Potential Protective Effect of N-Acetyl Cysteine on Renal Function during Cardiopulmonary Bypass in comparison to Manitol

Thesis

Submitted for Partial Fulfillment of M.D. Degree in Anesthesiology

Presented by

Mohammed Osama Mahmoud Elgohary
M.B., B.Ch., M.Sc., Anesthesiology
Faculty of Medicine, Ain Shams University

Supervised by

Dr. Amir Ibrahim Salah
Professor of Anesthesiology, Intensive Care and Agology
Faculty of Medicine - Ain Shams University

Dr. Ayman Mokhtar Kamaly
Professor of Anesthesiology, Intensive Care and Agology
Faculty of Medicine- Ain Shams University

Dr. Hadil Magdy Abdelhamid
Assistant Professor of Anesthesiology, Intensive Care and Agology
Faculty of Medicine- Ain Shams University

Faculty of Medicine
Ain Shams University
2016

*First and above all thanks to **ALLAH**.*

*I would like to express my endless gratitude and appreciation to my eminent professor, **Dr. Amir Ibrahim Salah,** Professor of Anesthesiology, Intensive Care and Agology, Faculty of Medicine – Ain Shams University, for giving me the honor to work under his supervision and from whom I did learn a lot. He encouraged me, removed all the obstacles from my way and pushed me to achieve success.*

My sincere thanks to ***Dr. Ayman Mokhtar Kamaly,*** *Professor of Anesthesiology, Intensive Care and Agology, Faculty of Medicine- Ain Shams University,* for his continuous guidance, honest help and endurance that made this thesis come to light.

*I would also like to express my gratefulness to **Dr. Hadil Magdy Abdelhamid,** Assistant Professor of Anesthesiology, Intensive Care and Agology, Faculty of Medicine- Ain Shams University, for her precious advice and support throughout this whole work.*

Mohammed Osama Mahmoud Elgohary

List of Contents

List of Abbreviations

ADQI ..... Acute Dialysis Quality Initiative
AKI ..... Acute kidney injury
All ..... Angiotensin ll
ANP ..... Atrial natriuretic peptide
AP ..... Alkaline phosphatase
ARF ..... Acute renal failure
ATN ..... Acute tubular necrosis
ATP ..... Adenosine triphosphatase
BUN ..... Blood urea nitrogen
CABG ..... Coronary artery bypass graft
CMV ..... Cytomegalovirus
CPB ..... Cardiopulmonary bypass
CSA ..... Cardiac surgery associated
DPP ..... Dipeptidyl peptidase
EF ..... Ejection fraction
FA ..... Folic acid
GFR ..... Glomerular filtration rate
GGT ..... Gamma glutamyl transferase
GST ..... Glutathione S transferase
IABP ..... Intra-aortic balloon pump
KIM 1..... Kidney injury molecule 1
LAP ..... Leucine aminopeptidase
LDH ..... Lactate dehydrogenase
L-FABP ..... Liver fatty acid binding protein
NAC ..... N-Acetyl Cysteine
NGAL ..... Neutrophil gelatinase associated lipocalin

List of Abbreviations (Cont…)

NO ..... Nitric oxide

NYHA ..... New York Heart Association

PARP ..... Poly adenosine diphosphateribose polymerase

PGs ..... Prostaglandins

RAS ..... Renin-angiotensin-aldosterone system

RBF ..... Renal blood flow

ROS ..... Reactive oxygen species

SIRS ..... Systemic inflammatory response syndrome

SNS ..... Sympathetic nervous system

TGF ..... Tubuloglomerular feedback

List of Tables

List of Figures

INTRODUCTION

Cardiovascular surgery with the use of cardiopulmonary bypass (CPB) is a common and life-saving procedure. It is the most frequent major surgical procedure performed in hospitals worldwide, with well over one million operations undertaken each year **(Albert and Antman, 2003).**

