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Интракоронарное введение эпинефрина и верапамила при рефрактерном феномене no-reflow у пациентов с острым инфарктом миокарда

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Несмотря на современные достижения в технике чрескожных коронарных вмешательств, рефрактерный синдром no-reflow остается серьезной проблемой, которая способствует ухудшению госпитального и долгосрочного прогноза. Адреналин в более низких дозах может проявлять сильные агонистические свойства бета-рецепторов, которые опосредуют коронарную вазодилатацию.

Цель. Исследование направлено на оценку эффективности и безопасности интракоронарного введения адреналина и верапамила, а также их комбинации по сравнению со стандартным лечением у пациентов с инфарктом миокарда с подъемом сегмента ST и рефрактерным коронарным синдромом no-reflow во время чрескожных коронарных вмешательств.

Материал и методы. Пациенты с инфарктом миокарда с подъемом сегмента ST и рефрактерным синдромом no-reflow будут рандомизированы в 4 группы: только стандартная терапия, интракоронарное введение адреналина, верапамила, адреналина + верапамила. У всех пациентов будет проведена оценка эпикардиального кровотока с использованием шкалы TIMI (Thrombolysis in Myocardial Infarction), MBG (Myocardial Blush Grade), пикового уровня тропонина, динамики сегмента ST, эхокардиографии, магнитно-резонансной томографии, динамической однофотонной эмиссионной компьютерной томографии.

Результаты. На основании фармакодинамических эффектов адреналина и верапамила ожидается, что их комбинация будет иметь более сильный сосудорасширяющий эффект.

Заключение. Если исследование EPIVER (Intracoronary administration of EPInephrine and VERapamil in the refractory no-reflow phenomenon) окажется успешным, появится новый более эффективный метод лечения рефрактерного феномена no-reflow, который обеспечит более полное сохранение систолической функции левого желудочка, улучшит прогноз и клиническое течение заболевания.

Ключевые слова: инфаркт миокарда с подъемом сегмента ST, чрескожное коронарное вмешательство, феномен no-reflow.

Отношения и деятельность: нет.

ID исследования: NCT04573751 (ClinicalTrials.gov Identifier).

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Intracoronary epinephrine and verapamil in the refractory no-reflow phenomenon in patients with acute myocardial infarction

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Despite modern advances in performing percutaneous coronary interventions, refractory no-reflow remains a serious problem that worsens in-hospital and long-term prognosis. Low-dose adrenaline may exhibit potent beta-receptor agonist properties that mediate coronary vasodilation.

Aim. To evaluate the efficacy and safety of intracoronary administration of epinephrine and verapamil, as well as their combination, compared with standard treatment in patients with ST-segment elevation myocardial infarction (STEMI) and refractory no-reflow during percutaneous coronary interventions.

Material and methods. Patients with STEMI and refractory no-reflow will be randomized into 4 groups: standard therapy, intracoronary adrenaline, intracoronary verapamil, intracoronary epinephrine + verapamil. All patients will be assessed for epicardial blood flow using the Thrombolysis in Myocardial Infarction (TIMI) and Myocardial Blush Grade (MBG) scales, peak troponin levels, ST segment changes, echocardiography, magnetic resonance imaging, and dynamic single photon emission computed tomography.

Results. Based on the pharmacodynamic effects of epinephrine and verapamil, their combination is expected to have a more potent vasodilating effect.

Conclusion. If the Intracoronary administration of EPInephrine and VERapamil in the refractory no-reflow phenomenon (EPIVER) study will be successful, a novel, more effective method for managing refractory

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no-reflow phenomenon will appear. This will ensure better preservation of left ventricular systolic function, as well as improve the prognosis and clinical course of the disease.

Keywords: ST-segment elevation myocardial infarction, percutaneous coronary intervention, no-reflow phenomenon.

Relationships and Activities: none.

Trial ID: NCT04573751 (ClinicalTrials.gov Identifier).

