar test and Mann–Whitney U test. A P value of less than 0.05 was considered statistically significant.

3. Results

Table 1.

Table 1. Sociodemographic and baseline data of the studied group (N = 60).

	N = 60 [n (%)]
Age (Y)	
Mean ± SD	54.7 ± 10.6
Sex	
Male	44 (73.3)
Female	16 (26.7)
DM	
Yes	32 (53.3)
No	28 (46.7)
Hypertension	
Yes	26 (43.3)
No	34 (56.7)
Dyslipidemia	
Yes	18 (30)
No	42 (70)
Smoking	
Yes	33 (55)
No	27 (45)
IHD	
No	57 (95)
IHD with previous PCI	3 (5)
IHD with previous CABG	0
CKD	
Yes	1 (1.7)
No	59 (98.3)
Stroke	
Yes	1 (1.7)
No	59 (98.3)
FH of ischemic heart disease	
Yes	9 (15)
No	51 (85)

CABG, Coronary artery bypass graft; **CKD**, chronic kidney disease; **DM**, Diabetes Mellitus; **FH**, family history; **IHD**, Ischemic heart disease; **PCI**, Percutaneous coronary intervention.

The mean age of the 60 Pts was 54.7 ± 10.6 years, 44 (73.3%) were males, 32 Pts (53.3%) were diabetics, 26 (43.3%) were hypertensive, one (1.7%) had CKD and a history of stroke, 33 (55%) smokers, 18 (30%) pts were dyslipidemic, and 9 (15%) had a positive FH of ischemic heart disease.

Table 2.

Fifty-seven Pts (95%) had KILLIP Class 1, 39 (65%) with anterior STEMI, 29 (48.3%) with 1 VD, and 39 (65%) with Culprit Vessel LAD. The mean onset-to-door time was 219.8 ± 103.1 min, while the mean door-to-balloon time was 77.6 ± 34.8 min. Four (6.7%) had thrombolytic therapy, 35 (58.3%) had balloon dilatation, 9 (15%) had Tirofiban, and none of the studied groups had thrombus Aspiration. The mean stenosis percentage before coronary intervention was 97.4 ± 13.1%. Before the coronary intervention, in most of the studied groups, 47 (78.4%) had 0 TFG, and 57 (95%) had 0 TMPG.

Table 3.

cTFC, TFG, and TMPG differed significantly after giving verapamil to pts. Following primary PCI to the culprit vessel, the number of pts that had no

Table 2. Cardiac-related characteristics of the studied group (N = 60).

	N = 60 [n (%)]
KILLIP Class	
1	57 (95)
2	3 (5)
Onset to door time (min) Mean ± SD	219.8 ± 103.1
Door to balloon time (min) Mean ± SD	77.6 ± 34.8
CK MB Mean ± SD	81.0 ± 45.6
ECG changes	
Anterior STEMI	39 (65)
Inferior STEMI	18 (30)
Lateral STEMI	3 (5)
Thrombolytic therapy	
Yes	4 (6.7)
No	56 (93.3)
CAD extent	
1 VD	29 (48.3)
2 VD	20 (33.3)
3 VD	11 (18.4)
Culprit Vessel	
LAD	39 (65)
RCA	17 (28.3)
LCX	3 (5)
OM	1 (1.7)
Balloon Dilatation	
Yes	35 (58.3)
No	25 (41.7)
Tirofiban administration	
Yes	9 (15)
No	51 (85)
Thrombus Aspiration	
Yes	0
No	60 (100)
Stenosis (%) before Coronary Intervention Mean ± SD	97.4 ± 13.1
TFG before Coronary Intervention	
0	47 (78.4)
I	5 (8.3)
II	3 (5)
III	5 (8.3)
TMPG before Coronary Intervention	
0	57 (95)
1	3 (5)

CAD, coronary artery disease; **LAD**, left anterior descending artery; **LCX**, left circumflex artery; **RCA**, right coronary artery; **STEMI**, ST elevation myocardial infarction; **TFG**, TIMI (thrombolysis in myocardial infarction) flow grade; **TMBG**, TIMI (thrombolysis in myocardial infarction) myocardial perfusion grade.

reflow (TFG <3) after PCI did not differ significantly after verapamil administration.

Table 4.

Bradycardia occurred in two (3.3%) pts, while none of them had cardiogenic shock or died.

