RISK CHARACTERISTICS AND INCIDENCE OF CONTRAST NEPHROTOXICITY IN PATIENTS EXPOSED TO INTRAVASCULAR CONTRAST AT KENYATTA NATIONAL HOSPITAL.

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DECLARATION

This study is being presented for part fulfillment of Masters Degree in Internal Medicine of the University of Nairobi.
I do hereby declare that this is my original work and has never been presented for a study in any other university.

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DEDICATION

This work is dedicated to my loving wife Catherine and my two children Keith and Faith for their sacrifice and unwavering support they gave me during my study.

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ABBREVIATIONS

ACEI	-	Angiotensin Converting Enzyme Inhibitor
ADH	-	Anti Diuretic Hormone
ANP	-	Atrial Natriuretic Peptide
ARF	-	Acute renal failure
CATHLAB	-	Cardiac Catheterisation Laboratory
CrCl	-	Creatinine Clearance
CIN	-	Contrast Induced Nephropathy
CCF	–	Congestive cardiac failure
CKD	-	Chronic kidney disease
CRF	-	Chronic Renal Failure
CT scan	-	Computerised Tomography Scanning
DM	-	Diabetes Mellitus
GRF	-	Glomerular Filtration Rate
HTN	-	Hypertension
HOCM	-	High Osmolar Contrast Media.
IV	-	Intravenously
KNH	-	Kenyatta National Hospital
LOCM	-	Low Osmolar Contrast Media.
MDRD	-	Modification of Diet in Renal Disease
MRI	-	Magnetic resonance imaging
mRNA	-	Messenger Ribonucleic Acid
NAC	-	N-AcetylCysteine
NaCl	-	Sodium Chloride/Normal Saline
NaHCO3	-	Sodium Bicarbonate
NFkB	-	Nuclear Factor kappa β
NO	-	Nitrous Oxide
NSAIDS	-	Non-Steroidal Anti-inflammatory Drugs.
PGE	-	Prostaglandin E.
UON	-	University of Nairobi
USA	-	United States of America

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ABSTRACT

BROAD OBJECTIVE: To determine the incidence and associated risk factors for developing contrast media induced nephropathy in adult patients undergoing intravascular contrast enhanced imaging procedures at Kenyatta National Hospital.

STUDY DESIGN: A prospective/descriptive survey

STUDY POPULATION: Adult patients above 13 years of age undergoing intravascular contrast enhanced imaging procedures at the radiology department and cardiac catheterization laboratory at Kenyatta National Hospital.

STUDY SETTING: This study was carried out in the departments of radiology and cardiac catheterization laboratory of Kenyatta National Hospital.

METHODOLOGY: Consecutive sampling of 177 patients undergoing contrast enhanced studies was done. Venous blood for serum creatinine sodium, potassium and urea levels determination was drawn at baseline, at 24 and 72 hours after contrast administration. A patient was considered to have developed contrast nephropathy if there were 44.2 µmol/L absolute increases in serum creatinine from the baseline within 72 hours of contrast administration.

DATA ANALYSIS: Data was analyzed using SPSS version 15.1

RESULTS: The results of serum creatinine changes at 24 and 72 hours were analyzed against patient's demographic data and known risk factors for contrast nephropathy. Contrast nephropathy was found to occur in 21.3% at 24hrs and 30.7 % at 72 hrs. Cumulative incidence was 32.8%.It was found to occur in increasing frequency with increase in the number of risk factors, age, amount of contrast and dehydration**.**

CONCLUSION: CIN is common in patients exposed to contrast at KNH

CIN is even more common in patients with known risk factors e.g. pre-existing renal insufficiency, eldely, dehydration, and exposure to large volumes of contrast load

Risk for CIN worsens with multiplicity of risk factors.

CIN incidence compares with others reported in other studies, inspite of differences in type of procedures most reported

STUDY PERIOD: September 2007-February 2008

LITERATURE REVIEW

CONTRAST MEDIA INDUCED NEPHROPATHY

INTRODUCTION

There is increasing use of contrast agents in both diagnostic imaging and interventional procedures in medicine worldwide. Contrast media are among the commonest used medication in the world. The contrast media creates an X-ray attenuation differential in tissues in order to increase the visualization of disease processes.[1]However, contrast media have no therapeutic effect and do cause substantial adverse effects of which contrast induced nephropathy (CIN) is one of them

CIN is now considered the third leading cause of hospital acquired acute renal failure (ARF) and makes approximately 12% of all cases [2].

Definition of Contrast Media Induced Nephrotoxicity.

CIN is commonly defined as an acute impairment or exacerbation of renal function impairment manifested by an absolute increase in the serum creatinine concentration of at least 44.2µmol/L or by a relative increase of at least 25% from baseline value, in absence of other causes, and occurs within 48-72 hrs after contrast administration[3].

However, serum creatinine typically peaks on the third to the fifth day after administration of contrast media and one may overlook a large group of patients in whom nephropathy develops up to a week after administration of contrast media.

The serum creatinine concentration usually peaks on the second or third day after exposure to contrast medium and usually returns to baseline value within 2 weeks. However, renal function may not return to its baseline level, contributing to increased risk of morbidity and mortality.

Ideally, the impairment of renal function should be measured by serial creatinine clearance but because this step may be neither practical nor cost-effective in many areas, most of the literature suggests the use of isolated measurements of serum creatinine levels, even though this parameter may be less sensitive at reflecting subtle early changes in renal function and may be slower to reach maximal sensitivity than creatinine clearance. Serum creatinine levels may prove more sensitive, however, in cases of pre-existing renal

impairment, in which tubular secretion of creatinine can lead to overestimation of the glomerular filtration

Other suggested definitions[4]

(a) A rise in serum creatinine more than 100%.

(b) A rise in serum creatinine of more than 88.4umol/L.

(c) Or acute renal failure requiring dialysis

Although it has been suggested that a low increment or change of serum creatinine levels may not be clinically important, this low increment allows studies of reasonable sample sizes. In addition a large cohort study by Levy et al, has shown that even apparently small decreases in renal function can lead to excessive mortality rates independent of other risks factors, and given that small rises in serum creatinine actually represent a significant drop in GFR, a definition set at the lower end of the accepted range has become the most quoted.[5] Hayman[6] has suggested that changes of 26.52umol/L are not statistically significant in many laboratories, hence contrast induced nephropathy has become most commonly defined as "a 25% increase in serum creatinine concentration from baseline value, or an absolute increase of at least 44.2 µmol/L, which appears within 48hrs after administration of radiographic contrast media, and is maintained for 2-5 days."

The definition may in part account for the large number of case reports showing only transient-elevation of serum creatinine levels or at least elevation that do not require dialysis. Although this large number has led to questioning of the clinical relevance of such rises, these subtle changes have been shown to be associated with significant morbidity rates[5] and in addition, may help to identify those with borderline renal function who may be at risk of developing fulminate renal failure in the future.[7]

THE MAGNITUDE OF THE PROBLEM

With the increasing use of contrast media in diagnostic and interventional procedures, nephropathy induced by contrast media has become the third leading cause of hospital acquired acute renal failure. It is also associated with significant risk of morbidity and mortality and accounts for appropriately 12% of all cases of ARF.

The risk of CIN continues to be considerable despite the use of newer and less nephrotoxic contrast agents in high-risk patients in recent years[8]

The rate of CIN reported in studies that included patients with pre-existing renal dysfunction or diabetic mellitus in whom a standard hydration protocol was not administered is between 12% and 26%[9,10]

The incidence of CIN in the general population is estimated to be 2-7% and as many as 25% among those with pre-existing chronic renal failure. The incidence of CIN in patients with normal renal function is <1% with intravenous and 2-7% with intra- arterial administration of contrast media.[9]

The incidence is 16% in nonazotemic diabetic patients. The incidence may be as high as 33% in patients with pre-existent azotemia [11]. An incidence of 3-16% has been reported in patients undergoing percutaneous coronary intervention (PCI).

Permanent impairment of renal function requiring dialysis can occur in up to 10% of patients with pre-existing renal failure who develop further reduction in renal function after coronary angiography or <1% of all patients who undergo percutaneous coronary intervention using contrast media [12].
In hospital mortality after acute renal failure requiring dialysis in these patients could reach 36% even if this rate might be due to the effects of eventual co-existing co morbidities[1].

CONTRAST MEDIA

The earliest contrast agents were ionic, containing a sodium atom that dissociated from the molecule in aqueous solution. Each molecule of the agent carried three iodine atoms. Therefore, these agents required two osmotically active particles to deliver three iodine atoms and they had an extremely high Osmolality of about 2000 mOsm/L. These agents are termed High Osmolar or ionic and were the predominant ones used until the 1980's.

The next generation which were introduced in 1980's and still the predominant contrast media in use are non-ionic, since they need only one osmotically active particle to deliver 3 iodine atoms, their osmolality is only about 600-900mOsm/L and they are termed low Osmolar.

Both types of agents are monomers, with one benzene ring and three iodine atoms. Dimer molecules consisting of 2 joined benzene rings contain a total of six iodine atoms per molecule.

There is one ionic dimer ioxaglate, which has 6:2 or 3:1 ratio of iodine atoms to osmotically active particles and has an osmolality of 300mOsm/L similar to other low osmolar contrast agents. The newest contrast agent iodixanol is a non-ionic dimer. The chemical structures of these agents allow six iodine atoms to be attached to one osmotically active particle resulting in an osmolality of 300mOsm/L which is iso-osmolar with normal plasma.

CLASSIFICATION

High Osmolality contrast media

These types of contrast media consist of a tri-iodinated benzene ring with 2 organic side chains and a carboxyl group. The iodinated anion, diatrizoate or iothalamate, is conjugated with a cation particles are present in solution (i.e. ratio of 3:2).

The Osmolality in solution ranges from 600mOsm to 2100 mOsm/ kg versus 290 mOsm/kg for human plasma. The Osmolality is related to some of the adverse effects. Ionic monomers are sub classified by the percentage weight of the contrast agent molecule in solution for example 30% or 76%.[1]

Low osmolality contrast media

Classified into 3 types.

1. Non-ionic monomers
2. Ionic dimers
3. Non ionic dimers

Nonionic Monomers

In nonionic monomers, the tri-iodinated benzene ring is made water soluble by the addition of hydrophilic hydroxyl group to organic side chains placed at the 1, 3 and 5 position.

Lacking a carboxyl group, nonionic monomers do not ionize in solution. Thus for every 3 iodine atoms, only 1 particle is present in solution (i.e. ratio of 3:1).

Thus at a given iodine concentration, non- ionic monomers have approximately one half the osmolality of ionic monomers in solution.

At normally used concentration, 25 – 76% non- ionic monomers are 290 – 860 mOsm/kg.

Nonionic monomers are sub- classified according to the number of milligram of iodine in 1ml of solution e.g. 240,300, or 370 mg/ml.