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EF — Ejection Fraction, IC — Intracoronary, LV — Left Ventricular, MRI — Magnetic Resonance Imaging, MVO — Microvascular Obstruction, PCI — Percutaneous Coronary Intervention, SPECT — Single-Photon Emission Computed Tomography, STEMI — ST Elevation Myocardial Infarction, TIMI — Thrombolysis in Myocardial Infarction.

Introduction

Current guidelines support the choice of percutaneous coronary intervention (PCI) as the preferred reperfusion strategy in patients with acute ST — segment elevation myocardial infarction (STEMI) [1, 2]. The aim of the procedure is the restoration of infarct-related artery patency and the achievement of microvascular reperfusion without delay. No-reflow syndrome is defined as the persistence of compromised myocardial perfusion in the area supplied by infarct-related coronary artery after restoration of epicardial artery patency. It can be attributed to the high resistance of microvascular blood flow developing on the background of infarct-related coronary artery opening. No-reflow syndrome may negate the benefits of early restoration of culprit artery patency, which translates into the suboptimal PCI results, leading to a worse in-hospital and long-term prognosis [3].

According to clinical guidelines, nitrates, adenosine, platelet IIb/IIIa receptor inhibitors and thromboextraction can be used to prevent and treat this complication. These methods have demonstrated the ability to improve coronary blood flow in experiment and small clinical trials [4, 5], however, limiting the zone of myocardial necrosis and improving disease outcomes have not been achieved [6-8].

The search for new methods of influencing the pathogenetic links of this complication is urgent. One of the main potentially reversible factors in the no-reflow phenomenon pathogenesis, along with microvascular obstruction (MVO), is microvascular arteriolar spasm [3]. Thus, this problem of emergency cardiology remains relevant and requires further research, new methods of prevention and treatment.

While the major effects of high-dose epinephrine administration constitute of positive inotropic and chronotropic actions mediated by beta-1 receptor stimulation, lower doses may induce coronary vasodilation owing to their beta-2 receptor agonist properties [9]. In 2002, a study was conducted, in which 29 patients with no-reflow phenomenon were injected with intracoronary adrenaline, which led to a significant improvement in coronary blood flow and the achievement of TIMI 3 (Thrombolysis in Myocardial Infarction) in 69% of cases [10]. The RESTORE study (The Efficacy and safety of intRacoronary Epinephrine versus conventional treatmentS alone in STEMI patienTs with refractORy coronary no-rEflow**)** included 30 STEMI patients who developed a refractory no-reflow phenomenon during primary PCI. Patients were randomized to either intracoronary epinephrine (n=14) or standard treatment (n=16). According to the study results, there was a significant improvement in coronary blood flow in the epinephrine group: TIMI-3: 28,6 vs 18,8% and TIMI-2: 64,3 vs 12,5% (p=0,004). The difference in the combined endpoint of death + heart failure reached statistical significance: 35,7 vs 81,25% (p=0,01). At the same time, left ventricular (LV) ejection fraction (EF) one day after the procedure in the adrenaline group increased significantly compared to the study before PCI: 44,57±8,20 vs 36,9%±13,9% (p=0,01), while the patients of the control group did not demonstrate such positive dynamics: 40,93±34,48 vs 38,31±14,70% (p=0,45) [11].

Another drug with a pronounced coronary vasodilation effect is verapamil. A meta-analysis that included 8 randomized studies with a total of 494 patients showed that intracoronary bolus administration of verapamil/diltiazem provided a statistically significant reduction in the manifestations of the no-reflow phenomenon and a decrease in MACE (Major Adverse Cardiac Events) within 6 months of observation [12]. Present trial aims to estimate the efficacy and safety of intracoronary (IC) epinephrine and verapamil administration, as well as their combination versus standard treatment in patients with STEMI and refractory coronary no-reflow despite conventional treatments during PCI.