Table 5.

Overall, 16 pts had less than 3 TFG after PCI but before verapamil administration (no reflow). In this subgroup, cTFC improved significantly, while the advance in TFG did not reach statistical significance.

Table 3. Comparing the angiographic characteristics of the studied group (N = 60).

	After PCI (N = 60) [n (%)]	After verapamil drug (N = 60) [n (%)]	P value
cTFC			
Mean ± SD	35.5 ± 27.2	26.5 ± 18.8	**<0.001**
cTFC categories			
<14	9 (15)	25 (41.7)	**<0.001**
14–40	36 (60)	23 (38.3)	
>40	15 (25)	12 (20)	
TFG			
0	1 (1.7)	0	**<0.001**
I	4 (6.7)	0	
II	11 (18.3)	9 (15)	
III	44 (73.3)	51 (85)	
TMPG			
0	21 (35)	15 (25)	**0.003**
1	10 (16.7)	7 (11.7)	
2	16 (26.6)	14 (23.3)	
3	13 (21.7)	24 (40)	
No reflow	16 (26.7)	9 (15)	**0.116**

cTFC, corrected TIMI (thrombolysis in myocardial infarction) frame count; **TFG**, TIMI flow grade; **TMPG**, TIMI myocardial perfusion grade.

Table 4. Complication occurrence among the studied group (N = 60).

	N = 60 [n (%)]
Bradycardia	
Yes	2 (3.3)
No	58 (96.7)
Cardiogenic shock	
Yes	0
No	60 (100)
Death	
Yes	0
No	60 (100)

Table 5. Comparing the angiographic characteristics of the Pts with 'no reflow' (n = 16).

	After PCI (N = 60) [n (%)]	After drug (N = 60) [n (%)]	P value
cTFC			
Mean ± SD	73.1 ± 25.7	51.5 ± 19.4	**0.001**[@]
cTFC categories			
<14	0	1 (6.3)	**<0.001**[$]
14–40	1 (6.2)	3 (18.7)	
>40	15 (93.8)	12 (75)	
TFG			
0	1 (6.3)	0	0.393
I	4 (25)	0	
II	11 (68.7)	9 (56.2)	
III	0	7 (43.8)	

cTFC, corrected TIMI (thrombolysis in myocardial infarction) frame count; **TFG**, TIMI (thrombolysis in myocardial infarction) flow grade.

4. Discussion

Some of the most common reasons for STEMI are an atherosclerotic plaque breaking, a thrombus forming, and a major epicardial coronary artery becoming fully blocked.[1]

IC Verapamil is a calcium channel blocker that has been investigated for its potential impact on coronary microcirculation in pts with primary PCI for STEMI. Verapamil's vasodilatory properties and ability to reduce calcium influx into vascular smooth muscle cells make it an appealing therapeutic option for improving microvascular perfusion in the post-stenting phase.[11]

This study includes 60 pts with STEMI indicated for primary PCI. This research targeted assessing the impact of IC verapamil on coronary microcirculation following implantation of stents in infraction-related vessels during primary PCI.

Most pts in our study were in Killip Class 1 (95%), suggesting a low risk of mortality. The mean onset-to-door time was 219.8 min, and the mean door-to-balloon time was 77.6 min, which were relatively longer than the recommendations in the guidelines for STEMI. The culprit vessel responsible for ACS was most commonly the left anterior descending artery (LAD) in 65% of Pts, followed by the right coronary artery (RCA) in 28.3% of cases. Most pts (58.3%) received balloon dilatation during the procedure and a small minority received IV thrombolytic therapy before PCI.

Before the coronary intervention, the majority of pts had a high degree of stenosis (97.4 ± 13.1%), and most of them had a TFG of 0 (95%). Postprocedure administration of Tirofiban (a glycoprotein IIb/IIIa receptor antagonist) was given in 15% of cases, possibly to improve platelet inhibition and enhance reperfusion. Thrombus aspiration was not performed in any of the cases.

Overall, the study reveals important clinical characteristics and treatment practices in Egyptian pts with STEMI who have primary PCI, which highlights the need to improve time-to-door and door-to-balloon times and adherence to appropriate reperfusion strategies.

