STUDY ON INCIDENCE AND RISK FACTORS OF CONTRAST INDUCED NEPHROPATHY IN PATIENTS UNDERGOING CARDIAC CATHETERIZATION STUDIES

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DECLARATION

I solemnly declare that this dissertation entitled "**STUDY ON INCIDENCE AND RISK FACTORS OF CONTRAST INDUCED NEPHROPATHY IN PATIENTS UNDERGOING CARDIAC CATHETERIZATION STUDIES**" is done by me at Madras Medical College and Government General Hospital during 2004-2007 under the guidance and supervision of **Prof.D.Rajasekaran, M.D.** This dissertation is submitted to Tamil Nadu Dr.M.G.R. Medical University, towards the partial fulfillment of requirement for the award of M.D. Degree General Medicine (Branch - I).

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CERTIFICATE

This is to certify that this dissertation entitled "**STUDY ON INCIDENCE AND RISK FACTORS OF CONTRAST INDUCED NEPHROPATHY IN PATIENTS UNDERGOING CARDIAC CATHETERIZATION STUDIES**" submitted by **Dr.R.RADHIKA** appearing for M.D. Branch I General Medicine Degree examination in March 2007 is a bonafide record of work done by her under my direct audience and supervision in partial fulfillment of regulations of the Tamilnadu Dr.M.G.R.Medical University Chennai, I forward this to the Tamilnadu Dr.M.G.R.Medical University, Chennai, Tamilnadu, India.

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INTRODUCTION

Nephropathy induced by contrast media is a significant yet underestimated problem in clinical practice. With the increasing use of contrast media in diagnostic and interventional procedures over the last 30 years, this form of nephropathy has become the third leading cause of hospital-acquired acute renal failure, accounting for 12% of all cases [1, 27].

The risk of contrast-medium nephropathy continues to be considerable, despite the use of newer and less nephrotoxic contrast agents in high-risk patients in recent years[2]. Affected patients are at increased risk of morbidity and death. They may require short-term hemodialysis, which can extend their hospital stay and increase the risk of permanent impairment of the renal function [1, 2, 3].

The rate of contrast-medium nephropathy reported in studies that included patients with pre-existing renal dysfunction or diabetes mellitus in whom a standard hydration protocol was not administered [4,7] is between 12% and 26%. Lower rates (3.3%) have been reported among patients without these risk factors [5]. The reason a number of patients develop acute renal failure following a cardiac procedure is the necessity to perform these procedures in the presence of pre-existing, and often non-modifiable, risk factors for renal impairment.

Many individual risk factors have been reported [4, 5] for the development of CIN. The combination of two or more risk factors is rather common in daily practice, the cumulative risk of several variables on renal function is recognized [20]. A simple risk score has been developed by which the risk of contrast induced nephropathy after PCI can be simply assessed using readily available information [12].

This study aims to assess the incidence of contrast induced nephropathy and identify the common risk factors of contrast induced nephropathy in patients undergoing percutaneous coronary intervention procedures.

AIMS OF THE STUDY

The main aims of this study are

1. To assess the incidence of contrast induced nephropathy, defined as a raise in post-procedural creatinine by >25% over the baseline, in patients undergoing cardiac catheterization studies.

2. To identify the common and important risk factors of contrast induced nephropathy in patients undergoing cardiac catheterization studies.

REVIEW OF LITERATURE

Contrast-medium nephropathy is usually defined as impairment of renal function occurring within 48 hours after the administration of the contrast media[4, 5, 6]. It is manifested by an absolute increase in the serum creatinine level of at least 44 µmol/L [5, 7, 8, 9] or by a relative increase of at least 25% over the baseline value [10, 11] in the absence of another cause. In patients with CIN, serum creatinine rises by 24 hours in about 60% of patients and by 72 hours in more than 90%. Most patients described in recent series are non-oliguric and a return to baseline occurs over 7-10 days [28, 29].

Physicochemical characteristics of various contrast media

Nonionic and ionic iodinated contrast media are currently classified, at the concentrations required for diagnostic or interventional radiologic and cardiac procedures, according to their osmolality compared with the osmolality of plasma. The high-osmolal contrast media (osmolality 1500–1800 mOsm/kg) are first generation agents. In fact, the so-called low-osmolal contrast media still have an increased osmolality compared with plasma (600–850 mOsm/kg), while the newest nonionic radiocontrast agents have a lower osmolality, ~ 290 mOsm/kg, iso-osmolal to plasma.

Ionic, osmolal and molecular characteristics of contrast media

Ionic, high-osmolal monomers (1500 to 1800 mOsm/kg)	Diatrizoate
Ionic, low-osmolal dimers (600 to 850 mOsm/kg)	Ioxaglate
Nonionic, low-osmolal monomers (600 to 850 mOsm/kg)	Iopamidol, Iomeprol, Iopromide, Iohexol, Iopentol
Nonionic, iso-osmolal dimers (approximately 290 mOsm/kg)	Iodixanol

Ionic monomers

These include diatrizoate, iothalamate, ioxithalamate and metrizoate, the first two being by far the most commonly used. All ionic monomers are salts with sodium or meglumine as the non-radioopaque cation and a radioopaque tri-iodinated fuly substituted benzoic acid ring as the anion. Each molecule completely dissociates in water solution into one anion and one cation. As each anion contains 3 atoms of Iodine each molecule of ionic monomer provides 3 Iodine atoms for 2 ions, giving Iodine:particle ratio of 3:2.

Non-ionic monomers

The first non-ionic tri-iodinated monomer was metrizamide, but was replaced by iohexol, iopamidol, iopromide, ioversol, ioxilan etc. Each of these molecules are tri-iodinated, non-ionising compounds therefore in solution they produce 3 atoms of iodine to every osmotically active particle producing an iodine :particle ratio of 3:1.

Ionic dimers

Ioxaglate (Hexabrix) is the only compound in this group. It is a mixture of sodium and meglumine salts of a mono-acidic double benzene ring having 3 atoms of iodine at C2, 4 and 6 positions. The total molecule therefore contains 6 atoms of Iodine and in solution each molecules dissociates to give 1 radioopaque hexa-iodinated anion and 1 non-radioopaque cation (sodium or meglumine). Ioxaglate therefore has an Iodine:particle ratio of 6:2 or 3:1.

Non Ionic dimers

Iotrolan (isovist) and Iodixanol (Visipaque) are both examples of non ionizing chemicals each molecule containing 2 non-ionic tri-iodinated benzene rings linked together. Each molecule therefore produces in solution 6 atoms of iodine for one particle to give an Iodine:particle ratio of 6:1.

Osmolality is dependent on the number of particles of solute in solution and radio-opacity is dependent on the Iodine concentration of the solution.

The experimental evidence obtained thus far after a 70 year search for a less toxic

compound indicates that the molecules and the physicochemical characteristics of currently available CM are not comparable. For example, nonionic, low-osmolal, monomeric agents appear to be less nephrotoxic than ionic, high-osmolal agents, at least in patients with pre-existing renal impairment[13, 14]. Some reviewers have hypothesized that nonionic, iso-osmolal dimers can offer some advantages when compared with nonionic, low-osmolar monomers, but there is limited evidence to support this hypothesis in the medical literature[15].

