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Coronary No-reflow Phenomenon: A Review of Therapeutic Pharmacological Agents

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Abstract

Coronary no-reflow phenomenon (CNRP) is one of the leading catastrophic consequences of percutaneous coronary intervention (PCI). Although several preventive strategies have been advised, yet CNRP is not entirely controlled with pharmacological agents after diagnosis. This study is a review of therapeutic pharmacological agents used in various studies for post-PCI-CNRP. Several pharmacological agents have been introduced for reducing the burden of adverse outcome, before or during PCI. Although most of these agents have shown a remarkable effect on post-PCI CNRP incidence reduction, and it seems more powerful are still needed for a better validation of the results. It appears that intra lesion and distal intracoronary administrations would have a less systemic effect, and therefore may be safer than catheter injection. Moreover, adenosine, sodium nitroprusside, and calcium channel blockers are among the most routinely used methods. However, we believe that the best approach in treating or preventing no-reflow post-STMI might be combinational therapy. By the way, although there have been numerous studies on different agents capable of lessening the noreflow phenomenon, yet there is no exact guideline for choosing the most appropriate drug. A systematic review and meta-analysis on all available or practiced combinational pharmacotherapies to prevent PCI-related no-reflow are needed to suggest the most appropriate therapy.

Keywords: Coronary no-reflow phenomenon, Pharmacotherapy, adenosine, nitroprusside, review

1. Introduction

Coronary no-reflow phenomenon (CNRP) occurs when, despite percutaneous coronary intervention (PCI) and opening up the occluded vessel, the myocardial reperfusion does not naturally happen [1]. This phenomenon may occur in more than 10% of the cases of primary PCI, worsening the survival rate of the patients [2]. Although the underlying pathogenic mechanism is not yet completely known, it is evident that thrombus in the human artery after PCI or stent placing may result in small distal emboli, thereby reducing coronary flow and no-reflow [3.4]. In addition, some clinicians believe that CNRP may be secondary to microvascular arteriolar spasm and abrupt flow stop after myocardial infarction, thrombolysis in myocardial infarction (TIMI) zero flow [5].

The CNRP may have long-term consequences, including myocardial necrosis lesion, which traps blood flow and results in a lack of normal existence of macrophages and hormones needed for removal of the debris and healing of the infarcted area. Moreover, CNRP may cause adverse left ventricle remodeling, resulting in heart failure and mortality [6]. Although several preventive strategies, such as thrombus aspiration before PCI or avoiding stent deployment at very high pressure, have been advised, CNRP is out of individual control and pharmacological treatment after diagnosis [5]. In recent years, several pharmacological agents have been identified as effective in the prevention and treatment of CNRP after PCI. Some of these pharmacological agents are now routinely administered and some are not. These agents can be either intracoronarily or intravenously administered. With this background in mind, the current study aimed to review all routinely and nonroutinely administered

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pharmacological therapeutic agents and their efficacy in CNRP.

2. Pharmacologic therapy

2.1. Adenosine

Adenosine is an endogenous nucleoside that is usually produced by the degradation of adenosine triphosphate (ATP) and made by occluded coronary vessels after the flow stoppage. It acts on smooth muscles of cardiac vessels through its vasodilator effect, improving coronary blood flow. Moreover, it antagonizes neutrophils as well as platelets and prevents calcium overload. In addition, it activates the one-way movement of potassium into cardiomyocytes [7, 8]. Therefore, hyperpolarization occurs and calcium-channel dependent action potentials become suppressed [9, 10]. Despite all adenosine known actions, the exact mechanism by which it affects no-reflow after PCI is yet not clear [11]. In a randomized controlled trial, Xiaowei et al. observed that intracoronary adenosine after PCI administration increased the coronary flow and reperfusion without adverse effects on cardiovascular outcomes [12]. Two previous randomized trials (i.e., AMISTAD [13] and AMISTAD II [14]) reported that intravenous adenosine infusion downturns infarct size. However, it was not effective in reducing the incidence of mortality and congestive heart failure in patients with acute myocardial infarction (AMI).