Methods/Design

This study is an open-label, randomized, single-center, prospective trial. Study intends to assess the safety and efficacy of IC administration of epinephrine and/or verapamil versus standard therapy following

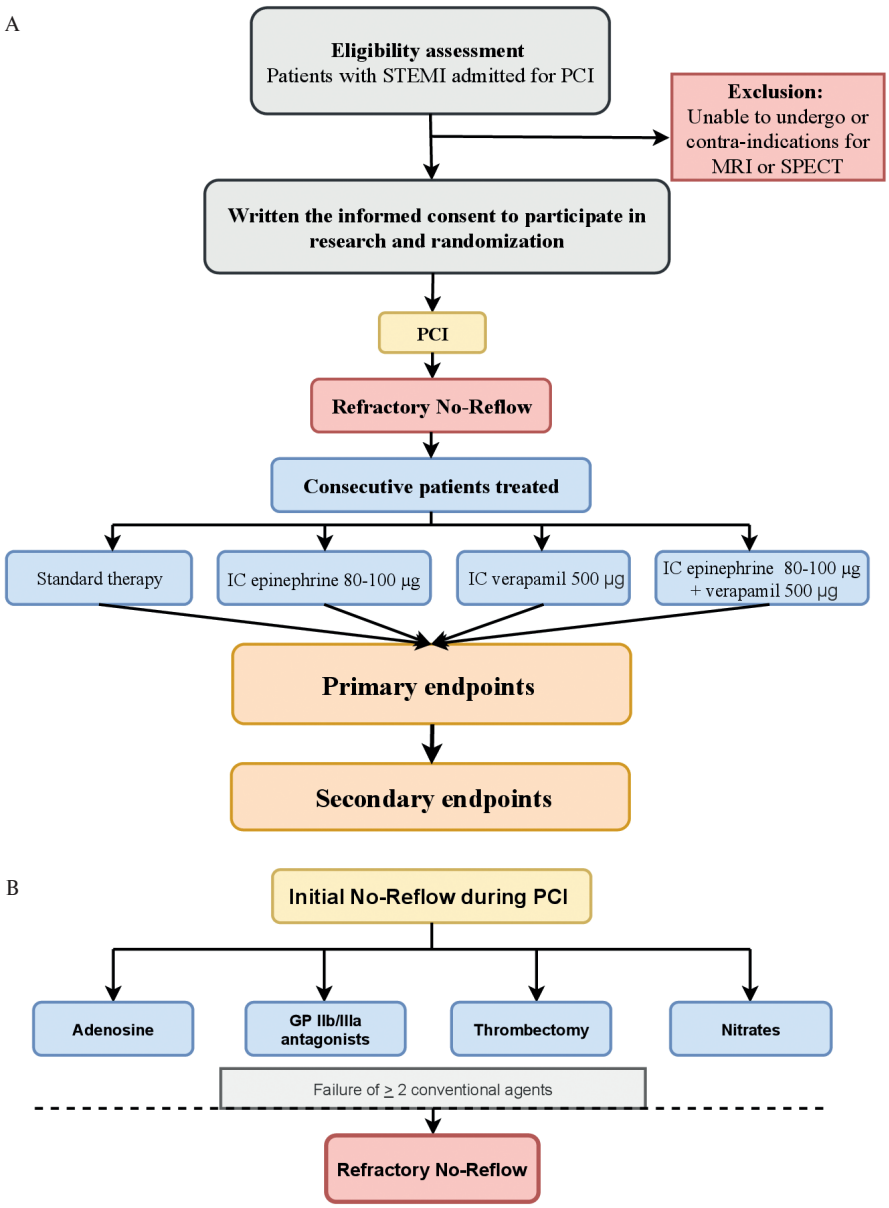

Figure 1 (*A*) Flow chart of the study design; (*B*) Flow diagram on the standard therapeutic procedures and and determination of refractory no-reflow. Note: BP — Blood Pressure, EDV — End-Diastolic Volume, ESV — End-Systolic Volume, EF — Ejection Fraction, GP — Glycoprotein, HR — Heart Rate, IC — Intracoronary, MRI — Magnetic Resonance Imaging, MVO — Microvascular Obstruction, SPECT — Single-Photon Emission Computed Tomography, PCI — Percutaneous Coronary Intervention, STEMI — ST Elevation Myocardial Infarction, TIMI — Thrombolysis in Myocardial Infarction.

