EFFECT ON KIDNEY FUNCTION OF INTRAVENOUS CONTRAST-ENHANCED CT USING ISO-OSMOLAR AND LOW-OSMOLAR IODINATED CONTRAST MEDIUM

BY

REGISTRATION NO. BS0119008

Dissertation

Submitted to

KLE Academy of Higher Education and Research, Belagavi, Karnataka

In partial fulfillment of the requirements for the degree of

M.D.
IN
RADIO-DIAGNOSIS

JAWAHARLAL NEHRU MEDICAL COLLEGE, BELAGAVI -590010, KARNATAKA

APRIL 2022

KLE ACADEMY OF HIGHER EDUCATION AND RESEARCH, BELAGAVI, KARNATAKA

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LIST OF ABBREVIATIONS

GLOSSARY	ABBREVIATIONS
ACEI	Angiotensin-converting enzyme inhibitors
AEs	Adverse events
AKI	Acute kidney injury
ARB	Angiotensin receptor blockers
CA-AKI	Chronic, acute kidney injury
CECT	Contrast-enhanced CT
CHF	Congestive heart failure
CI	Confidence interval
CI-AKI	Contrast-induced acute kidney injury
CIN	Contrast induced nephropathy
CKD	Chronic kidney disease
CM	Contrast media
	Computed tomography
CysC	Cystatin-C
DM	Diabetes mellitus
ESUR	European society of urogenital radiology
GFR	Glomerular filtration rate
HOCM	High-osmolar contrast media
ICA	Iodinated contrast agents
ICM	Ischemic cardiomyopathy
IOCM	Iso-osmolar contrast media
IQR	Interquartile range
IV	Intravenous
IVC	Inferior vena cava
KIDGO	Kidney disease: improving global outcomes guidelines
KIM-1	Kidney injury molecule-1
LCN2	Lipocalin-2
LOCM	Low-osmolar contrast media

mTAL	Medullary thick ascending limb
NADPH	Nicotinamide adenine dinucleotide phosphate
NGAL	Neutrophil gelatinase-associated lipocalin
NSAID	Nonsteroidal anti-inflammatory drugs
OD	Odds ratio
PC-AKI	Postcontrast acute kidney injury
PCI	Percutaneous coronary interventions
ROS	Reactive oxygen species
ROS	Reactive oxygen species
SCr	Serum creatinine
uNGAL	Urinary NGAL

ABSTRACT

Introduction: Iodinated contrast media (CM) are well tolerated, and their use is on the rise. The most life-threatening side effect of CM is acute renal damage. This study aimed to find the incidence of CI-AKI using iso-osmolar (IOCM) and low-osmolar contrast media (LOCM) in the general population.

Material and methods: This was hospital-based observational research with participants above the age of 18. An early increase in serum creatinine (SCr) concentration of at least 0.5 mg/dl or a 25% increase in creatinine from baseline were categorized as CI-AKI. The major outcome variable was serum creatinine levels. The key explanatory variable was the IV contrast agent. For quantitative variables, mean and standard deviation were used, whereas, for categorical variables, frequency and proportion were used.

Results: The final analysis involved 40 subjects. The group iodixanol (iso-osmolar) involved 37.50%, and iohexol (LOCM) involved 62.50%. The comorbidities recorded were diabetes in 17.50%, diabetes and hypertension in 15%, and hypertension in 12.50%. The mean baseline serum creatinine among the 2 groups showed insignificant difference (p-value 0.527) (iodixanol group -1.07 ± 0.33 (mg/dl) vs 1.01 ± 0.25 in Iohexol group). There was an insignificant difference in the mean serum creatinine between the 2 groups (1.09 ± 0.33 (mg/dl) in the iodixanol group VS 1 ± 0.25 in the Iohexol group, p-value 0.302). The connotation between comorbidities and IV contrast agent was insignificant (P value 0.412); the iodixanol group found a greater proportion (53.33%) compared to the Iohexol group (40%). In the overall study population majority of them (92.50%) had ≤ 1.4 creatine levels, and 7.50% had >1.4 creatine levels. The overall incidence of CIN was 7.50%. In 25 subjects in Iohexol IV contrast agent,12% showed positive for CIN.

Conclusion: The results of our study show that iodixanol to have no risk of CIN but Iohexol, found a 12% incidence of CIN.

Key words: iso-osmolar contrast media, low osmolar iodinated contrast media, contrast-induced nephropathy, serum creatinine.

