PLASMA RENALASE LEVEL AS BIOMARKER OF ISCHEMIC ACUTE KIDNEY INJURY FOLLOWING CARDIAC SURGERY

Thesis

Submitted for the partial fulfilment of MD Degree In Internal Medicine

By

Hussein Hassan Samir Mohammed Refaat
(M.B.B.CH, M.Sc.)

SUPERVISORS

Prof. Manal Mohammed Nabih ElDeeb
Professor of internal medicine
Faculty of Medicine- Cairo University

Prof. Amal abd elwahab moahmmed
Professor of chemical and clinical pathology
Faculty of medicine
Cairo University

DR. Ihab Abd ElRahman Ibrahim
Lecturer of Internal Medicine
Faculty of Medicine
Cairo University

DR. Hossam fathy ali sayed
Lecturer of cardiothoracic surgery
Faculty of medicine
Cairo University

Faculty of Medicine
Cairo University
2016

بسم الله الرحمن الرحيم

[وأنزل اللـه عليـك الكتــاب
والحكمة وعَلَّمَكَ مَا لَمْ تَكُن تَعْلَمُ
وكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيماً]

صدق الله العظيم

النساء .. آية ١١٣

Acknowledgement

*First of all, all gratitude is due to **God** almighty who guided and aided me to bring to light this work.*

*I would like to express my thanks to Dear Professor **Dr. Manal Eldeeb** Professor of internal medicine Faculty of Medicine Cairo University for her sound advice and guidance.*

*I am also really honored to express my deepest gratitude and indebtedness to **Dr. Ihab Abd Elrahman** Lecturer of Internal Medicine Faculty of Medicine Cairo University for his kind help, guidance, enthusiasm and encouragement for accomplishing this work.*

*Also I would like to express special thaks to **Prof. Dr. Amal Abd Elwahad** and **Prof. Dr. Hossam fathy** for their great help, that without it, this thesis will never come to light.*

Finally, I thank my family for their patience and support during this work, I would like to offer my thanks to my wife who kindly helped me.

Abstract

Background/Objective

Renal ischemia/reperfusion injury (IRI) is a major cause of acute renal failure. The scarcity of early biomarkers and validated risk models for predicting acute kidney injury (AKI) has hindered our ability to launch preventive and therapeutic measures in a timely manner. We tested the hypothesis that plasma renalase is an early biomarker for ischaemic renal injury after cardiac surgery.

Methods

This study prospectively evaluated 40 adult patients who underwent cardiac surgery at Cairo University Hospitals. Demographic factors, clinical data, operative and postoperative variables were evaluated. Plasma renalase levels, analysed by ELISA were measured before surgery and 18 - 24 hours after surgery. NGAL levels, analysed by ELISA. were measured 18 - 24 hours after surgery. The primary outcome measure was AKI diagnosed by the Acute Kidney Injury Network (AKIN) criteria.

Results

Of 40 patients, 25 patients (62.5 %) developed AKI after surgery. Plasma concentrations of renalase decreased significantly from a mean of 1.2 ± 0.46 ng/ml at baseline to 0.9 ± 0.42 ng/ml 18 - 24 hours after cardiopulmonary bypass, with a mean % change of 27 ± 14.8 in the AKI group. Univariate analysis showed statistically significant correlation between acute renal injury and the following: percent (%) change of plasma renalase levels, cardiopulmonary bypass time and Aortic cross-clamp time. Receiver operating characteristic (ROC) analysis revealed that for % change in plasma renalase concentrations at 18 - 24 h, the AUC was 0·9, sensitivity 0.92, specificity 0·87, PPV was 0.92, NPV was 0.87 and likelihood ratio of 7.07 for a cutoff value of 9 % change.

Conclusion

Plasma renalse percent (%) of change is more valid compared to renalse before or after procedure and NGAL in prediction of AKI and represents a sensitive, specific, and highly predictive early biomarkers for acute renal injury after cardiac surgery.