ADVERSE REACTIONS

Contrast media are known to produce reactions that can be minor (nausea, vomiting, urticaria, itching and sneezing), moderate (nephrotoxic effects, congestive heart failure and pulmonary edema), or severe (bronchospasm, anaphylaxis and even death). Most of the minor and moderate reactions decrease significantly by use of non-ionic contrast media.

Anaphylactoid reactions in the bodycan be: Idiosyncratic anaphylactoid reactions, Non idiosyncratic reactions, and a combination of the two.

Idiosyncratic anaphylactoid reaction

These are dreaded, serious and sometimes fatal reactions to contrast media as they occur rapidly and without warning. These reactions begin either during or immediately after the administration of injection of the contrast media. Anaphylactoid reactions are not dose dependent and death has been known to occur following as little as 1ml of intravenous contrast injection or after a full dose of contrast following a negative test dose.

Non idiosyncratic reactions

These may be divided into chemotoxic and osmotoxic reactions, reactions due to direct toxicity, vasomotor and vagal reactions. These non-idiosyncratic reactions are dose dependent and therefore related to osmolarity and concentration and volume of contrast medium injected.

RENAL HANDLING OF CONTRAST MEDIA

Renal haemodynamic changes

The injection of CM induces a biphasic haemodynamic response within the kidney, causing early, rapid renal vasodilatation followed by prolonged vasoconstriction, with an increase in intrarenal vascular resistances, a reduction of total renal blood flow (RBF) and a decrease in glomerular filtration rate (GFR). Conversely, the effect on the extrarenal vasculature is transient vasoconstriction that precedes a stable decrease in vascular peripheral resistances. The resulting renal ischaemia due to these haemodynamic effects is, in part, responsible for nephropathy[16].

The reduction in renal plasmatic flow is not uniform and occurs especially in the medulla, since medullar perfusion and partial O_2 pressure (PO_2) are much lower than in the cortex. The ascending limb of Henle's loop in the medulla is characterized by high metabolic activity and increased O_2 demand due to active ion transport through the membrane. Therefore, renal hypoxia may be a critical factor in the pathogenesis of CIN[17]. Alterations in regulatory intrarenal and systemic mechanisms, induced by mediators influenced by CM, seem to contribute to the reduced renal perfusion.

Since the urinary concentration of adenosine increases after CM administration, and seems to be related directly to CM osmolality, it is possible that adenosine contributes to the haemodynamic renal biphasic response and therefore to the pathogenesis of CIN [18].

Adenosine passes freely through membranes and induces vasoconstriction via links to A1 receptors, and vasodilatation via links to A2 receptors. This observation seems to be confirmed by the tubuloglomerular feedback mechanism that is activated by an increase in diuresis and natriuresis, secondary to the administration of compounds with high osmolality or tonicity, or both. Due to these compounds, the vasoconstriction of glomerular afferent arterioles causes an increase in intrarenal vascular resistance followed by a reduction in GFR

It has been suggested that the development of contrast induced nephropathy is affected by changes in renal hemodynamics because of the effects of the contrast medium on the action of many substances, including increased activity of renal vasoconstrictors (vasopressin, angiotensin II, dopamine-1, endothelin and adenosine) and decreased activity of renal vasodilators (nitric oxide and prostaglandins)[19].

The renal vasoconstriction induced by adenosine is accentuated during sodium depletion and is reduced during volume expansion. The interaction between adenosine and endothelins as mediators of renal haemodynamics is not yet well defined. It has been hypothesized that diuresis and natriuresis induced by endothelins play a role in determining increases in renal tissue-related values of adenosine. Experimental studies in diabetic animals have shown increases in adenosine-induced renal vasoconstriction; therefore, the higher incidence of CIN in diabetics has been attributed to the presumed hypersensitivity of renal vessels to adenosine [21].

Endothelial dysfunction

Active mediators such as nitric oxide and prostaglandins play an active role in the regulation of renal perfusion. The intrarenal production of these vasodilators is responsible for the maintenance of perfusion and oxygen supply in the medulla; therefore, reductions in the availability of these mediators can promote nephropathy. It has been suggested that a number of factors are implicated in this decrease in nitric oxide concentration during CIN, although the role of CM hyperosmolality or of cellular necrosis subsequent to the administration of CM is still doubtful. According to some recent studies, CM could induce a depletion of cofactors involved in nitric oxide synthesis, such as tetrahydrobiopterin, or modify substrates, such as L-arginine[22], or interfere with its synthesis through the nuclear factor κB (NFκB), which inhibits mRNA transcription of inducible nitric oxide synthase. Some authors have suggested that that role is played by vascular impairment of the endothelium, attributable to metabolic conditions (such as hypercholesterolaemia), which subsequently promotes acute renal impairment due to a decrease in nitric oxide after CM administration [23].

Experimental studies conducted in animals showed that prostaglandins (PG) also have a renal vasodilator effect. PGE_1 and PGE_2 are able to inhibit endothelin transcription implicated in vasoconstrictive mechanisms; PGE_1 in particular seems to have a direct cytoprotective effect[24].

It is highly probable that the endogenous vasoactive system of endothelins can contribute to CM-induced ischaemic renal damage. In numerous animal and human models, the

administration of CM in large volumes has been followed by increased plasma and urine endothelin levels, especially in the presence of diabetes mellitus and chronic renal failure.

The peptidic isoforms of the endothelin family—such as ET1, ET2 and ET3—are synthesized by a conversion enzyme starting from a common precursor. ET1 is produced in the kidney by endothelial cells, glomerular mesangial cells and by the epithelium of the renal tubules. There are two different endothelin receptor subtypes: ET_A, which is located on vascular smooth muscle cells and mediates vasoconstriction; and ET_B, which is located on endothelial cells and mediates vasodilatation through activating release of nitric oxide and prostacyclin. According to recent observations, both receptors may be involved in increasing vascular resistance[25], while the relative contribution of each receptor to the vasoactive effect could depend upon the specific vascular bed. Endothelins can promote natriuresis and diuresis by reducing the reabsorption of sodium in the proximal tubule.

Experiments on CIN in animals showed that endothelin receptor antagonists preserve haematic flow and reduce renal vasoconstriction due to the administration of CM. Since this also occurs in the presence of a concomitant inhibition of PG-mediated vasodilatation, it seems likely to support the role played by the endothelin system in CM-induced renal vasoconstriction. However, recent studies in patients with impaired baseline renal function have failed to demonstrate that endothelin receptor antagonists prevent CIN[26].

Vasoactive mediators

Studies by Arakawa K et al [30] in anaesthetized dogs without sodium restriction showed that pre-treatment with calcium channel blockers widens the initial phase of vasodilatation that follows the administration of CM and cancels the following vasoconstriction phase, thus preventing a reduction in renal flow and GFR. It is therefore likely that the calcium intracellular compartment is involved in the renal vasoconstriction that follows infusion of CM.

The calcium ion has a very important role in both tubuloglomerular feedback and the myogenic response of the afferent arteriole. The increase in intracellular calcium provokes a vasoconstrictive response in intrarenal circulation, and measures to reduce the entry of calcium ions into the animal's cells prevent the reduction in RBF and GFR secondary to vasoconstrictor stimuli.

