Intensive Insulin Therapy in Acute coronary syndromes

Title

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INTENSIVE INSULIN THERAPY IN ACUTE CORONARY SYNDROMES

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Abstract

Background

Elevated admission plasma glucose is associated with increased mortality in patients who are admitted with an acute coronary syndrome. This may be mediated by increased inflammation, apoptosis and coagulation, and by a disturbed endothelial function that can be found in hyperglycemic patients. Insulin has several characteristics that may potentially counteract these mechanisms.

METHODS:

A fifty selected critically ill adult patients admitted with acute coronary syndrome within 6 hours of presentation with admission hyperglycemia "RBS > 140 mg/dl" with or without previously known diabetes mellitus were enrolled in this study and the effect of intensive insulin therapy on decreasing infarct size, the incidence of complications as re-infarction, heart failure, arrhythmias, hemodynamic instability & death was monitored during ICU admission and 30 days follow up.

Results

Of 50 patients who were enrolled in the study 25 patients received insulin infusion , while the other 25 received insulin via S.C route if R.B.S exceeded 180 mg/dl. Each group composed of 25 cases of which 8 cases were diagnosed as having: Non ST-segment elevation acute coronary syndrome "Unstable angina + Non STEMI" "32%", 10 cases were diagnosed as having inf. STEMI." 40%", 7 cases were diagnosed as having anterior STEMI "28%". Mean age was 55.12±8.03 for Group A and 59.68±11 for Group B. The aim of tight glycemic control in the intensive insulin therapy arm group A was successfully achieved. The range of glycemic control during the 1st 24hs as well as during the rest of ICU stay was significantly lower in group A.

Heart failure at 7 and 30 days was 4% and 12%, respectively, for those receiving insulin infusion and 20% and 24%, respectively, for those who did not. Hemodynamic instability was 8% in group A vs. 28% in group B during the ICU stay. Mortality at 7 and 30 days was 0% and 0%, respectively, for those receiving insulin infusion and 4% and 12%, respectively, for those who did not.

Conclusion

Tight glycemic control in patients with acute coronary syndrome presenting with hyperglycemia at admission whether known or not known to be diabetic is

Key words

Intensive insulin therapy: Insulin actrapid infusion aiming at glycemic control between 80 – 130 mg/dl.

Acute coronary syndromes include patients with acute ST elevation myocardial infarction, patients with non ST elevation myocardial infarction & patients with unstable angina.

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List of abbreviations

ACC	American College of Cardiology
ACS	Acute coronary syndromes
AHA	American Heart Association
AV	Atrio ventricular
CAD	Coronary artery disease
CK	Creatine kinase
CMR	Cardiac magnetic resonance
DM	Diabetes mellitus
DSA	Digital substraction angiography
ED	Emergency department
EDWT	End diastolic wall thickening
EF	Ejection fraction
ESC	***the European Society of Cardiology***
GIK	Glucose-insulin -Potassium
GP IIb/IIIa	Glycoprotein IIb/ IIIa
IGC	Intensive glycemic control
LBBB	Left bundle branch block
LMWH	Low molecular weight heparin
LVA	Left Ventricular Aneurysm
LVMT	Left Ventricular mural thrombus
MBG	Myocardial blush grade
MCE	Myocardial contrast echo

MI	Myocardial infarction
NSTEMI	Non ST elevation myocardial infarction
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PKB/ Akt	Protein kinase B
PVCs	Premature ventricular contractions
RBBB	Right bundle branch block
RWMA	Regional wall motion abnormalities
Sign 93	Scottish Intercollegiate Guideline Network
SPECT	Sestamibi single photon emission computed tomography
STE	ST segment elevation
STD	ST segment depression
STEMI	ST elevation myocardial infarction
SWT	Systolic wall thickening
TIMI flow	Thrombolysis in myocardial infarction grading
TWI	T wave inversion
UA	Unstable angina
UFH	Unfractionated heparin
URL	Upper Reference limit
VFWR	Ventricular free wall rupture
VSR	Ventricular septal rupture
WHF	World Heart Federation

