INCIDENCE AND RISK FACTORS ASSOCIATED WITH ACUTE KIDNEY INJURY INDUCED BY RADIOLOGICAL CONTRASTS IN ADULT PATIENTS ADMITTED AT KUTH

“Prospective observation Cohort study”

A dissertation submitted to College of Medicine and Health Sciences, School of Medicine and Pharmacy in partial fulfilment for the requirements of award of a Masters` degree in Internal Medicine, University of Rwanda.

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Kigali, May 2019
DECLARATION

I, Dr BABANE Jean Felix, to the best of my knowledge hereby declare and certify that the work presented in this dissertation entitled “INCIDENCE AND RISK FACTORS ASSOCIATED WITH ACUTE KIDNEY INJURY INDUCED BY RADIOLOGICAL CONTRASTS IN ADULT PATIENTS ADMITTED AT KUTH” is entirely my own and original work and it has never been presented or submitted in whole or in part to any other university.

Dr. BABANE Jean Felix, Signature: …………… Date: 12/06/2019

Supervisors:

We, hereby declare that this dissertation has been submitted with my approval as the supervisor.

Dr BITUNGUHARI Leopold Signature: …………… Date: 12/06/2019

Dr LEWAY KAILANI Signature: …………… Date: 12/06/2019
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DEDICATION

To my son BERWA Hans Arthur whom I love the most

To my Wife

To my mother

To my irreplaceable father MUKINDIGIRI Damien (In memoriam)

To my brothers and sisters

To my friends Doctors and Nurses

I dedicate this work
ACKNOWLEDGEMENT

This work would not have been successful without joint efforts from different persons, including patients, nurses, doctors and laboratory technicians whom I express my gratitude.

I would like to thank the University of Rwanda, Kigali University Teaching Hospital (KUTH) and particularly the department of Internal Medicine, for supervision and assistance in different ways to make this research possible.

I would like to express my gratitude to Dr. BITUNGUHARI Leopold and Dr. LEWAY KAILANI, whom despite their busy timetable accepted to supervise and correct this work.

I would like also to thank patients who accepted to participate in this research by signing consent, providing needed information and giving the samples voluntarily.

Finally, my thanks are presented to all my colleagues, friends and relatives for their endurance and charity throughout my training.

Dr. BABANE Jean Felix
ACRONYMS

**CI-AKI:** Contrast induced acute kidney injury  
**KDIGO:** Kidney disease improving global outcome  
**CT-scan:** Computed tomography scan  
**KUTH:** Kigali university teaching hospital  
**USA:** United States of America  
**IV:** Intravascular  
**CSF:** Cerebro-spinal fluid  
**ATN:** Acute tubular necrosis  
**FENa:** Fraction excretion of sodium  
**STEMI:** ST elevation myocardial infarction  
**ROS:** Reactive Oxygen Species  
**CKD:** Chronic kidney disease  
**CMHS:** College of Medicine and health sciences  
**IRB:** Institution Review Board  
**SD:** Standard deviation  
**GO:** Gynecology and obstetric  
**ENT:** Ears, Nose and Throat  
**HIV:** Human Immunodeficiency Virus  
**IBM:** International Business Machine  
**SPSS:** Statistical Package for the Social Sciences  
**ERBP:** European Renal Best Practice
ABSTRACT

Background:

Contrast induced AKI is iatrogenic disease caused by intravenous contrast media. Its incidence is reported in some studies to have significantly reduced due to use of new agents which have low osmolality comparing to the old ones (hypo-osmolar agents). However it is reported in some studies to be on 3rd place among causes of hospital acquired AKI with incidence of 5% among patients who was previously showing normal renal function.

This study was done at KUTH with objectives of determining incidence of CI-AKI in hospitalized adult patients, identifying risk factors and generating data on patients who received Intra-venous contrasts.

Method:

This was a prospective observation Cohort study among hospitalized adult patients who received contrast for imaging purpose.

Study population and period

The study population included 204 patients who were 18 years old and above, who was hospitalized at KUTH, who received intravenous contrast products for radiological purpose and who accepted to consent for participation in the study and fulfil the inclusion criteria. The study was conducted from 15th February, 2018 to 30th December, 2018.

Results

This study recruited 204 patients from 5 different departments (Internal medicine, Surgery, Gynaecology-Obstetric, ENT and Emergency). Their mean age was 48.4 ± 18 years. Presumed risk factors were; Diabetes, heart failure, quantity of contrast received, concomitant use of nephrotoxic drugs, age above 65 years, quantity of pre and post contrast IV fluid received.

Among all those presumed risk factors, not receiving post contrast IV fluid was associated with risk of CI-AKI, with RR= 8.19 (3.4-19.5), p<0.001.
The incidence of CI-AKI was found 17.6%, with 7.8 had creatinine rise between 25% - 50% (low to be classified in AKI stage, but fulfil definition of CI-AKI as provided by KDIGO), 6.8% had AKI stage I, 2% AKI stage II and 1% stage III.

**Conclusion**

Incidence of CI-AKI is high in our population. This may be due to in part to lack of concise rehydration protocol in patients exposed to contrast.
CHAP I: INTRODUCTION

I.1. General Introduction and justification of study

Contrast induced acute kidney injury (commonly called contrast induced nephropathy) is iatrogenic kidney injury due to exposure to contrast media.

Over the last 60 years, use of intravenous contrast agents is becoming popular; the data in 2014 showed that around 2 million cardiac catheterization procedures[1] and nearly 30 million contrasts enhanced CT-scans were being performed annually in USA.