2.2. Calcium channel blockers

Calcium channel blockers (CCBs) are well tolerated far-reaching antihypertensive drugs [15], with beneficial cardiovascular effects on patients at high risk of cardiovascular diseases [16]. They are also used for the treatment of no-reflow following an AMI [12]. Impaired myocardial perfusion after blood flow obstruction is associated with vaster infarct size [17], worsened clinical outcomes, adverse remodeling of the left ventricle, and reduced left ventricular ejection fraction (LVEF) [18]. Vasodilator therapy with CCBs is a currently available treatment to avoid these consequences [19]. In a randomized controlled trial, Zhao JL et al. examined the efficacy of CCBs with adenosine in PCI-related no-reflow. They suggested that both could significantly lessen the size of the no-reflow area. However, in comparison to CCB, adenosine also positively affected the necrosis area [20]. That is why it is said that adenosine both structurally and functionally improves the no-reflow phenomenon [21, 20].

2.3. Sodium nitroprusside

Sodium nitroprusside (SNP) is considered a potent vasodilator in arterioles and venues. The SNP has to break down into circulation to release nitric oxide (NO) [22]. NO has a variety of activities, including antiplatelet as well as anti-inflammatory activities [23, 24]. It is assumed that SNP leads to the increase of reperfusion in PCI-related no-reflow as a result of vascular smooth muscle relaxation and hyperemia, due to the NO-releasing capacity of nitroprusside [25-27]. The results of another study showed that patients receiving nitroprusside had a better angiographic blood flow (P>0.01) and improved TIMI flow in 82% of cases [28, 29]. The combined therapy of adenosine and nitroprusside improved TIMI flow more than adenosine therapy (1.5±1 vs. 0.8±0.6; P<0.005) [28]. Moreover, although the systemic effect of distally-injected intracoronary nitroprusside is minor, it significantly improves blood flow [5].

Zhao et al. studied nitroprusside efficacy from the aspect of the improvement of ST-segment elevation resolution (STR), LVEF, TIMI flow grade, and adverse cardiac events in two groups, including tirofiban alone and tirofiban plus nitroprusside group, indicating an improvement with nitroprusside group [5]. Considering the fact that TIMI flow in the two groups was similar, it was concluded that myocardial blush grade is a more reliable strategy to define pharmacotherapy efficacy in reperfusion injury [5]. Statistically significant effect of SNP on the treatment of PCI-related reperfusion injury regarding TIMI frame count was also proven in comparison to that reported for nicorandil [30]. In another study, Parham et al. demonstrated that both adenosine and nitroprusside had a similar effect on hyperemia (and maybe no-reflow) although the improved results for blood flow development favored SNP [31].

In another study, the effect of prophylactic intracoronary injection of sole adenosine and adenosine plus SNP before PCI was investigated during a 6 months follow-up [32]. Thrombolysis in myocardial infarction flow grade (TFG) was higher in the control group (i.e., sole adenosine administration) than that reported for the nitroprusside plus anisodamine group (odds ratio [OR]: 1.85; 95% CI: 1.23-2.86). Furthermore, STR significantly reduced in comparison to that reported for anisodamine (OR: 0.36; 95% CI: 0.17-0.82) and nicorandil (OR: 0.37; 95% CI: 0.14-1.00). The LVEF in the control group was significantly lower than that of the nitroprusside group (95% CI: 6.18-0.27). Moreover, major adverse cardiac events (MACE) were less frequent in the nitroprusside group than those reported for the control group (OR: 1.23; 95% CI: 0.69-2.19) [32].

2.4. Glycoprotein IIb/IIIa inhibitors (i.e., eptifibatide, abciximab, and tirofiban)

The use of glycoprotein IIb/IIIa inhibitors is common

during PCI. These drugs are classified as antiplatelet and antithrombus formation glycoprotein IIb/IIIa antagonizes platelet aggregation by the inhibition of the glycoprotein IIb/IIIa receptor on the surface of the platelet [33]. One of the suggested mechanisms of post-PCI CNRP is platelet aggregation. These drugs inhibit the final pathway of platelet formation. Glycoprotein IIb/IIIa inhibitors could have potential benefits during PCI for the prevention of CNRP after acute coronary syndrome intervention [34]. A meta-analysis carried out by Tao Qin et al. evaluated the efficacy and safety of intracoronary tirofiban during PCI in the improvement of TIMI flow and MACE. The results of the aforementioned study showed that tirofiban significantly improved TIMI flow (OR: 0.24; 95% CI: 0.15-0.37; P<0.00001), compared to conventional pharmacological agents for NR [35]. Koon-Hou Mak et al. proved the association of 87% reduction in distal embolization with abciximab during percutaneous treatment in vein graft disease. They believed that it points to the fact that the most suggestive mechanism of distal emboli is platelet aggregation [36]. Benjie Sun et al. in a meta-analysis included six randomized controlled trials indicating that the intralesional administration of glycoprotein IIb/IIIa inhibitors gained better results in TIMI grade 3 flow (OR: 2.29; 95% CI: ; STR [OR: 1.55; 95% CI: 1.12-2.14; P=0.008) [37].

