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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Intracoronary adenosine administered during aortocoronary vein graft interventions may reduce the incidence of no-reflow phenomenon. A pilot randomised trial

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Abstract

Background: The results of percutaneous coronary intervention (PCI) for saphenous vein graft (SVG) disease are limited by distal embolisation and no-reflow which occurs in 10–43% of cases.

Aim: To examine the role of a new protocol of adenosine administration during PCI in SVG on immediate angiographic results and clinical course.

Methods: A prospective, single-centre, randomised placebo-controlled pilot trial in 32 consecutive patients after coronary artery bypass graft (aged 71 ± 12 years, 22 male) with stable and unstable angina (CCS II–IV), who were admitted to our hospital for SVG PCI, was conducted. Patients were randomised to two groups. Group A (16 patients) received two times adenosine (2 mg + 2 mg) to the SVG during PCI procedure, and Group B (16 patients) received a placebo.

Results: No reflow was observed in one (6.25%) patient in the adenosine group and six (37.5%) patients in the placebo group ($p = 0.0325$). TIMI 3 flow (94% vs. 63%; $p = 0.0322$) and corrected TIMI frame count < 28 (94% vs. 63%; $p = 0.0322$) at the end of the procedure were better in patients who received adenosine. Myocardial blush grade 2 and 3 at the end of the procedure was observed in 15 patients in the adenosine group and ten patients in the placebo group ($p = 0.083$). A trend toward a lower rate of myocardial infarctions in the adenosine group was observed (6% vs. 25%; $p = 0.144$).

Conclusions: Adenosine injections may be effective in preventing no-reflow in the setting of PCI of SVG. Adenosine administration seems to be associated with a more favourable clinical course.

Key words: adenosine, coronary artery bypass graft, percutaneous coronary intervention, no-reflow

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INTRODUCTION

The results of percutaneous coronary intervention (PCI) for saphenous vein graft (SVG) disease are limited by distal embolisation and no-reflow which occurs in 10–43% of cases [1–5]. The presence of no-reflow during SVG PCI has been associated with worsened short- and long-term outcomes and the risk of subsequent major adverse events, and its occurrence is associated with a 15% rate of mortality and a 31% rate of myocardial infarction (MI) [6–10]. At present, there are no uniform strategies for managing no-reflow during SVG interventions and the optimal medical therapy remains elusive [11–14]. Intravenous platelet glycoprotein (GP) IIb/IIIa receptor inhibition does not improve outcomes after PCI of bypass grafts, and in the absence of mechanical emboli protection may even be associated with a higher incidence of death and nonfatal ischaemic events [15]. Various treatment strategies, including the use of vasodilators such as verapamil, diltiazem, nitroglycerine and sodium nitroprusside, have been associated with an improvement in angiographic flow in several studies, but whether these treatment strategies affect clinical outcome, especially in SVG interventions, is not clear [5, 8, 9, 11, 12, 16, 17].

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We recently proposed a new and simple method of adenosine injection to prevent microvascular reperfusion injury and no-reflow in the setting of acute MI with ST segment elevation [18].

The aim of this study was to examine the role of our protocol of adenosine administration performed during PCI in SVG on immediate angiographic results and clinical course.

METHODS

Study plan

Patients with stable and unstable angina (CCS II–IV), who were admitted to our hospital for repeat coronary angiogram within the last 12 months with a history of coronary artery bypass graft (CABG), were considered for the study. Each patient received aspirin (300 mg) and clopidogrel (600 mg) at least 30 min before the procedure. Diagnostic coronary angiography was then performed using the femoral approach with the Judkins technique. If the culprit lesion suitable for PCI was present in the vein graft, and baseline Thrombolysis in Myocardial Infarction (TIMI) flow was good (TIMI flow 3), the patient was included in the study and randomised after informed consent had been obtained. Patients presenting with baseline TIMI 0–2 flow in the culprit graft were not included in the study. Patients with chronic obstructive pulmonary disease or asthma were also excluded. The study protocol was approved by the ethics committee of our institution, and informed consent was obtained from all patients.

Creatine kinase-MB (CK-MB) and troponins were assessed every 8 h during 24 h after index procedure, unless clinical events suggested repeat measurements. ECGs were performed immediately after the procedure and after 3, 12 and 24 h.

