ROSUVASTATIN FOR REDUCTION OF MYOCARDIAL DAMAGE DURING CORONARY INTERVENTION

Thesis
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List of abbreviations

abbreviations	Meaning
ACCF	American college of cardiology foundation
ACS	Acute coronary syndrome
AHA	American heart association
AKI	Acute kidney injury
ALT, AST	Aspartate aminotransferase/ Alanine aminotransferase
CABG	Coronary artery bypass grafting
CAD	Cronary artry disease
CCS	Canadian cardiovasculer society
CFR	Coronary flow reserve
CFVR	Coronary flow velocity reserve
CK-MB	Creatine phosphokinase MB isoenzyme
CPK	Creatine phosphokinase
CrCl	Creatinin clerance
CRP	C-reactive protein
CTnI	Cardiac troponin i
DM	diabetes mellitus
ESC	European society of cardiology
Factor-VIIa	F-VIIa
GP	Glycoprotein
HDL	High densty lipoprotin
HITS	High-intensity signals
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme a
HPPR	High post-treatment platelet reactivity
Hs-CRP	High sensitive C- reactive protein
ICTUS	Invasive versus conservative treatment in unstable coronary syndromes investigators
IL-6	Inter-leukin-6
IPC	Ischemic preconditioning
IVUS	Intravascular ultrasound
LAD	Left anterior descending
LCX	Left circumflex
LBBB	Left bundle branch block
LDL	Low densty lipoprotin
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
MRI	Magnetic resonance imaging
MVO	Micro vessel occlusion
NC	Necrotic core
NCDR Cath	National cardiac data registry catheter
NCEP	National cholesterol education panel
NIR	Near-infrared
NSTEACS	Non-st elevation acute coronary syndrome
OCT	Optical coherent tomography
PCI	Percutaneous coronary intervention

Continue of List of abbreviations

abbreviations	Meaning
PCI	Percutaneous coronary intervention
PMI	Peri-procedural myocardial injury
PTCA	Percutaneous transluminal coronary angioplasty
RCA	Right coronary artery
RIPC	Remote ischemic preconditioning
RPFA-ASA	Rapid platelet function assay-acetyl salicylic acid
SBO	Side branch occlusion
SCAI	Society for Cardiovascular Angiography and Interventions
SD	Standared deveation
SPSS	Statistical Product and Service Solutions
STEMI	St segment elevation myocardial infarction
SVGs	Saphenous vein grafts
TF	Tissue factor
TIMI	Thrombolysis in myocardial infarction
URL	Upper reference limit
VH	Virtual histology
VS	Versus

Abstract

Objectives: A high loading dose of statins has been showed to reduce post procedural events in patients undergoing percutaneous coronary intervention (PCI). In this study, we investigated the possible protective effects of rosuvastatin in Egyptian patients with stable or unstable angina undergoing PCI.

Patients & Methods: Our study was carried on 75 patients suffering from coronary artery disease (stable or unstable angina) who were planned for elective PCI and had no contraindication to statin therapy. The cases were divided into 3 groups, (Group I) included 35 patients who were not on statin therapy and received rosuvastatin 20 mg within 24 hours prior to PCI, (Group II) included 20 patients who were already on chronic statin therapy prior to PCI and continued on it & (Group III) included 20 patients who were not on statins and didn't receive any lipid lowering agent prior to PCI. Creatine kinase-MB, troponin-I, were measured at baseline , 8 and 24 hours after the procedure & additional samples were obtained if the patients showed signs or symptoms of myocardial ischemia. The study end point was the incidence of periprocedural myocardial injury in patients undergoing elective PCI.

Results: In our study, we found that loading dose of rosuvastatin 20 mg was associated with a reduction of periprocedural myonecrosis more than chronic statin therapy and both of them were associated with a reduction of periprocedural myonecrosis more than non-statins users in patients with stable or unstable angina. The postprocedural elevation in CK-MB and troponin-I at 8 hours and 24 hours was significantly lower in the rosuvastatin group compared with the chronic statin's group. Both statins groups showed significantly lower level of CK-MB and troponin-I, at 8 hours and 24 hours compared with non-statins users group.