2.5. Nitroglycerin

Nitroglycerin has been medically used as a potent vasodilator as it converts to nitric oxide (i.e., a potent vasodilator). Ischemia originates either from focal epicardial spasm or distal plaque embolization showing that nitroglycerin may be effective in epicardial-spasm ischemia [38]. A study carried out by Piana et al. investigated the patients undergoing PCI and intracoronary nitroglycerin administration just before PCI, followed by verapamil, and indicated that most of the patients did not respond to nitroglycerin. Two of the patients were treated with nitroglycerin alone plus balloon inflation, in which the partial improvement of TIMI flow was observed [37]. In another retrospective study, Sitaram et al. compared intracoronary administration of nitroprusside and nitroglycerin in STEMI patients undergoing PCI from the aspect of no-reflow incidence and TIMI flow. The incidence of no-reflow in the nitroprusside group was lower than that reported for the nitroglycerin group (19% vs. 36%; P=0.0442) and almost the same TIMI flow grade (III: II:I: 31:2:1:0 vs. 29:4:2:0; P=0.5524) and improved blush grade for the nitroprusside group [39].

2.6. Epinephrine

Epinephrine is a beta-2-agonist, with potent coronary vasodilatory effect and chronotropic and inotropic effect on the heart [40]. Aksu et al., in their retrospective study, suggested the use of intracoronary epinephrine as an alternative treatment for no-reflow post-primary PCI. The results of the aforementioned study showed that in 75% of patients treated with epinephrine, normal perfusion successfully returned. In addition, epinephrine did not have major adverse effects and was well tolerated [39].

2.7. Nicorandil

Nicorandil, as an anti-angina medication, has proven to have dual properties of nitrate and potassium (K^+) ATP channel agonist. It affects K^+ channels, promoting K^+ efflux as well as the ensuing hyperpolarization, and inhibits voltage-gated calcium channels, which leads to smooth muscle relaxation and vasodilation of the coronary arteries [41]. Nicorandil probably prevents reperfusion injury by blocking mitochondrial permeability transition pore (MPTP) [42]. Moreover, it seems that the effect of nicorandil on CNRP is due to its K^+ATP channel agonist action causing pharmacological preconditioning and providing cardioprotective effects against ischemia [43]. In another study, it is declared that intravenous nicorandil just before PCI was related to a lower incidence of CNRP, better ventricular function, and improved clinical outcomes [44].

Another clinical study investigated a combinational therapy of adenosine plus nicorandil resulting in the reduction of CNRP incidence and improved clinical outcome of AMI than sole adenosine administration [45]. Another study carried out by Tsuneo Mizumuraet al. demonstrated a relationship between the reduction of nicorandil infarct size and its KATP channel mechanism (not nitrate-like property) [46]. Another study assessed the efficacy and safety of nicorandil in comparison to verapamil indicating that nicorandil is both safer and more effective than verapamil in CNRP prevention [47]. Another study compared the use of nitroprusside and nicorandil for the treatment of CNRP and concluded a better TIMI flow grade for nitroprusside and almost the same efficacy in the improvement of blood flow for both agents [30].

2.8. Cyclosporine A

As a potential cardioprotective, cyclosporine A is an immunosuppressive agent blocking MPTP. Due to the aforementioned mechanism, Piot C et al. assessed intravenous cyclosporine administration during PCI and regarded it as an efficient agent in the improvement of no-reflow [48]. A study carried out by Kucukcelebi et al. also examined the efficacy of cyclosporine A in the improvement of reperfusion injury in rat skin island flaps. According to the results of the aforementioned

study, this agent is considered statistically beneficial in the improvement of survival rate due to the treatment or prevention of the no-reflow phenomenon [49].

2.9. Anticoagulants (dabigatran)

Dabigatran is an anticoagulant agent belonging to the category of direct thrombin inhibitors (DTIs) or novel DTIs functioning by directly inhibiting both free and fibrin-bound thrombin [50]. Spangle et al. in their study examined the blood samples of PCI candidates for ST-elevation myocardial infarction (STEMI) just before and at the end of PCI in addition to 2, 6, and 12 h after angiography. A rapid increase of thrombin occurred during PCI in 69% of patients, which is suggestive of the potential benefits of antithrombin agents for CNRP [51]. However, Hale SL et al. evaluated the efficacy of dabigatran in the no-reflow model and declared that dabigatran did not affect the improvement of blood flow to the infarct area [52].