The use of intravascular iodinated contrast media for diagnostic and therapeutic purposes is becoming more and more popular. Currently in Rwanda, nine sites can do images with use of intravascular contrast. Kigali University Teaching Hospital (biggest public hospital) can do more than 50 CT-scan with contrast per week for out and in patients including adults and paediatric population.

Intravenous contrast media may lead to acute kidney injury[2], although the majority of those cases are reversible, some cases may end up by having chronic kidney disease with associated fatal events.

Kidney disease improving global outcome (KDIGO) 2012 guidelines recognized the amplitude of contrast induced acute kidney injury (CI-AKI), and recommended pre and post contrast evaluation of renal functions for its early diagnosis and immediate management [3].

However during the last 2 decades efforts have been made to produce contrasts which are less nephrotoxic.

As the number of patients exposed on intra-vascular contrast media is increasing every year, there is need of conducting a study to assess their safety in order to improve their rational use. Thus the importance of this study is to evaluate incidence of CI-AKI.

I.2. Problem statement

In Rwanda, a country where the use of contrast media for radiological purpose is becoming popular since the last two decades, no recent epidemiological studies done to look for magnitude acute kidney injury induced by contrast products. This study will contribute to give preliminary data and ideas with regard to the use of IV Contrasts and related AKI as well as to highlight its risk factors in our setting.
I.3. Hypothesis

The risk of developing AKI after IV contrast use is high in our settings due to lack of pre and post-contrast preventive guidelines.

I.4. Objectives

To determine the incidence of IV Contrast related AKI in hospitalized adult patients who receive intravenous contrast for radiological purposes.

To identify risk factors for CI-AKI in hospitalised adult patients.

To generate data on patients who receive IV contrasts.

CHAP II: LITTERATURE REVIEW

II. 1. Contrast media

Contrast media are in group of chemical substances formed on the basis of 2,4,6-triiodinated benzene ring. They are classified on basis of their physical and chemical characteristics, including their chemical structure, osmolality, iodine content, and ionization in solution [4].

Due to their chemical properties, they are usually more viscous with high osmolality comparing to blood, plasma and CSF. These agents can be subdivided in two categories which are ionic and non-ionic. The ionic can break into cation and anion when are in solution and increase osmolality. This property is absent in non-ionic agents [4]. Ionic contrast are more nephrotoxic than non-ionic [5]. High osmolality of contrast media has been identified another factor to be associated with CI-AKI [6]. Thus ideal contrast agents are non-ionic, which can deliver most iodine with least effect on osmolality [4].

Renal toxicity of contrast media is not fully explained only by contrast properties and it is thought to be associated to several factors.

The most common used contrasts in our hospital are Iohexol-350 under trade name of Omnipaque-350 and Iopamidol-370 under trade name of Iopamiron-370. Although both have high osmolality comparing to serum, they are considered as low osmolar agents (osmolality around 900 mosm/kg H₂O) comparing to the old ones with osmolality around 1500 to 2000 mosm/kg H₂O [6].
Iohexol is a non-ionic, water-soluble, radiographic contrast medium with a molecular weight of 821.14 (iodine content count 46.36%). It is excreted by kidneys in 80-90%. It doesn’t dissociate in aqueous solution (non-ionic).

Omnipaque-350, its form commonly used in our setting contains 755mg of Iohexol with 350 mg of organic Iodine per ml. Its osmolality is 844 mOsm/kg water and specific gravity of 1.406 [7]. It is excreted by the kidney in 90%.

Iopamidol is a widely used non-ionic monomer, radiographic contrast material with low osmolality (796 mosm/kg) and iodine concentration of 300 mg iodine/ml. It has a half life of 2 hours, and in 90% is secreted by kidneys [8].

II. 2. Pathogenesis

The pathogenesis of CI-AKI is explained based on animal models. Studies on animals show evidence of acute tubular necrosis (ATN), but the mechanism by which it occurs is not fully understood [9]. The two main theories to explain ATN are medullary hypoxia due to renal vasoconstriction and cytotoxic effects of contrast agents to the tubular cells [10] [11]. Compared to other type of ATN, CI-AKI is usually characterized by rapid recovery of renal functions. The reasons thought to be behind such rapid recovery is that the degree of tubular necrosis is much less severe than seen in other settings on one hand and on the other hand the possibility of functional changes in tubular epithelial cells rather than necrosis. This phenomenon may be at least in part due to redistribution of membrane transport proteins from the basolateral to the luminal membrane [12]. Consistently low urinary sodium and fractional excretion of sodium (FENa) may be persistent in oliguric patients. FENa of less than 1% (not explained by ATN alone) was found to persist up to 5 days [13]. These findings raise the possibility that acute kidney injury secondary to contrast media may be mediated either by decreases in renal perfusion or by acute tubular obstruction.

Other intrinsic causes of medullary ischemia are increase oxygen consumption, increased intratubular pressure secondary to contrast induced diuresis, increased urinary viscosity and tubular viscosity and tubular obstruction, all frequently associated with dehydration and decrease the effective intravascular volume [6].
II.3. Definitions

To define contrast induced acute kidney injury, three components are important: An absolute or relative creatinine rise, exposure to contrast agents and exclusion of alternative causes of renal impairment [2]. Thus the definition of contrast induced-AKI is a relative increment of serum creatinine by 25% or more, or an absolute increase of 44μmol/l (>0.5 mg/dl) or more from baseline value, after 48-72 hours following exposure to IV contrast media [3]. CI-AKI is commonly a non-oliguric and asymptomatic, transient decline in renal function, generally start to occur within 24 hours of contrast administration [14].

Among patients who develop contrast induced AKI, 80% start to develop rise in creatinine in first 24 hours after exposure to contrast products [15].

