Original Article

Protective drugs against Risk of Intra-coronary Stent Restenosis

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ABSTRACT

Background: Intracoronary stent restenosis (ISR) is a famous catastrophe, always following percutaneous coronary interventions (PCI). Many investigations were performed to avoid this complication by the addition of many cytotoxic drugs to stent platform for prevention of neo-intimal hyperplasia and smooth muscle cell proliferation, or by finding a protective drug against this problem, such as dual antiplatelet therapy. Our research was conducted to detect the protective drugs against the risk of intracoronary stent restenosis among all drugs of medical treatment for ischemic heart diseases. Results: The study reported that 54, 26, 54, and 34% of patients respectively administrated by clopidogrel, nitrates, angiotensin-converting enzyme inhibitors (ACEI) and statins developed ISR after PCI when compared to the other group of patients who did not develop ISR. So, these drugs were protective against the risk of ISR (P value<0.001). We also reported that 74, 4, and 90% of patients administrated respectively by aspirin, warfarin, beta-1 blockers (BB) developed ISR after PCI when compared to the other group of patients who did not develop ISR. So, there was no association between these drugs and risk of ISR (P value>0.05). Conclusions: This study concluded that clopidogrel, nitrates, ACEI, and statins are protective drugs against the risk of ISR complications after PCI procedures.

Keywords: Intracoronary stent restenosis, percutaneous coronary interventions, angiotensin-converting enzyme inhibitors, adrenergic beta1 receptors blockers, clopidogrel, statins

Introduction

Intracoronary stent restenosis (ISR) is one of the most prevalent PCI complications.[1] ISR is a gradual restriction of the coronary vessel lumen after PCI more than 50% of the internal vessel diameter within the coronary stent or up to 5 mm from the stent edges.[2] Maneuvers of stent implantation during percutaneous coronary intervention result in vascular smooth muscle cells migration from tunica media to the intima and myofibroblasts from tunica adventitia to tunica intima to produce neointimal hyperplasia leading to restenosis. The enhancement of the extracellular matrix synthesis by deposition of collagens, proteoglycans, fibronectins and matrix proteins by vascular smooth muscle cells (VSMC) and fibroblasts is also involved in the procedure of neo-intimal hyperplasia.[3] The renin-angiotensin system (RAS) has been involved in the development and progression of neo-intimal hyperplasia by its bioactive peptide angiotensin II (Ang II).[4] Angiotensin-converting enzyme (ACE) converts angiotensin I (Ang I) to Ang II, which promotes the migration and proliferation of vascular smooth muscle cells, leads to vasoconstriction and thrombosis by its major cellular receptor, Ang II type 1 receptor (AT1R).[5] Statins have anti-inflammatory, anti-thrombotic, and antioxidant features, and also inhibit vascular smooth muscle cell migration and proliferation.[6] These compounds inhibit HMG-CoA reductase, a key enzyme in the synthesis of cholesterol.[7] They also decrease the development of Alzheimer's disease.[8] Nitrates play a key role in coronary

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vasodilatation, platelet disaggregation, endothelial protection and the prevention of vascular smooth muscle cell proliferation.[9] It has been reported that nitrates usually cause prompt relief of the pain in angina pectoris.[10] Dual antiplatelet therapy has a notable role in the prevention of in-stent thrombosis. In the present practice, patients undergoing PCI and stent deployment are prescribed clopidogrel 300–600 mg as a loading dose followed by 1 year of dual antiplatelet treatment (aspirin 75–100 mg and clopidogrel 75 mg daily) and continued with life-long aspirin intake.[11] Clopidogrel is an inactive pro-drug that needs two-step oxidation by the hepatic cytochrome P450 enzymes to transform into an active metabolite that further inhibits the ADP P2Y12 receptor, producing the anti-aggregation influence for platelets.[12] Beta-1 adrenergic receptors blockers (BBs) prevent the harmful effect of adrenaline on the cardiovascular system. So, BBs are used in the treatment of hypertension and abnormal heart rhythm. Some studies reported a protective role to BBs against the risk of ISR by coronaries vasodilatation, and vascular endothelial protection.[13] Since only a few studies have investigated the role of medical treatment drugs in protection from the risk of ISR, this study was designed to detect the protective ischemic heart disease drugs against the risk of ISR complications after PCI procedures.