Regarding the result of this study, the corrected thrombolysis in myocardial infarction frame count (cTFC), which is a measure of coronary blood flow, before verapamil administration, the mean cTFC was 35.5 ± 27.2, indicating suboptimal coronary blood flow. However, after verapamil treatment, there was a significant improvement in cTFC, with a mean of 26.5 ± 18.8 ($P < 0.001$). This finding suggests that verapamil had a beneficial effect on coronary blood flow, resulting in rabid blood flow through the coronary arteries following PCI.

Hang and colleagues categorized the cTFC values into three groups: cTFC less than 14, cTFC 14–40, and cTFC greater than 40. Before verapamil administration, the majority of pts (60%) fell into the intermediate cTFC range (14–40), indicating suboptimal blood flow. However, after verapamil treatment, there was a notable shift in the distribution, with 41.7% of pts achieving cTFC less than 14, representing improved coronary blood flow ($P < 0.001$). Additionally, 20% of pts had cTFC greater than 40 after verapamil, suggesting that some pts may not have responded as well to the treatment.[12]

Consistent with our result, Su and colleagues revealed that Verapamil treatment was significantly successful in the CTFC (weighted mean difference: −11.62; 95% CI: −16.04 to −7.21) and enhanced the TMPG (RR: 0.43; 95% CI: 0.29 to 0.64).[13]

In contrast with our results, Hang *et al*. revealed that there was no significant variance in post-PCI TIMI flow ($P = 0.68$) and CTFC ($P = 0.36$) between pts treated with verapamil and the control Pts.[12]

Also, thrombolysis in myocardial infarction (TIMI) flow grade (TFG) before and following verapamil administration was assessed in our study. Before verapamil treatment, the majority of Pts (73.3%) had TFG III, indicating normal blood flow. After verapamil, the percentage of Pts with TFG III increased (85%), indicating that verapamil significantly improves the overall TFG. However, it is essential to note that a majority of pts already had normal blood flow before the verapamil administration, limiting the potential for improvement.

Hang *et al*. indicated that when TIMI grade 3 flow was already attained following percutaneous transluminal coronary angioplasty, verapamil did not significantly enhance coronary flow.[12]

Werner *et al*. reported that TFG was enhanced in 87% of Pts by at least one category following verapamil administration.[8]

In our study, TMPG zero was found in 35% of Pts before verapamil compared with 25% of Pts after verapamil ($P = 0.003$). Conversely, the percentage of pts with TMPG 3 increased from 21.7% to 40% after verapamil treatment ($P = 0.003$).

In this study, no reflow after PCI occurred in 26.7% (16 pts), while the majority, 73.3% (44 pts), did not encounter this complication. Werner *et al*. found an incidence of no reflow of about 23 out of 212 Pts (10.8%).[8]

However, Piana and colleagues found that no-reflow occurs in 2% of coronary interventions. The discrepancy in the incidence of no reflow in our study compared with the others is possibly due to

the late presentation of Pts and underuse of thrombolysis (6.7).[14]

In our study, the TFG did not improve significantly after administration of verapamil (*P* 0.393). However, cTFC was significantly improved after verapamil administration (*P* 0.001) in Pts with no reflow.

In contrast to this, Tanzilli and colleagues concluded that verapamil as the first drug and on top of dipyridamole administration in Pts with no reflow did not induce significant improvement in the cTFC.[15]

Bradycardia was observed in 3.3% of pts, while the majority (96.7%) did not experience this condition. None of the pts developed cardiogenic shock or died during the study period. These findings suggest that bradycardia, cardiogenic shock, and mortality were infrequent in this cohort of pts with acute STEMI undergoing primary PCI.

Burlacu and colleagues revealed that the study identified that cardiogenic shock was an independent predictor of in-hospital mortality in acute myocardial infarction pts undergoing PCI. Additionally, the overall in-hospital mortality rate was found to be within the range of 5–10% after primary PCI.[16]

4.1. Conclusion

The results of this study show that giving verapamil after PCI significantly decreased cTFC values and increased TFG and TMPG, which means that blood flow and perfusion were improved. This study shows that giving verapamil IC after primary PCI to people with STEMI is safe, as there was a low rate of bradycardia, cardiogenic shock, and death.

Ethics information

Its was approved by faculty.

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Authorship

All authors have a substantial contribution to the article.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Conflicts of interest

The authors declared that there were no conflicts of Interest.

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