The large side chains increase the viscosity of non-ionic monomers compared with ionic monomers. The increased viscosity makes them harder to inject, but it does not appear to be related to the frequency of adverse events.

Common nonionic monomers are iohexol, iopamidol, ioversol and iopromide. The non-ionic monomers are the contrast agents of choice. In addition to their non-ionic nature and lower osmolatities they are potentially less chemotoxic than ionic monomers.[2]

Ionic dimers

These are formed by joining 2 ionic monomers and eliminating 1 carboxyl group. These agents contain 6 iodine atoms for every 2 particles in solution (ratio 6:2). The only commerciality available ionic dimer is ioxaglate**.**

It has a concentration of 59% or 320 mg/ml and an osmolality of 600mOsm/kg. Because of its high viscosity, ioxaglate is not manufactured at high concentrations. Ioxaglate is used primarily for peripheral arteriography.[2]

Non ionic Dimers

Non -ionic dimers consist of 2 joined non- ionic monomers. These substances contain 6 iodine atoms for every 1 particle in solution (i.e. ratio of 6:1) for a given iodine concentration, they have the lowest osmolality of all the contrast agents. At approximately 60% concentration by weight, they are iso-osmolar with plasma. They are highly viscous and thus have limited clinical usefulness. Examples are iotrol and iodixanol.[2]

RISK FACTORS FOR CONTRAST NEPHROPATHY

Many factors have been reported as influencing contrast induced nephropathy but few have been proven to be independent risk factors [14].

However it has been recommended that every known risk factor should be analyzed to properly evaluate a total cumulative risk of developing contrast induced nephropathy. Total risk increases as the number of risk factors increases [15.]

Reported risk factors for contrast induced nephropathy include;

1. Pre-existing renal impairment.
2. Diabetes Mellitus with Renal impairment
3. Reduced intravascular volume.
    - § Congestive cardiac failure
    - § Nephrotic syndrome

- § Diuretics especially furosemide
- § Abnormal fluid losses – Dehydration

4. Prolonged hypotension
    - § Concomitant use of diuretic and ACE inhibitors
5. Metabolic Disorders
    - § Diabetes Mellitus(DM)
    - § Hyperuricaemia
    - § Hypercholesterolemia
    - § Hypercalcaemia
6. Contrast media
    - § Large volumes
    - § High osmolality
    - § Repeated injection within 72 hours.
7. Multiple myeloma
8. Nephrotoxic drugs
    - § NSAIDS
    - § Aminoglycosides
    - § Amphotericin-B
    - § Cyclosporine- A
    - § Platinum based drugs
    - § Sulfonamides
9. Advanced age > 70 years
10. Hypertension
11. Proteinuria
12. Sepsis
13. Atopy /allergy

PRE-EXISTING RENAL FUNCTION IMPAIRMENT

Irrespective of cause, preexisting impairment of renal function appears to be the most important risk factor [16, 17.]

In one study, for instance, 50% of patients with a creatinine level of 176umol/l had deterioration in renal function [18].

Similarly, in two studies of a population with baseline serum creatinine averaging 220 µmol/l, contrast induced nephropathy was a complication in 30 – 50% of patients[19].

Davidson et al, in a series of 1,144 patients undergoing cardiac catheterization, found a low risk of contrast induced nephropathy in patients with normal renal function, but a high risk in those with pre-existing azotemia. The risk increased exponentially with serum creatinine concentration (e.g. 20% incidence in those with serum creatinine of 177 µmol/l[20].)

Moore et al found a highly significant relationship between an increasing baseline level of serum creatinine and the frequency of nephrotoxicity (varying from 2% in those with baseline creatinine < 1.5mg/l to 20% in those with levels of >2.5 mg/dl).[21]

DIABETES MELLITUS WITH ASSOCIATED RENAL INSUFFICIENCY

Diabetes Mellitus (DM) with associated renal insufficiency has been identified as an independent risk factor for contrast nephropathy, with as many as 56% of those who develop the condition progressing to irreversible renal failure. In addition, patients with chronic renal failure due to causes other than Diabetic nephropathy are at a significantly higher risk of developing CIN [22].

Some authors have suggested that DM alone may be an independent risk factor for development of CIN. More recent research has failed to corroborate this connection. For example, Palfreys et al in a prospective trial of patients with DM showed than none of 8 patients with DM and normal renal function, developed clinically significant renal impairment defined as an increase of >50% in serum creatinine level.[17]. However, given that those with DM alone were found to be at slightly higher risk of renal failure than general population, it is prudent to include DM in pre-procedural risk assessment.

NEPHROTOXIC DRUGS

Directly nephrotoxic drugs e.g. cyclosporine-A, Amino glycosides, amphotericin-B and cisplatin and those that inhibit local vasodilator effects of prostaglandins for example the non steroidal anti inflammatory drugs(NSAIDS) have been reported to render the kidney more vulnerable to nephrotoxic contrast agents.[15, 23, 24.]

NSAIDS may lead to acute tubulointerstitial nephritis, whereas aminoglycosides antibiotics exert a direct nephrotoxic effect. Combination with furosemide makes the effect more potent.

Chronic NSAID use may lead to chronic tubulo-interstitial nephritis.

Cyclosporine-A, is a direct cellular toxic drug that impairs lysosome function in both the proximal and distal tubules evoking tubulo interstitial changes.

Platinum derivatives such as cisplatin attach to sulfihydryl groups and impair proper enzyme function. Although all these medications are known to induce renal damage, their individual roles as independent risk factors for contrast induced nephropathy have yet to be determined in large prospective clinical trials.

REDUCTION OF EFFECTIVE INTRA-VASCULAR VOLUME.

Reduction of effective intravascular volume (due to congestive heart failure, liver cirrhosis or abnormal fluid losses), prolonged hypotension (especially when induced by intense antihypertensive treatment combined with ACE inhibitors and diuretics especially furosemide), and dehydration have been reported as contributing factors to prerenal reduction in renal perfusion, thus enhancing the ischemic insult of contrast media [22,24,,25]

MULTIPLE MYELOMA

Multiple myeloma has been reported as a risk factor for contrast induced nephropathy. It has been argued that high amounts of protein in the tubular lumen with concomitant contrast material load may cause an obstructive nephropathy, a mechanism that is thought to be central to the development of renal insufficiency in patients with nephrotic range proteinuria secondary to multiple myeloma [26, 27.] The patho-mechanism of this process has been explained by the precipitation of radiographic contrast molecules, together with Tamms- Hosfall Proteins and the abnormal proteins, tubular epithelial cells damaged and desquamated as a result of ischemia, direct contrast toxicity, or disturbed function of integrins. However, given that acute renal failure rarely occurs after contrast if dehydration is avoided and that a review of seven retrospective studies showed an incidence of contrast nephropathy of only 0.6- 1.25% in patients with myeloma, it seems unlikely that multiple myeloma in absence of other risk factors confers excessive risk of development of contrast induced nephropathy [28,29,30.] Despite this rare likelihood, because of hyperuricaemia, hypercalcaemia, volume depletion, amyloidosis and light chain nephropathy associated with multiple myeloma, patients are at an increased risk of renal failure for reasons other than those associated with contrast administration and should be included as part of risk assessments. The importance of hypercalcaemia, hyperuricaemia and proteinuria per se as independent risk factors is not clear [23.]

VOLUME AND TIMING OF CONTRAST ADMINISTRATION

Large doses and multiple injections of contrast media within 72 hours increase the risk of the patients developing contrast-induced nephropathy. The lethal dose 50% (LD_{50}) of diatrizoate, a high osmolar contrast medium, in mice is estimated to be 7.6g/kg whereas a lethal dose of iohexol, a low osmolar contrast medium is 24.2 g/kg but unfortunately mouse LD_{50} values do not directly predict how contrast media will affect the human kidney. Definitive cut off levels have not been established but Manske et al [22] reported that volumes of LOCM (iohexol or iopamidol) greater than 30ml were associated with markedly increased risk of contrast nephropathy (25%) increase in serum creatinine levels within 48 hours and for each 5ml increment, the risk of nephropathy increased by 65%. Mean volumes administered, range from 30ml to 140ml in various studies of low osmolar contrast medium.

ROUTE OF ADMINISTRATION

The route of administration is also important, with contrast media being more nephrotoxic when administered intra arterially [24]. This effect is thought to be due to the fact that the acute intra renal concentration of contrast media is higher after intra arterial rather than intravenous injection.

ADVANCING AGE

Advancing age is reported to predispose patients to renal sodium and water wasting due to reduction in renal mass, function and perfusion[24, 31]

OSMOLALITY

The osmolality of contrast media plays an important role with large clinical studies and meta-analysis indicating that the use of low osmolar contrast media (LOCM) substantially reduced the risk of nephropathy in high-risk patients compared with use of high osmolar contrast media (HOCM). However this benefit could be shown only in patients with pre existing renal dysfunction in who contrast material was administered intra-arterially. In contrast, no benefit was found among those with normal renal function (with or without DM) in who contrast material was given by intravenous route [32]. A recent study suggests that iodixanol, a non ionic dimeric isoosmolar contrast medium with lower toxicity than LOCM is of significant benefit in a group of patients known to be at high risk for the development of contrast induced nephropathy. However, further clinical trials are indicated to establish

properly the role of contrast osmolality as a risk factor, independent of the mode of administration. [33]

SEPSIS AND OTHERS

Sepsis, through direct damage by bacterial toxins to renal tubules and impairment of circulation, has also been reported as a risk factor, as have hypertension, peripheral vascular disease and atopy/ allergy[15, 34, 35].

PATHOPHYSIOLOGY OF CONTRAST MEDIA INDUCED NEPHROPATHY.

The underlying mechanism to contrast induced nephropathy is not clear, though several suggestions have been put forward.

It is thought that, most likely a combination of various mechanisms are responsible for the development of CIN.

HAEMORRHEOLOGIC ALTERATIONS-High osmolar ionic agents have been shown to diminish erythrocyte deformability and hence increasing their aggregation, and wall stiffness. This contributes to haematic resistance, viscosity and to the worsening of selective medullary hypoperfusion.

ACTIVATION OF TUBULOGLOMERULAR FEEDBACK RESPONSE- The tubulo glomerular feedback is a powerful mechanism in the control of renal vascular resistance and glomerular filtration. It is thought that the hyperosmotic contrast media causes diuresis, which activates the tubuloglomerular feedback and subsequently compromises renal blood flow and glomerular filtration.

HAEMODYNAMIC ALTERATIONS AND REGIONAL HYPOXIA The injection of contrast media induces early, rapid renal vasodilatation followed by a 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).