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INTRODUCTION

The use of contrast medium (CM) in diagnostic and interventional procedures is becoming more common. As a result, the frequency of iatrogenic renal function impairment due to CM exposure, also known as contrast-induced nephropathy (CIN), is increasing. Radiographic CM is the 3rd most common cause of renal failure after decreased renal perfusion and the use of nephrotoxic medicines, accounting for 11% of instances of hospital-acquired renal inefficiency. Coronary angiography and percutaneous coronary interventions (PCI) have the greatest risks of CIN among all procedures that use CM for diagnostic or therapeutic purposes.[1] The following three elements are required for the diagnosis of CIN: 1) a total or comparative rise in serum creatinine related to reference point values; 2) a sequential association among the increase in serum creatinine and revelation to a contrast agent, and 3) the elimination of other possible causes of renal impairment (e.g., "cholesterol embolism"). The most frequent definition of CIN nowadays is a 25 percent or greater rise in serum creatinine from the reference point, or a complete rise of 0.5 mg/dl or higher, 48–72 hours after exposure to CM.

The first 24 h post-exposure appear to be crucial in the development of CIN. A study of the trajectory of serum creatinine elevation in the randomized Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation trial indicated that in 80% of CIN cases, serum creatinine started to rise within the first 24 h post-CM exposure, and nearly all patients who progressed to serious renal failure (one needing either nephrology session or dialysis) had an increase in serum creatinine within this time frame.[2]

The majority of iodinated contrast media Adverse Events (AEs), such as nausea, vomiting, urticaria, and itching, are minor. Severe AEs, such as hypotensive shock, respiratory arrest, cardiac arrest, and convulsions, can occur. With the switch from High-Osmolar Contrast Media (HOCM) to Low-Osmolar Contrast Media (LOCM), the incidence of these AEs has fallen significantly; the incidence of AEs has been recorded as 5% to 15% for HOCM and 0.2 percent to 0.7 percent for LOCM.[3] Despite the fact that the overall rate of AEs has dropped, severe AEs continue to occur.

Patients with normal baseline renal function have a 2% chance of developing contrast-induced nephropathy (CIN), while those with a reference point creatinine >2 mg/dL had a 20% to 30% chance.[2] The most frequent definition of CIN is a 0.5 mg/dL absolute increase in serum creatinine (SCr) or a 25% increase from baseline, measured within 48 hours of the surgery.[4]

Clinical history, physical examination, and basic laboratory testing can reveal the majority of CIN risk factors. The most important pre-procedural risk factor for CIN is pre-existing chronic renal disease. Because a glomerular filtration rate of less than 60 mL/min per 1.73 m^2 is a major risk factor for CIN[5], a baseline estimated glomerular filtration rate should be obtained before any procedure involving contrast.

Diabetes mellitus, volume depletion, nephrotoxic medication usage, hypotension, age >75 years, advanced heart failure, left ventricular systolic function 45 percent, and anemia is all independent predictors of CIN.[6,7] To forecast the risk of CIN, various scoring schemes have been developed, but none has been thoroughly verified. When at-risk patients are identified, a variety of interventions can be offered to help them avoid CIN.

NEED FOR THE STUDY:

Contrast-induced acute kidney damage (CI-AKI) is a serious complication of using an iodine contrast medium for diagnostic or interventional procedures.[8] It is linked to higher rates of morbidity, death, increases in the duration of stay, and hospitalization expenses. [9] It's still up for debate if distinct contrast media types with different osmolarities are linked to a lower incidence of CI-AKI.[1] Despite significant advances in improving the quality of contrast media, doctors continue to be concerned about acute kidney impairment following intravascular contrast injection.

There's has been disagreeing results as to IOCM related to least risk of CI-AKI compared to LOCM.[1,10] The ESUR ("European Society of Urogenita Radiology"), and KIDGO ("Kidney Disease: Improving Global Outcomes guidelines") has suggested both LOCM and IOCM in subjects with greater risk of CI-AKI.[11,12] Diabetic (DM) disease is one of the most serious public health issues of the 21st century. In individuals with chronic kidney disease (CKD), especially when DM co-occurs, the risk of CI-AKI is dramatically increased.[13] The nephrotoxicity has been assessed across LOCM and IOCM, especially in subjects with diabetes, by numerous studies.[14,15] However, whether there are any substantial changes in renal safety between IOCM and LOCM is still unknown. As a result, we conducted a study to see how IV contrast-enhanced CT with iso-osmolar and low-osmolar iodinated contrast medium affected kidney function.

AIM AND OBJECTIVES

- To determine the incidence of Contrast-Induced Nephropathy (CIN), which is defined as a rise in serum creatinine of more than 25% over baseline or more than 0.5 mg/dL above baseline due to intravenous contrast media delivery (Iso-osmolar contrast media and low-osmolar contrast media).