However, there are areas of uncertainty in this definition, as some of the risk factors for CI-AKI can be independent causes of AKI. For example dehydration which facilitates increase of serum osmolality when you give IV contrasts consequently increases risk of CI-AKI, can cause itself pre-renal AKI. Another area which has been subject of debate is the choice of threshold of 25% creatinine increment, which normally is low in comparison to the definition of AKI in general (relative creatinine increment of 50%) [16].

II.4. Epidemiology

AKI induced by contrast media is iatrogenic condition. It is considered as the 3rd cause of hospital acquired acute kidney injury (after surgery and hypotension) and accounting 12% of all cases [17]. CI-AKI also count around 5% of hospitalized patients who had normal renal functions before using contrasts [18]. The above results may not be generalized for Rwandese population where the main causes of hospital admission are infectious and few centres are using high volume IV contrast and currently agents being used are with low osmolality and non-ionic.

CI-AKI is common in patients with pre-existing renal impairment and is more exacerbated when the last one is due to diabetic nephropathy [19]. This justifies the importance of assessing kidney functions before exposing a patient on contrast products.

As evidenced in percutaneous coronary intervention for STEMI, high contrast volume is associated with high rates of CI-AKI and mortality [20]. But no study to look if limiting contrast would improve
outcome. A lot of formula have been established to calculate safe volume taking into account contrast osmolality, as contrasts with different osmolalities, can have different risks despite using the same volume [21][22].

The type of contrast agent may alter the risk. Hyper-osmolar and ionic contrast products are associated with high rate of nephrotoxicity [23][5]. In current practice, these agents are being abandoned.

However, the procedure behind the use of IV contrast can be the reason to explain the development AKI. The risk is high in interventional comparing to diagnostic coronary angiography, particularly in setting of myocardial infarction.

**II.5. Clinical presentation and diagnosis**

The major clinical manifestations of CI-AKI are an increase in serum creatinine generally in non oliguric patients [5]. The creatinine increase is generally observed within 24 to 48 hours after contrast exposure [2]. In severe renal impairment, signs and symptoms of hyperkalemia, acidosis and hyperphosphatemia may be present.

Microscopic urinary sediment may show classic findings of acute tubular necrosis, including muddy brown, granular and epithelial cell casts and free renal epithelial cells. However the absence of these urinary findings doesn’t exclude CI-AKI like it is the case in other type of ATN[24]. Protein excretion on presentation is absent or mild. Some iodinated radio-contrast agents may induce false-positive results when either dipstick or sulfosalicylic acid is used to detect proteins in urine [25]. Consistently low urinary sodium and fractional excretion of sodium (FENa) may be persistent even if the patient is oliguric.

**II.6. Management and outcome**

In one small study including 21 patients with 70 years and above, who developed CI-AKI 57% returned to baseline renal function and 19% had partial recovery within five to seven days, 24% had persistent renal dysfunction at the time of discharge [26]. The sample size and age selection put in doubts results of this study. CI-AKI associated percutaneous coronary intervention is independently associated with risk of short- and long-term ischemic and hemorrhagic events [27]. CI-AKI after administration of contrast medium is associated with increased mortality. The risk is higher in
patients whom contrast medium is administered intra-arterially [28]. It was noticed also, small
increase in serum creatinine which doesn’t meet the criteria of AKI was associated with increased
risk of in-hospital mortality [29].

II.7. Prevention

Common methods used to prevent CI-AKI are IV hydration [30]. Reasons advanced are prevention of
renal vasoconstriction and associated hypoxia due to contrast agents. Use of normal saline prior to
contrast products normalize plasma volume and reduces osmotic diuresis [31][32]. By frequent urine
elimination, it reduces time of exposure of contrasts to epithelial cells of renal tubules, consequently
reduce its cytotoxicity. Use of 100ml per hour for at least 4 hours pre-contrast and 24 hours post
contrast use has been accepted by some protocols as standard [33][16]. Few randomized trials have
examined the effect of intravenous fluids in the absence of other interventions. In small randomized
trial including 53 patients underwent nonemergency cardiac catheterization, IV saline decrease the
risk of CI-AKI compared with unrestricted oral hydration (4% versus 35 %), the study was stopped
early due to high rate of acute kidney injury in the last group [32]. IV saline hydration during primary
percutaneous coronary intervention reduced the risk of CI-AKI to 48% [30]. In these studies it’s
difficult to conclude if the lower incidence can be attributed to prevention of dehydration or direct
protection of the kidney.

Another prevention measures include, minimizing concomitant use of nephrotoxic drugs and
avoidance use of contrasts when unnecessarily. It has been advised to use minimal effective quantity
of contrasts to avoid CI-AKI [17].

Potentially nephrotoxic drugs (Aminoglycosides, Dipyridamole, and NSAIDs) should be
discontinued at least 24 hours before radiographic procedure [14]. If Aminoglycosides are mandatory
to use, the European Renal Best practice recommends a single dose per day and monitoring drug level
[16].

Use of anti-oxidant drugs has been suggested seeing the role played by ROS in nephrotoxicity by
iodinated radio-contrast agents. N-Acetylcysteine has been the first tested anti-oxidant, considering
its double properties, as a free radical scavenger and as well as drug able to increase the vasodilating
effect of Nitric Oxide [34]. Conflicting results have been obtained with the use of anti-oxidant
ascorbic acid. In recent meta-analysis with 1536 patients who completed the trial, patient who received Ascorbic acid had 33% less risk of developing [35].

**CHAP III: METHODOLOGY**

**III.1. Study design**

This study was prospective observation cohort, among patients who received contrast products. It used qualitative and quantitative strategies of data collection.