GENERATION OF REACTIVE OXYGEN SPECIES - It has not been shown that contrast media induced hemodynamic alteration of the renal vessels is directly related to the synthesis and release of active mediators such as nitric oxide and prostaglandins, although their active role in the regulation of renal perfusion is well known. The intra-renal production of these vasodilators is responsible for the maintenance of perfusion and oxygen supply in the medullar; therefore, reductions in the availability of these mediators can promote nephropathy. It is highly probable that the endogenous vasoactive system of endothelium can contribute to medium ischaemic renal damage**.**

TUBULAR TOXICITY AND IMMUNOLOGICAL MECHANISMS

Many authors have made the hypothesis that; contrast media induced nephropathy may be due to direct tubular toxicity resulting from alterations in the integrity of plasma and mitochondrial damage[37.] Contact of the contrast media with tubular cells seems to cause rapid loss of cellular protein in the suspension medium including the loss of cell membrane proteins such as Na+/K+ ATPase pump and careolin, as well as mitochondrial proteins such as cytochrome-C.

FREE RADICALS AND REPERFUSION DAMAGE

There is some evidence that reactive oxygen species,, such as hydrogen peroxide, hydroxyl radicals, hypochlorous acid, superoxide anion, play a role in CN and that an endothelial dysfunction is partly due to oxygen free radical generation during post ischaemic reperfusion. Post ischaemic reperfusion may also lead to realkalization injury which has been observed after the induction of immediate post ischaemic correction of PH value.

CLINICAL PRESENTATION

Contrast nephropathy may occur after any radiographic procedure in which intravenous or intra arterial iodinated contrast agents are used, including excretory urography, computerized tomography, coronary, aortic, pulmonary, cerebral, peripheral angiography and cholangiography [38].

Acute renal failure caused by contrast media is generally non-oliguric and reversible. The serum creatinine level usually increases within 24-48 hours after contrast administration, reaches a peak value at 3-5 days (generally an increase 44.2 µmol/L and then returns to baseline within 7-10 days.

Urinalysis is often compatible with acute tubular necrosis, demonstrating renal tubular epithelial cells and coarse granular casts. Low urinary sodium and fractional excretion of Na+ <1% have been reported to be distinctive.

Contrast nephropathy may also present as a more severe acute renal failure, particularly in high risk patients. In this situation, oliguria may develop within 24 hours of contrast medium administration, with peak increase in creatinine exceeding 440mmol/L), sometimes necessitating dialysis. Fortunately, the incidence of severe contrast nephropathy requiring dialysis is fairly low (<1%), but recent studies have confirmed that associated mortality for this group of patients is 29%-36% [(39, 40).]

IDENTIFICATION OF PATIENTS WITH ABNORMAL RENAL FUNCTION

The **glomerular filtration rate (GFR)** is an index of functional renal mass.

Normal glomerular filtration rates are;

120 ± 25ml/min for males

and

95 ± 20ml/min for females.

In clinical settings, **serum creatinine** is used as a measure of **GFR.** While it is true that serum creatinine does vary inversely with **GFR,** it is important to recognize that this relationship is largely dependent on factors which affect muscle mass and creatinine production; age, sex and body weight. Therefore in those patients with diminished muscle mass (e.g. elderly, females) even mild elevation in serum creatinine may indicate significant impairment of renal function.

An alternative method is use of **creatinine clearance** to measure GFR. Although a true measured **creatinine clearance** requires **a 24- hour urine collection**, estimated creatinine clearance from serum creatinine is fairly simple, correlates well with **GFR**, and incorporates age, sex and body weight into the calculation.

CALCULATION OF CREATININE CLEARANCE

Cockroft-Gault formula

Creatinine clearance **(Ccr)** may be estimated in patients with stable creatinine utilizing the **Cockroft- Gault equation.**

Males
Creatinine Clearance

$$\text{CrCl (ml/mm)} = \frac{[140 - \text{Age}) \times \text{Lean body weight (kg)}]}{\text{Serum Creatinine (mg/dl)} \times 72}$$

Females

$$\text{CrCl (ml/mm)} = \frac{(140 - \text{Age}) \times \text{Lean body weight} \times 0.85}{\text{Serum Creatinine (mg/dl)} \times 72}$$

Estimation of lean body weight

Males- 50kg + [2.3kg x (each inch of height >5ft)]

Females 45.5 + (2.3kg x each inch of height > 5 ft)

It must however be noted that the Cockcroft and Gault formula is less accurate at a GFR of > 60ml/min and thus this limitation may not influence treatment of prediction of renal insufficiency. This formula often underestimates the glomerular filtration rate for patients older than 70 years and thus overestimates renal insufficiency. Nevertheless, the estimate it

provides has been used in several studies and is still a better estimate of GFR and renal function than serum creatinine alone.

Cockcroft -Gault formula is not applicable in children [41]

Abbreviated Modification of diet in renal disease study equation (MDRD) [42].

This is used to estimate GFR in patients with established chronic kidney disease and in stable function. It is more accurate than GFR and it tends to underestimate GFR in absence of kidney disease.

GFR= 186 x [Scr mg/dl] $^{-1.154}$ x Age $^{0.203}$

Modifiers- Female- Multiply GFR by 0.74 Males - Multiply GFR by 1.210.

Serum Cystacin – C

Cystacin C- is a cationic non-glycosylated low molecular weight cysteine protease that is produced by all nucleated cells at a constant rate, is not metabolized in the serum, and is freely filtered by the renal glomeruli[43, 44].

Serum concentration of Cystacin-C has been reported to be superior to serum creatinine with regard to assessment of GFR and to be independent of age, sex and muscle mass.

A recent study provided evidence for the usefulness of Cystacin (as a marker of contrast nephropathy[45].

Unfortunately, there are other factors than renal function influencing Cystacin C levels e.g. malignant tumours or elevation of C- reactive protein (CRP).

PREVENTIVE STRATEGIES OF CONTRAST MEDIA NEPHROPATHY.

Risk stratification

Several attempts have been made in developing a clinical tool for the purposes of risk stratification, but none have been validated prospectively.

Two risk scores for CN developed from large international cardiology databases may be the most generalisable to the cardiology patient sub population.

A simple scoring method that integrated 8 baseline clinical variables was developed by Mehran et al to assess risk of CN after percutaneous coronary intervention:

	Risk factors	Integer score
(I)	Hypotension	5
(II)	Use of intra -aortic balloon pump	5
(III)	Congestive heart failure	5

(IV)	Serum creatinine > 133µmol	4
(V)	Age > 75 years	4
(VI)	Anemia	3
(VII)	Diabetes mellitus	3
(VIII)	Volume of contrast used 1 for 100ml used	

The total score would give the patients

Risk category	**Total score**
Low	≤ 5
Moderate	6-10
High	11-15
Very high	≥ 16

Based on pathogenic mechanisms which have been proposed, several drug interventions have been tested in trials for prophylaxis against the development of contrast induced renal dysfunction.

General measures to minimize incidence of contrast nephropathy include

1. Carefully considering whether the contrast examination is absolutely needed, especially in high risk patients;
2. Using the minimum effective dose
3. Eliminating potentially nephrotoxic drugs at least 24 hours before study.
4. Use of alternative diagnostic procedures especially those at High risk e.g. sonography, MRI or CO_2 angiography.

Role of Hydration

Adequate hydration is the simplest and most effective way of protecting renal function. High risk patients should be administered normal saline by IV infusion at a rate of 1ml/kg/hour, adjusted appropriately for the patients' current fluid status and cardiovascular condition. This should be commenced 6-12 hours before the procedure and continued for up to 12-14 hours after the radiographic examination.

Eisenberg et al [46] in retrospective study of 537 patients reported that CIN was avoided by the administration of 550ml of normal saline and 250ml of heparanised saline flush per hour during the 295 cerebral and 242 abdominal or peripheral angiograms. Contrast doses

varied with an average of 115ml of meglumine iothalamate being given for cerebral angiograms and an average of 210 ml of either meglumine iothalamate, diatrizoate, or metrizoate being given for abdominal and peripheral studies.

Solomon et al[11] conducted a prospective trial in 78 patients with CRF in whom simple fluid therapy (1ml/kg hr of 0.45 %) Saline for 12 hrs before and after coronary angiography) was shown to be beneficial in reducing renal dysfunction after contrast administration.

More recently, a prospective single centre randomized trial of 119 patients by Merten etal[47] has suggested that use of sodium bicarbonate hydration is superior to sodium chloride hydration. Rates of contrast induced nephropathy were significantly lower in the sodium bicarbonate group (1.7%; n=1) when compared with sodium chloride group (13.6% n=8) when both cohorts were administered 154 meq/L of solution intravenously.

Although somewhat limited by its small sample size, drop out rates and its single centre nature, the authors argue that the bicarbonate ion is more efficacious than chloride. They suggest that free radical formation is promoted by an acidic environment and thus can be inhibited by increasing the PH of normal extracellular fluid by use of bicarbonate.

A confirmation of these findings is needed in larger multicentre trials. Inspite of absence of large controlled randomized trials with sufficient statistical power, it is almost universally accepted that hydration is an appropriate and safe measure to prevent contrast induced nephropathy.

Free radical scavengers

N- acetyl-cysteine (NAC)

This thiol containing anti- oxidant is thought to act either as a free radical scavenger or as a reactive sulphhydryl compound that increases the reducing capacity of the cell. It may also increase the biologic effects of NO by combining with NO to form S- Nitrosothiol which is a more stable form and a potent vasodilator. This interaction may limit the production of the damaging peroxynitrite radical because NAC would compete with the superoxide radical for NO. It also increases the expression NO synthase and may also improve blood flow. [48]Recent studies have suggested that NAC has vasodilatory effects, blocks expression of vascular cell adhesion molecule –1 (VCAM-1) and activation of nuclear factor $\Re$- β in glomerular and mesangial cells [49]

Tepel et al[50] - found that the incidence of CN after CT in patients with CRF was greatly reduced with NAC. This was also supported by results from the Acetylcysteine to Prevent

Angiography Related Renal Tissue Injury Trial in which the incidence of CIN was found to be 28%, risk ratio 0.18 with 95% confidence interval [5l.]

However, a few trials have shown negative results in use of NAC e.g. Durham et al [52] and Allaqabad etal [53.] A recent in depth and comprehensive meta-analysis of all studies to date on NAC including all those mentioned previously has shown that overall; NAC reduced the occurrence of CIN after non-ionic contrast medium administration by half in high risk patients. Seven trials including 805 patient found NAC plus hydration reduced the relative risk of CIN by 56% (0.435; P=0.02)[54]

Another recent study has shown that NAC may have other additional (cardiovascular benefits other than its reno- protective effects, in patient with end stage renal disease [55.]

These recent studies, coupled with the favourable side effect profile of NAC and its low cost, mean that NAC has gained favour in many centres as a preventive therapy, especially in high risk groups undergoing coronary intervention. An oral dose of 600mg twice daily the day before and the day of procedure is the commonest used regimen.

Intravenous doses of 150mg/kg over half an hour before the procedure or 50mg/kg administered over 4 hours have more recently been gaining popularity for use in critically ill patients or in those who are unable to take NAC orally.