2.10. Liraglutide

Liraglutide is a derivative of human incretin (i.e., metabolic hormone) glucagon-like peptide-1 (GLP-1) that is used as a long-acting GLP-1 receptor agonist. This agent binds to the same receptors, as does the endogenous metabolic hormone GLP-1, stimulating insulin secretion [53]. Based on the results of their clinical study, Wei Ren Chen et al. suggested that liraglutide is associated with lower incidence of CNRP in patients undergoing PCI for STEMI in comparison to that reported for the control group (5% vs. 15%; P=0.01). Wei Ren Chen et al. also confirmed the efficacy of liraglutide in the reduction of myocardial injury and improvement of reperfusion [54].

2.11. Anisodamine

Anisodamine, an anticholinergic and alpha-1 adrenergic receptor antagonist, is a tropane alkaloid observed in some plants of the Solanaceae family. Many fundamental studies have proven the efficacy of anisodamine in the improvement of microvascular flow [55]. In a meta-analysis carried out by Niu et al., it was demonstrated that the intracoronary administration of anisodamine would help to improve myocardial reperfusion, clinical outcomes, cardiac function, and TFG with no MACE [56]. A clinical study conducted by Fu XH et al. studied a group of nitroglycerin intracoronary administration and a group treated by intracoronary anisodamine after nitroglycerin. The results of the aforementioned study showed that anisodamine might have a significant effect on relieving microvascular spasm in addition to the MACE effect [57].

2.12. Melatonin

Melatonin is a hormone produced by the pineal gland which is involved in the circadian rhythm as well as being a potent free radical scavenger and electron donor [58]. Due to the anti-inflammatory, antioxidant, and lipid regulatory actions of melatonin, it is imaginable to regard it as an effective agent in post-PCI coronary flow improvement [59]. RJ Reiter declared that melatonin could prevent ROS and therefore might have a potential role in overcoming cardiovascular diseases and reperfusion injury [60].

2.13. Atorvastatin

Atorvastatin is a lipid-lowering agent of the statin drug class which is routinely prescribed for the prevention of cardiovascular diseases [61]. As most of the no-reflow cases present a high serum lipoprotein, there might be an association between hyperlipidemia and reperfusion injury. A previous trial showed that high-dose statin therapy before PCI promoted prognosis and decreased CNRP incidence [62]. In another study, high doses of atorvastatin at least days before elective PCI was related to lower incidence of myocardial infarction (the incidence of myocardial infarction in the atorvastatin group reported as 9.5% and in the control group without prophylactic atorvastatin reported as 15.8%; OR: 0.56; 95% CI: 0.35-0.89; P=0.014) [63].

2.14. N-acetyl cysteine

N-acetyl cysteine (NAC) is a prodrug of L-cysteine, which in addition to other properties, provides antioxidative effects. Younes Nozari et al. assessed the potential role of NAC (due to its anti-oxidant action) and observed remarkable improvement of myocardial reperfusion [64]. Another study carried out by Neil P Andrews et al. evaluated the effect of NAC on blood flow change and compared the differences in two postmyocardial infarction reperfusion groups. Firstly, when patients received adenosine and secondly when they received NAC following adenosine. The vasodilation effect pattern of adenosine neither increased nor decreased after NAC administration; however, NAC could improve coronary and vascular function [65]. In another study, the improvement of lung blood flow injury after other organ's transplantati.

3. Conclusion

The CNRP is an essential consequence of PCI for reperfusion, leading to impaired blood flow, increasing infarct size, reducing LVEF, and increasing the mortality rate. Several pharmacological agents have been introduced for reducing the burden of this adverse outcome before or during PCI. Although most of these agents have shown a remarkable effect on the reduction of post-PCI CNRP incidence, it seems more powerful are still required for a

better validation of the results. It appears that intralesional and distal intracoronary administrations would have a less systemic effect and therefore may be safer than catheter injection. Moreover, adenosine, SNP, and CCBs are among the most routinely used agents. However, it is believed that the best approach in the treatment or prevention of no-reflow post-STMI might be combinational therapy. In addition, although there have been numerous studies carried out on different agents capable of lessening the no-reflow phenomenon, there is no exact guideline for the selection of the most appropriate drug. It is required to carry out a systematic review and meta-analysis on all available or practiced combinational pharmacotherapies for the prevention of PCI-related no-reflow to suggest the most appropriate therapy.

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