Iso-Osmolar versus Low-Osmolar Contrast Media in Reducing Contrast Induced Nephropathy in Patient with Renal Impairment Undergoing Coronary Angiography or Intervention.

Thesis submitted for partial fulfillment of master degree in cardiology

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بِسْمِ اللهِ الَرحمَن الرحيم

أَلَم تَرَ أَنَّ اللهَ أَنزَلَ مِنَ السَّمآءِ مَآءً فَأَخرَجنَا بِهِ ثمراتٍ مُخْتلفاً ألوانُها وَمِنَ الجِبالِ جُدَدٌ بِيضٌ وَحُمرٌ مُّختلِفٌ ألوانُها وغرَابيبُ سُودٌ ﴿27﴾ ومِنَ النَّاسِ والدَّوابِّ والأنعامِ مُختلفٌ ألوانُهُ كَذلِكَ إنَّما يَخشَى اللهَ مِن عبادِهِ العُلَمآءُ إنَّ اللهَ عزيزٌ غفور﴿28﴾.

صَدَق اللهُ العَظيمْ

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ABSTRACT

OBJECTIVES

This study was undertaken to compare the renal safety of iso-osmolar iodixanol vs. low-osmolar iopromide in patients with chronic kidney disease (CKD) undergoing coronary angiography and /or intervention.

BACKGROUND

With the growing number of contrast-enhanced procedures being performed for coronary artery disease management, the safety and efficacy of iodinated contrast media (CM) have come under increased scrutiny. Contrast-induced nephropathy (CIN) is a common cause of in-hospital renal failure. A prior meta-analysis and studies was conflicting about the safety of iodixanol (IOCM) compared with iopromide (LOCM) in reduce the incidence of CIN in patients with chronic kidney disease (CKD) undergoing coronary interventions.

METHODS

One hundred ten patients with CKD (eGFR $\leq$ 60 mL/min/1.73m^2) were randomized in 1:1 fashion to receive either iso-osmolar contrast agent (iodixanol =55) or low-osmolar contrast agent (iopromide =55) with proper hydration. Serum creatinine levels were measured at baseline and 48–72 hours after contrast administration. Contrast-induced nephropathy (CIN) was defined as an increase in serum creatinine (SCr) $\geq$25% or 0.5 mg/dL within 72 hr of CM administration.

ABSTRACT

RESULTS

The overall incidence of CIN expressed as a relative ≥ 25% increase in SCr was significantly lower in iodixanol group than iopromide group (7patients (12.7%) vs. 17 patients(29.1%), P= 0.035). Similarly when expressed as an absolute ≥0.5 mg/dL increase in SCr the incidence of CIN was significantly lower in patients who received iodixanol: 8 patients (14.5%) compared with those who received iopromide: 19 patients (34.5%); P= 0.015. Among all variables in the study, female gender (HR=0.29; 95% confidence interval 0.1 to 0.7, P=0.008), use of iopromide (HR=3.59; confidence interval 1.3 to 9.3, P=0.008) and DM appeared to be associated with higher risk of CIN by >25% and ≥0.5 mg increase SCr from baseline.

CONCLUSIONS

In patients with impaired renal function undergoing coronary catheterization, use of iso-osmolar contrast medium, iodixanol is associated with lower risk of contrast induced nephropathy than the low-osmolar contrast medium, iopromide. Among many clinical and procedure related variables, only female gender and use of contrast medium iopromide are associated with increased risk of contrast induced nephropathy.

Key Wards: Renal impairment - Coronary Angiography – iodinated contrast media- Contrast induced Nephropathy

List of abbreviations

ACC	American College of Cardiology
ACE-I	Angiotensen Converting Enzyme Inhibitors
ACS	Acute Coronary Syndrome
AHA	American Heart Association
AKD	Acute Kidney Disease
ANP	Atrial Natriuretic Peptide
BB	Beta Blockers
BMI	Body Mass Index
BSA	Body Surface Area
CABG	Coronary Artery Bypasses Grafting
CAD	Coronary Artery Disease
CCB	Calcium Channel Blockers
CI	Confidence Interval
CIN	Contrast Induced Nephropathy
CKD	Chronic Kidney Disease
CM	Contrast Media
COX_2	Cyclooxygenase 2
CT	Computed Tomography
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
DSA	Digital Subtraction Angiography
EACTS	European Association for Cardio-Thoracic Surgery
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
EDTA	Ethylene Ediamine Tetra Acetic Acid
gI/kg	Gram iodine / kilogram
HF	Heart Failure
HOCM	High Osmolar Contrast Media
HR	Hazard Ratio
HVCM	High Viscosity Contrast Media