Methods:

This investigation was carried out in the Cardiology and Medical Biochemistry Departments at Zagazig University in the period from March 2017 to March 2019. The research design was confirmed by the Institutional Review Board (IRB) and included (200) patients with ischemic heart disease.

Inclusion criteria:

The inclusion criteria were ischemic heart disease patients who undergo the previous revascularization to coronary arteries, with bare metal stent (BMS) implantation more than 12 months ago, then re-admitted to coronary catheterization due to recurrence of myocardial ischemic symptoms, with positive non-invasive cardiac stress tests. The coronary catheterization showed ISR as restriction of the coronary vessel lumen more than 50% of the internal vessel diameter within the bare metal stent or up to 5 mm from the stent edges.

Exclusion criteria:

The exclusion criteria included patients developed ISR after drug eluting stent (DES) implantation or before the period of 12 months after stent implantation.

We divided all patients into two groups: the first group included 100 patients with ISR, and the second group included 100 patients with patent coronary stents. All patients were exposed to history taking, emphasis on good adherence to medical treatment drugs during the period of coronary stenting, physical examination, laboratory investigations, resting ECG, and coronary angiography.

Statistical study:

Data were collected and analyzed utilizing Microsoft Excel and Statistical Package for the Social Sciences (SPSS version 20.0) software. We utilized the Chi-square test (X2) to test differences for significance, difference, and association of qualitative variables. P-value was set at <0.05 for significant results.

Results:

The current study revealed that 54 patients (54%) with ISR and 78 patients (78%) without ISR were on clopidogrel therapy. We found that clopidogrel was significantly protective against the risk of ISR ($P<0.01$; Table 1). Our results found that 26 patients (26%) with ISR and 58 patients (58%) without ISR were on nitrates therapy. We found that nitrates were significantly protective against the risk of ISR ($P<0.01$). According to the results of ACEI, 54 patients (54%) with ISR, and 76 patients (76%) without ISR were on ACEI therapy. We found that ACEI was significantly protective against the risk of ISR ($P<0.01$). Based on the results, 34 patients (34%) with ISR, and 60 patients (60%) without ISR were on statins therapy. We found that statins were significantly protective against the risk of ISR ($P<0.01$). The results of the current study also found that 74 patients (74%) with ISR and 80 patients (80%) without ISR were on aspirin therapy. We found that aspirin therapy did not have any significant association with the risk of ISR ($P=0.31$). Besides, 90 patients (90%) with ISR and 88 patients (88%) without ISR were on BB therapy. We found that BB therapy did not have any significant association with the risk of ISR ($P=0.65$). Regarding warfarin therapy, our study found that 4 patients (4%) with ISR and 6 patients (6%) without ISR were on warfarin therapy. We found that warfarin therapy did not have any significant association with the risk of ISR ($P=0.51$; Figure 1).

Table 1: distribution of medical treatment drugs between studied groups

		ISR		NO		P-value
		N	%	N	%	
Clopidogrel	Yes	54	54	78	78	0.00**
	No	46	46	22	22	
Aspirin	Yes	74	74	80	80	0.31
	No	26	26	20	20	
Nitrates	Yes	26	26	58	58	0.00**
	No	74	74	42	42	
Warfarin	Yes	4	4	6	6	0.51
	No	96	96	94	94	
Beta blockers (BB)	Yes	90	90	88	88	0.65
	No	10	10	12	12	
Angiotensin converting enzyme inhibitors (ACEI)	Yes	54	54	76	76	0.001**
	No	46	46	24	24	
Statins	Yes	34	34	60	60	0.00**
	No	66	66	40	40	

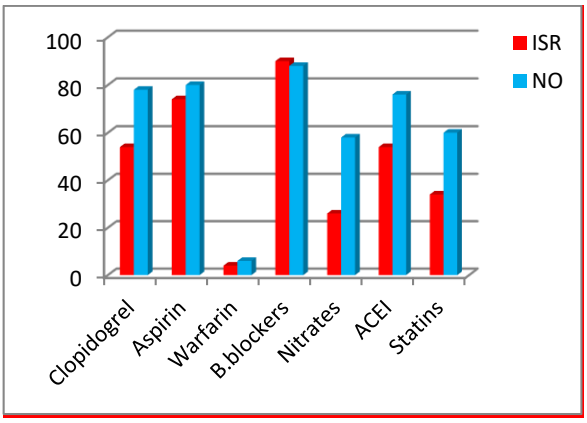

Figure 1: The difference between studied groups regarding medical treatment drugs.