**III. 2. Study population and period**

The study population included 204 patients who were 18 years old and above, who was hospitalized at KUTH, who received intravenous contrast products for radiological purposes and who accepted to consent for participation in the study and fulfilled the inclusion criteria. The study was conducted from 15<sup>th</sup> February, 2018 to 30<sup>th</sup> December, 2018 with interruption of 32 days due to technical problem in radiological unit.

**III. 3. Sampling and sample size**

To calculate the sample size, Slovin’s formula was used:

\[ n = \frac{N}{1 + Ne^2} \]

\( n \): Study sample size

\( N \): Total number of patients who fulfilled criteria to be included in the study, on predefined study period as seen above. In our study we estimated it to be 400, based on data in radiological record of 2017, where 407 hospitalised adults’ patients underwent CT imaging with contrasts.

\( E \): Error tolerance, which in our study will be 0.05

\[ n = \frac{N}{1 + Ne^2} = \frac{400}{1 + 400(0.05)^2} = 200 \]

In total 204 patients have been enrolled in our study.
III. 4. Inclusion criteria

Patient who were 18 years and above, who received IV contrast for radiological purposes, whom Pre-contrast and post-contrast creatinine (between 48-72 hours) were available, and who were hospitalized for at least 48 hours after receiving contrasts and accepted to sign consent for participation himself or by surrogate.

III. 5. Exclusion criteria

- Refusal to sign consent by patient or surrogate for any reason
- Patients with pre-existing renal disease (AKI or CKD)
- Patients with incomplete data
- Patients who were bleeding for any reason
- Trauma patients
- Patients who were on inotropes
- Critically ill patients in terminal phase, whom it was mentioned do not resuscitate.

III. 6. Data collection

To collect data, a questionnaire was used. The entrance point was in radiological department. And after, patients were followed in their respective primary departments. The samples for pre and post-contrast serum creatinine were analysed at KUTH laboratory. A relative increment in serum creatinine of 25% from baseline was considered as CI-AKI. Clinical data including all demographic data, clinical signs and para-clinical investigations were recorded by using a questionnaire. For every patient the name and dose of contrast received were documented. The reason of imaging for each patient was identified and at the end grouped in main category such as cardio-vascular + thromboembolic, neoplastic, infectious, metabolic and others (auto-immune, spinal cord compression, inflammatory, intestinal obstruction).

III. 7. Statistical analyses

Data were entered using EpiData 3.1 and exported to IBM SPSS statistics version 25 for analysis. Descriptive statistics have been used to present the measures. Univariate and multivariate analyses were performed using Logistic regression. T-test was used to compare the difference between means.
A p value <0.05 was statistically significant. The principle dependable outcome was CI-AKI as defined by KDIGO-2012 guidelines. Presumed risk factors were quantity of supplemental IV fluid received at least 12 hours pre and 24 hours post contrast exposure (reference being 500ml and 2500ml respectively), concomitant use of nephrotoxic drugs, quantity of contrast received, age above 65 years, and comorbidities like diabetes and heart failure.

III. 8. Ethics

An approval of this study was obtained from University of Rwanda ethical and research committee (CMHS IRB) and the permission to conduct it at the level of the hospital was given by KUTH ethic committee (find annexed copies of both).

The involved patients have provided written consents themselves or through their surrogates after being given sufficient explanations on the purpose of this study and reassured that the information provided will be kept confidential. Patients’ initials were used instead of their names and patients’ identifiers and corresponding data were kept confidential and no patient name appeared anywhere from the study conduction up to publication. For cases of confirmed AKI, collaboration with treating team was done for early and appropriate management.

CHAP IV: DATA PRESENTATION AND ANALYSIS

IV.1. Patients enrollment

<table>
<thead>
<tr>
<th>260 patients were Eligible</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14 patients didn’t (or can’t) provide consent</td>
</tr>
<tr>
<td></td>
<td>8 patients received contrast before getting baseline creatinine.</td>
</tr>
<tr>
<td></td>
<td>5 patients deteriorate to require inotropes before controlling creatinine.</td>
</tr>
<tr>
<td></td>
<td>10 patients underwent surgery before controlling creatinine (4 of them had high output colostomy).</td>
</tr>
<tr>
<td></td>
<td>10 patients were discharged before controlling creatinine.</td>
</tr>
<tr>
<td></td>
<td>4 patients had incurable disease in terminal phase.</td>
</tr>
<tr>
<td></td>
<td>5 patients received contrast for the second time before 48 hours.</td>
</tr>
</tbody>
</table>

Total of 204 participants were enrolled in the study.
IV.2. Descriptive phase

Table 1: Clinical characteristics

<table>
<thead>
<tr>
<th>Descriptive phase</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>115</td>
<td>56.4</td>
</tr>
<tr>
<td>Female</td>
<td>89</td>
<td>43.6</td>
</tr>
<tr>
<td><strong>Age (Mean ± SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>48.4 ± 18 years</td>
<td></td>
</tr>
<tr>
<td><strong>Department</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>158</td>
<td>77.5</td>
</tr>
<tr>
<td>Surgery</td>
<td>24</td>
<td>11.8</td>
</tr>
<tr>
<td>G.O.</td>
<td>9</td>
<td>4.4</td>
</tr>
<tr>
<td>Emergency</td>
<td>8</td>
<td>3.9</td>
</tr>
<tr>
<td>ENT</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Groups of presumed diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td>78</td>
<td>38.2</td>
</tr>
<tr>
<td>Malignancy</td>
<td>70</td>
<td>34.3</td>
</tr>
<tr>
<td>Cardio-vascular and thrombo-embolic</td>
<td>40</td>
<td>19.6</td>
</tr>
<tr>
<td>Metabolic</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Others</td>
<td>14</td>
<td>6.9</td>
</tr>
<tr>
<td><strong>Co-morbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>26</td>
<td>12.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13</td>
<td>6.4</td>
</tr>
<tr>
<td>Heart failure</td>
<td>12</td>
<td>5.9</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>23</td>
<td>11.2</td>
</tr>
<tr>
<td>Other co-morbidities</td>
<td>25</td>
<td>12.2</td>
</tr>
</tbody>
</table>

