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The Role of Dexmedetomidine in decreasing Acute Kidney Injury in Children with Acyanotic Heart Disease Undergoing Total Correction by a New Urinary Biomarker Kidney Injury Molecule-1

Thesis

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Abstract

Cardiac surgery with cardiopulmonary bypass (CPB) is the most frequent major surgical procedure worldwide. Acute kidney injury (AKI) is a common and serious complication encountered in 30–40% after CPB.

Once AKI is established, there is no effective treatment for human AKI, and dialysis merely provides supportive care. There in lies the Achilles' heel of AKI management ; the paucity of early biomarkers has lead to an unacceptable delay in initiating therapy in humans¨

Serum creatinine is insensitive for the early detection of AKI. KIM-1 is one of the most highly induced proteins in the kidney after AKI in animal models, and a proteolytically processed domain of KIM-1 is easily detected in the urine soon after AKI. In a small human cross-sectional study, KIM-1 expression was markedly induced in proximal tubules in kidney biopsies from patients with established AKI (primarily ischemic), and urinary KIM-1 measured by ELISA distinguished ischemic AKI from prerenal azotemia and chronic renal disease .

In a case-control study of children undergoing CPB, urinary KIM-1 levels were markedly enhanced in subjects who subsequently developed AKI. Thus, KIM-1 represents a promising candidate for inclusion in the urinary "AKI Biomarker Panel", with NGAL being most sensitive at the earliest time points and KIM-1 potentially adding specificity at slightly later time points. One advantage of KIM-1 as a urinary biomarker is the fact that its expression seems to be limited to the injured or diseased kidney, and no systemic source of KIM-1 has been described .

Perioperative administration of alpha2-adrenergic agonist dexmedetomidine, has been shown to reduce anesthetic requirements, enhance hemodynamic stability and provide sedation during postoperative recovery following coronary artery bypass. Dexmedetomidine-induced sympatholysis might attenuate harmful hemodynamic events resulting in prevention of AKI. In fact, alpha2-adrenoceptor activation does produce some potentially renal protective effects including inhibition of renin release,increased glomerular filtration and increased secretion of sodium and water . Moreover, pretreatment with clonidine, the archetype of alpha2-adrenergic agonists, has shown beneficial renal effects after cardiac surgery .In an earlier study it was found that urine output tended to be greater in patients receiving dexmedetomidine than in those receiving placebo in post-coronary artery bypass grafting (CABG) patients .

To date, no single pharmacological regimen has conclusively proved its efficacy in preventing AKI and any potential means to decrease the number of cardiac surgery patients encountering this deleterious adverse effect should be sought.

The present study is directed to examine the renal protection of dexmedetomidine as tested by KIM-1 , and the study included 72 pediatric patients of average age 6 months -8 years and average weight of 6-20 kilograms. Different elective pediatric cardiac surgeries of average duration 3-5 hours were undergone for these patients under general anesthesia. The patients were randomly assigned and divided into 2 groups namely Dexmedetomidine group (n=36) and Control group (n=36).

There was no significant rise in level of KIM-1 between both groups , but there was significant difference indicating AKI in control group in patients with prolonged bypass .There was significant rise in level of KIM -1 between the baseline sample and 24 hour sample within the same group .In prolonged bypass only ,the number of patients diagnosed with AKI in control group was double the number of patients with AKI in group Dex .

Data obtained in this study showed that dexmedetomidine has renal protective value by decreasing AKI in patients with prolonged by pass more than 90 minutes . KIM-1 is more sensitive than serum creatinine in diagnosing AKI

Key words: Dexmedetomidine , Cardiopulmonary bypass, Pediatric , AKI, KIM-1.

Aim of The Work

The aim of the work is to detect the effect of dexmedetomidine in decreasing AKI in children with acyanotic congenital heart diseases undergoing corrective cardiac surgery using cardio-pulmonary bypass, as early as possible, by measuring KIM- 1 - a novel urinary biomarker - to allow for early management and thus decreasing morbidity and mortality in those children .