A few studies on the action of angiotensin II, also involved in tubuloglomerular feedback, have been done on sodium-depleted dogs, in which this depletion accentuates both the magnitude and duration of the vasoconstrictive phase of the renal blood flow response to injection of CM, and the blockade of the intrarenal renin–angiotensin system shortens the duration of this response[30]. Animal models of acute renal failure have been induced by administration of a CM bolus, following activation of the renin–angiotensin system by sodium restriction and PG synthesis inhibition with indomethacin [31]. Activation of the renin–angiotensin system could cause vasoconstriction of the efferent glomerular arteriole while at the same time increasing the *ex novo* synthesis of vasodilator prostaglandins resulting in almost stable or slightly increased intrarenal resistance. The CM inhibition of PG synthesis negates the

vasodilator response that in turn increases renal resistance, and reduces kidney perfusion and the GFR.

Blood volume expansion and osmotic load following CM injection provoke a release of atrial natriuretic peptide (ANP) and antidiuretic hormone (ADH), respectively, with a counteraction that provokes direct renal effects *in vivo*. While vasoconstriction induced by ADH can increase CM-induced ischaemia, the vasodilatory effects of ANP may play a protective role. It has been observed that the altered plasma concentrations of these mediators following CM injection are modest and transient; therefore, it does not seem probable that they are the determining cause in the pathogenesis of renal impairment[32]. ANP increases hydrostatic pressure and GFR, with dilatation of the afferent arteriole and vasoconstriction of the efferent arteriole. This peptide blocks tubular sodium reabsorption, induces redistribution of the renal medullar flow, hinders endothelin-induced vasoconstriction and offers resistance to tubuloglomerular feedback. It has been observed that this mediator is capable of preventing renal ischaemia and nephrotoxicity in rats and dogs after CM injection [33]. However, the increased serum concentration of atrial natriuretic peptide does not reach values high enough to prevent vasoconstriction of the afferent arteriole [34].

Haemorheological factors

Experimental studies performed on rats who have undergone CM administration have shown decreases in capillary blood flow in the renal papilla, reductions in erythrocyte velocity and O_2 tension and increases in erythrocyte aggregation. The hypertonic effect of high osmolality CM reduces the volume and deformability of the erythrocyte membrane,

contributing to an increase in haematic viscosity and to the worsening of selective medullar hypoperfusion: in fact, the plasma hyperviscosity can alter RBF particularly in the inner medulla, where the haemoconcentration is usually increased. Therefore, most authors agree that the peculiar viscosity of some CM can play a role in the pathogenesis of CIN, at least in animal studies [35].

Free radicals and reperfusion damage

Tsao PS et al [36] showed in animal studies that reactive O_2 species, such as hydrogen peroxide, hydroxyl radicals, hypochlorous acid and superoxide anion, play a role in CIN, and that endothelial dysfunction is partly due to oxygen free-radical generation during post-ischaemic reperfusion. During the pathogenesis of CM-induced renal damage an association has been observed between endothelial dysfunction and post-ischaemic syndrome. Alterations in vasoconstriction and perfusion in the external medulla seem to be partially dependent on the production of free radicals and a subsequent decrease in or deactivation of nitric oxide, or both. Free oxygen radicals, particularly the superoxide anion, react with nitric oxide to produce peroxynitrite, an oxidative and very reactive nitrosative species capable of further reducing the bioavailability of nitric oxide, thereby increasing tissue damage. This reactive species also exerts its oxidative and nitrosative effects on the sulf hydrylic groups and aromatic rings of proteins, cellular membrane lipids and nucleic acids, and can contribute to the acute vasoconstrictive effects of CM as well: this occurs through the nitrosation of tyrosine residues of enzymes, such as prostacycline synthase and nitric oxide synthase, which are involved in the synthesis of medulla vasodilators. The latter may play a critical role in vascular tone control in the external medulla, where CM ischaemic damage seems to prevail. In fact, CM administration

in humans is followed by increased production of 3-nitrotyrosine, a stable marker of peroxynitrite generation [37]. Patients with chronic renal failure, diabetes mellitus and heart failure show alterations in nitric oxide activity, a fact that may explain the greater susceptibility of these patients to develop CM-induced nephrototoxicity.

The connection between vasoactive mediators and free radicals is indirectly demonstrated by the ability of adenosine to induce the production of O_2-reactive species during its metabolization to xanthine and hypoxanthine. Methylxanthines, such as theophylline and aminophylline, could behave both as adenosine antagonist and scavengers of hydroxyl groups and inhibitors of superoxide release. In clinical practice, premedication with methylxantine before CM administration has not produced satisfying results.

Despite the many animal models of CIN that provide evidence for the involvement of free radicals, there is only indirect evidence of free radical involvement in humans. In patients with moderate renal failure, the administration of N-acetylcysteine, an antioxidant and scavenger of oxygen free radicals, might reduce the incidence of CIN, even if this finding has not been uniformly demonstrated by currently available trials [38,39].

Tubular toxicity and immunological mechanisms

In an experimental study conducted on mice, Zager RA et al [40] made the hypothesis that direct tubular toxicity may result from alterations in the integrity of the plasma and mitochondrial membranes.

Contact of the CM with tubular cells seems to cause a rapid loss of cellular proteins in the suspension medium, including the loss of cell membrane proteins, such as the sodium–potassium ATPase pump and caveolin, as well as mitochondrial proteins, such as cytochrome C.

The hypothesis that tubular toxicity is associated with CM hyperosmolality seems to be supported by the potential of other hyperosmolal substances, such as mannitol and hypertonic saline solution, to induce analogous morphological and enzymatic alterations. Moreover, in dogs some CM reduce paraaminohippurate secretion by 30–40% - a fact that is not evident with noniodinated hypertonic solutions.

Intratubular precipitation of the Bence Jones protein was one of the first hypotheses to explain CIN associated with concomitant multiple myeloma. This theory has never been confirmed. It has been confirmed that in vitro CM administration precipitates the Tamm Horsfall protein, which is the major physiological constituent of the urinary casts.

RISK FACTORS

Risk factors for contrast-medium nephropathy are related to patient characteristics and to the contrast medium used.

Patient related factors

The most important patient-specific risk factors are pre-existing renal insufficiency and diabetes [5] especially in combination [4]. A history of congestive heart failure is an independent risk factor for contrast-medium nephropathy and contributes an even greater risk in patients

with diabetes or renal disease [5, 42], probably because of the effect of low cardiac output on renal blood flow. Other predictors of contrast-medium nephropathy include the presence of hypertension, increased age [20], acute myocardial infarction within 24 hours before administration of the contrast agent [5], hemodynamic instability and use of an intra-aortic balloon pump during percutaneous coronary intervention [12, 43]. Certain medications, including angiotensin- converting-enzyme (ACE) inhibitors [44] and NSAIDs, have been implicated by their effects on regional renal hemodynamics. However, data are sparse and conflicting, some evidence suggests that inhibition of angiotensin II may prevent CIN [45, 46] but, in general, support their role in the risk of CIN[47,48].

Other factors

Risk factors not related to the patient include the type and amount of contrast medium administered. The use of hypo-osmolar or iso-osmolar contrast media has been found to be beneficial in reducing the incidence of contrast-medium nephropathy among high-risk patients but not among patients without risk factors [14, 49].

The volume of contrast medium administered correlates with the risk of nephropathy [4, 5, 50]. In a series of consecutive patients undergoing coronary angiography, each 100 mL of contrast medium administered was associated with a significant increase of 12% in the risk of nephropathy. [5] Adjustment of the volume to the patient's body weight and serum creatinine level has been found to minimize the risk [51].