REVIEW OF LITERATURE

Contrast-Induced Nephropathy

Contrast-induced nephropathy (CIN) is becoming a more common cause of iatrogenic acute kidney injury (AKI), which is linked to higher healthcare resource utilization by lengthening hospital stays, growing long and short-term mortality and hastening the advance of underlying (chronic kidney disease) CKD.[16] It's a common reversible and transitory origin of hospital-attained renal failure, with rates ranging from 0% to 24% depending on the patient's risk factors, the quantity and kind of agent given, and the sorts of radiological tests conducted.[17]

CIN is defined as a 25 percent increase in serum creatinine from a reference point or a 0.5 mg/dL increase in complete serum creatinine value within 48–72 hours of contrast material delivery (measured as a 25 percent rise in serum creatinine from reference point or a 0.5 mg/dL increase in total serum creatinine value). CIN may be avoidable; high-risk patients may usually be identified ahead of time, and most contrast procedures are performed on a non-emergent basis, providing plenty of time to take measures.[18]

Recent research has shown that using low or iso-osmolar medicines at the lowest effective dose and administering a pre-procedure IV isotonic crystalloid solution reduces the incidence of CIN in high-risk subjects. Some of the postulated pathophysiologic causes of CIN include intrarenal vasoconstriction with the generation of reactive oxygen species, medullary hypoxia, and direct renal tubular noxiousness.[19]

Indications for using contrast in CT,

Contrast media definition:

CM is a chemical molecule that improves the image quality of various body sections, helps to identify diseases from vigorous tissues, and helps to define vascular structures. Although CM can be given orally, intravenously, or through other luminal organs, the absorption and nephrotoxic effects of CM given other than intravenously may be minimal.[20]

Anatomy, Physiology of Kidney,

Surgical anatomy of kidney:

Because of the placement of the liver, the right kidney is roughly 1–2 cm lower than the left kidney. The diaphragm covers the upper part of the kidneys posteriorly, where it also has a strong association with the pleura, which continues to the 12th rib level. The liver and the right colonic flexure border the right kidney from the front. The right renal hilum is overlain by the descending section of the duodenum, which includes the head of the pancreas. The left colonic flexure forms an anterior boundary for the left kidney. The pancreas and the splenic arteries are anatomically near to the left renal hilum. The adrenal gland abuts the upper pole of the kidneys, which may cover the kidney or support the renal hilum, particularly on the left. The psoas muscle supports the kidney's rear side.[21] As a result, it's critical to understand that the higher pole is positioned medially and in a posterior plane in relation to the lower pole. CT slices are normally recorded at 90 degrees to the body, but due to the above-mentioned angulation of the kidney, this is not always the case. As a result, an upper-pole tumour may look on CT scans as a mid-renal tumour on

occasion. As a result, proper cross-sectional CT slice modification is essential for accurate imaging, taking into consideration the angulation of the kidney.[22]

The adrenal gland, perinephric fat, and kidney and are all enclosed by Gerota's fascia. Laterally, Superiorly and medially but not inferiorly, its layers are united. A single renal vein and artery and the renal pelvis are the traditional features of the hilum, which run from anterior to posterior. Because of the psoas muscle, the hilar area is turned somewhat anteriorly.[23]

Arterial system:

In around 75% of instances, a single renal artery originates bilaterally from the lateral part of the abdominal aorta, immediately caudal to the origin of the superior mesenteric artery. Duplication of renal arteries is more common on the right side, with the exception of auxiliary renal arteries, which occur in about 25% of individuals (Fig. 1). The calibre of duplicate arteries is frequently the same. These auxiliary arteries, which often subtend the poles, are usually formed by the aorta.[24]

Auxiliary arteries are any arteries that branch off from the main artery and reach the kidney. If the artery does not reach the kidney at the hilum, it is called aberrant (e.g., “enters the parenchyma at a pole”). As a result, there's a chance that an auxiliary artery will be abnormal. The auxiliary arteries of the upper pole are characteristically reduced in diameter than those of the lower pole. The right renal artery runs behind the inferior vena cava.

The renal artery has two divisions in respect to the renal pelvis: an anterior division that carries 75% of the blood supply and a posterior division that carries 25% of the blood supply. The majority of these divisions occur outside of the renal hilum.[24]

It's possible to tell the difference between extra- and intraparenchymal artery sections (Fig. 2). The avascular plane (Brödel's line) runs along the lateral edge of the kidney, amid the arterial divisions, and is placed along the axis of the posterior. This avascular plane is slightly posterior to the mid-lateral region of the kidney rather than in the exact mid-lateral portion. For avascular access for an endophytic malignancies, atrophic nephrolithotomy and Brödel's line can be employed.[22]

Figure 1: Two right renal arteries are shown on a computed tomography image.[22]