List Of Abbreviations

ACTH : adrenocorticotropic hormone
AKI : acute kidney injury
AKIN : acute kidney injury network
ANP : atrial natriuretic peptide
ARF : acute renal failure
ATP : adenosine triphosphate
AUC : area under the curve
AVP : arginine vasopressin
BNP : brain-type natriuretic peptide
BUN : blood urea nitrogen
CABG : coronary artery bypass graft
cAMP : cyclic adenosine monophosphate
CBP : cardiopulmonary bypass
CK : creatinine kinase
CKD : chronic kidney disease
CRRT : continuous renal replacement therapy
DHCA : deep hypothermic circulatory arrest
ECG : electrocardiogram
ECMO : extra corporeal membrane oxygenation
FDA : food and drug administration
GABA : gamma-aminobutyric acid
GFR : glomerular filtration rate
GGT : glutamyltranspeptidase
HAVCR-1 : hepatitis A virus cellular receptor-1
HK2 : human kidney proximal tubular cells
ICAM-1 : intercellular adhesion molecule-1
ID : internal diameter
IHD : intermittent hemodialysis
IL-18 : interleukin-18
IRI : ischemic reperfusion injury

JAK/STAT : janus kinase / signal transducer and activator of transcription
KIM-1 : kidney injury molecule-1
Lcn2 : lipocalin 2
L-FABP : liver fatty acid binding protein
MCP-1 : monocyte chemoattractant protein-1
MUF : modified ultrafiltration
NaCl : sodium chloride
NAG : N-acetyl-β-glucoosaminidase
Na-K-ATPase : sodium potassium ATPase
NGAL : neutrophil gelatinase-associated lipocalin
NSAIDs : non steroidal anti-inflammatory drugs
NYHA : NewYork Heart association
PAH : para-aminohippurate
PCR : polymerase chain reaction
PI3K-Akt : phosphatidylinositol 3-kinase
RBF : renal blood flow
RCTs : randomized control trials
RIFLE : risk, Injury, Failure, Loss and End-stage
ROC : receiver-operating characteristic
RRT : renal replacement therapy
SLED : Sustained low-efficiency dialysis
TFEC : S-(1,1,2,2-tetrafluoroethyl)-l-cysteine
TIM-1 : T-cell immunoglobulin mucin
TMN : tuberomamillary nucleus
TNF : tumor necrosis factor
VLPO : ventrolateral preoptic nucleus

Contents

List of Tables

List of Figures

Chapter One

Pathophysiology of AKI

Renal Physiology

The kidneys contain approximately 2×10^6 nephrons, each of which consists of a glomerulus and a tubule, which empties into a collecting duct. These functional units collectively enable the kidneys to maintain a stable interior milieu despite large fluctuations in fluid and solute intake. Together, they regulate intravascular volume, osmolality, and acid-base and electrolyte balance and excrete the end products of metabolism and drugs. Urine is formed by the combination of glomerular ultrafiltration and tubular reabsorption and secretion. The nephron also elaborates hormones that contribute to fluid homeostasis (renin, prostaglandins, kinins), bone metabolism (1,25-dihydroxycholecalciferol), and hematopoiesis (erythropoietin).

GLOMERULUS (RENAL CORPUSCLE)

The glomerulus consists of five distinct components: capillary endothelium, glomerular basement membrane, visceral epithelium (which together make up the filtration barrier), parietal epithelium (Bowman's capsule), and mesangium (interstitial cells). The glomerular tuft, a highly convoluted series of capillary loops, is fed by the afferent arteriole and drains into the efferent arteriole . The capillary endothelium has fenestrations about 70 to 100 nm in diameter and lies atop the glomerular basement membrane. The visceral epithelium, which is applied to the underside of the basement membrane, consists of podocytes with filamentous, interdigitating foot processes that contain contractile actin filaments.

Glomerular ultrafiltration is governed by the balance of Starling's forces regulating fluid flux across the filtration barrier. The glomerular filtration rate