Among 204 patients who participated in this study, Males and females were respectively 56.4% and 43.6%. They were coming in 5 different departments with 77.5% from internal medicine, 11.8% from surgery, 4.4 from gynaecology and obstetrics, 3.9% from emergency and 2.5 from ENT. Infections were on top of working diagnosis with 38.2%, followed by malignancy 34.3%, cardio-vascular and thrombo-emboli 19.6% and the remaining with 7.9%.
Table 2: Descriptive analysis of presumed risk factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of contrast</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iopamiron-370</td>
<td>50</td>
<td>24.5</td>
</tr>
<tr>
<td>Omnipaque-350</td>
<td>154</td>
<td>75.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20</td>
<td>9.8</td>
</tr>
<tr>
<td>Concomitant use of nephrotoxic drugs</td>
<td>17</td>
<td>8.3</td>
</tr>
<tr>
<td><strong>Type of nephrotoxic drug</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td>8</td>
<td>3.9</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>IV fluid received in 12 hours before contrast</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥500ml</td>
<td>154</td>
<td>75.5</td>
</tr>
<tr>
<td>Nothing</td>
<td>50</td>
<td>24.5</td>
</tr>
<tr>
<td><strong>IV fluid received in 24 hours post contrast</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>44</td>
<td>21.6</td>
</tr>
<tr>
<td>0-1 litre</td>
<td>29</td>
<td>14.2</td>
</tr>
<tr>
<td>≥2.5 litres</td>
<td>131</td>
<td>64.2</td>
</tr>
</tbody>
</table>

The most common used contrast was Iohexol-350 with 75.5% and followed by Iopamidol -370 24.5%. Among patients who participated in this study 17 (8.3%) were on nephrotoxic drugs and no systematic interruption noted as recommended in some guidelines. 64.2% received fluid in 24 hours fulfilling recommendation of European Renal Best Practice, (ERBP) at least 100 ml per hour in 24 hours and 21.6% didn’t receive any fluid. However, 14.2% received quantity between 0-1 litre.
IV. 3. Incidence of CI-AKI

Table 3: Incidence using KDIGO definition of CI-AKI

<table>
<thead>
<tr>
<th>Measures</th>
<th>AKI (25% Rise of baseline creatinine)</th>
<th>D (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CI-AKI (+), n=36</td>
<td>CI-AKI(-), n=168</td>
<td></td>
</tr>
<tr>
<td>Baseline creatinine</td>
<td>59.5 ± 22.4</td>
<td>64.5 ± 26.8</td>
<td>-5 (-4.4-14.4)</td>
</tr>
<tr>
<td>Control creatinine</td>
<td>99.3 ± 62.6</td>
<td>60.8 ± 26.1</td>
<td>38.5 (25.7-51.2)</td>
</tr>
<tr>
<td>Incidence of AKI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>36/204 = 17.6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Severity of CI-AKI

<table>
<thead>
<tr>
<th>KIDGO CLINICAL STAGE</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not classified (1.25-1.49 times)</td>
<td>16</td>
<td>7.8%</td>
</tr>
<tr>
<td>Stage 1 (1.5-1.9 times)</td>
<td>14</td>
<td>6.8%</td>
</tr>
<tr>
<td>Stage2 (2.0-3.0 times)</td>
<td>4</td>
<td>≈2%</td>
</tr>
<tr>
<td>Stage 3 (&gt;3.0 times)</td>
<td>2</td>
<td>≈1%</td>
</tr>
</tbody>
</table>

Considering relative creatinine increment of 25% as threshold for definition of CI-AKI, the incidence was 17.6%. However 7.8% of them had mild increment (between 25% - 50%) which doesn’t fulfil the criteria for definition of AKI in general (creatinine increment of at least 50%). Among the remaining 9.8% of involved patients, 6.8 had AKI stage I, 2% AKI Stage II and 1% AKI stage 3.
Table 5: Bivariate analysis of presumptive risk factors for CI-AKI between CI-AKI (+) and CI-AKI (-)