Keywords:

Plasma renalase - biomarker - acute renal injury - cardiac surgery

Contents

Abbreviations

ADQI:	**The Acute Dialysis Quality Initiative**
AKI:	**acute kidney injury**
AKIN:	**Acute Kidney Injury Network**
ANP:	**atrial natriuretic peptide**
ARF:	**acute renal failure**
ATN:	**acute tubular necrosis**
AUC:	**area under this curve**
AXT:	**Aortic cross-clamp time**
CABG:	**coronary artery bypass grafting**
CCU:	**coronary care unit**
CKD:	**chronic kidney disease**
CM:	**Contrast Media**
CPB time:	**cardiopulmonary bypass time**
CRRT:	**continuous venovenous hemofiltration**
Crry:	**complement receptor related protein**
DAMPs:	**damage-associated molecular patterns**
DIC:	**disseminated intravascular coagulation**
ELISA:	**enzyme-linked immunosorbent assay**
EPO:	**erythropoietin**
ESRD:	**End stage kidney disease**
GFR:	**glomerular filtration rate**
GN:	**glomerulonephritis**

HMBG1: high mobility group box protein 1

ICAM-1: intracellular adhesion molecule 1

IGF: insulin-like growth factor

IR: Ischemia reperfusion

Kd: kilodalton

KDIGO: Kidney disease improving global outcome

KIM-1: kidney injury molecule-1

NGAL: neutrophil gelatinase-associated lipocalin

NGAL: Neutrophil Gelatinase-Associated LipocaliN

NPV: Negative predictive value

PAMP: pathogen-associated molecular patterns

PPAR: peroxisome proliferator-activated receptor

PPV: Positive predictive value

RAD: The renal assist device

RCT: randomized controlled trials

RIPC: Remote ischemic preconditioning

ROC curves: Receiver operating characteristic

RPGN: rapidly progressive glomerulonephritis

STS: The Society of Thoracic Surgery

TIMP2: tissue inhibitor of metalloproteinases-2

TLR: Toll-like receptors

TMA: thrombotic microangiopathy

TNF: tumor necrotic factor

List Of Tables

List of Figures

INTRODUCTION

The term ‘‘acute kidney injury/impairment’’ has been proposed to encompass the entire spectrum of the syndrome from minor changes in markers of renal function to requirement for renal replacement therapy (RRT). **(Mehta RL et al. 2007)**

The Acute Kidney Injury Network AKIN proposed the term acute kidney injury (AKI) to represent the entire spectrum of acute renal failure. The proposed diagnostic criteria are an abrupt (within 48 hours) absolute increase in the serum creatinine concentration of ≥0.3mg/dL (26.4 micromol/L) from baseline, a percentage increase in the serum creatinine concentration of ≥50 percent, or oliguria of less than 0.5mL/kg per hour for more than six hours **(Levin A etal., 2007).**

Creatinine is currently the most widely used marker of renal function. Its use in the diagnosis of AKI remains a problem; however, as it often requires as much as a 50% loss in renal function before creatinine levels rise. **(R. Bellomo etal.2004)**

Renal ischemia reperfusion (IR) injury is a frequent cause of clinical AKI, with the incidence of AKI exceeding 50% after major cardiac, hepatobiliary, or aortic surgery. **(Bove T etal. 2004) (Elapavaluru S, etal. 2007).** Ischemic AKI is frequently complicated by multi-organ dysfunction, systemic inflammation, sepsis, and death **(Jones DR etal. 2008).**

Acute kidney injury (AKI) is a frequent complication of cardiac surgery **(Rosner MH, etal. 2006).** Patients who double their serum creatinine or need acute dialysis have a two- to five-fold higher risk of death **(Zanardo G, et al. 1994 and Chertow GM, et al. 1998)** and patients who recover their kidney function remain at increased risk of chronic kidney disease (CKD) and premature death **(Coca SG, et al.2009 and Hobson CE, et al. 2009)**

A number of novel plasma and urinary early postoperative biomarkers have recently been proposed to assess the risk of postoperative AKI on the assumption that early detection of renal damage may limit its progression to overt renal failure with appropriate therapeutic interventions **(Hall IE, et al. 2011).**