Physicians in charge of patients in the coronary care ward were informed of the angiographic results of PCI, but were blinded to the study treatment administered during the procedure. Patients received standard pharmacological treatment including aspirin, clopidogrel, beta-blockers, angiotensin-converting enzyme inhibitors and statins, unless contraindicated. Significant major cardiac events within hospital stay including death and MI were recorded. Death included mortality from all causes. MI was defined as: (1) evolutionary ST-segment elevation, development of new Q waves in ≥ 2 contiguous electrocardiographic leads, or new left bundle branch block on ECG; or (2) biochemical evidence of myocardial necrosis, manifested as (a) CK-MB ≥ 3 times the upper limit of normal or (b) troponin value above $> 5 \times 99^{th}$ percentile of upper reference limit.

The primary study end points were: 1) the incidence of no-reflow (final TIMI flow grade at the end of procedure); 2) TIMI frame count at the end of the procedure; and 3) myocardial blush grade (MBG) at the end of the procedure. Secondary end-points were: 1) the feasibility and safety of the new protocol of intracoronary adenosine administration in the setting of SVG PCI; and 2) the composite end-point of death and MI within hospital stay.

Patients were also followed for cardiac events (death, MI, heart failure and reinterventions) at six months after hospital discharge (telephone interview).

PCI procedure

The PCI procedure was started with an intravenous administration of heparin (100 U/kg). After placing the guiding catheter in the ostium of venous graft, either adenosine (2 mg in 10 mL 0.9% NaCL) or saline (10 mL 0.9% NaCl) was rapidly hand-injected through the guiding catheter. The stenosis of the venous graft was then crossed with a filter device (FilterWire™, Boston Scientific), which was opened in the distal part of the graft. Immediately after crossing the lesion again, either adenosine (2 mg in 10 mL 0.9% NaCL) or saline (10 mL 0.9% NaCl) was rapidly hand-injected into the graft through the guiding catheter. After 1 min, the balloon catheter was advanced to the stenotic segment, positioned at the level of the obstruction, and dilated with low-pressure (4–6 ATM) for a few seconds. The dilation procedure was completed according to the standard technique. Stenting of the predilated vein graft segment was performed in all cases with drug-eluting stents. After the end of the procedure (defined for that study as completion of the dilation procedure and filter device removal), a second contrast injection for the assessment of TIMI flow and MBG was performed. The invasive procedure was limited to the culprit lesion in all patients. Choice of medication(s), the dose and the route of injection, and the order of different drugs (including GP IIb/IIIa inhibitors) in the case of no-reflow after the end of the procedure were made at the discretion of the operator.

The angiograms were reanalysed as a single group, in chronological sequence, by two observers who had not participated in the invasive procedure and were blinded to the treatment received. TIMI flow grade was assessed as defined previously. No reflow was defined as TIMI flow grade 0, 1, or 2 following stent implantation and removal of filter device not caused by an abrupt closure, spasm or significant stenosis at the target lesion as well as distal macroembolisation with angiographic filling defect. Degenerated SVG was defined as luminal irregularities or ectasia involving more than 50% of its total length. SVG lesion was called diffuse if it measured > 20 mm in length, and discrete or focal if < 10 mm. Thrombus was judged to be present if angiography demonstrated a discrete, intraluminal filling defect with defined borders, largely separated from the adjacent wall, with or without contrast staining.

An analysis of coronary flow was done according to the TIMI frame count method as described by Gibson et al. [11, 19]. MBG was assessed by the method described by Van't Hof et al. [20]. MBG was assessed by two observers who were blinded to each other and to the clinical data.