Ascorbic acid

A recent randomized trial showed that use of ascorbic acid was associated with a significant reduction of 62% in the rate of CIN among patients with renal insufficiency undergoing coronary angiography with or without intervention[56].

Choice of Contrast Media

Improvements of contrast media in recent years have centred on the principles of eliminating ionicity, lowering osmolarity, increasing hydrophilicity and counting the number of iodine atoms per molecule. The osmotic effects of contrast media is central to the development of contrast induced nephropathy and is described in terms of the ratio of iodine atoms to dissolved particles. The higher the ratio, the better the attenuation of X-rays as there are more iodine atoms for fewer particles of contrast agent. Media with a ratio of 1.5:1 are Higher Osmolar Contrast Agents (HOCM), media with ratio 3:1 are Low Osmolar Contrast Media (LOCM). Agents with ratio 6:1 are Iso Osmolar Contrast Agents.

A meta analysis of 31 trials concluded that the use of LOCM rather than HOCM was beneficial to patients with preexisting renal failure[33] . Recently, interest has grown in a new, non-ionic, dimeric Iso-Osmolar contrast media - iodixanol, which has shown reduced incidence of CIN than LOCM.

Diuretics

It has previously been recommended that furosemide or mannitol administered together with saline infusion offers better protection of renal function, but consistent results have not been obtained. Clinical trials have been similarly unconvincing. Anton et al.[57]claimed protective effect of mannitol in an early study of 37 patients with CRF who were hydrated before and after urography and were given 250 mls of 20% mannitol 1 hr after contrast administration, when compared with 40 patients with history of CRF who received hydration alone. Solomon et al.[11], report simple fluid therapy to be superior to fluid therapy plus either furosemide or mannitol.

Weinstein et al[58]. - found a worsening of renal function in 8 patients with pre-existing azotemia who were treated with furosemide and hydration versus a control group of 10 patients who did not have a deterioration in renal function and in whom hydration was left to the discretion of the referring clinician.

Antinatriuretic peptide (ANP)

ANP, with or without saline, has been reported to reduce incidence of contrast induced nephropathy by increasing GFR and glomerular hydrostatic pressure by dilating afferent arterioles and constricting efferent arterioles while blocking tubular re-absorption of sodium and thus disrupting the tubuloglomerular feedback mechanism [59,60].

The Auriculin Anaritide Acute Renal Failure study group, a multi-centred randomized double blind placebo controlled trial of aniritide (the synthetic form of ANP) in 504 critically ill patients with acute tubular necrosis, suggested improvements in dialysis free survival in patients with oliguria[61] .

A few other studies have shown no benefit in use of Aniritide in preventing CIN. [62]

Calcium channel blockers

The role of calcium as a mediator of contrast induced nephropathy, thought to be related to its positive effect on haemodynamics and their cytoprotective influence on renal cells, was investigated by Neumayer etal[63] in a randomized double blind study of Nitrendipine. Nitrendipine was found to attenuate contrast induced decline in GFR with a return to baseline in 48 hrs. Solomon et al [11] found no benefit for a single pre-procedural dose of calcium channel blocker in their series of 78 patients with CRF undergoing angiography. Given the lack of resoundingly positive results in human trials, calcium channels blockers have failed to gain wide use as a prophylactic tool to date.

Adenosine antagonists

Adenosine is a portent vasoconstrictive agent and has been implicated as a mediator in tubuloglomerular feedback, a mechanism that may have a role in the pathogenesis of contrast induced nephrotoxicity. Experimental studies of acute renal failure in different animal models reveal a nephroprotective effect of adenosine antagonism.

Theophylline acts as a non-specific adenosine receptor antagonist and may be given I.V. bolus of 2.5 - 5 mg/kg of body weight before administration of contrast agent or orally for 3 consecutive days before contrast injection [64]. The use of theophylline as a prophylactic agent for contrast-induced nephropathy was first assessed by Erley et al.

45 patients were given i.v. Theophylline or a placebo. 4 hr inuline clearance and 48 hrs creatinine clearance were stable or minimally reduced in the theophylline group but diminished in the placebo group[65, 66]

More recently a study of 100 patients with serum creatinine levels of 1.3mg/dl or greater and who received either 200mg of I.V. theophylline or a placebo 30minutes before administration of 100ml or more of LOCM arterially, 72% or IV 28% showed the benefit of pre-treatment with the adenosine antagonist. The incidences of contrast induced nephropathy were significantly reduced in the theophylline group 4% vs. 16%, P= 0.046 with minimal change in the mean serum creatinine levels whereas the placebo group had a significant increase in 24 hr serum creatinine level[66].

Kapoor et al confirmed these findings in a cohort of 70 patients with DM undergoing coronary angiography[67].

A few studies have shown no benefit of adenosine antagonists. Abizaid et al[68] randomized 60 patients undergoing coronary angiography to receive saline, dopamine or aminophylline and found no differences among the three groups. A study by Shahmas et al[69] found no appreciable differences when compared with the same number of matched control subjects.

In the wake of lack of consensus in clinical studies, coupled with potential side effects of theophylline and the narrow therapeutic index, adenosine antagonism cannot be recommended for routine prophylactic use. A definitive multi-centre prospective trial is warranted to confirm or deny the encouraging findings from earlier studies.

Dopamine Agonists

Dopamine is a potent vasodilator of the renal arteries. Hans et al[70] used a dopamine infusion of 2.5mg/kg/min, and reported protection against contrast mediated renal dysfunction.

Evidence suggests that selective Dopamine type 1 receptor agonist fenoldopam mesylate may be useful in preventing contrast induced nephropathy[71].

Endothelin receptor blockers

Bosentan, an orally active endothelin antagonist may attenuate the contrast mediated reduction of renal function in the isolated perfused rat kidney. On the contrary, a recent prospective randomized trial has shown that endothelial receptor antagonists actually exacerbate radiographic contrast induced nephrotoxicity.[72, 73]Prostaglandins

A report on a pilot study of 117 patients receiving 3 separate dosages of prostaglandin E, (aprostidil) or a placebo suggested that contrast induced nephropathy was reduced in the prostaglandin group but at higher doses, PGE, caused frequent hypotension and a higher rate of nephropathy[73].

Preventive Haemodialysis or Haemofiltration

Removal of contrast by haemodialysis after the procedure in patients with pre-existing renal failure has been shown to have no effect on contrast induced nephropathy and is unwarranted as a routine practise[75]. Vogt et al. evaluated prophylactic haemodialysis and showed no beneficial effect compared with using saline hydration alone. [74].

Marenzi et al. investigated haemofiltration and showed significant benefits in prophylaxis against CIN. He found that in a cohort of 114 patients undergoing coronary angiography, serum creatinine increases of greater than 25% from baseline were found to occur less frequently in the haemofiltration group. They attributed the beneficial results to the preservation of haemodynamic stability, maintenance of circulating blood volume and prevention of renal hypoperfusion by the haemofiltration.[75]

The widespread use of haemofiltration is limited by its relatively high cost.

RESEARCH QUESTION:

What is the burden of contrast induced nephropathy and independent risk characteristics of patients undergoing intravascular contrast imaging procedures at Kenyatta National Hospital?

Study justification and rationale

There is now widespread use of radio contrast material in various imaging modalities. This widespread use predisposes patients, who already have co morbid conditions, to the risks of renal injury by the radio-contrast material. Unfortunately, very few clinicians take cognisance of these risks.

There are currently no data on the prevalence of CIN locally and hence no guiding protocols on its prevention. This study will thus raise awareness amongst clinicians and radiologists on this common risk.

This study will also provide data for future studies on this area.

Broad objective

TO DETERMINE THE INCIDENCE OF CONTRAST NEPHROPATHY IN ADULT IN PATIENTS UNDERGOING INTRAVASCULAR CONTRAST IMAGING PROCEDURES AT THE KENYATTA NATIONAL HOSPITAL.

Specific objectives

1. To determine the incidence of contrast nephropathy in adult inpatients undergoing intravascular contrast imaging procedures.
2. To determine the burden of independent risk factors for developing contrast nephropathy i.e.
    - Age
    - Hydration status
    - Pre-existing renal impairment
    - Diabetes mellitus,
    - Volume and type of contrast used

3. To determine the commonest indications/procedures for patients undergoing contrast enhanced imaging.

MATERIALS AND METHODOLOGY

STUDY DESIGN

A prospective and descriptive cross sectional study.

STUDY SUBJECTS

This study identified and recruited by consecutive sampling 177 adult inpatients over period of 6 months (September 2007 to February 2008) at Kenyatta National Hospital.

Patients undergoing intravascular contrast enhanced imaging procedures e.g. CT scanning, Angiography, Cardiac catheterization, intravenous urography etc were eligible for screening and recruitment.

STUDY SITE

This was a hospital based study conducted at

(1) X-ray department and

(2) Cardiac Catheterization laboratory, of Kenyatta National Hospital (KNH).

KNH is a tertiary referral hospital for Kenya and the neighboring countries located on north western side of Nairobi; the political and business capital city of Kenya.

Patient selection

Inclusion Criteria

1. Adult (>13years) inpatient at KNH.
2. Patient who gave an informed consent or whom their guardians gave consent.

Exclusion criteria

1. Any patient or guardian who declined to give consent
2. Patient with documented history of allergy to contrast materials
3. Documented acute renal failure

SAMPLE SIZE AND SAMPLING

Sample size was calculated using a sample size formula for prevalence study i.e.

$$N = Z^2 P (1-P) \div d^2$$

Prevalence of CIN reported in studies that included patients with pre-existing renal dysfunction or type 2 diabetes mellitus in which a standard hydration protocol was not administered is between 13% and 26%. Lower rates of 3.3% have been reported among patients without these risk factors

Prevalence (P) contrast nephropathy= 0.13

Confidence Interval of 95% (Z= 1.96)

Precision level **(d)** = 0.05

Thus sample size **N**= $(1.96^2 \times 0.13)(0.87)$

0.0025

= 174

CASE DEFINITION

An adult inpatient at KNH, who had been exposed to a contrast medium in the last 72 hours and had an absolute increase of 44.2umol/L in serum creatinine, was considered to have developed contrast induced nephrotoxicity

CONTRAST INDUCED NEPHROTOXICITY AT 24HRS

A patient who at **24** hours had an absolute increase of **44.2** µmol/l in serum creatinine from the baseline was considered to have CIN at **24** hrs.

CONTRAST INDUCED NEPHROTOXICITY AT 72 HOURS

A patient who at **72** hours had an absolute increase of **44.2** µmol/l in serum creatinine from the baseline was considered to have CIN at **72** hours.

CUMULATIVE CIN

Any patient who at anytime during the **72** hours of the study period had an absolute increase of **44.2** µmol/l in serum creatinine from the baseline was considered to have cumulative CIN. (E.g. a patient, who had CIN at **24** hrs but resolves, may be missed at **72** hours thus underestimate the cumulative incidence.)

METHODOLOGY

Patient's selection and recruitment

Eligible patients were recruited by consecutive sampling.