Similarly, it has been shown that exceeding a patient-specific maximum volume of contrast medium (recommended to be 5 mL X[body weight (kilograms)/serum creatinine level (micromoles per litre) ÷ 88.4]) is associated with a 12-fold increase in risk of hemodialysis[50].

In several large studies, the benefit of nonionic contrast media was limited to patients with pre-existing renal dysfunction [52,53,55], whereas a third study showed no benefit of nonionic over ionic contrast agents in patients either with or without pre-existing renal dysfunction [54]. A recent trial by Aspelin P et al that included diabetic patients with preexisting renal disease undergoing coronary and aortic angiography supports the fact that the lowest-osmolality agents, ie, iso-osmolar agents (290 μOsm/kg), provide the best protection from CIN [14].

Risk stratification

Mehran.R and colleagues developed a simple scoring method that integrates 8 baseline clinical variables to assess the risk of contrast-medium nephropathy after percutaneous coronary intervention [12]. Each risk factor found to be statistically significant was given a weighted integer and the sum of the integers was considered the total risk for that patient.

Hypotension during the procedure, use of IABP during or immediately after the procedure and presence of congestive heart failure was assigned a score of 5 each.

Age more than 75 years was assigned a score of 4, anaemia and diabetes were assigned a score of 3 each, volume of contrast medium used was assigned a score of 1 per 100ml used, serum creatinine of >1.5mg/dl was assigned a score of 4 or if e-GFR was calculated by Levey

modified MDRD formula [105] a score of 2 was assigned for a e-GFR of 40-60, 4 for 20-40 and 6 for <20 ml/min/1.73m^2.

They found that contrast induced nephropathy was strongly associated with an increased risk score: the incidence was 7.5% among patients with a low score and 57.3% among those with a high risk score.

CLINICAL PRESENTATION OF CIN

CIN can occur following any radiographic procedure where intravenous or intraarterial contrast agents are used. Acute renal failure caused by contrast medium is usually non-oliguric and reversible. The serum creatinine value increases by 48-72 hours following administration of contrast medium, peaks by 3-5 days (0.5-3.0mg/dl) and returns to baseline by 7-10 days.

CIN may also present as a more severe acute renal failure, particularly in high risk patients. In such situations, oliguria may develop within 24hrs of contrast administration and serum creatinine may rapidly increase sometimes exceeding 5mg/dl necessitating dialysis. Most studies though indicate that incidence of CIN requiring dialysis is very low (<1%) but with a slightly higher mortality in this group.

It is also important to note that patients with atherosclerotic disease undergoing angiographic studies are also at a risk of developing acute renal failure secondary to atheroembolic disease. In contrast to CIN, renal failure due to atheroembolic disease has a delayed onset (7 days to several weeks), and is associated with a brief period of eosinophilia, hypocomplementemia and other evidence of embolic phenomena.

PARAMETERS TO MONITOR RENAL FUNCTION AFTER CONTRAST MEDIUM ADMINISTRATION

Serum creatinine

Serum creatinine is an insensitive measurement in patients with normal kidneys as more than 50% reduction in GFR may occur before any rise is observed. However it can be used as an accurate test in patients with renal impairment to assess any further deterioration in renal function after administration of contrast medium [106].

Creatinine clearance

Creatinine clearance is often used as a measurement of GFR. However creatinine is not a perfect marker for GFR as it is both filtered by the glomerulus and secreted by the tubules. However this measurement remains the most acceptable method for assessing renal function in clinical practice[80]

GFR is calculated by a formula by Cockroft and Gault[94] using serum creatinine, body weight and age.

$$CrCl = [(140 - age) \times IBW] / (Scr \times 72) \quad (\times 0.85 \text{ for females})$$

Measurement of urinary enzymes

Urinary excretion of proximal tubular brush border enzymes (alanine aminopeptidase α-glutamyl transferase and alkaline phosphatase), lysosomal enzymes (β-glucuronidase, N-acetyl

β-D-glucosaminidase) and cytosol enzymes (lactate dehydrogenase, leucine aminopeptidase, β-glucosidase) are often raised following administration of contrast medium.

Enzymuria peaks during the first 6 hours following contrast medium administration and recovers ain 24-48 hours. It represents the Normal response of the kidneys to contrast medium exposure and is of little importance in the assessment of CIN.

PREVENTION

Modification of risk factors

In order to minimize the risk of CIN, when possible the administration of contrast media should be delayed in patients with circulatory collapse or congestive heart failure until their hemodynamic status is corrected. Administration should be delayed for 24 hours after myocardial infarction. Repeated exposure should be delayed for 48 hours in patients without risk factors for contrast-medium nephropathy, and for 72 hours in those with diabetes mellitus or pre-existing renal dysfunction. NSAIDs, diuretics (when feasible) and possibly ACE inhibitors should be discontinued 1–2 days before administration of contrast media.[56] Most importantly, the smallest possible amount of nonionic, hypo-osmolar or iso-osmolar contrast medium should be used in patients with risk factors.

THERAPEUTIC APPROACHES TO PREVENTION OF CIN

Saline hydration and forced diuresis:

A standardized saline hydration protocol has been proven effective in reducing the risk of contrast induced nephropathy and has been recommended for use routinely [7, 57, 58, 59]. In a study of the effectiveness of saline, mannitol and furosemide in preventing contrast-medium nephropathy after cardiac angiography in patients with renal insufficiency, the incidence of nephropathy was significantly lower among patients who received saline alone (11%) than among those who received saline plus mannitol (28%) or saline plus furosemide (40%). It was also considerably lower than the incidence reported among patients with similar pre-existing renal diseases who did not receive hydration in a standardized fashion [4,61] These results were confirmed by the Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation (PRINCE) Study [57], which found no benefit to forced diuresis with intravenous crystalloid, furosemide, mannitol or low-dose dopamine therapy over hydration alone in patients exposed to contrast media who were at risk for nephropathy.

In a recent prospective randomized studies by Merten GJ et al hydration with sodium bicarbonate was found to be significantly more effective than hydration with sodium chloride in preventing contrast-medium nephropathy (incidence of nephropathy 1.7% v. 13.6% respectively) [60]. However, further studies are required to clarify the role of hydration with sodium bicarbonate in preventing such nephropathy.

VASODILATORS

1. Fenoldopam

Fenoldopam mesylate is a selective dopamine-1 receptor agonist that produces systemic, peripheral and renal arterial vasodilatation. The drug exhibits many desirable renal effects

including decreases in renal vascular resistance and increases in renal blood flow, glomerular filtration rate, and sodium and water excretion [62]. The benefit of fenoldopam for the prevention of contrast-medium nephropathy has been demonstrated in a dog model and in nonrandomized clinical studies [62,63]. In a small double-blind, randomized controlled pilot trial, fenoldopam plus normal saline was found to attenuate reductions in renal blood flow induced by contrast media; it was also associated with a lower incidence of contrast-medium nephropathy than was normal saline alone, although the difference between the 2 groups was not significant [65]. In 2 recent large studies comparing fenoldopam with N-acetylcysteine, treatment with fenoldopam either had a similar, nonsignificant effect as that of N-acetylcysteine[66] or was inferior to it [67]. Therefore, the routine use of fenoldopam cannot be recommended at the present time.