onset of severe refractory no-reflow despite guideline-directed conventional pharmacologic and device-based treatment. The study was approved by the biomedical ethics committee of the Cardiology Research Institute, Tomsk National Research Medical Center. Protocol No 203 on October 14, 2020. Trial registration: ClinicalTrials.gov Identifier: NCT04573751; registered on October 19, 2020.

Written informed consent for the intervention will be obtained from all patients upon admission prior to enrollment in the study. Patients enrolled have rights to withdraw at any time point and the reasons will be documented.

Consecutive patients with STEMI and refractory no-reflow will be randomized by the envelope method into 4 groups: standard therapy only, epinephrine, verapamil, epinephrine + verapamil. IC epinephrine will be administered at a dose of 80-100 μg and verapamil at a dose of 500 μg. The dose of IC epinephrine was selected empirically and based on the experience of previous studies [10, 11, 13]. The dose of IC verapamil was selected based on the experience of previous studies [12, 14]. All patients will undergo an assessment of epicardial blood low by TIMI and MBG (Myocardial Blush Grade) before and after a bolus of epinephrine and/or verapamil, peak troponin level, ST segment

dynamics, echocardiography on 1-3 and 7-10 day, magnetic resonance imaging (MRI) on 2 day, dynamic Single-photon emission computed tomography (SPECT) on 7 day (Figure 1 A). A flow diagram describing the temporal phases of standard therapeutic procedures relative to the diagnosis of no-reflow onset prior is shown in Figure 1 B. Patient clinical, laboratory and instrumental data will be taken from the medical record, 30-day clinical outcomes will be obtained by calling. Baseline and follow-up evaluation is shown in Figure 2. Graphical Abstract is shown in Figure 3.

Sample size

Taking into account the results of previous studies assessing the use of epinephrine in the setting of no-reflow phenomenon [11] and Using the Bland-Alrman method [15, 16] for sample size calculation, we determined the minimum necessary number of patients enrolled in each group to be 30 (total 120), in order achieve 80% power with 0,05 statistical significance level.

Inclusion Criteria:

— Patients with ST-elevation myocardial infarction.

— Infarct-related artery TIMI flow grade 0-2 during the interventional procedure after the initial opening of the vessel.

— Written informed consent to participate in research.

Exclusion Criteria (for all groups):

— Inability to undergo or contra-indications for MRI or dynamic SPECT.

Determinations

We will define refractory no-reflow as the no-reflow episode not resolving with the combined administration of at least two conventional strategies including nitrates, thrombectomy, glycoprotein IIb/IIIa inhibitors and adenosine.