The principal investigator assisted by a study assistant visited the radiology department and cardiac catheterization laboratory every morning at 8.00 am and checked for inpatient's bookings for a contrast enhanced imaging procedure for the next day.

Consecutive sampling of patients booked for the procedure was done.

The PI and the study assistant then visited the sampled patients in the wards and obtained an informed consent, the required data and blood samples for baseline creatinine levels.

A complete medical history and physical examination was done on all the sampled patients. All the necessary demographic data i.e. age sex, occupation, residence; anthropometric measurements such as height, weight, body mass index, lean body weight and drug history i.e. use of NSAIDS, Amino glycosides, Amphotericin-B, ACE inhibitors, Platinum based, Sulfonamides and Sulphonylureas were recorded in a validated study proforma. The PI studied the patient's files for other co- morbid conditions. A thorough clinical examination was done and the level of hydration assessed as per the WHO guidelines.

3mls of venous blood was then drawn aseptically for baseline urea and creatinine, sodium and potassium. A repeat blood sampling was done at 24 hours and 72 hours after the administration of the contrast material.

ETHICAL CONSIDERATIONS

1. Permission to carry out the study was obtained from **the Department Of Medicine University of Nairobi and given on 2nd November 2006 and Ethics and Scientific Research Committees of the Kenyatta National Hospital approved it on 11th July 2007**
2. Patients' **identities** were kept confidential all along the study.
3. Participation was entirely voluntary **and after giving a written consent.**
4. **Informed consent** for inclusion in the study was obtained from the patients or if too ill to give consent, was obtained from the guardian or next of kin.
5. The entire procedures were carried out maintaining **strict aseptic techniques.**
6. Prior patient preparation and need for prophylactic strategy was at the discretion of the attending primary care team or the primary physician. However, the principal investigator may gave limited suggestions in cases found ethically wanting and such cases were excluded from the study.
7. Results of the study were in a few cases relayed back to the patient, the radiologist and the primary physician and all were advised accordingly.
8. Patients found to have contrast nephropathy were referred to the renal clinic through the usual hospital referral system.

RESULTS

A total of 174 patients were recruited in the study. All patients were analyzed at 24 hrs and 140 (80.5%) were analyzed at 72hrs with a drop out rate of 34 (19.5%) patients. (Figure 1 below)

FIGURE 1: STUDY FLOW CHART

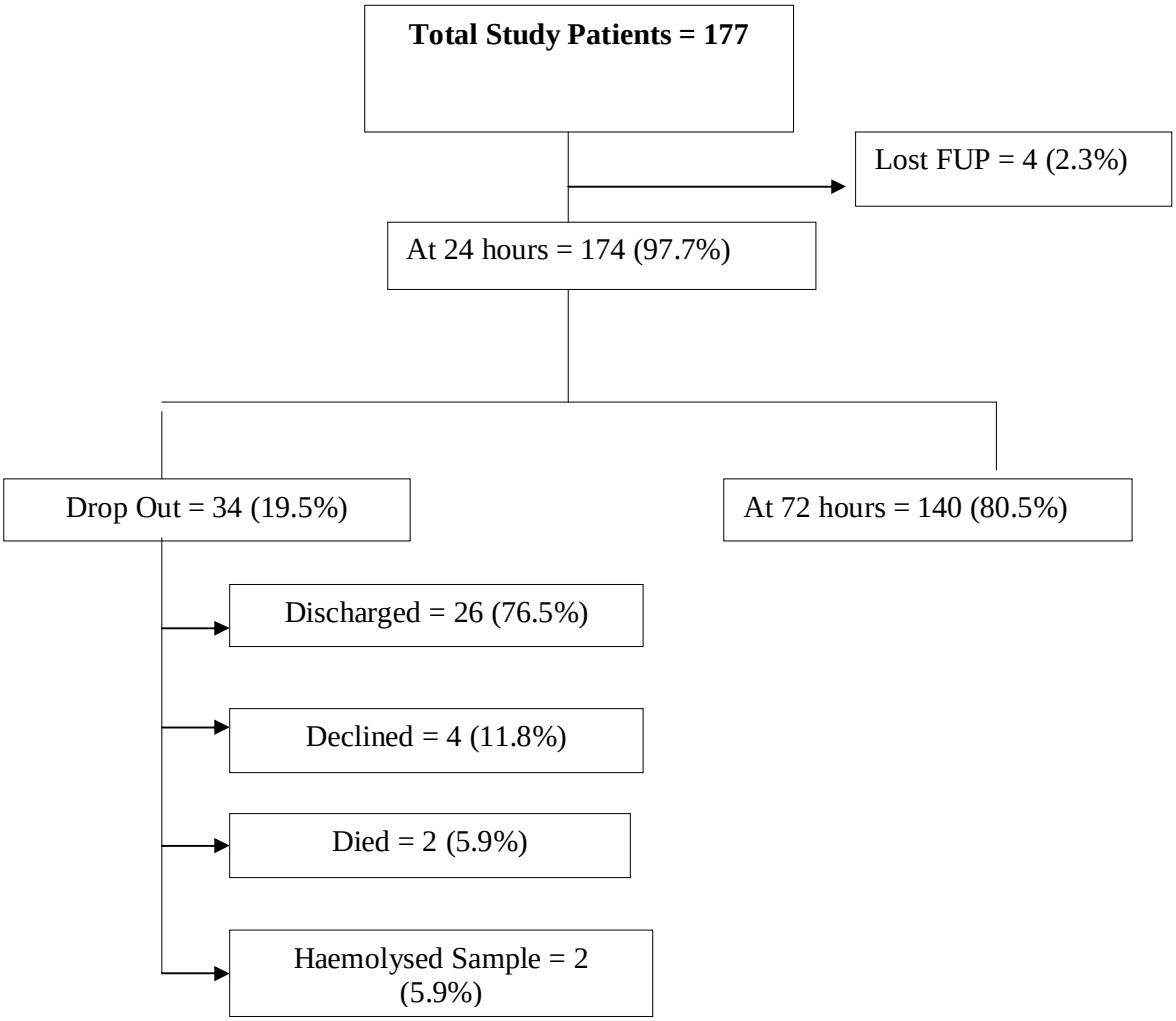


Table 1: Baseline characteristics of the study population (n = 177)

Factor	Frequency	Percentage
Sex		
• Male	83	46.9
• Female	94	53.1
Age (in Years)		
• ≤ 19	18	10.2
• 20 – 29	23	13.0
• 30 – 39	51	28.8
• 240 – 49	26	14.7
• 50 – 59	25	14.1
• 60 – 69	19	10.7
• 70 +	15	8.5
Employment Status		
• Formally Employed	72	40.7
• None	105	59.3

As per Table 1 above a total of 94 (53.7 %) were females and 83 (46.3 %) males. Most patients 51 (28.8%) were aged between 30 and 39 years. The mean age was 42.59, Median age was 39, Mode age was 32 year and the range was 14 – 80 years. About 60% of the total patients had no formal employment.

Table 2: Co-morbid conditions among the study population (n = 177)

Medical condition	Frequency	Percentage
HTN	46	26.0
CKD	23	13.0
Malignancies	23	13.0
DM	20	11.3
Dyslipidaemea	20	11.3
CCF	19	10.7
Connective tissue disease	10	5.6
Nephrotic syndrome	6	3.4
Asthma	4	2.3
Hyper-uricaemia	2	1.1

Ten co-morbid medical conditions were found among patients presenting for various imaging procedures, with the highest condition being HTN at 46 (26.0%) and the least being hyper-uricaemia at 2 (1.1%) (Table 2 above).

Table 3: Combination of co-morbid medical conditions in the study population (n = 177)

Combinations of conditions	Frequency	Percentage
CKD	23	13.0
CKD + DM	12	6.8
CKD+HTN	17	9.6
CKD+DM +HTN	12	6.8
CKD + DM+HTN+CCF	5	2.8
DM	20	11.3
DM + HTN	19	10.7
DM + CCF	8	4.5

Multiple risk factors for CIN were noted with 17(9.6%) patients having both CKD and HTN.6.8% had CKD, HTN and DM.(Table 3 above)

A total of 121 (68.4%) patients had varied degrees of renal impairment with creatinine clearance below 90 ml/kg/24 hrs.

Table 4: Hydration Status (n = 177)

Level	Frequency	Percentage
Well hydrated	129	72.9
Dehydrated	48	27.1
Mild	34	70.8
Moderate	12	25.0
Severe	2	4.2
Total	**177**	**100.0**

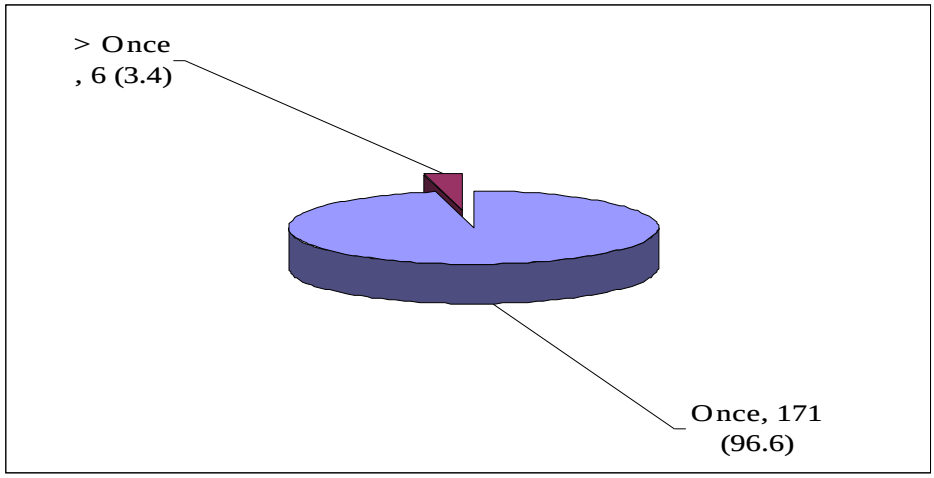
A total of 129 (72.9%)(table 4 above) were well hydrated and the remaining 48(27.1%) had different levels of dehydration as indicated in table above.