Conclusions: A single, high loading dose (20 mg) of rosuvastatin within 24 hours prior to PCI reduces periprocedural myocardial injury in patients with stable or unstable angina

Keywords: *Rosuvastatin; Stable or Unstable Angina; Elective PCI; Chronic statins therapy*

Introduction

There is increasing evidence that early and aggressive statin therapy in patients with acute coronary syndrome (ACS) can decrease periprocedural myocardial infarction (MI) and adverse cardiovascular events.[1]

The incidence of elevated biomarkers of myocardial damage after percutaneous coronary intervention (PCI) is 1-30%. There is an increasing consensus that troponin is probably the most relevant biomarker but the prognostic impact of troponin elevation after PCI is still debated.[2,3]

The relevance of cardiac marker elevation during and after PCI has been debated by interventionalists for some years. However, using CK-MB, it became clear that patients with enzyme elevation > 5 times upper reference limit (URL) had clear impact on subsequent prognosis.[4]The impact of elevation of CK-MB to levels (<5 times URL) was less clear. More recently detailed studies have shown the link between elevated troponin post PCI and areas of new myonecrosis on MRI scanning. These studies have definitively shown that the issue of troponin elevation should not be ignored.[5]

The occurrence of peri procedural MI defined by the new universal definition confers an adverse prognosis both in hospital and over the next 18 months.[5] The Joint ESC/ACCF/AHA/WHF Task Force Universal definition of myocardial infarction 2007[6] defined PMI during PCI, as an elevation of serum biomarkers (preferably cardiac troponins) above the 99th percentile (URL) after PCI, assuming a normal baseline troponin value. According to these published guidelines, an elevation in serum cardiac enzyme to more than three times the 99th percentile URL has been defined as a type 4a PCI-related myocardial infarction.

Several studies published in the last few years suggested different approaches aiming at reducing the risk of myocardial damage after elective PCI. Pre-treatment with high dose statins appeared to significantly reduce procedural myocardial injury in elective coronary intervention.[7,8]

Several randomized studies demonstrated the beneficial effects of therapy with HMG-CoA reductase inhibitors (statins) in patients with coronary disease or in normal subject with hypercholesterolemia[9,10],and retrospective observational studies have suggested that pretreatment with statins might reduce the incidence of periprocedural myocardial infarction after coronary intervention.[4,11]

Despite their multifaceted properties, statins continue to remain underused in the treatment of stable and unstable coronary artery disease. The available evidence creates a convincing argument for statins treatment before coronary procedures. Given the strong biological rationale and the sum of the clinical data, no patient should undergo coronary procedures without statin therapy unless clear contraindications exist.[12]

Up to our knowledge, there are no randomized and controlled studies to date to evaluate the effect of statins given before coronary intervention on preventing myocardial injury in egyptian patients.

A study is needed to evaluate the cardioprotective role of high dose statins given before elective coronary intervention in egyptian patient.

Aim of the work

To confirm the hypothesis that statins may lower the risk of procedural myocardial injury in patients undergoing elective PCI.

Chapter 1

Percutaneous Coronary Intervention

Coronary balloon angioplasty, or percutaneous transluminal coronary angioplasty (PTCA), was first performed by Andreas Gruentzig in 1977 using a fixed-wire balloon catheter. The procedure was initially limited to the fewer than 10% of patients with symptomatic CAD who had a single, focal, non-calcified lesion of a proximal coronary vessel.[13,14]