2. Low dose dopamine

Low-dose dopamine has been used to maintain renal perfusion and function in patients with renal insufficiency who have circulatory or hemodynamic instability. However, studies evaluating low-dose dopamine (2–5 μg/kg per minute) for the prevention of contrast-medium nephropathy have shown conflicting results [68,69,70]. These different results may be related to the simultaneous activation of the dopamine receptor type 2 (DA_2), which, in contrast to the DA_1 receptor, reduces renal blood flow and the glomerular filtration rate.

3. Adenosine antagonists

Contrast media stimulate the intrarenal secretion of adenosine, which binds to the renal adenosine receptor and acts as a potent vasoconstrictor, reducing renal blood flow and increasing the generation of oxygen free radicals as it is metabolized to xanthine and

hypoxanthine. Studies evaluating the adenosine antagonists (aminophylline and theophylline) have shown inconsistent results [70,71,72,73], and therefore the use of these antagonists are not routinely recommended for the prevention of contrast-medium nephropathy.

4. Other vasodilator therapies

The calcium-channel antagonists verapamil and diltiazem have been found to attenuate the renal vasoconstrictor response after exposure to radiocontrast media [74]. However, when the efficacy of the dihydropyridine calcium-channel blockers felodipine, nitrendipine and nifedipine was evaluated, results were inconsistent [75,76].

Endothelin-1, a potent endogenous vasoconstrictor, is thought to play a role in the development of contrast-medium nephropathy. However, the use of a mixed endothelin A and B antagonist (SB 290670) was associated with a significantly higher incidence of nephropathy than was placebo [77]. Prostaglandin E_1 (PGE_1) has vasodilatory effects that may be beneficial in preventing contrast-medium nephropathy. In one study, 130 patients were randomly assigned to receive either placebo or 1 of 3 doses of PGE_1. All of the patients received 2 L of fluid before and after the contrast procedure. The increase in serum creatinine level was smaller in all of the 3 PGE_1 groups than in the placebo group, but the difference was significant only in the medium-dose PGE_1 group (20 ng/kg per minute) [78].

Antioxidants

N-acetylcysteine

N-Acetylcysteine is an acetylated amino acid (L-cysteine) with reactive sulfhydryl groups that confer antioxidant properties. N-acetylcysteine reduces renal damage by scavenging oxygen free radicals, generated as a result of toxic damage to renal tubules [8]. In a randomized placebo-controlled clinical trial, N-acetylcysteine significantly reduced urinary levels of 15-isoprostane $F2_t$, a specific marker of oxidative stress [79]. N-acetylcysteine may also have direct vasodilating effects on the kidneys through an increase in the biologic effects of nitric oxide, which is a potent and stable vasodilator contributing to improved renal hemodynamics [79].

In a study comparing oral administration of N-acetylcysteine plus standard saline hydration with hydration alone in patients with chronic renal insufficiency undergoing coronary angiography with intravenous administration of 75 mL of a nonionic, hypo-osmolar contrast agent[8], the incidence of contrast-medium nephropathy was significantly lower in the *N*-acetylcysteine group than in the control group.

Subsequent trials of N-acetylcysteine in patients with chronic renal insufficiency have provided conflicting results[9,66,81,82]. A meta-analysis of the first 7 reported trials showed that, compared with peri-procedural hydration alone, administration of N-acetylcysteine plus hydration reduced the risk of contrast-medium nephropathy by 56% among patients with chronic renal insufficiency [83].

A meta-analysis by Goldenberg I et al in 2004 showed an overall benefit of the drug, but only in patients with more severe renal dysfunction (serum creatinine level > 221 μmol/L) or when a nonstandard or incomplete hydration protocol was used [84].

Given the mixed results of N-acetylcysteine studies and the lack of evidence-based consensus, only a general recommendation for the use of the drug is made at this time by most authors. It may be used to prevent contrast-medium nephropathy in high-risk patients and as an abbreviated oral or intravenous regimen in patients requiring emergency diagnostic procedures using contrast media. An oral dose of 600 mg twice daily the day before and the day of procedure is the most commonly used regimen. IV doses of 150 mg/kg over half an hour before the procedure or 50 mg/kg administered over 4 hr have more recently been gaining popularity for use in critically ill patients or in those who are unable to take NAC orally [85].

Ascorbic acid

A recent randomized trial showed that the use of ascorbic acid was associated with a significant reduction of 62% in the rate of contrast-medium nephropathy among patients with renal insufficiency undergoing coronary angiography with or without intervention [86]. Further prospective studies are needed to validate these preliminary results.

Haemofiltration and Haemodialysis

In a study by Vogt B et al, hemodialysis immediately after exposure to contrast media has not been shown to be effective in preventiing nephropathy in patients with pre-existing renal insufficiency, and it may even increase the risk of nephropathy [87]. Marenzi et al published a paper in 2003 studying the use of hemofiltration as a prophylactic measure to prevent CIN [88]. In a higher-risk patient population (mean serum creatinine level 265 μmol/L), hemofiltration seems to have a protective effect, including significant reduction in in-hospital and 1-year mortality compared with routine hydration. However, the expense and complexity

of hemodialysis may prevent its general application in procedures that require the use of contrast media.

METHODS AND MATERIALS

STUDY POPULATION

All patients included in the study were patients who underwent cardiac catheterization studies during the period from Jan 2005- July 2006 in the Department of Cardiology, Government General Hospital. All procedures were elective, no emergency procedure was included in the study, thereby ruling out patients with MI within the previous 72 hours from the study. None of the patients included in the study had any prior angiographic study within the previous week. Hydration status was assessed clinically. No specific hydration protocol was followed in the patients.

STUDY DESIGN

Contrast induced nephropathy was defined as an increase in post-procedural creatinine by more than 25% from the baseline. All patients who had an increase in post-procedural creatinine by more than 25% over baseline were diagnosed to have Contrast Induced Nephropathy. Serum creatinine was estimated by ERBA XL 300 automated analyzer using Alkaline picrate method in our Biochemistry department. Serum creatinine values were followed up in the patients before coronary angiogram was performed and at 24 and 48 hours after the procedure, and peak serum creatinine levels were considered for calculation of increase from baseline.

Patients were identified as hypertensives if already diagnosed and on treatment or newly detected with a Blood pressure of 140/90 or more as defined by JNC 7 [(89)].

Patients with Diabetes mellitus were defined as known diabetics on treatment or patients with a random blood sugar value of >200mg/dl as defined by ADA guidelines [92, 93]. Blood glucose level was measured using Glucose oxidase and Pyruvate oxidase methods by the automated analyzer.

"Anemia" was defined using World Health Organization criteria: baseline hematocrit value <39% for men and <36% for women[90].

Serum cholesterol was measured using enzymatic method, serum triglyceride using enzymatic colorimetric method and serum HDL-C using Polyethylene Glycol-CHOD-PAP method by the automated analyzer. Dyslipidemia was defined by ATP3 guidelines [91] as Total cholesterol > 200mg/dl, LDL-C >130mg/dl, HDL-C < 40 in men and <50 in women, TGL > 150mg/dl. Lipoprotein anaysis was performed on serum obtained after a 12 hour fast. Total cholesterol, HDL-C and TGL were measured and LDL-C was calculated using the Friedwald's formula

$$\text{LDL-C} = \text{Total cholesterol} - \text{HDL-C} - (\text{TGL}/5)$$

Height and weight of all patients was documented and Body Mass Index calculated using the formula

$$\text{BMI} = (\text{weight in kg})/ (\text{Height in metres}^2)$$

Urine output of the patient was monitored. Urine albumin, echocardiogram for quantification of Left Ventricular function and renal angiogram was also performed to rule out possibility of renal artery stenosis. All patients were screened with a urine examination for albuminuria and an ultrasound of the abdomen to rule out underlying primary renal disease.