Table 1. Baseline clinical characteristics of the two study groups

	Adenosine (n = 16)	Placebo (n =16)	P
Age [years]	69 ± 11	72 ± 13	0.4865
Male sex	12 (75%)	10 (62.5%)	0.4456
Hypertension	10 (62.5%)	11 (68.8%)	0.7074
Diabetes mellitus	8 (50%)	7 (43.8%)	0.7253
Hypercholesterolaemia	10 (62.5%)	9 (56.3%)	0.7210
Smoking	5 (31.3%)	4 (25%)	0.6919
Prior myocardial infarction	13 (81.3%)	12 (75%)	0.6663
Left ventricular ejection fraction [%]	45.3 ± 13	43.4 ± 12	0.6706
Heart failure (NYHA II–IV)	5 (31.3%)	5 (31.3%)	1.000

Table 2. Lesion/procedural characteristics of the two study groups

	Adenosine (n = 16)	Placebo (n = 16)	P
Time since CABG [years]	8.5 ± 5.3	9.1 ± 4.4	0.7300
Location of graft:			
Left anterior descending artery	4 (25.0%)	3 (18.8%)	0.6715
Left circumflex artery	6 (37.5%)	5 (32.2%)	0.7531
Right coronary artery	6 (37.5%)	8 (50.0%)	0.4760
Lesion characteristic:			
Diffuse	12 (75.0%)	11 (67.8%)	0.6522
Focal	4 (25.0%)	5 (32.2%)	0.6522
Thrombus	4 (25.0%)	3 (18.8%)	0.6715
Degenerated graft	4 (25%)	3 (18.8%)	0.6715
Treatment site:			
Ostial	4 (25.0%)	4 (25.0%)	1.000
Body	10 (62.5%)	9 (56.2%)	0.7168
Distal	2 (12.5%)	3 (18.8%)	0.6238
Percutaneous coronary intervention:			
Mean stents (n)	1.4	1.3	
Mean stent(s) (length)	32.0 ± 15.3	31.0 ± 14.8	0.8522
Mean stent(s) (diameter)	3.6 ± 1.3	3.5 ± 1.5	0.8417

CABG — coronary artery bypass grafting

Statistical analysis

Data was expressed as means ± standard deviation for continuous variables and as percentage for categorical variables. Continuous variables were compared with the use of non parametric tests (Mann-Whitney U test). Chi-square test or Fisher's exact test was used to compare categorical variables. A p value of < 0.05 was considered significant. Statistical analysis was performed using Statistica version 8.0.

RESULTS

Thirty two patients (aged 71 ± 13 years, 22 male) were included in the study. Patients were randomised to two groups based on a computer-generated randomisation schedule. Group A (16 patients) received two times adenosine to the SVG during PCI procedure, and Group B (16 patients) received a placebo. Baseline clinical and angiographic characteristics of the two groups were similar (Tables 1, 2).

No reflow was observed in one (6.25%) patient in the adenosine group and six (37.5%) patients in the placebo group ($p = 0.0325$) (Fig. 1). TIMI 3 flow and corrected TIMI frame count (CTFC) at the end of the procedure were better in patients who received adenosine (Fig. 2).

MBG 2 and 3 at the end of the procedure was observed in 15 (93.75%) patients in the adenosine group and ten (62.5%) patients in the placebo group ($p = 0.083$) (Fig. 3).

The injections of adenosine or saline directly to the vein grafts were well tolerated and free of significant side effects. No patients complained of worsening of chest pain