Table 5: Current medication (n = 177)

Drug	Frequency	Percentage
NSAIDs	54	30.5
ACE-I	29	16.4
Sulphonamindes	22	12.4
Sulphonylureas	21	11.9
Amino glycosides	12	6.8
AmphotericinB	8	4.5
Platinum Based	4	2.3

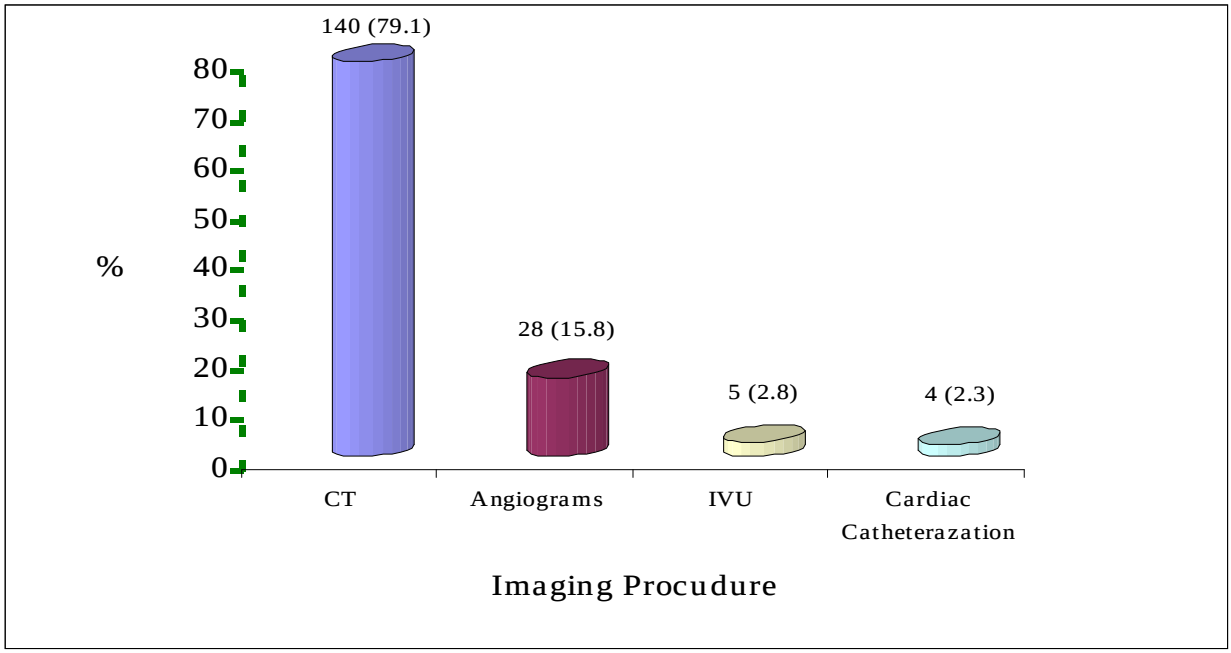
The table 5 above shows that NSAIDs were the mostly used medication at 54 (30.5%) followed by ACE-I at 29 (16.4%) and the least medication being the platinum based compounds at 4 (2.3%).

Figure 2: Exposures (n = 177)



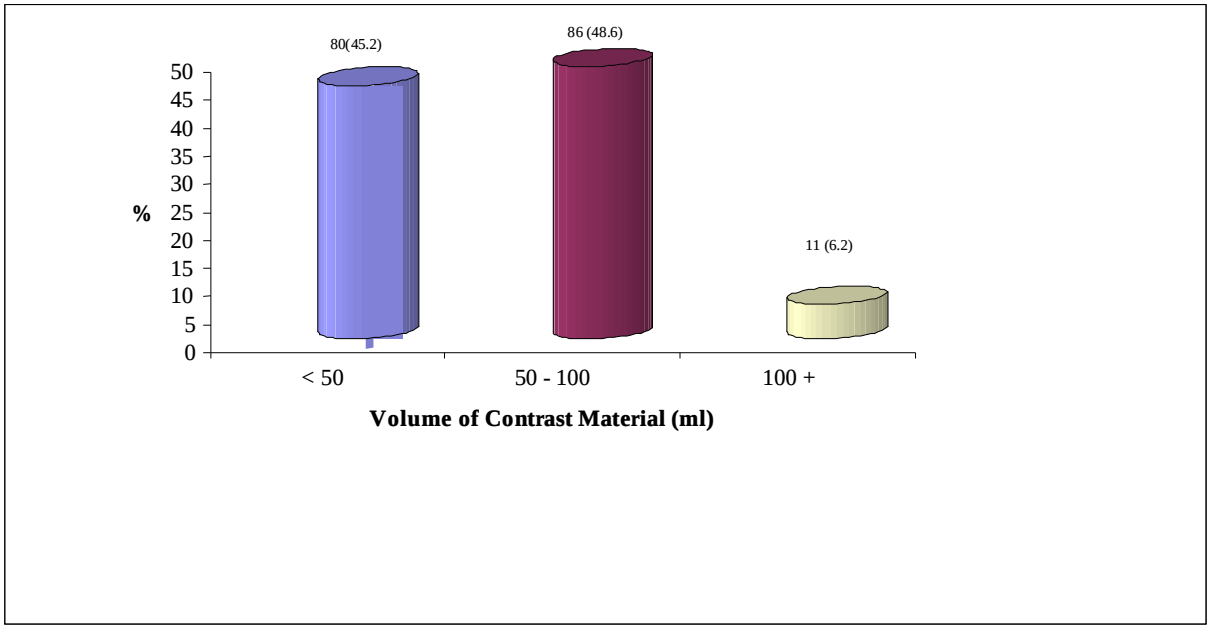
Only 6 (3.4%) patients had had prior exposure to contrast material.

Figure 3: Distribution by Imaging procedures (n = 177)



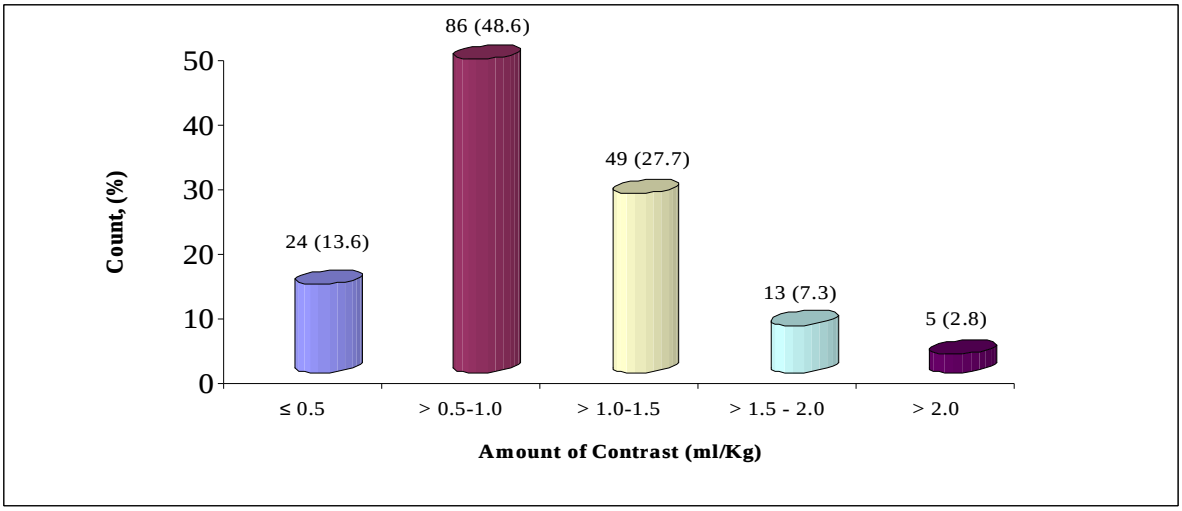
Most patients (Figure 3) 140(79.1%) studied underwent contrast enhanced CT scans of various regions of the body, 28 (15.8%) had angiography done and 5(2.8%) IVU.

Figure 4: Volume of intravascular Contrast Given (n = 177)



Most patients 86 (48.6%) received between 50 and 100 ml of contrast with only 11 (6.2%) recieving more than 100 mls of contrast.

Figure 5; Contrast load in mls /kg given to each study subject



Amount of contrast material given ranged from 20mls to 140 ml of 370mg/l strength of low osmolar iodinated of contrast, with 48.6 per cent receiving between > 0.5 and 1.0 ml per kg being the highest. (Figure 5 above)

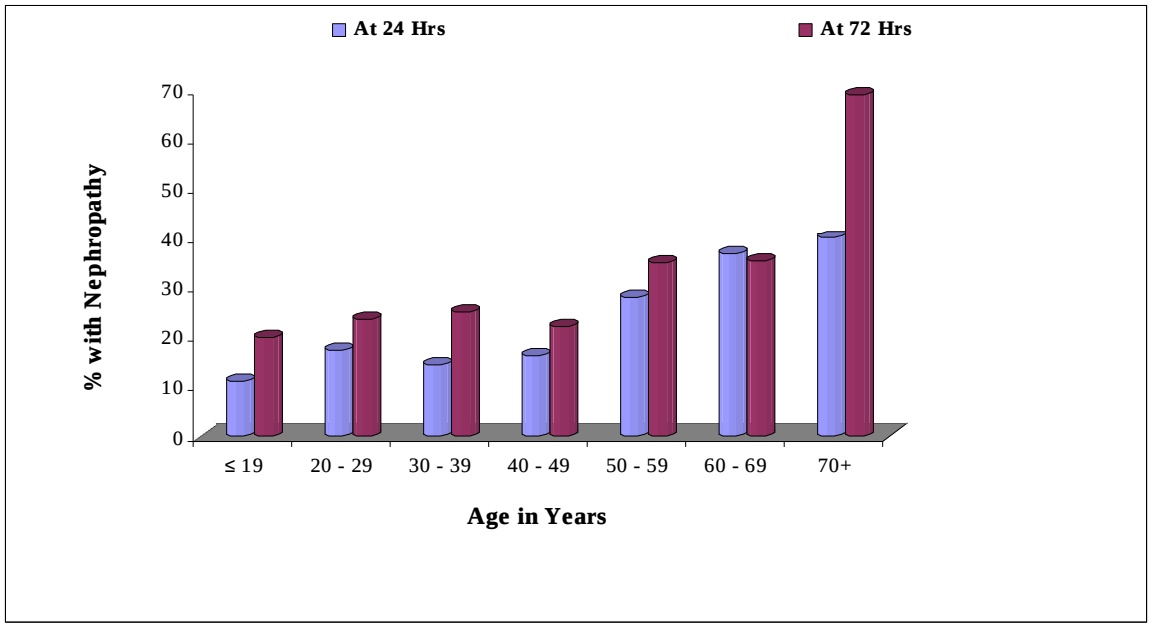
Prevalence of Contrast Nephropathy

Table 6: Incidence of Contrast Nephropathy (based on an increase of 44.2 µmol/l)

Period	Frequency	Prevalence
At 24 hours (n=174)	37	21.3
At 72 hours (n=140)	43	30.7
Any CIN(within 72 hours)	57	32.8

The incidence of CIN was 21.3% and 30.7% at 24 hours, 72 hours respectively. Cumulatively the incidence was found to be 32.8 %.(Table 6 above).

Figure 6: Distribution of Contrast Nephropathy per Age



The risk of developing contrast nephropathy was found to increase with the age of the patient as shown in the Figure 6 above.

The mean age of patients who developed CIN at 24 hrs was 49.7(±2.9) years while those who did not develop CIN were 40.8 (±1.14). There was a significant difference in mean age between those who developed CIN, with mean difference of 9 years, 95%CI of 2.9 – 15.0 and p-value of 0.004 at 24 hours.