None of the patients included in the study had underlying renal disease.

The contrast media used were ionic monomer Diatrizoate (high osmolar) and non-ionic monomer Iohexol (Low osmolar). Use of high or low osmolar contrast medium was subject to availability and presence of Left Ventricular dysfunction or renal failure in view of the high cost of low-osmolar contrast medium.

All patients were observed for development of hypotension, anaphylactoid reactions to contrast medium, or any other procedural complication during and immediately after the angiogram. None of the patients in the study developed any significant hypotension during the procedure requiring inotropic support and no patient developed any serious reaction to the contrast medium.

No specific prophylactic measure was used towards prevention of contrast induced nephropathy.

STATISTICAL ANALYSIS

Statistical analysis was carried out for 122 subjects after categorizing each variable. Baseline data were collected from all patients. Age, sex, presence of hypertension, diabetes, BMI, serum creatinine, creatinine clearance, type and amount of contrast medium, number of coronary vessels diseased, presence of dyslipidemia and left ventricular ejection fraction were analyzed with respect to development of CIN.

Results are presented as mean ± SD or a percentage of the total. The significance of difference in means between two groups was calculated by means of Student's *t* test and the significance of difference in proportions were compared with Pearson's χ^2 (chi-square) test. Statistical significance was taken to be significant at 1% level when P value was ≤ 0.001, significant at 5% level when P value was between 0.011 to 0.05, and not significant at 5% level when P value was >0.05.

Logistic regression was used to identify correlates of CIN. Models were developed with stepwise techniques and by consideration of variables that were clinically relevant. Variables included are baseline creatinine value, type of contrast used, amount of contrast used, hypertension, baseline creatinine clearance and number of diseased coronary vessels. Statistical analysis was carried out using standard formulae SPSS (Statistical package for Social Sciences) for Windows Dos.

OBSERVATIONS

BASELINE CHARACTERISTICS OF STUDY POPULATION

n = 122

		Frequency	Percentage
Sex	Male	104	85%
	Female	18	15%
Age Group	≤ 50	47	39%
	51-60	53	43%
	> 60	22	18%
Hypertension		56	46%
Diabetes		41	34%
BMI	< 25	87	71%
	≥ 25	35	29%

Out of the total population studied, females were fewer in number forming only 15%. Patients aged >60 years formed 18% of the study population. Patients with risk factors like hypertension and diabetes mellitus formed 46% and 34% of the study population respectively.

AGE GROUPS

Variable	CIN		No CIN		p
	n	%	n	%	

Age	≤50	6	12.8%	41	87.2%	0.005**
	51-60	4	7.5%	49	92.5%	
	>60	8	36.4%	14	63.6%	

Among patients aged >60 years the incidence of CIN was 36.4% which was found to be statistically significant with a p- value of 0.005.

SEX

Variable		**CIN**		**No CIN**		**p**
		n	**%**	**n**	**%**	
Sex	M	15	14.4%	89	85.6%	0.800
	F	3	16.7%	15	83.3%	

The incidence of CIN among females was marginally more than that among males, but this was found to be statistically not significant.

HYPERTENSION

Variable	**CIN**		**No CIN**		**p**
	n	**%**	**n**	**%**	
HT	11	19.6%	45	80.4%	0.160

The incidence of CIN in hypertensives was 19.6% which was also statistically not significant.

DIABETES MELLITUS

Variable	CIN		No CIN		p
	n	%	n	%	
DM	9	22.0%	32	78.0%	0.110

22% among the diabetics developed CIN which was not statistically significant with a p-value of > 0.05

BODY MASS INDEX

Variable		CIN		No CIN		p
		n	%	n	%	
BMI	< 25	13	14.9%	74	85.1%	0.930
	≥ 25	5	14.3%	30	85.7%	

Patients were grouped based on BMI of ≥25 (overweight). There was no significant difference in the incidence of CIN between the two groups.

BASELINE SERUM CREATININE

Variable		CIN		No CIN		p
		n	%	n	%	
Creatinine	< 1.5mg/dl	15	13.2%	99	86.8%	0.003**
	≥ 1.5mg/dl	3	37.5%	5	62.5%	

A baseline pre-procedure serum creatinine of >1.5 mg/dl was found to be a statistically significant risk factor with an incidence of CIN of 37.5% and a p-value of 0.003

LEFT VENTRICULAR EJECTION FRACTION

Variable		CIN		No CIN		p
		n	%	n	%	
LVEF	< 40%	5	38.5%	8	61.5%	0.011*
	≥ 40%	13	11.9%	96	88.1%	

A decreased Left ventricular ejection fraction of <40 % was found to be significant at 5% level with an incidence of CIN of 38.5% and a p-value of 0.011

DYSLIPIDEMIA

Variable	CIN		No CIN		p
	n	%	n	%	
Dyslipidemia	5	27.8%	13	72.2%	0.091

The incidence of CIN in patients with an abnormal lipid profile was 27.8% which was not statistically significant.

TYPE OF CONTRAST MEDIUM USED

Variable		CIN		No CIN		p
		n	%	n	%	
Contrast	HOCM	16	15.4%	88	84.6%	0.640
	LOCM	2	11.1%	16	88.9%	

The incidence of CIN in patients with use of HOCM was higher at 15.4% compared to 11.1% with LOCM, though statistically not significant.

NUMBER OF CORONARY VESSELS DISEASED:

Variable		CIN		No CIN		p
		n	%	n	%	
Cor. Vessels	≤ 1	2	7.1%	26	92.9%	0.196
	> 1	16	17.0%	78	83.0%	

Multivessel disease increased the incidence of CIN compared to normal coronary vasculature by angiogram or single vessel disease. P-value was 0.196 making it statistically not significant.

Student's t test was performed for the difference between two means for the following variables:

	CIN		No CIN		p
	Mean	**±SD**	**Mean**	**±SD**	
Sugar	104.22	28.13	95.05	23.12	0.135
Urea	25.67	6.1	24.28	4.86	0.284
Creatinine	1.18	0.29	0.97	0.22	< 0.001**
Cr Clearance	67.89	24.75	83.23	17.04	0.001**
Hb	11.57	0.85	11.54	1.09	0.923
PCV	34.22	3.1	34.05	3.48	0.842
ESR	13.67	5.75	16.24	7.24	0.156
LVEF	51.83	14.04	55.53	11.2	0.216
Amount of Contrast	82.22	13.09	55.19	13.44	< 0.001**

* indicates statistical significance at 5% level

** indicates statistical significance at 1% level

The average values of baseline parameters including blood sugar, urea, serum creatinine were higher among the patients who developed CIN than among those who did not. The LVEF and creatinine clearance at baseline were noted to be less among patients with CIN than those without. The average amount of contrast used in patients who developed CIN was 82 ml compared to an average of 55 ml in those who did not develop CIN. Among these variables studied, baseline serum creatinine, creatinine clearance and amount of contrast used were found

to be statistically significant risk factors.

Logistic regression was performed by entering the following variables for predicting CIN. The variables were, serum creatinine, creatinine clearance, type of contrast used, amount of contrast used, presence or absence of hypertension and presence or absence of multivessel disease. The development of CIN could be predicted to an overall accuracy of 94% with a 78% correct chance of predicting development of CIN with these variables.

