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Potential Protective Effects of Intravenous N-acetylcysteine on Myocardial Ischemia - Reperfusion Injury in Coronary Artery Bypass Graft Surgeries

Thesis

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Mohamed Salah El-Deen Badawii Eissa

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List of Abbreviations

Abbr.	Title
AAGP	α1-acid glycoprotein
ACC	Aortic Cross Clamp
AF	Atrial Fibrillation
ATP	Adenosine triphosphate
BAX	Bcl-2-Associated X protein
BMI	Body Mass Index
Bpm	Beat per minute
CA	Cardiac Arrest
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CK-MB	Creatinine Kinase-MB
CLcr	Creatinine Clearance
CMR	Cardiac Magnetic Resonance imaging
CO	Cardiac Output
CPB	Cardiopulmonary Bypass
CPD	Citrate-Phosphate-Dextrose
CRP	C-reactive protein
CVP	Central Venous Pressure
D.BP	Diastolic Blood Pressure
DC	Direct Current defibrillator
DM	Diabetes Mellitus
ECG	Electrocardiogram

EF	Ejection Fraction
eNOS	Endothelial Nitric Oxide Synthetase
GIK	Glucose/Insulin/Potassium
GLP1	Glucagon Like Peptide-1
GSH	Reduced Glutathione
GSSG	Oxidized Glutathione
GUARDIAN	Guard During Ischemia Against Necrosis
Hb	Hemoglobin
HCT	Hematocrit
HR	Heart Rate
Ht	Height
HTN	Hypertension
ICU	Intensive Care Unit
IL-1β	Interleukin-1 Beta
IL-6	Interleukin-6
IMMEDIATE	Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency care
INR	International Normalized Ratio
IQR	Inter Quartile Range
IRI	Ischemia Reperfusion Injury
IV	Intravenous
KFT	Kidney Function Test
LFT	Liver Function Test
LPS	Lipopolysaccharide
LV	Left Ventricular
MDA	Malondialdehyde

MI ..... Myocardial Infarction

MitoK_{ATP} ..... Mitochondrial K_{ATP}

MPO ..... Myeloperoxidase

MPTP ..... Mitochondrial Permeability Transition Pore

NAC ..... N-Acetylcysteine

NADP ..... Nicotinamide Adenine Dinucleotide Phosphate

NADPH ..... Reduced Nicotinamide Adenine Dinucleotide phosphate

NO ..... Nitric Oxide

NOS ..... Nitric Oxide Synthetase

NYHA ..... New York Heart Association

OHG ..... Oral Hypoglycemic

$PaCO_2$ ..... Arterial partial pressure of carbon dioxide

PC ..... Preconditioning

PCI ..... Percutaneous Coronary Intervention

PKC ..... Protein Kinase C

PKG ..... Protein Kinase G

PLT ..... Platelets

Pr ..... Pressure

PT ..... Prothrombin Time

PTT ..... Partial Thromboplastin Time

RBS ..... Random Blood Sugar

ROS ..... Reactive Oxygen Species

RR ..... Respiratory Rate

S.BP ..... Systolic Blood Pressure

S.GOT ..... Serum Glutamic Oxaloacetic Transaminase

S.GPT ..... Serum Glutamic Pyruvic Transaminase

SD..... Standard Deviation

SPSS ..... Statistical Program for Social Science

STEMI ..... ST Elevation Myocardial Infarction

SWMA ..... Segmental Wall Motion Abnormality

THAM ..... Tris-Hydroxymethyl-Aminomethane

TNF-α ..... Tumor Necrosis Factor Alpha

UOP ..... Urine Output

WBCs ..... White Blood Cells

Wt ..... Weight

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Introduction

Myocardial protection during cardiopulmonary bypass (CPB) and cardioplegic arrest (CA) has continued to be refined since its introduction in the 1950s ***(Fischer et al., 2003)***.

After the ischemic period reentry of the blood to tissue causes massive release of oxygen free radicals. These free radicals trigger enzymatic reactions, such as peroxidation of polyunsaturated fatty acids or plasma lipoproteins, which leads to oxidative destruction of cell membranes and the productions of toxic reactive metabolites and cell injury involving DNA, proteins, and lipids. All of these events are called ischemia reperfusion injury (IRI) ***(Erturk, 2014).***

Despite numerous advances the heart may still exhibit evidence of IRI, such as arrhythmias, microvascular damage, edema, myocardial stunning, and cell death ***(Dhalla et al., 2000).***

Several studies have been performed using antioxidants to eliminate or at least diminish the effects of oxygen free radicals associated with CPB/CA ***(Belboul et al., 2001).***

N-acetylcysteine (NAC) has been used for almost half a century to treat congestive and obstructive lung diseases, and since the mid-1970's it has also been used to treat

paracetamol intoxication. Several recent reports have suggested that its use may be extended to manage clinical conditions as diversified as IRI, inflammation related complications after CPB and renal damage provoked by radiographic contrast. As an extensively used and relatively safe drug, NAC may be a useful adjuvant for the protection of the myocardium in cardiac surgery ***(Rodrigues et al., 2004).***

Aim of the work

The aim of this work is to evaluate the potential effects of intravenous infusion of NAC on myocardial protection against IRI after bypass during coronary artery bypass grafting (CABG) operations.

Ischemia Reperfusion Injury

Although recent advances in anesthetic and surgical techniques currently allow most patients to undergo coronary artery bypass grafting (CABG) procedures without substantial mortality, more than 25% of this surgical population may still experience significant morbidity related to adverse perioperative cardiovascular outcomes ***(Shernan, 2003).***

The myocardium may be particularly vulnerable to ischemia during CABG surgery because of underlying coronary artery disease (CAD), perioperative hemodynamic instability, inadequate protection during cardiopulmonary bypass (CPB), coronary artery embolization, or technical complications (ie, incomplete revascularization and graft spasm or kinking). Although prolonged myocardial ischemia alone can jeopardize the structural and biochemical integrity of the cells, limited oxygen deprivation (< 20 minutes) is usually associated with only transient depression of myocardial contractility. Paradoxically, the restoration of blood flow after sustained myocardial ischemia (> 45 minutes) results in a phenomenon known as myocardial ischemia reperfusion injury (IRI), where in the tissue injury after reperfusion is greater than that produced by ischemia alone ***(Shernan, 2003).***