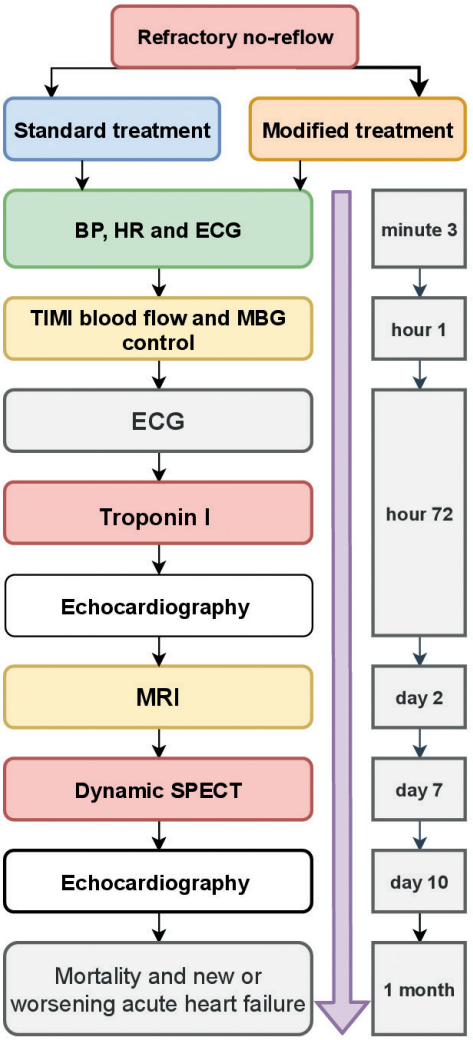

Figure 2 Baseline and follow-up evaluation.
Note: BP — Blood Pressure, ECG — Electrocardiography, HR — Heart Rate, MBG — Myocardial Bluch Grade, MRI — Magnetic Resonance Imaging, SPECT — Single-Photon Emission Computed Tomography, TIMI — Thrombolysis in Myocardial Infarction.

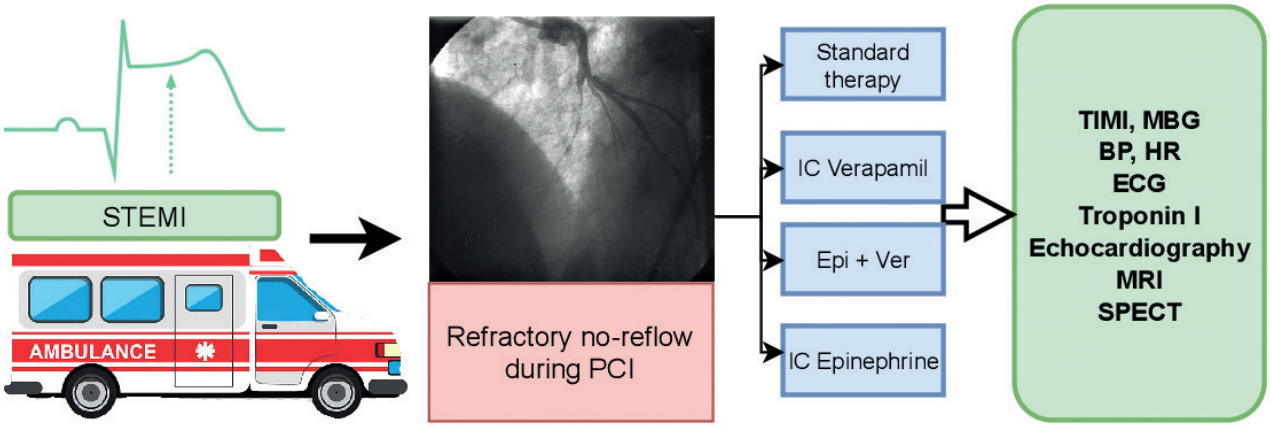

Figure 3 Graphical Abstract.
Note: BP — Blood Pressure, HR — Heart Rate, ECG — Electrocardiography, MBG — Myocardial Bluch Grade, MRI — Magnetic Resonance Imaging, SPECT — Single-Photon Emission Computed Tomography, STEMI — ST Elevation Myocardial Infarction, PCI — Percutaneous Coronary Intervention, TIMI — Thrombolysis in Myocardial Infarction.

The MVO assessment will be performed using MRI within 2 days from PCI.