All the above mentioned parameters were found to be predictors of CIN by this model.

DISCUSSION

Our study has attempted to assess the incidence of contrast induced nephropathy in patients undergoing cardiac catheterization studies in our hospital and to identify the major risk factors for developing CIN in this population.

The major findings of this study are that the incidence of contrast nephropathy is as high as 14.75% among the population undergoing cardiac catheterization studies at our Institute. The rates of contrast induced nephropathy reported in various studies that included patients with pre-existing renal dysfunction or diabetes mellitus in whom a standard hydration protocol was not administered is between 12% and 26 % [4, 7, 12]. No patient in our study developed acute renal failure necessitating Haemodialysis. The incidence of ARF requiring haemodialysis has been reported in most studies as <1%.

McCullough PA et al also reported an increase in serum creatinine by 25% in 14.5% of patients who underwent coronary angiography (95 percent confidence interval, 12.9 to 16.1 percent) [4]. An incidence of 16.5% was reported by Iakovou I et al [20], who also reported an increased incidence of CIN among females. In our study females form only 15% of the study population but the incidence of CIN among them was 16.6%, higher than the incidence among males (14.4%), comparable with the incidence reported by Iakovou et al though not found to be statistically significant.

Most studies performed internationally have found that the risk of CIN increases with increasing age and age >75 years was a significant risk factor for development of CIN. The study by Mehran et al in 2004 puts the incidence at as high as 21.8% among those aged >75

years [12]. The cause is probably multifactorial and related to alterations in renal glomerular and tubular functions and perhaps to renovascular disease. Our study shows that incidence of CIN does increase with increasing age, with the population above 60 years having an incidence as high as 36%. Age has also been found to be a statistically significant factor in development of CIN in our study.

That osmolality is an important factor in contrast-medium–induced nephropathy is supported by several studies. In a prospective, randomized study involving 1196 patients who underwent angiocardiography, Rudnick et al [52] found no differences in the incidence of nephropathy (defined as an increase of 0.5 mg per deciliter or more in the serum creatinine concentration within 72 hours after the administration of contrast medium) between patients receiving iohexol (low-osmolar; 780 mOsm per kilogram of water) and patients receiving diatrizoate (high-osmolar; 1870 mOsm per kilogram of water) among low-risk patients (patients without diabetes who had a base-line serum creatinine concentration of less than 1.5 mg per deciliter [133 µmol per liter]). However, among patients without diabetes whose serum creatinine concentrations were higher than 1.5 mg per deciliter, the incidence of nephropathy was reduced from 27.0 to 12.2 percent by the use of iohexol [52] Among patients with diabetes, the incidence was reduced from 47.7 to 33.3 percent. Overall, patients receiving high-osmolar contrast medium were 3.3 times as likely to have nephropathy induced by contrast medium as those receiving low-osmolar contrast medium [52]. Barrett and Carlisle performed a meta-analysis to determine the relative nephrotoxicity of contrast mediums using the results of 14 trials and concluded that the use of low-osmolar contrast medium rather than high-osmolar contrast medium was beneficial to patients with preexisting renal failure [49]. A similar pattern

was observed by Aspelin et al in a study conducted in 2003[14]. Our study revealed a slightly higher incidence of CIN among patients in whom HOCM was used was 15.4% compared to an incidence of 11.1% among those in whom LOCM was used. But the figures were not statistically significant. The type of contrast was found to be an predictor of renal function deterioration by logistic regression.

Use of LOCM was restricted to patients in whom there was significant left ventricular dysfunction or elevated renal parameters. Its use was mainly limited by cost factors. LOCM was used in only 15% of the study population especially those with high risk.

In most studies, the volume of contrast medium administered during coronary angiography correlates with the risk of CIN [5, 51, 96, 100]. A study of more than 7000 patients by Rihal CS et al showed that each 100 mL of contrast medium administered correlates with a hazard ratio for CIN of 1.12 [5]. In our study, the average amount of contrast used among those patients who developed CIN was more than that used among patients who did not develop CIN (82ml vs 55 ml). This was also found to be statistically significant with a p-value of <0.001. The amount of contrast used was also found to be an independent predictor of CIN by logistic regression. The lesser the amount of contrast used, the lesser the incidence of CIN expected.

Baseline renal insufficiency is also an important risk factor for CIN. Several studies have shown an increased incidence of CIN among patients with pre-existing renal failure [95, 5]. Rihal et al in a study observed 22.4% incidence of CIN among patients with baseline serum creatinine of between 2-2.9mg/dl, and 30.6% among those with baseline value of >3.0mg/dl[5].

Murphy SW et al also noted that the individuals with chronic renal insufficiency (Serum creatinine >= 2.0mg/dl) were at a greater risk of contrast induced renal injury [16].

In many studies preexisting renal disease has been the greatest independent predictor of CIN, and its severity (as measured by serum creatinine concentration) directly correlating with the incidence of CIN [5, 13, 20]. In a study by Gruberg et al that included 439 patients with serum creatinine levels of 1.8 mg/dL or higher before coronary angiography, the incidence of CN was 37%; 7.1% and 0.9% of the patients underwent short-term and long-term dialysis, respectively [98]. Similar pattern was also noted in studies conducted by Mehran et al [12], Manske CL et al [96].

Our study also showed a similar pattern, with a baseline serum creatinine value of ≥1.5mg/dl being observed to be a statistically significant risk factor for the development of CIN. It was also noted in our study that the baseline creatinine clearance as calculated by the Cockroft and Gault formula was lower (67.89 ml/min) in the study population who developed CIN compared to those who did not (83.23ml/min). Creatinine clearance was also observed to be a statistically significant risk factor with a p-value of 0.001. It was also found to be a significant independent predictor of deterioration of renal function by logistic regression.

Diabetics were found to have a higher incidence of CIN in our study. Most studies also report a similar picture [5, 12]. Mehran et al reported an incidence of 19.2% in diabetics [12]. CIN incidence rates among diabetics have been reported to be between 5%- 30% in various studies [42, 97]. In our study diabetes was not found to be a statistically significant risk factor though the incidence of CIN was 22% among the diabetics. A study by Gruberg L et al also reports diabetes as not being a statistically significant risk factor in univariate analysis [98].

Hypertension was reported to be an independent predictor of CIN in the study conducted by Iakovou I et al [20]. The study by Mehran R et al also finds hypertension to be a significant predictor of CIN with 15.9% among hypertensives developing CIN [12]. The study by Gruberg L et al does not find a statistically significant association between hypertension and CIN [98]. In our study the incidence of CIN in hypertensives was 19.6% but there was no statistically significant association between hypertension and CIN. However it was found to be a significant risk factor in predicting development of CIN by logistic regression.

Body Mass Index was not found to be a statistically significant risk factor in our study. No study has been done to correlate BMI with CIN. There has been one study by Omer Toprak et al published in March 2006 which showed an increased risk of CIN among patients with metabolic syndrome. In this group of patients it was reported that impaired fasting glucose, high triglyceride levels were independent predictors of risk of CIN [106].

Dyslipidemia in our study defined as per ATP 3 guidelines was found to be statistically not significant as a risk factor for CIN. 27.8% of patients with dyslipidemia developed CIN in our study. Hypercholesterolemia has been shown to be a significant risk factor for the development of CIN in the study by Mehran R et al with an incidence of CIN being 13.2% [12]. Hypertriglyceridemia has been shown to be a significant risk factor for CIN in the study by Omer Toprak et al [102]. There has also been an animal study by Andrade L et al which shows that hypercholesterolemia in rats aggravates radio contrast nephropathy [103].