Discussion:

According to our results, clopidogrel, nitrates, ACEI, and statins were protective drugs against ISR. RAS could play a significant role in the pathophysiology of ISR by activation of migration and proliferation of vascular smooth muscle cells, vasoconstriction, expression of adhesive inflammatory molecules, and thrombosis. So, RAS inhibitors as ACEI, angiotensin receptors blockers (ARBs) decrease the risk of ISR complication after PCI by improving endothelial function, enhancing bradykinin levels, a decrease of vascular smooth muscle cells proliferation, as well as inhibition of inflammation and thrombosis.[14] Statin therapy was related to a lower risk for restenosis of coronary stents after implantation. The impact of statins seems to be independent of their lipid-lowering influences. However, it depends on the pleiotropic impacts on the vascular wall. Statins lower the oxidized low-density lipoproteins (LDL) content of the arterial wall and reduce the expression of cell adhesion molecules, tissue factor, and the amount of inflammatory cells. Statins have also antioxidant role against oxygen free radicals and endothelial injury. They also activate nitric oxide synthase, decrease C reactive protein levels, and inhibit proliferation and migration of vascular smooth muscle cells.[15] The current study observed a strong association between long-term administrations of nitrates in patients re-vascularized by stenting of coronary vessels and lower rates of ISR complication. This may be related to the role of nitrates in coronary vasodilatation, platelet disaggregation, endothelial protection, and prevention of vascular smooth muscle cell proliferation.[16] Dual antiplatelet therapy has an important role in the prevention of in-stent thrombosis. Patients undergoing PCI and stent deployment, who are prescribed clopidogrel 300–600 mg as a loading dose followed by 1 year of dual antiplatelet therapy, have a lower risk for ISR.[17] The pathophysiology of neo-intimal hyperplasia of ISR restenosis consists of three phases: thrombosis (within 24 h), recruitment (3–8 days), and proliferation, which starts on day 8 of PCI. Early starting of clopidogrel therapy inhibits the initiation phase of ISR and neo-intimal hyperplasia by prevention of thrombosis. Clopidogrel is the most protective therapy against the risk of ISR and should be started as soon as possible after PCI procedure.[18] Our results found that clopidogrel is more important than aspirin in protection against the risk of ISR. The study did not find any protective value for patients against the risk of ISR when oral anticoagulants such as warfarin were combined with dual antiplatelet therapy, but there was an increase in the bleeding risk. BB drugs block the effect of adrenaline on the cardiovascular system. Some studies reported a protective role for BBs against the risk of ISR by coronaries vasodilatation and their antioxidant value against endothelial injury.[19] Although confirmation from good adherence of the patients to medical treatment drugs was a major limitation in our study, we could not find any role for BB drugs in the process of ISR after PCI procedures.

Conclusion:

Our study found that clopidogrel, nitrates, ACEI, and statins are protective drugs against the risk of ISR complications after PCI procedures.

-Abbreviations: ISR: Intracoronary stent restenosis, PCI: percutaneous coronary intervention, ACEI: angiotensin-converting enzyme inhibitors, BB: beta-1 adrenergic receptors blockers, RAS: renin-angiotensin system.

Declarations:

Ethics approval and consent to participate: The research design was approved by the Institutional Review Board (IRB). Full written consents were taken from participant patients in this investigation and all patients were informed by the goal of the research. Our investigation did not have any adverse effects or harmful event against participant patients.

Consent for publication:

Not applicable

Availability of data and material:

The datasets utilized and analyzed during the current investigation are available from the corresponding author on reasonable request.

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