Acute renal failure (ARF) occurring around the time of surgery is a serious complication associated with considerable morbidity and mortality. Appropriate perioperative strategies are required to protect renal function to optimize patient outcome. Patients undergoing cardiac and vascular surgery are at particular risk of developing Acute Renal Failure (ARF) that commonly results in a poor outcome (**Hertzer *et al.*, 2002).**

Factors are involved in the development of ARF:

1. Renal hypo-perfusion outside the limits of auto-regulatory reserve, particularly during cardiopulmonary bypass (CPB), is a major determinant of (Acute tubular necrosis) ATN.
2. The systemic inflammatory response syndrome (SIRS) triggered by major surgery results in cell-mediated and cytotoxic injury.
3. ATN may also be exacerbated by renal embolic injury: aortic atheroma disrupted by operative manipulation and

thrombus, air, lipid, and tissue may contribute to the embolic load during surgery.

4. Prolonged surgery produces haemolysis: renal excretion of haem derivatives may result in renal tubular injury.

5. Toxic injury from the administration of nephrotoxic drugs may also contribute to post-operative ARF. Patients who present for non-elective cardiac surgery shortly after pre-operative cardiac catheterization are at increased risk related to both the radiocontrast load and surgery itself (**Kellum, 2008).**

The identification of high-risk patients and the implementation of prophylactic measures are the goals of perioperative renal protection. Strategies to reduce the occurrence of renal injury in patients without evidence of acute renal dysfunction are referred to as primary prevention (**Thakar *et al.*, 2005).**

Mannitol is a traditionally osmotic diuretic with several suggested benefits in the perioperative period. Theoretically, it increases intravascular volume, improving preload and cardiac output, increases blood to the kidneys through the release of atrial natriuretic peptide, and facilitates the flushing of debris from renal tubules by increasing urinary output. ***Mannitol*** is known to have additional properties as a free radical scavenger,

which may help attenuate the effects of reperfusion injury. **(Gude & Jha, 2007)**.

Substantial evidence supports the prophylactic use of the antioxidant ***N-Acetyl Cysteine*** (NAC), along with intravascular volume expansion, for the prevention of radio-contrast nephropathy (**Tepel *et al.*, 2000).** In experimental studies, NAC has attenuated renal dysfunction through different anti-inflammatory and antioxidant effects such as antagonism of tumor necrosis factor and inhibition of the vascular cell adhesion molecule expression. Furthermore, NAC has been shown to prevent cardio- pulmonary bypass pump–induced inflammatory response (**Sucu *et al.*, 2004).**

Cystatin C is a cysteine protease inhibitor. Serum level of cystatin C is a reflection of GFR, making changes in serum and urine levels a reflection on changes in GFR. **Cystatin C** levels are not significantly affected by age, race, sex , muscle mass, or infection, making it a better measure of GFR than serum creatinine **(Dharnidharka, Kwon *et al.* 2002).**

AIM OF THE STUDY

The aim of this study is to explore the potential protective effect (s) of N-Acetyl Cysteine and Mannitol on renal functions for patient undergoing on pump cardiac surgery using the renal biomarker Cystatin C, serum creatinine and serum sodium (Na+).

PATHOPHYSIOLOGY AND RISK FACTORS

Perioperative renal failure is not an uncommon clinical problem after major cardiovascular surgery and relentlessly continues to be associated with poor outcomes; mortality rates for new patients requiring dialysis are similar to several decades ago. Barriers that have precluded effective clinical studies are caused in part by inconsistencies in defining the entity and an incomplete understanding of the pathophysiology in the clinical setting, both of which contribute to the lack of success in prevention and treatment of this disease (**Bouman *et al.*, 2010).**

The term acute kidney injury (AKI) was adopted in by the American Society of Nephrology Renal Research Group to reflect the entire spectrum of the disease from minimal elevations in serum creatinine to anuric renal failure, from functional deviations to structural changes, and from prerenal azotemia to acute tubular necrosis (**Dennen *et al.*, 2010).**