<table>
<thead>
<tr>
<th>Variables</th>
<th>CI-AKI (+)</th>
<th>CI-AKI (-)</th>
<th>RR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 years</td>
<td>4 (10.3%)</td>
<td>35 (89.7%)</td>
<td>1.9 (0.7-5.0)</td>
<td>0.186</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (20.9%)</td>
<td>91 (79.1%)</td>
<td>1.6 (0.8-3.0)</td>
<td>0.17</td>
</tr>
<tr>
<td>Female</td>
<td>12 (13.5%)</td>
<td>77 (86.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (30.0%)</td>
<td>14 (70.0%)</td>
<td>2.2 (0.78-6.18)</td>
<td>0.134</td>
</tr>
<tr>
<td>Fever</td>
<td>1 (4.8%)</td>
<td>20 (95.2%)</td>
<td>0.24 (0.03-1.7)</td>
<td>0.102</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (15.4%)</td>
<td>11 (84.6%)</td>
<td>0.86 (0.23-3.2)</td>
<td>0.825</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (19.2%)</td>
<td>21 (80.8%)</td>
<td>1.1 (0.5-2.6)</td>
<td>0.821</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4 (33.3%)</td>
<td>8 (66.7%)</td>
<td>2.0 (0.8-4.9)</td>
<td>0.143</td>
</tr>
<tr>
<td>Use of nephrotoxic drugs</td>
<td>3 (15.8%)</td>
<td>16 (84.2%)</td>
<td>0.88 (0.3-2.6)</td>
<td>0.824</td>
</tr>
<tr>
<td>No pre-contrast IV fluids</td>
<td>11 (22.0%)</td>
<td>39 (78.0%)</td>
<td>1.35 (0.72-2.5)</td>
<td>0.353</td>
</tr>
<tr>
<td>Post-contrast IV fluids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>19 (43.2%)</td>
<td>25 (56.8%)</td>
<td>8.19 (3.4-19.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0-1 liter</td>
<td>6 (20.7%)</td>
<td>23 (79.3%)</td>
<td>2.54 (0.93-8.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>≥2.5 liters</td>
<td>11 (8.4%)</td>
<td>120 (91.6%)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Name of contrast</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iopamiron-370</td>
<td>5 (10.0%)</td>
<td>45 (90.0%)</td>
<td>0.49 (0.2-1.2)</td>
<td>0.103</td>
</tr>
<tr>
<td>Omnipaque-350</td>
<td>31 (20.1%)</td>
<td>123 (79.9%)</td>
<td>D (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Quantity of contrast (M ± SD) in ml</td>
<td>62.9 ± 13.8</td>
<td>59.8 ± 8.9</td>
<td>3.1 (0.4-6.4)</td>
<td>0.091</td>
</tr>
</tbody>
</table>

The presumed risk factors were diabetes, heart failure, quantity of contrast received, and concomitant use of nephrotoxic drugs, quantity of pre and post contrast IV fluids, age above 65 years and quantity of contrast received.

Among all the presumed risk factors, Not receiving post contrast IV fluid was the only to be associated with CI-AKI with RR=8.19 (3.4-19.5), p value < 0.001, reference range being 2.5 litres in first 24 hours (≈100ml/h).
However, among the presumed risk factors, not receiving pre-contrast IV fluid, Age>65, Heart failure had an RR >1 but with p value > 0.05. This may be explained by sample size and number of these particular patients with those risks involved in our study.

There was no difference between both types of contrast in matter of causing CI-AKI, with an RR=0.49(0.2-1.2) and a p=0.103.

V. RESULTS DISCUSSION

This study has found the incidence of CI-AKI to be 17.6% using definition provided by KDIGO 2012 (high comparing with incidence found in other studies). However, as it has been criticized in recent articles, including European Renal Best Practice, this problem may be overlooked due to low threshold used in case CI-AKI Vs AKI in general (25% Vs 50%), and no patho-physiological or epidemiological reasons to explain why it should be different. Consequently, by using AKI general criteria, that incidence fall to 9.8%, with 6.9% in stage I (1.5-1.9 times the baseline creatinine), 2% in stage II (2.0-3.0), and 0.9% in stage III (> 3times).

The most determinant risk factor was quantity of supplemental IV fluid received after IV contrast exposure and there was association between CI-AKI and not receiving supplemental IV fluid, with RR=8.19 (3.4-19.5) and p value <0.001. Due to lack of gold standard diagnostic tool to differentiate CI-AKI and other causes of AKI in general, it’s difficult to conclude if the kidney injury was due the contrast received alone or poor fluid intake which subsequently leads to reduced circulating volume and pre-renal AKI particularly in hospitalised and sick patients.

This study didn’t find association between CI-AKI and diabetes, as it was reported in some studies, RR=0.86 (0.23-3.2), with p value = 0.825. The low number of patient with diabetes (13 patients) may be one of the reasons. It didn’t also find an association between CI-AKI and concomitant use of presumed nephrotoxic drugs (NSAID, Amphotericin B and Aminoglycosides) despite that the treatment was not interrupted for 24 hours as recommended by some guidelines RR=0.88 (0.3-2.6) with p value=0.824. For Amphotericin B, all patients were following a strict rehydration plan as recommended by local guidelines.
Despite a small difference of contrast volumes between two groups 3.1 (0.4-6.4) ml and patients who develop CI-AKI being the one to receive high volume, there was no statistical significance associated to that difference with p value = 0.091 (using T-test).

Finally, the volume of contrast received in both groups in milliliters (62.9±13.8 for CI-AKI (+) Vs 59.8 ± 8.9 for CI-AKI (-)) was low in comparison to the volume given in patient with coronary angiography (mostly > 100ml) and didn’t have significant impact on incidence of CI-AKI p=0.091.

VI. CONCLUSION AND RECOMMENDATION

VI. A. Conclusion

Despite areas of uncertainty surrounding the definition and diagnosis of CI-AKI, which actually didn’t escape available literature, the incidence of CI-AKI is high in our population (9.8-17.6% depending on threshold chosen Vs 5%). This may be due to in part due to lack of concise rehydration protocol in patients exposed to contrast. However, noticed cases of CI-AKI, are not severe to require dialysis immediately.

VII. B. Recommendation

Establish clinical guidelines governing rehydration plan following IV contrasts use and available international guidelines may serve as prototype.

Monitor creatinine on regular bases, at least 48 hours after receiving contrast.

Document contrasts received on medication chat to facilitate for CI-AKI risk stratification.