Multiple coronary vessels being diseased as detected by coronary angiogram was not a significant risk factor statistically. Incidence of CIN in patients with two and three vessel

disease was 17 %. However by logistic regression it was an independent predictor of CIN. It has also been documented as a significant risk factor for CIN in studies by Mehran R et al [12] and Omer Toprak et al [102, 104].

Studies have shown that reduced left ventricular ejection fraction (≤49%), advanced congestive heart failure (New York Heart Association class III or IV), or any history of congestive heart failure are independent risk factors for CN and contribute even greater risk in patients with diabetes or renal disease [5, 96, 98] A recent study conducted by Marenzi.G et al has reported a Left ventricular ejection fraction of <40% as being a significant risk factor for development of CIN following primary angioplasty [101]. The risk associated with congestive heart failure is likely due to derangements in renal blood flow due to low cardiac output. The risk is probably increased by this population's use of specific medications such as angiotensin-converting enzyme (ACE) inhibitors, diuretics, and aspirin[99]. Our study showed an incidence of CIN to be 38.5% among patients with an LVEF <40%, which was statistically significant at 5% level with a p-value of 0.011.

Apart from these factors, acute hyperglycemia defined as a blood sugar value of ≥150mg/dl has been shown to be a significant risk factor in the development of CIN in one study by Diane.B.Turcot et al [64]. There were only 5 patients in our study with a blood sugar value ≥150 mg/dl, out of which only one developed CIN. This parameter was not assessed due to very small numbers.

This study has shown that risk factors for CIN are an elevated baseline creatinine, a low creatinine clearance, the type and amount of contrast medium used, and the presence of

multivessel CAD. Identification of these risk factors before subjecting the patient to angiogram gives us an opportunity to use prophylactic measures to prevent CIN and also anticipate CIN in high risk patients.

OUR STUDY HAD SEVERAL LIMITATIONS

Patient's hydration status was assessed clinically, central venous pressure monitoring was not done for patients due to resource constraints. All patients were on overnight starvation before the procedure, some were on diuretics for their cardiac condition, and no patient was given intravenous fluid infusion. Dehydration has been consistently identified to be a significant risk factor for CIN in most studies. A more careful assessment of hydration is required to study statistical significance of dehydration as a risk factor.

Almost all patients were on ACE inhibitors for their cardiac condition which could be a confounding factor in the study. Studies regarding the role of ACE inhibitors have been conflicting.

There was also no strict protocol with regard to the type of contrast medium used as it was dependent essentially on availability due to cost factors.

CONCLUSION

The conclusions that can be drawn from this study are:

There is a significant risk of contrast induced nephropathy in patients undergoing cardiac catheterization studies especially among the elderly, and among those with pre-existing renal failure.

* The risk of CIN is also increased by the presence of multivessel coronary disease by angiogram and by the presence of left ventricular dysfunction

* There were no patients in this study who developed renal failure needing Haemodialysis.

* The type of contrast and amount used also determine development of CIN.

* Risk of CIN can be predicted before the procedure based on risk factors and suitable precautions can be taken including use of low or iso-osmolar contrast media, minimizing the amount of contrast medium used.

SUMMARY

Contrast induced nephropathy is a significant problem in clinical practice with the increasing use of contrast media in diagnostic and interventional procedures. In our hospital we conducted a study of the incidence of contrast - induced nephropathy among the patients undergoing cardiac catheterisation studies, based on the increase in post - procedural serum creatinine from the baseline.

It was noted that among the 122 patients followed up in the Department of Cardiology 18 developed CIN (14.75%). Among the patients who developed CIN, it was noted that common risk factors were increased Age, elevated baseline serum creatinine, low baseline creatinine clearance, and multi-vessel coronary disease. It was also noted that incidence of CIN was higher among patients with hypertension, diabetes, poor LV function, and among the patients who underwent studies with high osmolar contrast medium and in whom higher amounts of contrast medium was used. Identification of these risk factors before subjecting the patient to angiogram studies gives us an opportunity to anticipate development of CIN and to use prophylactic measures to prevent CIN.

SCOPE FOR FUTURE STUDIES

This study identifies only potential risk factors of Contrast Induced Nephropathy. Further studies need to be done regarding possibility of preventing CIN, various prophylactic measures that might be useful in a Government Hospital setting. This study has not included patients undergoing emergency angiographic procedures like PTCA etc. In such conditions the risk factors are likely to be more and unique to the situation. A study in such a setting will help define the risks better. A long term follow up of patients who develop CIN could be done to determine the degree of residual renal damage and possibility of permanent renal dysfunction leading to Chronic Kidney Disease. A thorough study regarding the relationship between atheromatous disease load and CIN can also be done considering the fact that dyslipidemia, multivessel CAD have been known to predispose to CIN.

ABBREVIATIONS AND ACRONYMS

CIN	-	Contrast Induced Nephropathy
PCI	–	Percutaneous Intervention
CM	–	Contrast Medium
HOCM	-	High Osmolar Contrast Medium
LOCM	-	Low Osmolar Contrast Medium
RBF	-	Renal Blood Flow
GFR	-	Glomerular Filtration Rate
PG	-	Prostaglandin
ANP	-	Atrial Natriuretic Peptide
ADH	–	Anti-diuretic Hormone
ACE	–	Angiotensin Converting Enzyme
NSAID	–	Non Steroidal Anti-Inflammatory Drugs
IABP	–	Intra Aortic Balloon Pump
Sr.Cr.	-	Serum Creatinine
CrCl	–	Creatinine Clearance
MDRD	–	Modification Of Diet in Renal Disease
HDL-C	–	High Density Lipoprotein
LDL-C	–	Low Density Lipoprotein
TGL	–	Triglycerides
BMI	–	Body Mass Index
HT	–	Hypertension
DM	–	Diabetes Mellitus
LVEF	–	Left Ventricular Ejection Fraction
Hb	–	Haemoglobin
PCV	–	Packed Cell Volume
ESR	–	Erythrocyte Sedimentation Rate
CAD	–	Coronary Artery Disease

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PROFORMA

Name

Age

Sex

Occupation

Hospital IP no.

Admitting diagnosis:

Procedure planned:

Indication for procedure:

Risk factors:

1. Hypertension:
2. Diabetes mellitus:
3. Drug intake(nephrotoxic):

General examination:

Ht:
Wt:
Hydration status:
Vitals: Pulse:
Blood pressure:
Respiratory rate:

Investigations at admission:

1. Blood sugar:
2. Blood Urea:
3. Sr. Creatinine:
4. Sr. Potassium:

5. Sr. Sodium:

6. Hb:

7. PCV:

8. ESR:

9. Urine Albumin:

10. USG abdomen:

11. Echocardiogram:

12. Sr. Lipid profile:

Procedure done:

Contrast used:

Amount of contrast used:

Osmolality of contrast:

No. of coronary vessels involved:

Renal Artery Stenosis (>50%): Y/N

Post-procedure:

	Day 0	24hrs	48/72hrs
Urine output			
Sr creatinine			
Creatinine clearance *			

* as calculated by Cockroft and Gault formula

Peak Sr.creatinine:

% increase from baseline: