Efficacy of Atorvastatin in Prevention of Contrast induced Nephropathy in Patients Undergoing Coronary Angiography

Thesis

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List of Contents

List of Tables

Table No.	Title	Page No.

List of Figures

List of Abbreviations

Abb.	Full term
AKI	*Acute Kidney Injury*
AKIN	*Acute Kidney Injury Network*
ATN	*Atorvastatin*
CA	*Coronary Angiography*
ESC	*Europeans society of cardiology*
CIN	*Contrast-Induced Nephropathy*
CRP	*C-Reactive Protein*
GMSC	*CM Safety Committee*
HOCM	*High-Osmolar Contrast Media*
ICAM-1	*Intracellular Cell Adhesion Molecule 1*
ICM	*Iodinated Contrast Media*
IL-1β	*Interferon-1 Beta*
IL6	*Interleukin 6*
LVEF	*Left Ventricular Ejection Fraction*
MHC	*Major Histocompatibility Complex*
MM	*Multiple Myeloma*
NAC	*N-acetylcysteine*
NFG	*Normal Fasting Glucose*
NGAL	*Neutrophil Gelatinase-Associated Lipocalin-2*
NO	*Nitric Oxide*
PCI	*Percutaneous Coronary Intervention*
PGE2	*Prostaglandin E2*
pPCI	*Primary Percutaneous Coronary Intervention*
ROS	*Reactive Oxygen Species*
SCr	*Serum Creatinine*
STEMI	*ST Elevation Myocardial Infarction*
VCAM-1	*Vascular Cell Adhesion Molecule*
β2M	*Beta-2Microglobulin*
ACR	*American Association of Radiology*

INTRODUCTION

The use of radiocontrast media has increased greatly from the past decades for diagnostic radiography and interventional procedures and it is estimated that approximately 60 million people in the world are used radiocontrast media each year ***(Assareh et al., 2016).***

On the other hand, the administration of radiocontrast media may lead to acute kidney injury (AKI) that begins soon after the contrast is administered. Contrast-induced nephropathy (CIN) is defined as the impairment of renal function measured as either a 25% increase in serum creatinine (SCr) from baseline or a 0.5 mg/dL (44 μmol/L) increase in absolute SCr value within 48-72 hours after intravenous contrast administration ***(KDIGO et al., 2016).***

Contrast-induced nephropathy (CIN) is of concern after the use of radiocontrast media for coronary angiography (CAG) and percutaneous coronary intervention (PCI). Many studies has studied the incidence of CIN and its risk factors in patients undergoing CAG ***(Kumar et al., 2016).***

Interaction between inflammatory mechanisms and oxidative stress are involved in the pathogenesis of CIN ***(Hossain et al., 2016).***

Statins may decrease inflammation and improve endothelial function, decreasing expression of endothelial adhesion molecules, and increasing NO bioavailability ***(Syed et al., 2016).***

Aim of the Work

The aim of this study was to evaluate the efficacy of atorvastatin (ATN) 80 mg in the prevention of CIN in patients undergoing angiography.

CONTRAST-INDUCED NEPHROPATHY

The European Society of Urogenital Radiology defines kidney injury as CIN (well received by the radiological community) if there is an increase in serum creatinine of 0.5mg/dL or > 25% of the baseline within 72 hours of contrast administration (3, 5-8) in the absence of an alternative etiology ***(Wichmann et al., 2015).***

Definition of contrast induced nephropthy is not uniform, with the used criteria showing discrepancies. According to the Acute Kidney Injury Network (AKIN), CIAKI is defined as an increase in serum creatinine > 0.3mg/dL or > 50% of the baseline within 48 hours after the administration of intravenous contrast ***(Moura et al., 2017)***.