IOCM	Iso Osmolar Contrast Media
IV	Intra Venous
LV	Left Ventricle
LOCM	Low Osmolar Contrast Media
LVCM	Low Viscosity Contrast Media
LVED	Left Ventricular end Diastolic Pressure
LVEF	Left Ventricular Ejection Fraction
LVSP	Left Ventricular Systolic Pressure
MACE	Major Adverse Cardiac Events
MI	Myocardial Infarction
mpa-s	Millipascal seconds into Centipoise
mOsm/kg H2O	Milli-Osmoles per Kilogram Water
NAC	N- Acetyl Cystain
NO	Nitric Oxide
$NSAID_S$	Non Steroidal Anti Inflammatory Drugs
NSTEMI	Non ST Elevation Myocardial Infarction
NYHA FC	New York Heart Association Functional Class
OMT	Optimal Medical Therapy
PCI	Percutaneous Coronary Intervention
PO_2	Partial Oxygen Pressure
PVD	Peripheral Vascular Disease
SBP	Systolic Blood Pressure
SCr	Serum Creatinine
STEMI	ST Elevation Myocardial Infarction
UA	Unstable Angina
Δ	Delta

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Introduction and Aim of the work

Introduction

Over the past several decades, coronary angiography (CA) has undergone tremendous growth. It remains the gold standard for identification and diagnosis of coronary stenosis due to coronary artery disease (CAD).

CA has several indications and also has some reported complications. Among these reported complications is the contrast induced nephropathy (CIN).

Several methods and strategies were used aiming at preventing this unpleasant complication with it's consequences. These efforts included, Identification of risk factors, hydration forced dieresis, use of drugs such as vasodilators and, N-acetylcysteine, and choice of the type of the contrast media.

The aim of this study

1) - Compare between the iso-osmolar CM iodexanol with the low-osmolar CM iopromide in prevention of CIN in patients with CKD.

2) - Identification of the predictors for deterioration of renal function after coronary catheterization.

Contrast angiography

Introduction

Diagnostic and interventional cardiac angiography has undergone tremendous growth over the past several decades. Iodinated contrast media (CM) are utilized in an estimated 80 million diagnostic and interventional cardiovascular and non-cardiovascular procedures worldwide; annually [(1)]. A great deal of this growth has been facilitated through an increased ability to perform these procedures safely. This would have not been possible without the design and development of several generations of intravascular contrast agents [(2)].

Contrast enhanced x-ray imaging remains essential to the diagnosis and treatment of many types of cardiac and vascular diseases. Despite the rapid advancement in less invasive imaging technique, only traditional angiography provides a high resolution, real time, dynamic view of vascular structures [(3)].

Historical Background:

Soon after the discovery of X-rays by Roentgen, it was recognized that iodine was radio-opaque. The attenuation of X-rays by iodine-containing media during radiographic examinations resulted in the name “contrast” media. In 1901, Marcel Guerbet, Professor of Toxicology at the School of Pharmacy in Paris, developed Lipiodol, the first organic contrast compound. [(4)] However, it was not until 1921–1922 that this iodinated oil compound was used in radiology procedures, following myelography studies by Jacques Forestier and Jean-Athanase Sicard. [(5)] In 1928, Moses Swick developed the first water-soluble iodinated CM suitable for intravenous use. After his initial attempts to find a soluble and stable CM compound, Swick and colleagues went on to develop a number of more effective, safer compounds.[(6)] The first use of CM in cardiac catheterization was by Sven- Ivar Seldinger,[(7)]a young radiologist working at the Karolinska Clinic in Stockholm in 1956. By that time, the forerunner of contemporary CM containing a tri-iodinated benzene ring compound (sodium diatrizoate) had been produced.

Early CM was ionic, monomeric and high osmolar. In 1968, the first nonionic, monomeric, low-osmolar CM, metrizamide, was developed by a Swedish radiologist, Torsten Almen, in an effort to improve the safety profile of CM.[6] He believed that the dissociation of ionic CM in solution and the resulting effects on the osmolality of the solution were primarily responsible for their untoward hemodynamic effects. Since metrizamide was unstable in solution, other low-osmolar CM was developed. One of the first stable low-osmolar CM, ioxaglate, was marketed in the United States [8] in 1985. More recently, nonionic, dimeric, iso-osmolar CM were developed in an attempt to further reduce their osmolality to that approaching plasma. However, the dimeric structure of these agents resulted in a substantial increase in their viscosity [9].

Contrast Agents in Use Today:

Contrast media differ significantly with regard to their physical and biochemical properties.