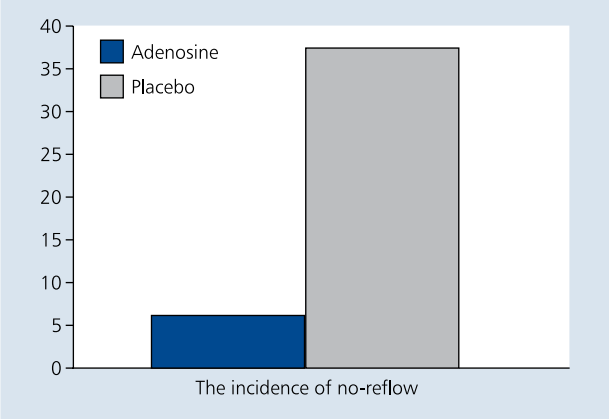
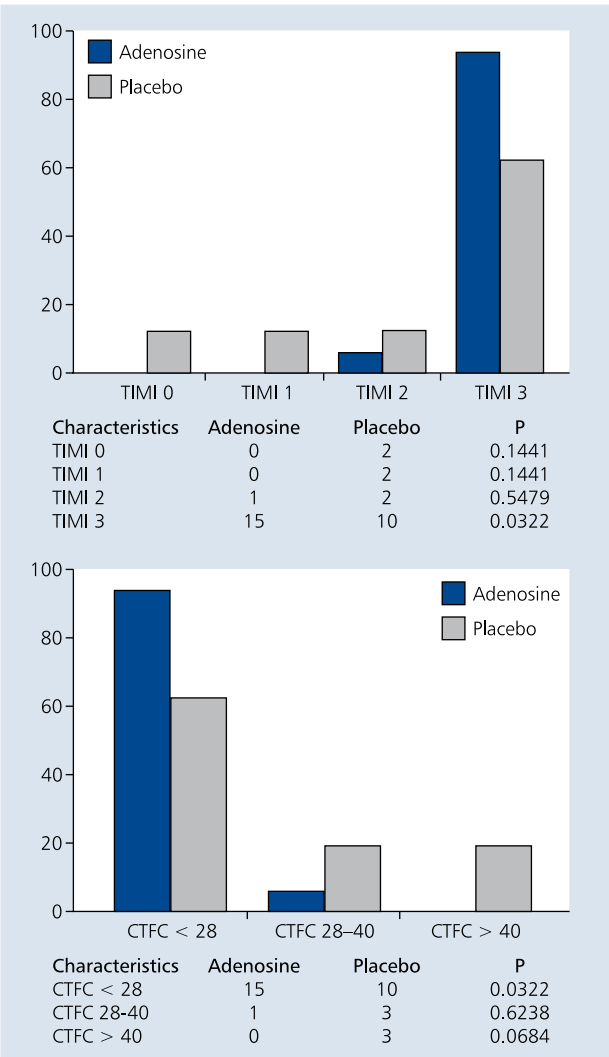


Figure 1. The incidence of no-reflow at the end of the procedure (% of patients with TIMI flow grade 0, 1 and 2)



Characteristics	Adenosine	Placebo	P
TIMI 0	0	2	0.1441
TIMI 1	0	2	0.1441
TIMI 2	1	2	0.5479
TIMI 3	15	10	0.0322

Characteristics	Adenosine	Placebo	P
CTFC < 28	15	10	0.0322
CTFC 28-40	1	3	0.6238
CTFC > 40	0	3	0.0684

Figure 2. Angiographic results — Thrombolysis in Myocardial Infarction (TIMI) flow and TIMI frame count at the end of the procedure in the two study groups (% of patients within a certain category of TIMI flow or corrected TIMI frame count — CTFC)

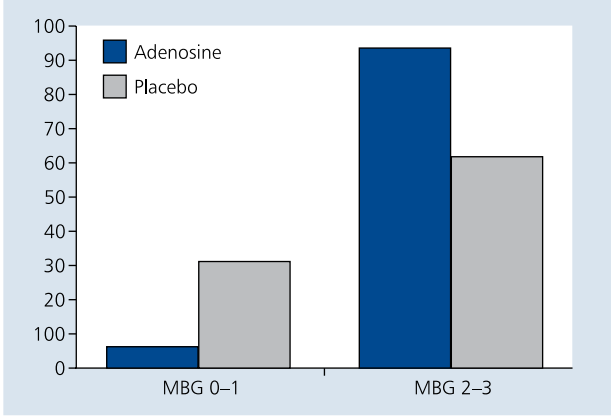


Figure 3. Angiographic results — myocardial blush grade (MBG) at the end of the procedure in the two study groups (% of patients within certain categories of MBG: MBG 0–1 vs. MBG 2–3)

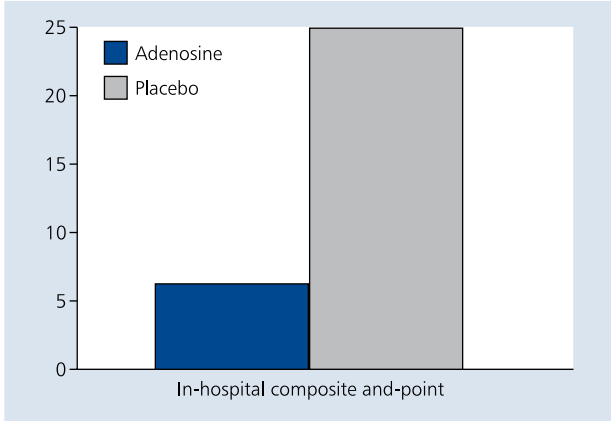


Figure 4. The composite end-point of death and myocardial infarction in the adenosine group and the placebo group during hospital stay (% of patients with the event)