A consensus definition of AKI was proposed by the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) group, which published a classification system for AKI based on changes in serum creatinine and/or urine output criteria. This is a 5-stage classification, the first 3 of which define grades of increasing

severity of AKI (risk, injury, and failure) on the basis of changes of serum creatinine or glomerular filtration from baseline as well as a decline in urine output. The last 2 stages are outcome variables (loss and end-stage kidney disease), thus the acronym RIFLE classification (**Bellomo *et al.*, 2010).**

These criteria have since been modified by the Acute Kidney Injury Network (AKIN), which proposed a timeframe of 48 hours within which AKI has to occur and 3 classes describing increases in serum creatinine relative to baseline. In recognition of findings that even minimal increments in serum creatinine adversely affect outcomes, the AKIN definition includes lesser degrees of serum creatinine elevation (_0.3 mg/dL or _50% above baseline within 48 hours) (**Lassnigg *et al.*, 2008)**.

The Acute Dialysis Quality Initiative (ADQI) group recently proposed a consensus definition specifically aimed at AKI after cardiac surgery using these modified criteria, subdividing the AKIN diagnostic and staging criteria into "early" (within the first 7 days) and "late" (occurring between 7 and 30 days after cardiac surgery) **(Hoste *et al.*, 2008).**

Table (1): A comparison of RIFLE and AKIN classification of AKI (**Haase et al., 2009).**

RIFLE Criteria*			AKIN Criteria†		
Stage	GFR or Creatinine	Urine Output	Stage	Creatinine	Urine Output
Risk	GFR decrease > 25% or S Cr increase x 1.5 (baseline)	UO < 0.5 ml/kg/h for > 6 h	1	0.5 to 2 times (baseline) or Increase of > 0.3 mg/dl	UO < 0.5 ml/kg/h for > 6 h
Injury	GFR decrease > 50% or S Cr increase x 2 (baseline)	UO < 0.5 ml/kg/h for 12 h	2	2 to 3 times (baseline)	UO < 0.5 ml/kg/h for > 12 h
Failure	GFR decrease > 75% or S Cr increase x 3 (baseline) or level of 4.0 mg/dl with an acute increase of 0.5 mg/dl	UO < 0.5 ml/kg/h for 12 h	3	> 3 times (baseline) or level of 4.0 mg/dl with an acute increase of 0.5 mg/dl or RRT	< 0.3 ml/kg/h for 24 h or anuria for 12 h
Loss	Persistent AKI = loss of renal function > 4 weeks				
ESKD	End stage kidney disease > 3 months				

The pathophysiology of AKI during cardiac surgery

With respect to the pathophysiology of cardiac surgery associated AKI (CSA-AKI), although the mechanisms of injury are well established in preclinical trials, direct proof of causation in humans is less feasible. Manipulation of individual pathways is not possible in clinical trials as it is in animal or in vitro studies; rather, the mechanisms and pathways are inferred by association. Therefore, 6 general pathophysiologic processes were concluded to be most likely to contribute to CSA-AKI: exogenous and endogenous toxins, metabolic factors, ischemia reperfusion, neurohormonal activation, inflammation, and

oxidative stress, which are all most likely interrelated and probably synergistic (**Fontaine *et al.*, 2009).**

The concept of prerenal azotemia currently is questioned by leading authors in nephrology. The traditional paradigm that prerenal azotemia and acute tubular necrosis are separate clinical entities is no longer held; rather, they are both part of a dynamic response of the kidney to physiologic and pathophysiologic changes and encompass early reversible conditions through to established disease (**Kellum *et al.*, 2007**).

Although the term prerenal azotemia is outmoded, the condition itself is encompassed in the current definitions of AKI because the AKIN definition allows for small increases in serum creatinine and reductions in urinary flow. Rather than the term prerenal azotemia, the ADQI and AKIN groups favor the concept of **volume-responsive AKI,** emphasizing that although these early stages of AKI may be reversible, even minor increases above baseline are associated with adverse outcomes and any degree of renal insufficiency no matter how small has significant clinical consequences even in the absence of complete loss of function (**Levin *et al.*, 2008).**

Volume-responsive AKI

The current conceptual model of AKI presents the idea of volume-responsive AKI as a reduced glomerular filtration rate