PCI in patients with chronic stable angina

Coronary artery angioplasty is indicated (Class I) for improvement of symptoms in patients with one-vessel coronary artery disease who are eligible for invasive treatment and have symptoms that are not controlled by medication (and in whom the periprocedural risk does not exceed the expected benefit). In multi-vessel disease, without high-risk coronary artery anatomy in patients with moderate to severe symptoms, angioplasty improves symptoms and also has a Class I indication. Angioplasty has a class IIa indication in patients with only one-vessel disease, eligible for invasive treatment, with mild to moderate symptoms that are not tolerated. In multi-vessel disease with mild to moderate symptoms, PCI also has a Class IIa indication when the patient cannot tolerate the symptoms.[15,16]The corresponding guidelines of the American College of Cardiology and the American Heart Association recommend PCI with a Class IIa indication in patients with asymptomatic ischemia or angina in Canadian cardiovasculer society(CCS) class I or II, with one or more significant stenosis in one or two coronary arteries that supply a moderate to large region of viable myocardium, or are associated with a moderate or severe degree of ischemia on non-invasive examination.[15,16,17] PCI received a Class IIa indication in patients with asymptomatic ischemia , or CCS class I or II angina and restenosis after angioplasty in an artery that

supplies a large region of viable myocardium, or in the presence of high-risk criteria on non-invasive examination. Angioplasty is also recommended in patients with asymptomatic ischemia, or angina of CCS class I or II, with significant stenosis of the left main coronary artery (>50%) that cannot be treated surgically (Class IIa). In patients with CCS class III angina, angioplasty is recommended in those with one-vessel disease or multi-vessel disease who have one or more significant stenosis in one or more arteries suitable for PCI (Class IIa indication). It is also recommended in those with angina CCS class III with significant left main coronary artery disease who cannot undergo surgery,or in surgically treated coronary arteries with multiple stenosis in grafts that are not susceptible to reoperation (Class IIa).[17]

PCI in patients with unstable angina

The main difference between management of the patient with stable angina and the patient with unstable angina is that the impetus for revascularization is stronger in the setting of unstable angina, because myocardial ischemia occurring as a part of an ACS is potentially life threatening, and associated angina symptoms are more likely to be reduced with a revascularization. Thus, the indications for revascularization are strengthened by the acuity of presentation, the extent of ischemia, and the ability to achieve full revascularization. [18,19,20]

Indication of PCI in patients with unstable angina

1. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is indicated in unstable angina patients who have refractory angina or hemodynamic or electrical instability (without serious co morbidities or contraindications to such procedures).[20,21,22]

2. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is indicated in initially stabilized unstable angina

patients (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events.[22,23,24]

3. The selection of PCI or CABG as the means of revascularization in the patient with ACS should generally be based on the same considerations as those without ACS. [24,25,26,27]

Adjunctive Drug Therapy in PCI

Platelet inhibitors have to be administered at the latest at the inception of the procedure.[28] Acetylsalicylic acid is standard. Clopidogrel, a thienopyridine, is also advocated, preferably starting a few days before the procedure or with a 600 mg or greater oral loading dose [29,30], intravenous direct glycoprotein IIb/IIIa receptor blockers (abciximab, tirofiban, or eptifibatide) used in truly acute coronary syndromes documented by troponin elevation but is not necessarily superior to that of clopidogrel.[31] Heparin is part of the standard regimen. Doses vary, but they are usually weight adjusted and are assessed by activated clotting times to be increased in lengthy procedures. Low-molecular-weight heparin has been tested in the setting of PCI; it has proved at least as effective as un-fractionated heparin, and it causes fewer propensities to bleeding.[32,33] Of the direct thrombin antagonists, bivalirudin has proved equivalent or superior to a combination of un fractionated heparin and a glycoprotein IIb/IIIa receptor blocker in general cohorts [34,35,37] , as well as in patients with diabetes [37] or renal failure.[38]

PCI outcomes

Definitions of PCI success

The success of a PCI procedure is best defined by 3 inter-related components: angiographic findings, procedural events, and clinical outcomes [39-42].