or suffered from haemodynamic instability. Bradyarrhythmias including asystole and 3 degree atrioventricular block were observed in four patients. They were observed only after adenosine injection, lasted for a few seconds (max. 20 s), resolved spontaneously or after patients' cough, and did not require temporary pacing in any patient.

There were no deaths in our study group. We noted a trend (although not statistically significant) toward a lower rate of MI in the adenosine group (one patient) than in the placebo group (four patients) ($p = 0.144$) (Fig. 4). MI was diagnosed based on biochemical evidence of myocardial necrosis, manifested as CK-MB $\geq$ 3 times the upper limit of normal (four patients — all from the placebo group) or troponin value $> 5 \times 99^{th}$ percentile of upper reference limit (five patients — four from the placebo group and one from the adenosine group). Peak CK-MB was 31 $\pm$ 20 U/L in the adenosine group and 86 $\pm$ 55 U/L in the placebo group

(p = 0.0893). Also peak troponin levels were not different between the two study groups — peak troponin I in the adenosine group was 1.8 ± 1.7 ng/mL and 6.5 ± 5.0 ng/mL in the placebo group (p = 0.1893). New ECG changes with development of new Q waves in ≥ 2 contiguous electrocardiographic leads were observed only in one (6.25%) patient from the placebo group.

Five patients who developed no-reflow (all from the placebo group) were treated with multiple (average 3.2 ± 1.2) repeated and rapid boluses of adenosine (1–2 mg in 10 mL 0.9% NaCL). This resulted in restoring TIMI 3 flow in two of these patients. Since the TIMI flow was not completely re-established in the remaining three patients, GP IIb/IIIa inhibitors (abciximab) were given (at the discretion of the operator) to those patients — however, that did not result in a significant improvement of TIMI flow in any of these patients. The intraaortic balloon pump was not used in any patient.

There were no cardiac deaths in our study group during the six-month follow-up. Recurrent nonfatal MI were observed in three patients (one in the adenosine group and two in the placebo group) (p = 0.5479). During the six-month follow-up, 17 patients presented heart failure symptoms (NYHA class II–IV) compared to ten patients before intervention — six from the adenosine group and 11 from the placebo group (p = 0.0760). Heart failure symptoms developed in four patients from the placebo group in whom no-reflow was observed during initial intervention (three with persistent no-reflow and one with no-reflow reversed with multiple repeated boluses of adenosine). Clinically driven reintervention (PCI) was necessary in four patients (two from the adenosine group and two from the placebo group) (p = 1.0000).

DISCUSSION

The major observation from our pilot study is that our new, simple protocol of relatively high dose adenosine injections through a guiding catheter is effective in preventing no-reflow in the setting of PCI of SVG and gives additional benefits, even in the presence of distal protection devices. We have noted significantly better TIMI flow and CTFC in the adenosine group compared to the placebo group. Adenosine usage was also associated with a borderline improvement in the presence of MBG grade 2–3 at the end of the procedure compared to the placebo.

The no-reflow phenomenon occurs at a high rate after degenerated SVG interventions [2–7]. This is particularly true if the lesions are diffuse, with angiographic haziness, filling defects or ulcerations [1]. The strict definition of no-reflow in this study (TIMI flow < 3) may have overestimated the incidence of no-reflow, however even 'slow flow episodes' (TIMI 2 flow), if prolonged, have been associated with significant ischaemia and myocardial necrosis, as in our study and placebo groups.

Intracoronary adenosine injection may be followed by transient atrioventricular block. However, injections of relatively high-dose adenosine directly to the vein graft, as in our study protocol, were well tolerated and free of significant side effects. Our safety findings are in accordance with other studies which used similar protocols of adenosine infusions [17, 18, 21–24]. The composite secondary end-point of death and MI was lower, although not significantly, in the adenosine than in the placebo group. It must be pointed out, however, that all these MI (except one) were diagnosed based on biochemical parameters such as CK-MB and/or troponins, but they may also be associated with an adverse prognosis, as previously demonstrated [4–7, 16]. Also, six-month follow-up data may suggest some beneficial effects of adenosine, especially with regards to the development of heart failure.