There is a need of conducting a randomised trial to confirm these findings and do a study with aim of long term outcome (who developed CKD, who recovered completely).
REFERENCES


[26] Rich MW et al “Incidence , Risk Factors , and Clinical Course of Acute Renal Insufficiency After Cardiac Catheterization in Patients 70 Years of Age or Older Prospective Study,” Arch Intern Med 1990 June; 150(6):1257-42


ANNEXES I: INFORMED CONSENT

Dear Participant,

My name is Dr BABANE Jean Felix, I am a student in University of Rwanda (UR), pursuing Masters of Medicine (MMed) in Internal medicine. I am principle investigator in the study entitled:

“Incidence and risk factors associated with acute kidney injury induced by radiological contrasts in patients admitted at KUTH”

Acute kidney injury induced by radiological contrasts is a type of acute kidney injury caused by exposure of intravenous contrast product. In some settings its incidence is 5% in patients with normal renal functions prior to exposure to contrasts. 57% of patients who had this condition recover within 5 days. 19% can still have partial recovery and 24% can still have persistent dysfunction at the time of discharge. As the use of CT-scan with contrast is becoming popular we need to know the magnitude of this condition in our settings.

We will be testing creatinine in blood. To get blood, the procedure can be painful but we will try not to harm you.

Participation in this study is voluntary and you can choose not to answer any individual question or all of the questions and you have the right to withdraw from the study at anytime.

The decision of not participating in this study or withdrawing from it for any reason will not affect your daily medical care. However, we hope that you will participate in this study.

Whatever information you provide will be kept strictly confidential and no reference to your name or other family members will be made anywhere. We do not anticipate that there would be any harmful event that would occur with this study, for any query you can refer to the Chairperson of the CMHS IRB (0788 490 522) or the Deputy Chairperson (0783 340 040) or research committee (researchcenter@ac.ur.rw Tel +250 788563311).

Thank you.
I, ......................................................, understand the explanation received from .............................................................. about the risks and benefits of this research on “Incidence and risk factors associated with acute kidney injury induced by radiological contrasts in patients admitted at KUTH”

I accept willingly to participate in this research.

Participant’s signature                                         Researcher’s signature

Date: ......../....../.........                                              ..............................................
Kwemera kujya mu bushakashatsi
Numero.............................................

Muvandimwe wemeye gusubiza,

Nitwa Dogiteri BABANE JEAN FELIX, ndi umunyeshuri muri Kaminuza y’ u Rwanda mu ishami ry’ ubuvuzi , agashami karyo k’ ubuvuzi bw’ indwara zo mu mubiri, mu cyiciro cya gatatu. Nd’ gukora ubushakashatsi ku kugabanuka kw’ imikorere y’ impyiko biturutse ku miti ite rw忙 urwayi ugiye kunyura mu cyuma kugira ngo amafoto agaragare neza.

Ukugabanuka kw’ imikorere y’ impyiko biturutse ku miti iterwa urwayi ugiye guca mu cyuma ni ikibazo gishobora kubaho ku kigero cya 5% mu barwayi basanzwe nta kibazo cy’ impyiko basite. Gishobora kwikizaugera ku kigero cya 57%, ku bagera kuri 19% by’ abakigize kiba kitarakira neza mu minsi itanu, naho 24% bashobora gusezererwa kitarakira neza.

Tuzajya dufata ibipimo bya creatinine mu maraso (duheraho tubona imikorere y’impyiko bigereranywe n’ ibyafashwe mbere yo guca mu cyuma.


Gusa ni ubufasha ku muryango mugari, n’ abandi barwayi batugana kugira ngo tumenye uburemere bw’ iki kibazo mu bitaro byacu.

Ubu bushakashatsi bwateguwe ku buryo udahutazwa, kandi nta ngaruka mbi buzakugiraho. Gusa mu gufata maraso ushobora kubabara bidakabije.

Ama kuru n’ibisubizo by’ ibipimo byawe bizagirwa ibanga ubu ndetse na nyuma y’ ubu bushakashatsi, kandi uzabimenyeshwa igihe cyose ubikeneye.

Mu gihe utanyuzwe wakwiyambaza ikigo gishinzwe ubushakashatsi ubinyujije kuri aba bakurikira:
Chairperson of the CMHS IRB (0788 490 522), Deputy Chairperson (0783 340 040), research committee (researchcenter@ac.ur.rw) Tel +250 788563311).

Tubaye tubashimiye.
Njyewe………………………………………, maze gusobanurirwa na …………………………….
Ingaruka n’inyungu kuri ubu bushakashatsi, nemeye nta gahato kubujyamo.
Umukono w’uwitabiriye ..................................................................................................
Umukono w’uwamusobanuriye .....................................................................................

………………………………                                                  …………………………………..

Itariki ........../........../........
ANNEXE II: QUESTIONNAIRE

I. IDENTIFICATION
1. Patient initials:
2. Department:
3. Ward:
4. Bed:
5. Hospital identification number:
6. Age:
7. Sex:
8. Weight (If not taken estimate)
9. Study ID number

II. PATIENT BASELINE BEFORE CONTRAST
10. Suspected diagnosis:

11. Known diabetes/newly diagnosed  yes □  no □
12. Hypertension  yes □  no □
13. Chronic kidney disease  yes □  no □
   (If yes eGFR or Baseline creatinine=……………….)
14. Heart failure  Yes □  no □
   (If known recent Ejection Fraction…………………………)
15. Another unmentioned illness:  ………………………………………………………………………
16. Initial creatinine  …………………………………………………………………………………
17. Current medications:  ……………………………………………………………………………
18. Any medication(s) stopped before contrast  …………………………………………………

II. CONTRAST RELATED INFORMATION
19. The time at which the patient received contrast  …………………………………………
20. Name of contrast