Physicochemical Properties of Contrast Media

Contrast media have traditionally been classified by their physical and biochemical properties, including structure, ionicity, osmolality and viscosity [10]. Although intimately related, these properties are distinct and are best discussed separately.

Structure is related to the number of benzene rings per molecule. The basic structure of all currently used CM consists of a 2, 4, 6 tri-iodinated benzene ring. The structural composition of iodinated CM is either a single tri-iodinated benzene ring (monomer) or 2 bound benzene rings (dimer). Monomers and dimers can be either ionic or nonionic depending on their side chain constituents.

Ionicity refers to the conjugation of the benzene ring structure (anion) with a non-radio-opaque cation resulting in a water-soluble compound. Ionic monomeric CM dissociate (ionize) in solution (*i. e.*, in the bloodstream) into 1 anion and 1 cation, resulting in an iodine-to-particle ratio of 3:2 (3 iodine atoms for 2 ions). Nonionic monomeric CM consist of tri-iodinated benzene rings with hydrophilic hydroxyl groups and organic side chains placed at the 1, 3, 5

positions, which do not ionize in solution, resulting in an iodine to particle ratio [11] of 3:1. Dimeric CM can be composed of either 2 bound nonionic monomers or a bound nonionic and ionic monomer, resulting in iodine-to particle ratios of 6:1 and 6:2, respectively. The iodine-to-particle ratio and the concentration of iodine-bearing molecules in solution affect the osmolality and amount of radio-opacity of a given CM, respectively. Based upon these differences in structure and ionicity, iodinated CM are often grouped into 4 major categories: ionic monomers, nonionic monomers, ionic dimers, and nonionic dimers [12]. The chemical structures of these prototypic CM are illustrated in figure 1.