There are neither preoperative biomarkers nor validated risk models that predict AKI not requiring dialysis. Preoperative biomarkers offer the potential to target and develop therapeutic intervention aimed at blocking the initial sequence of events that lead to AKI **(Endre ZH et al. 2011).**

Renalase is a 38-kD, flavin adenine dinucleotide–dependent amine oxidase synthesized and secreted by the renal proximal tubules. (Xu J, etal.2005). Renalase degrades circulating catecholamines and regulates systemic BP in rodents and humans **(Desir G et al. 2012).**

Plasma catecholamines and systemic BP are elevated in patients with chronic kidney dysfunction or end stage renal insufficiency **(Schlaich MP et al., 2009).**

Recent studies suggest that renalase deficiency in patients with chronic renal insufficiency leads to increased plasma catecholamine levels and systemic BP. **(Li G et al., 2008; Desir GV et al., 2009; Desir GV et al., 2011 and Desir G et al., 2012)**

In mice, renalase deficiency resulted in exacerbated cardiac ischemia reperfusion (IR) injury and exogenous renalase administration reduced myocardial necrosis **(Wu Y et al., 2011).**

A recent study showed that ischemic AKI in **mice** leads to renalase deficiency it also showed that exogenous administration of recombinant human renalase directly protects against ischemic AKI in mice and this might represent a novel approach to combat ischemic AKI **(Lee HT et al., 2013).**

The aim of this study to assess the plasma Renalase levels as predictor biomarker for early diagnosis of acute kidney injury in patients following cardiac surgery.

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is a clinical syndrome denoted by an abrupt decline in glomerular filtration rate (GFR) sufficient to decrease the elimination of nitrogenous waste products (urea and creatinine) and other uremic toxins. This has traditionally been referred to as acute renal failure (ARF), but in recent years, an effort has been made to implement the term AKI instead of ARF and to develop a standardized definition of AKI. **(Mehta RL, et al. 2007)**

One offered definition of AKI, is a decline in kidney function during 48 hours as demonstrated by an increase in serum creatinine of more than 0.3 mg/dl, an increase in serum creatinine of more than 50%, or the development of oliguria. **(Mehta RL, et al. 2007)**

The Acute Dialysis Quality Initiative (ADQI) was formed by a group of expert intensivists and nephrologists to develop consensus and evidence based guidelines for the treatment and prevention of acute renal failure **(Ronco C, et al. 2001).**

Recognizing the need for a uniform definition for ARF, the ADQI group proposed a consensus graded definition, called the RIFLE criteria **(Bellomo R, et al.2004)**

A modification of the RIFLE criteria was subsequently suggested by the Acute Kidney Injury Network, which included the ADQI group as well as representatives from other nephrology and intensive care societies **(Levin A, et al. 2007; Molitoris BA, et al. 2007 and Mehta RL, et al. 2007).**

Rifle Criteria

The RIFLE criteria consists of three graded levels of injury (Risk, Injury, and Failure) based upon either the magnitude of elevation in serum creatinine or urine output, and two outcome measures (Loss and End-stage renal disease). The RIFLE strata are as follows (Levin A, et al. 2007)

Risk — 1.5-fold increase in the serum creatinine or GFR decrease by 25 percent or urine output <0.5mL/kg per hour for six hours

- Injury — Twofold increase in the serum creatinine or GFR decrease by 50 percent or urine output <0.5mL/kg per hour for 12 hours
- Failure — Threefold increase in the serum creatinine or GFR decrease by 75 percent or urine output of <0.3mL/kg per hour for 24 hours, or anuria for 12 hours
- Loss — Complete loss of kidney function (eg, need for renal replacement therapy) for more than four weeks
- ESRD — Complete loss of kidney function (eg, need for renal replacement therapy) for more than three months

A review of 13 studies verified a stepwise increase in the relative risk of death in patients who met the RIFLE criteria for various stages of AKI, Compared to patients who did not have AKI, patients in the RIFLE stages of "risk," "injury," and "failure" had increased relative mortality risks of 2.4 (CI 1.94-2.97), 4.15 (CI 3.14-5.48), and 6.37 (CI 5.14-7.9**).(Ricci Z, et al.2008)**