21. Osmolarity of contrast:  hyperosmolar □  Isosmolar □  Hyposmolar □

22. Is the contrast anionic?  Yes □  not □

23. Quantity of contrast received in milliliters

24. Quantity of pre-contrast IV or Oral fluid received:  None □  <500ml □  ≥500ml

III. PATIENT CLINICAL INFORMATION AFTER CONTRAST

25. History of vomiting after sampling initial creatinine  yes □  no □
   (If yes how many times)

26. History Diarrhea after sampling initial creatinine  Yes □  no □
   (If yes how many times)

27. Bleeding after sampling initial creatinine  Yes □  no □
   (If yes how much)

28. Fever/sweating after taking creatinine   Yes □  no □
   (If yes what was the highest temperature recorded)

29. Any recent use of NSADS/Aminoglycoside/ Amphotericine  Yes □  No □
   (If yes for how long)

30. Part of the body to be imaged

31. Control creatinine taken between 48-72 hours

32. Post contrast IV or Oral fluid received in 24 hours following IV contrast:
   None □  <2500ml □  >2500ml □

THANKS
ANNEXE III: ETHICAL APPROVALS

Dr BABANE Jean Felix
School of Medicine and Pharmacy, CMHS, UR

Approval Notice: No 006 /CMHS IRB/2018

Your Project Title “Incidence And Risk Factors Associated With Acute Kidney Injury Induced By Radiological Contrasts In Patients Admitted At KUTH” has been evaluated by CMHS Institutional Review Board.

<table>
<thead>
<tr>
<th>Name of Members</th>
<th>Institute</th>
<th>Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof. Kato J. Njunwa</td>
<td>UR-CMHS</td>
<td>Yes</td>
</tr>
<tr>
<td>Prof. Jean Bosco Gahutu</td>
<td>UR-CMHS</td>
<td>Yes</td>
</tr>
<tr>
<td>Dr Brenda Asiimwe-Kateera</td>
<td>UR-CMHS</td>
<td>Yes</td>
</tr>
<tr>
<td>Prof. Ntaganira Joseph</td>
<td>UR-CMHS</td>
<td>Yes</td>
</tr>
<tr>
<td>Dr Tumusiime K. David</td>
<td>UR-CMHS</td>
<td>Yes</td>
</tr>
<tr>
<td>Dr Kayonga N. Egide</td>
<td>UR-CMHS</td>
<td>Yes</td>
</tr>
<tr>
<td>Mr Kanyoni Maurice</td>
<td>UR-CMHS</td>
<td>Yes</td>
</tr>
<tr>
<td>Prof Munyanshongore Cyprien</td>
<td>UR-CMHS</td>
<td>Yes</td>
</tr>
<tr>
<td>Mrs Ruzindana Landrine</td>
<td>Kicukiro district</td>
<td>Yes</td>
</tr>
<tr>
<td>Dr Gishoma Darius</td>
<td>UR-CMHS</td>
<td>Yes</td>
</tr>
<tr>
<td>Dr Donatilla Mukamaa</td>
<td>UR-CMHS</td>
<td>Yes</td>
</tr>
<tr>
<td>Prof. Kyamanywa Patrick</td>
<td>UR-CMHS</td>
<td>Yes</td>
</tr>
<tr>
<td>Prof. Condo Umatesi Jeannine</td>
<td>UR-CMHS</td>
<td>Yes</td>
</tr>
<tr>
<td>Dr Nyirazinyozi Laetitia</td>
<td>UR-CMHS</td>
<td>Yes</td>
</tr>
<tr>
<td>Dr Nkeramuligo Emmanuel</td>
<td>UR-CMHS</td>
<td>Yes</td>
</tr>
<tr>
<td>Sr Maliboi Marie Josee</td>
<td>CHUK</td>
<td>Yes</td>
</tr>
<tr>
<td>Dr Mudenge Charles</td>
<td>Centre Psycho-Social</td>
<td>Yes</td>
</tr>
</tbody>
</table>

After reviewing your protocol during the IRB meeting of where quorum was met and revisions made on the advice of the CMHS IRB submitted on 8th January 2018, Approval has been granted to your study.

Please note that approval of the protocol and consent form is valid for 12 months.
You are responsible for fulfilling the following requirements:

1. Changes, amendments, and addenda to the protocol or consent form must be submitted to the committee for review and approval, prior to activation of the changes.
2. Only approved consent forms are to be used in the enrolment of participants.
3. All consent forms signed by subjects should be retained on file. The IRB may conduct audits of all study records, and consent documentation may be part of such audits.
4. A continuing review application must be submitted to the IRB in a timely fashion and before expiry of this approval.
5. Failure to submit a continuing review application will result in termination of the study.
6. Notify the IRB committee once the study is finished.

Sincerely,

Date of Approval: The 8\textsuperscript{th} January 2018
Expiration date: The 8\textsuperscript{th} January 2019

Professor Kato J. NJUNWA
Chairperson Institutional Review Board,
College of Medicine and Health Sciences, UR

Ce:
- Principal College of Medicine and Health Sciences, UR
- University Director of Research and Postgraduate Studies, UR
Review Approval Notice

Dear Babane Jean Felix,

Your research project: “Incidence and risk factors associated with acute kidney injury induced by Radiological contrasts in patients admitted at CHUK.”

During the meeting of the Ethics Committee of University Teaching Hospital of Kigali (CHUK) that was held on 09/02/2018 to evaluate your protocol of the above mentioned research project, we are pleased to inform you that the Ethics Committee/CHUK has approved your protocol.

You are required to present the results of your study to CHUK Ethics Committee before publication.

PS: Please note that the present approval is valid for 12 months.

Yours sincerely,

Dr. Rusingiza Emmanuel
The President, Ethics Committee,
University Teaching Hospital of Kigali

<<University teaching hospital of Kigali Ethics committee operates according to standard operating procedures (Sops) which are updated on an annual basis and in compliance with GCP and Ethics guidelines and regulations>>.