Contrast-induced nephropathy (CIN) is defined as the impairment of renal function measured as either a 25% increase in serum creatinine (SCr) from baseline or a 0.5 mg/dL (44 µmol/L) increase in absolute SCr value-within 48-72 hours after intravenous contrast administration ***(van der Molen et al., 2018).***

Table (1): Shows definitions of contrast nephropathy ***(Moura et al., 2017)***

Criteria		Definition	
CIN		Increase in sérum creatinine of 0.5mg/dL or > 25% of the baseline within 72 hours of contrast administration	
CIAKI		Increase in sérum creatinine > 0.3mg/dL or > 50% of the baseline within 48 hours after administration of intravenous contrast	
KDIGO staging	1	1.5 X	Increase in sérum creatinine level
	2	2 X	
	3	3 X	

Despite technological advances, CIN remains responsible for a third of all hospital-acquired acute kidney injury (AKI) and affects between 1% and 2% of the general population and up to 50% of high-risk subgroups following coronary angiography (CA) or percutaneous coronary intervention (PCI) ***(Mehran et al., 2006).***

Contrast-induced nephropathy (CIN) is a common complication of primary percutaneous coronary intervention (pPCI) and is associated with high mortality and morbidity and long hospital stay in patients with ST elevation myocardial infarction (STEMI) ***(Rencuzogullari et al., 2018).***

Table (2): Shows severity grading of contrast nephropathy ***(Harjai et al., 2013)***

Table 1 CIN severity grading system (adapted from Harjai *et al*[16])

CIN grade	Change in serum creatinine	6 month outcomes
Grade 0	SCr increase <25% and <0.5 mg/dL above baseline	MACE 12.4% Mortality 10.2%
Grade 1	SCr increase ≥25% and <0.5 mg/dL above baseline	MACE 19.4% Mortality 10.4%
Grade 2	SCr increase ≥0.5 mg/dL above baseline	MACE 28.6% Mortality 40.9%

CIN, contrast-induced nephropathy; MACE, major adverse cardiovascular event; SCr, serum creatinine.

PATHOGENESIS OF CONTRAST NEPHROPATHY

Inspite of an unclear understanding of the mechanisms underlying CIN, tubular toxicity and endothelial vasoconstriction, together with reactive oxygen species (ROS), are implicated in the pathogenesis of CIN ***(Seeliger et al., 2012).***

Contrast induced tubular toxicity:

Iodinated contrast media directly injures the renal tubular epithelium by producing ROS radicals that cause intra-renal vasoconstriction leading to ischaemia and death of tubular cells. Contrast media is characterized by high osmolality and increased viscosity (thickness), even the iso-osmolar contrast media is extremely hyperviscous compared to plasma ***(Chao et al., 2013)***. Increased hyperviscosity and osmolality cause direct damage to renal tubules and with increased intratubular pressure consequently lead to compromised renal blood flow and decreased glomerular filtration rate. Previous studies have reported a positive association between contrast media administration and tubular cell vacuolation ***(Mitchell et al., 2010).***

a. Endothelial dysfunction in CIN:

An imbalance of vasoconstrictors and vasodilators plays a critical role in mediating CIN. Contrast media suppresses intra-renal vasodilators i.e. nitric oxide (NO) and prostaglandin E2 (PGE2) and increases intra-renal vasoconstrictors that decrease blood flow to the renal medulla leading to hypoxic ischaemia, production of ROS and death of tubular cells ***(Azzalini et al., 2016).***

Vasoconstriction in CIN is mediated by adenosine and endothelins acting on A1 and E1 receptors respectively. Endothelin receptor stimulation is associated with decreased GFR ***(Deng et al., 2015).***

b. Medullary hypoxia and CIN:

In CIN, the presence of hypoxia in the outer medulla of the kidney is essential in the pathogenesis of CIN ***(Geenen et al., 2013).*** Following contrast administration, the outer medullary renal blood flow exhibits two phases; a brief period characterized by increased flow that is later followed by an almost 25% sustained decrease in renal blood flow that ultimately impacts poorly on oxygen delivery to the medulla.The partial pressure of oxygen decreases to as low as 10-15 mmHg post contrast administration ***(Seeliger et al., 2012).***