The coronary reserve area will be assessed using dynamic SPECT within the first 7 days. Dynamic SPECT will be performed as follows: the passage of a radiopharmaceutical bolus through the cavities of the heart and myocardium at rest and during infusion of adenosine at a dosage of 140 mcg/kg/min (for 4 min) will by recorded. At the peak of the stress test (after 2 min of adenosine administration) 5 ml (dose 260-444 MBq) of technetium 99m-labeled methoxy-isobutyl isonitrile (99mTc-Technetril) will be infused at a rate of 1 ml/s. Immediately after the end of tracer administration, 30 ml of 0,9% NaCl will be infused. A scintigraphic recording of the study will be begined 5 sec before the administration of the radiopharmaceutical preparation. On the next day, the study at rest will be carried out — Scintigraphic images will be recorded in tomographic mode with ECG synchronization for 600 s, at listmode. Image acquisition will be carried out on dedicated cardiac gamma-camera with ultrafats CZT detectors (DiscoveryNM530c, GE Healthcare Israel, Tirat Hacarmel, Israel).

Primary endpoints

— Mortality events at 30 days

— Hospitalization for new or worsening acute heart failure events at 30 days. Congestion characterized by dyspnea, edema, rales, jugular venous distention and need to increase diuretic doses is a hallmark of acute heart failure prompting hospitalization [17].

Secondary parameters

— The rate of patients (percent) who achieved TIMI 3 coronary blood flow after percutaneous coronary intervention;

— Change in systolic/diastolic blood pressure values, heart rate values;

— Frequency of arrhythmias (atrial fibrillation, atrial fluttery, supraventricular tachycardia, premature ventricular contractions, ventricular tachycardia, conduction disorders and other heart rhythm disorders) after intracoronary administration verapamil and/or epinephrine;

— Concentration of troponin I;

— Degree of ST segment resolution on ECG;

— LV EF by echocardiography;

— LV end-diastolic and end-systolic volumes;

— LV wall motion score index;

— Total volume of MVO, myocardial necrosis, edema, and hemorrhagic impregnation according to MRI data;

— Coronary reserve will be measured by cardiac SPECT with 99mTcMIBI at rest and during pharmacological stress-test (counts).

Statistical analysis

All data will be statistically analyzed using Statistica 10.0 software (Stat Soft Inc., Tulsa OK, USA). Data that are normally distributed will be expressed as mean, standard deviation, minimum value, and maximum value. Data that are non-normally distributed will be expressed as the lower (Q1), median, and upper quartile (Q3). Rates and frequencies of occurrence will be expressed as percentages (%). Data will be compared between groups using Student's t-test; nonparametric variables will be compared between groups using the Friedman test and Median Test. A value of $p<0,05$ is considered statistically significant.

Discussion

Based on the pharmacodynamic effects of epinephrine and verapamil, their combination is expected to have a more potent vasodilating effect, due to the additive type of synergistic interaction, which will improve coronary microcirculation after PCI in patients with acute myocardial infarction and refractory no-reflow phenomenon.

According to the data from large thrombolysis trials, patients with TIMI 1 and 2 flow have equally poor prognosis when compared to those achieving TIMI 3 flow [18]. This fact can serve as a rationale for myocardial infarction reperfusion no-reflow diagnosis in the setting of TIMI flow of <3. Additionally, findings from the studies [19, 20] that utilized myocardial contrast echocardiography as a mean to assess the area of compromised perfusion, suggest that TIMI 2 flow is associated with a large no-reflow zone, which further supports the TIMI 3 flow as the only single indicator of successful reperfusion.

Currently, in clinical practice, there is a possibility of very sensitive diagnosis of MVO using MRI, as well as the area of the coronary reserve according to dynamic perfusion scintigraphy of the myocardium. It is advisable to evaluate the effectiveness of treatment of the no-reflow phenomenon using these methods.

Conclusion

Coronary no-reflow is a potentially lethal complication of PCI. The optimal approach to restore coronary reflow during PCI is still controversial. If the EPIVER study proves to be successful, a new effective method of managing refractory no-reflow will appear, which would ensure more preserve left ventricular systolic function and improve the prognosis and clinical course of the disease.

Trial Status

At the time of application, 12 patients were included in the study.

Competing interests. All authors declares no potential conflicts of interest warranting disclosure in this article.

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