Mean age of those who developed CIN cumulatively was 48.3 years while those who did not was 39.4 (p-value = 0.002).

Table 7: Distribution of Contrast Nephropathy by Risk Factors

Risk Factors	At 24 hrs (n = 37)	At 72 hrs (n = 43)
CKD	11 (29.7)	10 (23.3)
CCF	10 (27.0)	13 (30.2)
DM	10 (27.0)	9 (20.9)
HTN	20 (54.1)	21 (48.8)
Dyslipidaemia	9 (24.3)	10 (23.3)
Nephrotic Syndrome	0	1 (2.3)
Asthma	0	3 (7.0)
Hyperuricaemia	1 (2.7)	2 (4.7)
Malignancy	5 13.7)	7 (16.3)
CTD	3 (8.1)	4 (9.3)

Table 7 above shows that at 24 hours of the 37 cases with contrast nephropathy 11(29.7%) had pre-existing renal insufficiency, 10 (27%) CCF, 10 (27%) DM and 20(54%) HTN. At 72 hours of the 43 cases with contrast nephropathy 10(23.3%) had pre-existing renal insufficiency, 13(30.2%) CCF, 9 (20.9%) DM and 21(48.8%) had HTN.

Table 8: Combination of Risk Factors and Risk for Contrast Nephropathy

	Risk for CN		OR (95%CI)	P-value
At 24 hours	(n)	Yes, n (%)		
CKD	(23)	11 (47.8)	-	-
CKD, DM	(12)	7 (58.3)	1.5 (0.3 – 7.9)	0.815
CKD,DM,HTN	(12)	7 (58.3)	1.5 (0.3 – 7.9)	0.815
CKD,DM,HTN,CCF	(5)	3 (60.0)	1.6 (0.2 – 17.5)	1.000
At 72 hours				
CKD	(20)	10 (50.0)	-	-
CKD,DM	(10)	6 (60.0)	1.5 (0.3 – 9.2)	0.709
CKD, DM, HTN	(10)	6 (60.0)	1.5 (0.3 – 9.2)	0.709
CKD, DM, HTN, CCF	(4)	3 (75.0)	3.0 (0.2 – 89.6)	0.598
Any CIN				
CKD	(23)	14 (24.6)	3.9 (1.6-9.7)	**0.002**
CKD, DM	(12)	7 (15.8)	7.1 (1.8-27.5)	**0.001**
CKD, DM,HTN	(12)	7 (15.8)	7.1 (1.8-27.5)	**0.001**
CKD, DM, HTN, CCF	(5)	5 (100.0)	0	**0.001**

Patient with multiple risk factors had higher risk of developing CIN but this was not found to be statistically significant (Table 8 above). At 72 hrs, a patient with CKD and DM had 1.5 higher risk of developing CIN (OR 1.5, (p-0.709) than a patient with CKD alone. This was the same (OR 1.5, (p-0.709) if the patient had hypertension too. The risk was tripled if the patient had co-existing heart failure (OR 3.0, p-0.596). However, this was not statistically significant.

When the analysis is done on occurrence of CIN, within 72hrs, there was increasing risk with occurrence of multiple risk factors with statistical significance e.g. in a patient with CKD and DM, the risk is 7.1 times that of a patient with CKD alone.

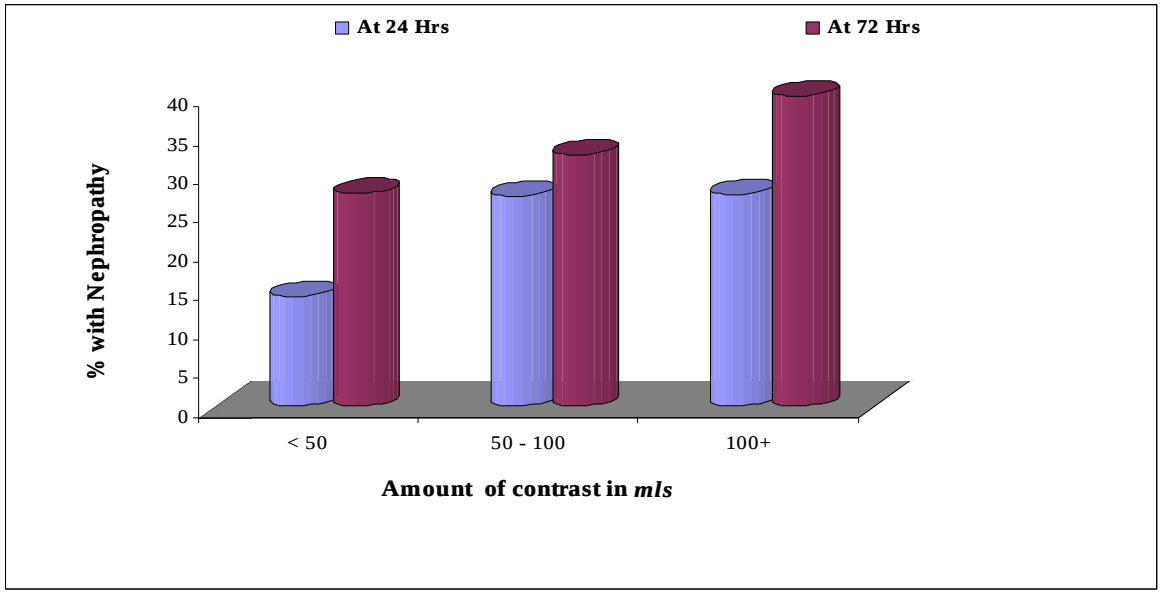
Table 9: Dehydration and Risk for Contrast Nephropathy				
	Risk for CIN		**OR (95%CI)**	P**-value**
At 24 hours	(n)	Yes, n (%)		
Dehydrated	(46)	15 (32.6)	2.3 (1.0 – 5.0)	*0.028*
Hydrated.	(128)	22 (17.2)		
At 72 hours				
Dehydrated	(38)	16 (42.1)	2.0 (0.9 – 4.4)	0.075
Well Hyd.	(102)	27 (26.5)		

At 24 hours 15 (32.6%) of the patients who had dehydration were 2.3 time likely to develop CIN (p=0.028) while at 72 hours 16 (42.1%) who had dehydration were 2.0 time likely to develop CIN (p=0.075).

Table 10: Dehydration and Risk for Contrast Nephropathy				
	Risk for CIN		**OR (95%CI)**	*P***-value**
At 24 hours	(n)	Yes, n (%)		
Mild	(34)	9 (26.5)		
Moderate	(11)	5 (45.5)	-	0.176
Severe	(1)	1 (100.0)		
At 72 hours	(n)	Yes, n (%)		
Mild	(28)	11 (39.3)		
Moderate	(9)	4 (44.4)	-	0.476
Severe	(1)	1 (100.0)		
Any CIN		Yes, n (%)		
Mild		15 (71.4)		
Moderate		5 (23.8)	-	0.543
Severe		1 (4.8)		

The risk of CIN with dehydration increased with severity of dehydration, however this was not statistically significant (p>0.05).

Figure 7: Contrast nephropathy vs. Volume of contrast material



The mean volume of contrast in those who developed CIN at 24 hrs was 71.5 (±4.5) mls while those who did not develop CIN were 58.3 (±2.5). There was a significant difference in mean amount between those who developed CIN, with mean difference of 13.24, 95%CI of 2.9 – 23.7 and p-value of 0.013 at 24 hours.

The mean amount of contrast in those who developed CIN at 72 hrs was 64.3 (±4.5) mls while those who did not develop CIN were 60.5 (±3.00). There was not significant difference in mean amount between those developing CIN and those without, with a mean difference of 3.79, 95%CI of -6.9 – 14.5 and p-value of 0.486 at 72 hours.

Mean amount of contrast for those who developed any CIN was 0.98mls/kg years while those who did not was 0.91mls/kg (p-value = 0.322).

Table 11: Drugs and Risk for Contrast Nephropathy

	Risk for CIN	OR (95%CI)	P-value
At 24 hours (n)	Yes, n (%)		
NSAIDs	(54) 15 (27.8)	1.7 (0.8 – 3.6)	0.156
Aminoglycocides	(12) -	-	-
Amphotericin	(8) -	-	-
ACEI	(29) 13 (44.8)	4.1 (1.7 – 9.6)	***0.001***
Platinum based	(4) -	-	-
Sulfonamides	(20) 3 (15.0)	0.6 (0.2 – 2.3)	0.467
Sulphonylureas	(21) 9 (42.9)	3.3 (1.3 – 8.7)	***0.001***
At 72 hours (n)	Yes, n (%)		
NSAIDs	(44) 15 (34.1)	1.3 (0.6 -2.7)	0.55
Aminoglycocides	(9) 2 (22.2)	0.6 (0.1 – 3.2)	0.568
Amphotericin	(4) 1 (25.0)	0.7 (0.1 – 7.4)	0.802
ACEI	(22) 13 (59.1)	4.2 (1.6 – 10.9)	***0.003***
Platinum based	(4) 1 (25.0)	0.7 (0.1 – 7.4)	0.802
Sulfonamides	(14) 3 (21.4)	0.6 (0.2 – 2.2)	0.427
Sulphonylureas	(18) 9 (50.0)	2.6 (0.9 – 7.1)	0.057

At 24hrs, patients on NSAIDS were 1.7 times at risk of developing CIN while those on ACEI were 4.1 times at risk. This risk was only statistically significant in those on ACEI and sulphonylureas.At 72hrs, only patients on ACEI had statistically significant increased risk of CIN.

DISCUSSION

This is a hospital based study done over a period of 6 months and in which 177 inpatients were recruited, with various co-morbidities and no prior protocol pre-contrast preventive strategies. Requesting doctors were allowed to make their own non-standardized preparation of patients.

A high (32.7%) cumulative incidence of CIN was found at 72 hrs. The incidence is higher than what is reported in various studies. The incidence of CIN in the general population is estimated to be 2-7% and as high as 25% among those with pre-existing chronic renal failure.[7] Rates may vary from 0% to 90%[9] and depend on definition used and other variable such as the procedure performed, the dose and type of contrast agent used, number and type of risk factors and the length of patient follow up. Reasons that may explain the higher incidence in this study include-the fact that there was no standardized pre contrast preparation, the population studied had a bigger proportion (121 (68.4%) of the subjects having various stages of CKD, and the definition used in this study may also have overestimated the prevalence of CIN. (Most studies have used an absolute increase of 25% in serum creatinine from the baseline).

Patients in this study were relatively younger (mean age-43years) compared to most other studies predominantly from the West. Many studies available are mainly on an elderly population with multiple co-morbid conditions and in who the procedures done are mainly cardiovascular such as Coronary angiography. This study population; however, was quite representative of the population seen at the KNH. Co-morbidities among recruited patients were high with many patients having more than one co- morbid condition.

