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قسم

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Pharmacological Study Of The Therapeutic Outcomes Of Rosuvastatin And Beta-Blocker Combination In Isoprenaline-Induced Myocardial Infarction In Rats

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ABSTRACT

Introduction: Myocardial infarction (MI) is a major form of ischemic heart disease characterized by an inequity of coronary blood supply and demand, leading to cardiac ischemia and cardiomyocytes degeneration. Rosuvastatin has been shown to activate PI3K/Akt/Nrf2/HO-1 pathway, which plays a pivotal role in promoting cell survival in the myocardium. **Method:** The present study investigated the therapeutic benefit of adding rosuvastatin (RSV 20 mg/kg; orally) to low-dose carvedilol (CAR 2 mg/kg; orally) in protection against myocardial infarction (MI) induced by Isoprenaline (ISP) in rats. **Results:** The results showed that low-dose CAR and/or RSV pre-treatment prevented ECG changes and histopathological alterations induced by ISP. Also, the same treatments significantly reduced the infarct size, heart index, serum creatine kinase-MB (CK-MB), cardiac troponin-I (cTn-I), and C-reactive protein (CRP) levels. In addition, pre- treatment with low-dose CAR and/or RSV replenished the antioxidant defense systems, superoxide dismutase (SOD) and total antioxidant capacity (TAC) with subsequent reduction in heart tissue lipid peroxides. Further, pre-treatment with RSV and/or CAR showed lower expression level of the inflammatory transcription factor NF-κB (p65) and a significant increase in phosphorylated PI3K and Akt, which may in turn activate the anti-apoptotic signaling events as evidenced by the decrease in active caspase-3 level. The combination therapy has more significant and potent effect in the most studied parameters as compared to their monotherapy. The protective effect of the proposed combination may be, at least partly, via activation of Nrf2/HO-1 signaling and the involvement of the PI3K/Akt pro-survival signaling pathway. **Conclusion:** This study highlights the potential benefits of combining RSV with low-dose CAR in affording myocardial protection against ISP-induced MI in rats; via attenuating oxidative stress, inflammation and apoptosis. Furthermore, the activation of Nrf2, by RSV in combination with low-dose CAR, suggests that targeting Nrf2 activation may represent a novel therapeutic approach in the treatment of myocardial infarction.These findings provide experimental evidence for extending the use of this combination to the clinical practice.

Keywords: Rosuvastatin; carvedilol; isoprenaline; myocardial infarction; PI3K/Akt/Nrf2/HO-1.

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List of Abbreviations

ACS	Acute coronary syndrome
AD	Alzheimer's disease
AF	Atrial fibrillation
AIF	Apoptotic inducing factor
Akt	Protein kinase B
AMI	Acute myocardial infarction
ANOVA	Analysis of variance
AP-1	Activator protein-1
Apaf-1	Apoptotic protease activating factor-1
ARE	Antioxidant responsive element
AT-II	Angiotensin II
ATP	*Adenosine triphosphate*
BCRP	Breast cancer resistance protein
BSA	bovine serum albumin
Ca^{+2}	Calcium
CAD	coronary artery disease
CAR	Carvedilol
Caspases	Cysteinyl aspartate–specific proteases
CAT	Catalase
CHD	Coronary heart diseases
CHF	Congestive heart failure
CK-MB	Creatine kinase Myocardial Band

List of Abbreviations

Cl^-	Chloride
CO	Carbon monoxide
COMT	Catechol-O-methyltransferase
CRP	C-reactive protein
cTn-I	Cardiac troponin I
cTn-T	Cardiac troponin T
CVDs	Cardiovascular diseases
CX3CR1	CX3 chemokine receptor 1
DISC	Death-inducing complex
DNA	Deoxyribonucleic acid
DTI	Direct thrombin inhibitors
ECG	Electrocardiography
EndoG	Endonuclease G
eNOS	endothelial nitric oxide synthase
g	Gram
G6PDH	glucose-6-phosphate dehydrogenase
GPx	Glutathione peroxidase
GR	Glutathione reductase
GSH	Glutathione
GSSG	Glutathione disulfide
GST	Glutathione-*S*-transferase
H&E	**Hematoxylin and eosin**
HF	**Heart failure**

List of Abbreviations

HK	Hexokinase
HMG-CoA	Hydroxymethylglutaryl-coenzyme A
HO-1	Heme oxygenase-1
H2O2	Hydrogen peroxide
HR	Heart Rate
HRP	Horseradish peroxidase
IFN	Interferone
IGF-1	insulin-like growth factor-1
IHD	Ischemic heart disease
IKK	Inhibitory protein Kappa B kinase
IL	Interleukin
iNOS	Inducible nitric oxide synthase
INR	international normalized ratio
I/R	Ischemia/reperfusion
ISP	Isoprenaline
IκB	Inhibitory protein Kappa B
Keap1	Kelch-like ECH-associated protein 1
LAD	Left anterior descending coronary artery
LDH	Lactate dehydrogenase
LMWH	Low molecular weight heparin
LOX-1	Lectin like ox- LDL receptor
LPA	Lipoprotein–A
LV	Left ventricle

List of Abbreviations

MDA	Malondialdehyde
MI	Myocardial infarction
miRNA	Micro ribonucleic acid
mPTP	Mitochondrial permeability transition pore
NADH	*Nicotinamide adenine dinucleotide (reduced form)*
NADPH	Nicotinamide adenine dinucleotide phosphate
NBT	Nitroblue tetrazolium
NF-κB	Nuclear factor kappa-B
NIK	Nuclear factor kappa-B -inducing kinase
NO	Nitric Oxide
Nrf2	Nuclear factor erythroid 2p45 (NF-E2)-related factor 2
NSTEMI	Non-ST-Elevation myocardial infarction
NQO1	NAD(P)H quinone oxidoreductase 1
OATP-1B1	organic anion transporting polypeptide-1B1
OD	Optical density
ox-LDL	Oxidized low-density lipoprotein
PDK1	phosphoinositide-dependent kinase-1
P-gp-1	P-glycoprotein-1
P-gp	P-glycoprotein
PH	pleckstrin homology
PI3K	phosphatidylinositol 3-kinase
PIP2	phosphatidylinositol 4,5-diphosphate
PIP3	phosphatidylinositol 3,4,5-trisphosphate

List of Abbreviations

PT	prothrombin time
PTEN	Phosphatase and Tensin Homolog
PVDF	Polyvinylidene Difluoride
RIPA	Radio-immunoprecipitation assay
RNS	Reactive nitrogen species
ROIs	Reactive oxygen intermediates
ROS	Reactive oxygen species
RyR	Ryanodine receptor channel
RSV	Rosuvastatin
SEM	Standard error of mean
S.C.	Subcutaneous
SDS-PAGE	Sodium Dodecyl Sulfate PolyAcrylamide Gel ELectrophoresis
SERCA	Sarco / endoplasmic reticulum Ca^{2+}ATPase
SGOT	serum glutamic-oxaloacetic transaminase
SOD	Superoxide dismutase
STEMI	ST-Elevation myocardial infarction
TAC	Total antioxidant capacity
TBA	Thiobarbituric acid
TBARS	Thiobarbituric acid reactive substances
TBST	Tris-Buffered Saline with Tween 20
TCA	Trichloroacetic acid
TEMED	Tetra methyl ethylene diamine