To date, the optimal prophylaxis and management of the no-reflow phenomenon remains unknown. Since it occurs in a variety of clinical settings and is likely to have multiple mechanisms, it is unlikely that a single definitive treatment would be a sufficient therapy for all cases [8, 10–12, 16].

We can only speculate as to the mechanism with which adenosine reduced the no-reflow phenomenon in our study group. Although the mechanisms responsible for microvascular injury with subsequent decrease in myocardial blood flow are complex and diverse, adenosine appears to be a crucial counter-regulatory compound in the maintenance of microcirculatory flow due its numerous pharmacological actions.

Adenosine could decrease mechanical obstruction of capillary channels caused by neutrophil adherence and neutrophil-mediated cellular damage. The potent arteriolar vasodilator properties of adenosine would oppose the effects of vasoconstrictor substances present in the vascular bed, such as endothelin, leukotriens and platelet activating factor [17]. Adenosine is also an important modulator of neutrophil function. It markedly inhibits superoxide anion production by neutrophils and decreases the number of neutrophils in the reperfused bed. In addition, the ability of adenosine to reduce inflammation by inhibiting multiple cell types involved in cellular immunity may also contribute to tissue protection [17]. Adenosine moreover possesses a number of physiological effects that may reduce free radical formation following ischaemia and it also restores calcium homeostasis [17].

Several studies have investigated the benefits of preventive use of intracoronary adenosine during and after reperfusion therapy for acute MI on angiographic parameters, including no-reflow, and its clinical course. A summary of these studies is presented in Table 3 and was also described in detail in a review article which has been published by our group just recently [25–27].

Although data regarding the usage of adenosine in the setting of SVG interventions is very limited, it has been shown that no-reflow can be safely and effectively reversed by the delivery of intragraft adenosine. Fischell et al. [28] in a small study group of eight patients showed that rapid and repeated high-velocity intragraft administration of adenosine

Table 3. Summary of randomised trials comparing intracoronary adenosine to placebo in patients with acute myocardial infarction with ST segment elevation treated with primary percutaneous coronary intervention

Study/ /author	Journal [year]	Number of patients	Reper-fusion strategy	Route of adenosine	Dose of adenosine	Follow-up time [months]	Short summary of results
Marzilli et al. [21]	Circulation (2000)	54	PCI	IC	4 mg (1 min)	In-hospital	Improved angiographic flow and ventricular function Less MACE
Stoel et al. [23]	Catheter Cardiovasc Int (2008)	51	PCI	IC	60 mg (5–10 min)	12	Better ST segment resolution, TIMI flow, TFC and MBG No difference in MACE
Grygier et al. [18, 33]	Am J Cardiol (2011) Cardiology (2013)	70	PCI	IC	2–4 mg (quickly)	12	Better ST segment resolution, TIMI flow, TFC and MBG Less MACE
Fokkema et al. [25]	Circ Cardiovasc Int (2009)	448	PCI	IC	2 × 120 μg (quickly)	1	No difference in ST segment resolution, TIMI flow and MBG No difference in MACE
Desemet et al. [26]	Eur Heart J (2011)	110	PCI	IC	4 mg (quickly)	12	No difference in ST segment resolution, TIMI flow and MBG No difference in MACE