No comparative studies from Africa on this subject were found despite an extensive literature search

Preexisting renal insufficiency

29.7% of patients with preexisting renal insufficiency developed CIN. This compared well with other reported studies where it is said to be extremely high, ranging from 14.8 to 55%.[8, 9, and 11] Other studies show even higher prevalences.Heyman S. N. showed prevalence of 50% in a patient population with baseline serum creatinine of 176 µmol/l.In two other studies in which the population had baseline serum creatinine averaging 220 µmol/l, CIN was a complication in 30-50%.[19]

Pre-existing renal disease with an elevated level of serum creatinine is the most crucial risk factor in the development of CIN. Focus has been on prevention of CIN in this predisposed group where it has been shown that prophylactic hydration with normal saline reduces the

risk of CIN significantly. (Solomon et al[11] conducted a prospective trial in 78 patients with CRF in whom simple fluid therapy (1ml/kg /hr of 0.45 % Saline for 12 hrs before and after coronary angiography) was shown to be beneficial in reducing renal dysfunction after contrast administration).

2. Diabetes mellitus

We found an incidence of 27%of CIN in patients diagnosed to have diabetes mellitus. Patients with DM and renal insufficiency had 1.5 times increased risk than those with diabetes mellitus alone.

Diabetes Mellitus with/without renal failure has been identified as an independent risk factor for CIN with as many as 56% of those who develop the condition progressing to irreversible renal failure.

Our study findings are at variance with findings of Palfreys' et al in a prospective trial of patients with DM who showed than none of 8 patients with DM and normal renal function, developed clinically significant renal impairment defined as an increase of >50% in serum creatinine level.[17].This might be due to the small numbers of patients in his study. His patient population was drawn from a population with prior pre-procedural rehydration and in whom no major co-morbidities existed. Palfreys used a much more stringent criteria in defining CIN (>50%increase in serum creatinine). Diabetic patients represent a significant proportion of patients undergoing contrast exposure due to high prevalence of diabetes in the general population and the ability of the disease to cause a broad spectrum of cardiovascular diseases that require radiological procedures using contrast media.

4. **AGE**

The risk of developing contrast nephropathy was found to increase with the age of the patient. Mean age of those who developed any CIN was 48.3 years while those who did not was 39.4 (p-value = 0.002).This was statistically significant.

Although our study population was made up of predominantly younger age, there was a significant difference in the risk for CIN. This is in concurrence with many other studies from the west[24].

The reasons for higher risk to develop CIN in elderly are not studied specifically and probably are multifactorial, including age-related changes in renal function (diminished glomerular filtration rate, tubular secretion, and concentrating ability).

This may also be explained by the presence of various risk factors with advancing age.

4. Dehydration

Dehydrated patients had a twofold risk of CIN. Increasing severity of dehydration was associated with increasing risk of CIN.

Adequate hydration is the simplest and most effective way of protecting renal function. High risk patients should be administered normal saline by IV infusion at a rate of 1ml/kg/hour, adjusted appropriately for the patients' current fluid status and cardiovascular condition. This is indeed feasible even in resource poor settings.

5. Combination of medical risk factors

Co-existing risk factors increased risk of CIN significantly. For example, a patient with CKD and DM, the risk is 7.1 times that of a patient with CKD alone.

Apart from the known unfavorable combination of diabetes and renal insufficiency, the presence of two or more other risk factors for CIN also had an additive influence on the rates of CIN

In one study, for example, CIN occurred in 1.2% of the patients without risk factors, 11.2% with one risk factor (contrast volume greater than 200 ml, serum albumin level of 35 g/l, diabetes mellitus, serum sodium level of 135 mmol/l, and serum creatinine level ≥133 µmol/l), and in 42% of the patients with two or more risk factors.[7]

Patients with multiple risk factors had higher risk of developing CIN.[9] This necessitates algorithms and pre contrast risk assessment of the patients.

6. Amount of contrast material

The mean amount of contrast volume in those who developed CIN at 24 AND 72hours was 71.5 mls and 64.3 mls respectively with significant volume differences (p-value of 0.013). Mean amount of contrast for those who developed any CIN was 0.98mls/kg while those who did not was 0.91mls/kg (p-value = 0.322).

The volume of contrast media is a main modifiable risk factor in the development of CIN. The correlation between the amount of contrast media and the risk of CIN is well documented.[9,21,25] Most of the studies indicate that higher volume of contrast media is especially deleterious in the presence of other risk factors.

Even relatively low doses of contrast (less than 100 ml) can cause CIN.

INDICATIONS FOR CONTRAST IMAGING PROCEDURE

Most patients 140(79.1%) studied underwent contrast enhanced CT scans of various regions of the body, 28 (15.8%) had angiography done and 5(2.8%) IVU. Studies in the literature have been mainly in patients undergoing coronary angiography who are thought to be at slightly higher risk for CIN due to high contrast load and existence of other co-morbidities. Inspite of the commonest procedure being computed tomography scans CIN was still found to be quite prevalent. This may be attributable to the large number of patients who had significant renal derangement (121 (68.4%) patients with Cr Cl<90ml/min/kg) and the fact that no pre procedural preventive measures had been taken in the study population.

STUDY LIMITATIONS

This study has certain limitations;

The acute deterioration of renal function (ARF) was assumed to be due to contrast agent renal toxicity and not any other cause after contrast administration. No further evaluation for the cause for the acute renal failure was done. This study might have included a number of patients who possibly developed ARF from other causes such as the more common pre-renal ARF or even drug induced.

This study population was small and drawn from a single institution, which reduces the external validity of our findings.

This study recruited only inpatients for convenience and may thus have missed out on a number of out patients with similar characteristics and predisposed to contrast nephropathy.

The study also recruited a biased sample of inpatients, excluding outpatients, which are more likely to have a multiplicity of risk factors for contrast nephropathy.

No standardized prophylactic protocols have been developed and thus this study population was made up of a mixed picture of patients.

CONCLUSIONS

CIN is common in patients exposed to contrast at KNH

CIN is even more common in patients with known risk factors e.g. pre-existing renal insufficiency, high volume of contrast media, contracted intravascular volume and advancement in age.

Risk for CIN worsens with multiplicity of risk factors.

CIN incidence compares with others reported in other studies, inspite of differences in type of procedures most reported

Recommendations

In view of the findings of a higher incidence of CN, it is recommended in normal practice that all patients going for any contrast enhanced imaging procedure should be screened for risk factors and stratified accordingly. Alternative studies such as MRI with less nephrotoxic gadolinium may thus be recommended in those at high risk.

Simple preventive procedures, such hydration in our set up, should be instituted for every patient going for imaging procedure and in whom contrast enhancement is anticipated.

Protocols should be designed for individual patients undergoing contrast imaging procedure

Further studies should be undertaken on outcomes of these patients who develop CIN i.e. need for dialysis or even mortality.

Further studies on effect of contrast on other organ systems may be interesting considering its effect on the renal system

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APPENDIX 1

PATIENT'S GENERAL INFORMATION

This is a study to determine the prevalence of radio contrast agent effect on kidneys. This study will involve you or your next of kin answering a questionnaire where details of your medical and drug examination will be noted. A thorough physical examination with be done on you or your next of kin. After that I will draw some blood from your forearm / elbow for urea, creatinine and other electrolytes which will help analyze your baseline renal function.

You will again be requested to allow for repeat blood samples after 24 hours and again after 48 hours.

Benefits:

This study will help in detecting any early deleterious effects to your kidneys and hence allow us to intervene if need be.

The results of this study will also help in laying the basis for future policies on patients undergoing contrast enhanced imaging studies.

Risks

There will be no additional risks involved but there will be some pain at the puncture site

Participation.

This will be totally voluntary and no medical service or advice will be denied to you if you decline to participate in the study.

Costs

There will be no additional monetary costs on you for the laboratory tests.

Confidentiality

Your identify and test results will be kept confidential

APPENDIX 2

CONSENT-FORM

I ---------- do hereby consent to participate in the proposed research on prevalence of contrast media nephropathy.

I am aware that the study will involve a clinical examination and blood laboratory investigations.

I understand that my identity and results of the investigation will be kept strictly confidential.

I have also been explained the benefits of this study for myself and others undergoing similar examination.

---------- ----------

Signature of participate Date

Signature of investigator

Telephone number- 0722-492185.

Appendix 3

SERUM CREATININE DETERMINATION.

The 3mls of venous blood drawn from the patient will be put in are a red capped blood specimen container and using the Jaffe reaction (creatinine reacts with alkaline picrate to produce a reddish colour which is measured photo metrically at 500 nm). Serum creatinine will be determined by the Technicon RA+1000 machine in the KNH. Renal laboratory.

Appendix 4

STUDY PROFORMA

PERSONAL HISTORY

Patients Name _____ **Study no** _____

/INPATIENT NO _____

Sex **Male** ☐ **Female** ☐

Age (years) _____

Residence _____

Occupation _____

IMAGING PROCEDURE _____

INDICATION/DIAGNOSIS; _____

Medical History	**(NO=0)**	**(YES I)**
1. Chronic Kidney Disease	☐	
2. Diabetes mellitus(Type1 and 2)	☐	
3. Congestive cardiac failure	☐	
4. Nephrotic syndrome	☐	
5. Hypertension	☐	
6. Asthma/Allergies	☐	
7. Documented Dyslipidaemia	☐	
8. Documented Hyperuricaemia	☐	
9. Malignancies	☐	
If yes specify		
9 Connective tissue disease	☐	
If yes specify		

Drug History

1. NSAIDS	☐	
2. Amino glycosides	☐	
3. Amphotericin-B	☐	
4. ACE – inhibitors	☐	
5. Platinum based	☐	
6. Sulfonamides	☐	
7. Sulphonylureas	☐	
Contrast material	(Once=O,	>Once=1
1. Number of exposures	☐	
2. Osmolality of contrast		
HOCM	☐	

LOCM ☐

1OCM ☐

3. Amount given strength _____ mg of iodine/ml)

_____ Mls

Physical examination
Blood pressure (mmHg)
Height
Weight
Calculated body mass index

Level of hydration

1. Well hydrated ☐
2. Dehydrated ☐

If dehydrated

- Mild dehydration ☐
- Moderate dehydration ☐
- Severe dehydration ☐

Serum creatinine

Baseline _____ µmol/L

At 24 hours _____ µmol/L

At 72 hours _____ µmol/L

CALCULATED CREATININE CLEARANCE

(As per Cockroff -Gault formula)

At baseline _____ mls/min

At 24 hours _____ mls/min/kg

At 72 hours _____ mls/min/kg

APPENDIX 5

STUDY BUDGET

Proposal Development	–	20,000
Laboratory tests	-	177,000
Laboratory assistant	-	20,000
Study assistant	-	30,000
Data analysis	-	20,000
Thesis write up	-	10,000
		277,000/=

The whole budget was incurred by the principal investigator.

Ethical approval