Introduction

Approximately 85% of patients who present with ACS have some degree of dysglycemia. ***(Mathew et al 2010)***. An increase of 1 mmol/L above normal blood glucose is associated with an increase in mortality of 4% in non diabetic patients and 5% in known diabetic patients ***(*Standers *et al 2004).***

Acute hyperglycemia is associated with endothelial dysfunction, platelet hyper-reactivity, impaired microcirculatory function, increased cytokine activation, increased free fatty acid levels, and increased oxidative stress, all of which adversely affect outcome in AMI **(Zarich et al 2007).** The oxidative stress induced by increasing levels of intramuscular nuclear factor β and by activation of proinflammatory transcription factors is also associated with hyperglycemia. Furthermore in patients with AMI, acute hyperglycemia is associated with decreased microvascualr perfusion, as demonstrated by reduced thrombolysis in myocardial infarction flow and myocardial blush grades ***(Timemr et al 2005).*** Also reduced left ventricular function and cardiac arrhythmia has been described with hyperglycemia ***(Ishihara et al 2003).***

The ACC-AHA guidelines on management of unstable angina/NSTEMI have aggressive glycemic management in accordance with current standards of diabetes care and this has been endorsed by the American Diabetes Association and the American College of Endocrinology. Their pre-prandial glucose target is <110 mg/dl (<6.1 mmol/L), a maximum blood glucose target of <180 mg/dL (10 mmol/L). European society of cardiology guidelines on management of AMI

suggests achieving glycated hemoglobin A1c < 6.5% in diabetic patients. None of these guidelines recommends a best method to achieve these glycemic targets ***(Mathew et al 2010).***

Cardio metabolic regulation in acute myocardial infarction has largely taken 2 forms. One approach is to deliver a metabolic "Cocktail" such as glucose – insulin-potassium "GIK") to all patients without regard to the level of glycemia, and the other is to specifically target only these patients with hyperglycemia (with a "physiological" continuous infusion of insulin). ***(Diaz et al 2007).***

Insulin has been shown to increase microvascular blood flow through the release of nitric oxide by the endothelium and to suppress the expression of inflammatory mediators such as intra cellular adhesion molecule-1, monocytes chemotactic protein-1, and nuclear factor-κβ binding. Overall, insulin promotes beneficial effects in endothelial and platelet function, which can ultimately be potentially pharmacologic tools beyond glycemic control to improve cardiovascular outcome in the setting of AMI. ***(Opie 2008).*** The delivery of intravenous insulin to normalize glucose levels has been shown to improve outcomes in STEMI and in patients in intensive care unit settings. ***(Chung et al 2006).*** For every 6 mmol/L reduction in glucose post admission, there is an 8% reduction in mortality in patients with AMI***. (Goyal et al 2006).***

Aim of the work

Our aim is to test the hypothesis that insulin is cardioprotective in patients with acute coronary syndrome and hyperglycemia because of its anti-inflammatory, profibrinolytic, antioxidant, antiapoptotic, vasodilatory and anti-aggregatory actions and that these effects are enhanced by lowering glucose into the normoglycemic range using intensive insulin therapy.

ACUTE CORONARY SYNDROMES

Definition:

Patients with ACS include those whose clinical presentations cover the following range of diagnoses: unstable angina, non–ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). This ACS spectrum concept is a useful framework for developing therapeutic strategies. ***(Fenton 2010).***

Patho-physiology: Supply-demand mismatch, Plaque disruption or rupture, Thrombosis, Vasoconstriction, Cyclical flow**.** ***(Topol et al 2000).***

Supply-demand mismatch

The incidence of unstable angina, like all tissue ischemia, results from excessive demand or inadequate supply of oxygen, glucose, and free fatty acids. ***(Murphy et al 2003).***

Plaque disruption

Accumulation of lipid-laden macrophages and smooth muscle cells; foam cells, occurs within atherosclerotic plaques. The oxidized low-density lipoprotein cholesterol (LDL-C) in foam cells is cytotoxic, procoagulant, and chemotactic as shown in figure 1. ***(Peters et al 2003).***