IV — intravenous; IC — intracoronary; MACE — major adverse cardiac events; MBG — myocardial blush grade; TIMI — Thrombolysis in Myocardial Infarction; TFC — TIMI frame count

promptly reverses no-reflow events complicating PCI and stenting of diseased SVG. Sdringola et al. [29] examined the efficacy of adenosine boluses (24 μg each) to reverse no-reflow events. Reversal of no-reflow was observed in 91% of patients who received high doses of adenosine (≥ 5 boluses) and only in 33% of those who received low doses (< 5 boluses). Moreover, final TIMI flow was significantly better in the high dose than in the low dose group. Also the results of our study suggest that repeated boluses of relatively high dosage of adenosine may have some beneficial effects on reversing no-reflow in at least some of the patients. Other authors have suggested that combined therapy with adenosine and nitroprusside [30] or nicorandil [31] may provide better improvement in coronary flow compared to intracoronary adenosine alone in case of impaired flow during coronary interventions. Figures regarding the prevention of no-reflow with different drugs including adenosine are even weaker [10–12, 15, 16]. Sdringola et al. [29] reported that prophylaxis with multiple doses of adenosine was ineffective in preventing no-reflow in this setting. However, the dosage of adenosine in that study was very low (24 to 48 μg) compared to our treatment group. So it is possible that the dose and method of administration of adenosine were not adequate to prevent no-reflow in that study. On the other hand, intracoronary adenosine bolus (24 to 48 μg) administered during rotational atherectomy significantly reduced the incidence of no-reflow [32].

Limitations of the study

It should be emphasised that this report is intended to be a relatively rapid publication of a pilot randomised trial. It is not intended as a definitive scientific study of the prevention of no-reflow in cases of SVG interventions. The major limitation of the study was the sample size. Also the primary end-points were mostly surrogate end-points (no-reflow, TIMI flow, CTFC, MBG). The assessment of TIMI flow and MBG could be subjective, although our interpreters were blinded to treatment. The study follow-up was limited to only six months after the procedure. Larger studies are necessary to confirm these observations.

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CONCLUSIONS

Adenosine injections may be effective in preventing no-reflow in the setting of PCI of SVG. Adenosine administration seems to be associated with a more favourable clinical course.

Conflict of interest: *none declared*

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Podawanie adenozyny w trakcie zabiegów na pomostach wieńcowych może zmniejszać częstość występowania zjawiska *no-reflow*: pilotażowe badanie randomizowane

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Streszczenie

Wstęp i cel: Celem badania była ocena nowego protokołu podawania adenozyny stosowanego w trakcie zabiegów przezskórnej interwencji wieńcowej (PCI) w pomostach żylnych na bezpośrednio oceniane parametry angiograficzne i rokowanie kliniczne.

Metody: Prospektywne, jednoośrodkowe, randomizowane i kontrolowane placebo badanie przeprowadzono w grupie 32 kolejnych chorych po zabiegu bezpośredniej rewaskularyzacji serca (CABG) (71 ± 12 lat, 22 mężczyzn), przyjętych do szpitala z powodu dławicy piersiowej stabilnej lub niestabilnej (CCS II–IV), w celu wykonania koronarografii i angioplastyki pomostu żylnego. Pacjentów randomizowano do jednej z dwóch grup. Chorzy w grupie adenozyny (Grupa A, n = 16) otrzymywali 2-krotnie adenozynę (Grupa B, 2 mg + 2 mg) bezpośrednio do pomostu żylnego w trakcie zabiegu angioplastyki, natomiast chorym w grupie placebo (n = 16) podawano placebo.

Wyniki: Zjawisko *no-reflow* zaobserwowano u 1 (6,25%) chorego w grupie adenozyny i u 6 (37,5%) osób w grupie placebo (p = 0,0325). Przepływ TIMI 3 (94% *vs*. 63%; p = 0,0322) oraz CTFC < 28 (94% *vs*. 63%; p = 0,0322) po zakończeniu zabiegu były lepsze w grupie adenozyny niż placebo. Prawidłowe zmatowienie miokardium (MBG 2 i 3) po zakończeniu procedury zaobserwowano u 15 chorych w grupie adenozyny i 10 w grupie placebo (p = 0,083). Zanotowano także trend w kierunku niższego odsetka zawałów serca w grupie adenozyny niż placebo (6% *vs*. 25%; p = 0,144).

Wnioski: Podawanie adenozyny w trakcie zabiegów angioplastyki na pomostach wieńcowych może zmniejszać częstość występowania zjawiska *no-reflow*. Adenozyna wydaje się korzystnie wpływać na rokowanie kliniczne.

Słowa kluczowe: adenozyna, pomostowanie aortalno-wieńcowe, przezskórna interwencja wieńcowa, zjawisko *no-reflow*

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