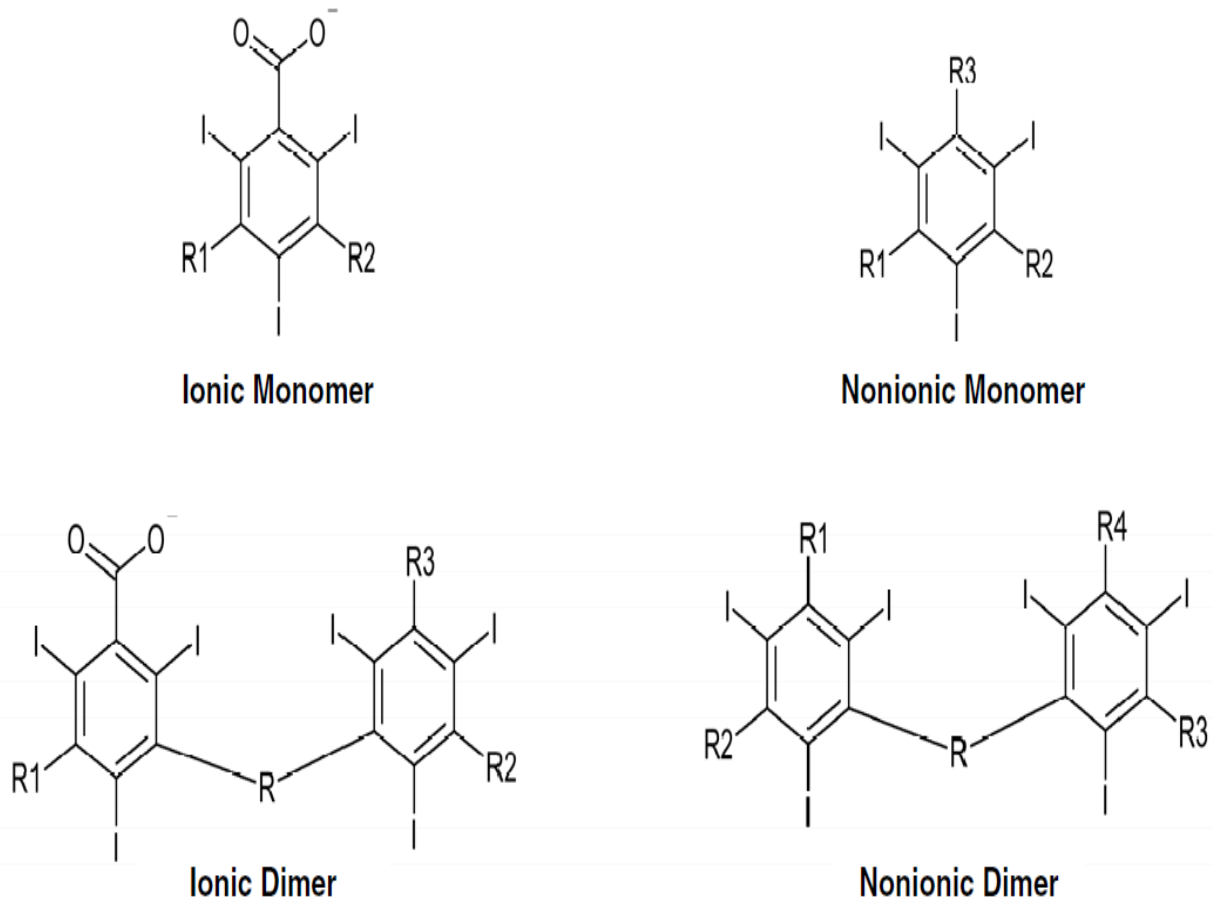

Figure .1 Prototypic structures of contrast media [13].

Osmolality refers to the concentration of osmotically active particles in a solution. The normal osmolality of blood is 280–295 mOsm/kg H2O. Contrast media used in cardiovascular procedures are often referred to as high osmolar (HOCM, typical osmolality 1400–2016 mOsm/kg H2O), low osmolar (LOCM, typical osmolality 600–844 mOsm/kg H2O) or isosmolar (290mOsm/kg H2O).[13]

Viscosity refers to the intrinsic resistance of a material to changing form and is determined primarily by the chemical structure of CM, differences in organic side chain composition, iodine concentration and temperature. Factors, such as molecular size and complexity of side chains, may lead to steric hindrance of bond torsion angles, restricting rotation and resulting in a more rigid molecule with higher viscosity. In general, viscosity is directly related to particle size and inversely related to osmolality. As with osmolality, CM may be categorized as high viscosity CM (HVCM) or low-viscosity CM (LVCM). The viscosities of select currently available CM for iodine concentrations used in cardiac catheterization and percutaneous coronary intervention (PCI) vary widely from 15.7–26.6 mPa.s at 20˚C [13]. The relationship between viscosity and osmolality of select LOCM is summarized in figure 2.

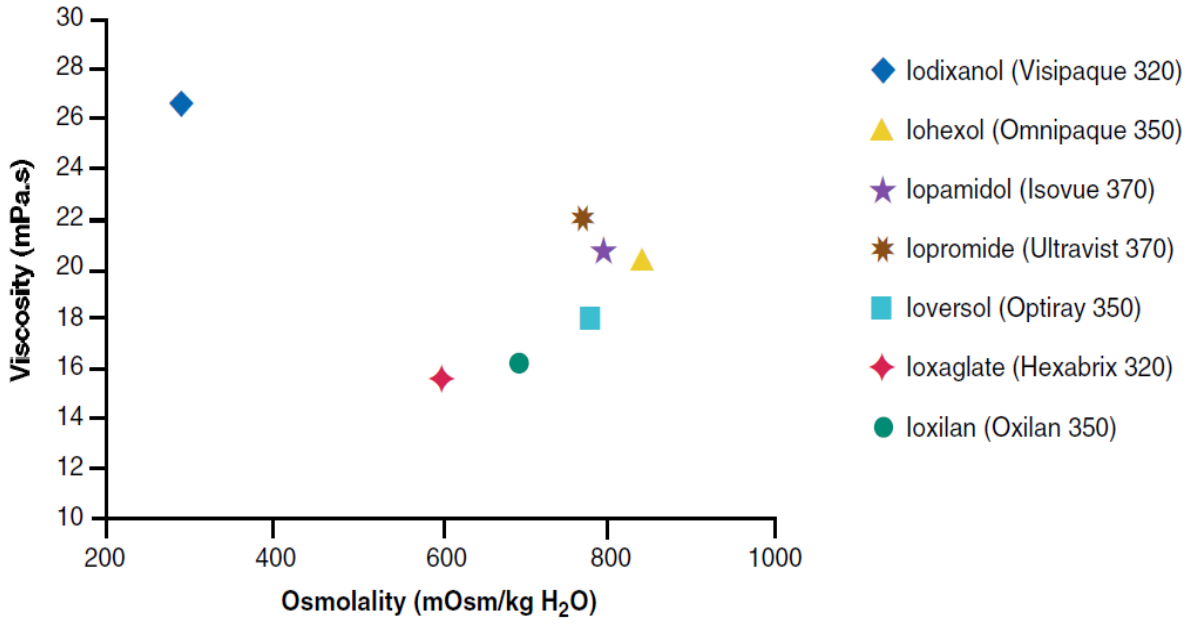

Figure .2 Viscosity and osmolality of selected contrast media at 20 °C [13].