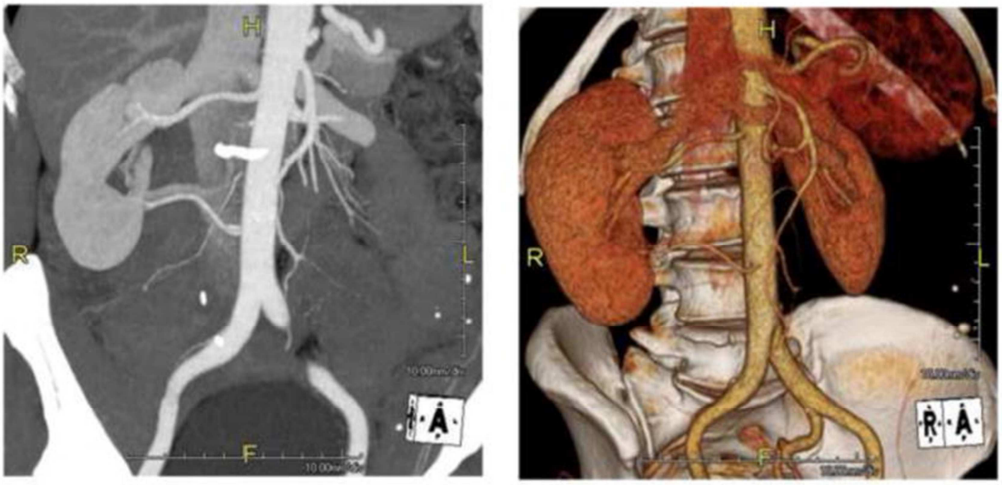
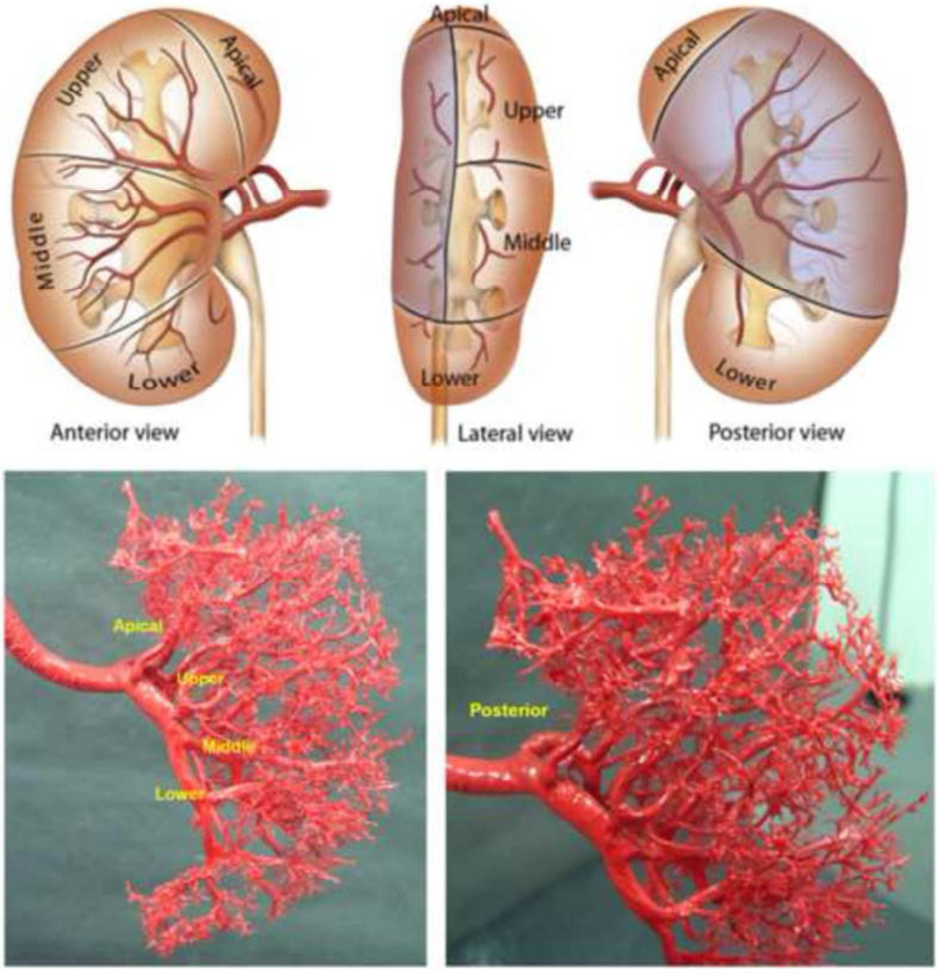


Figure 2: "According to Graves, segmental renal arteries are classified anatomically. In addition to the traditional variety, a considerable number of patients have anatomic variants".[22]

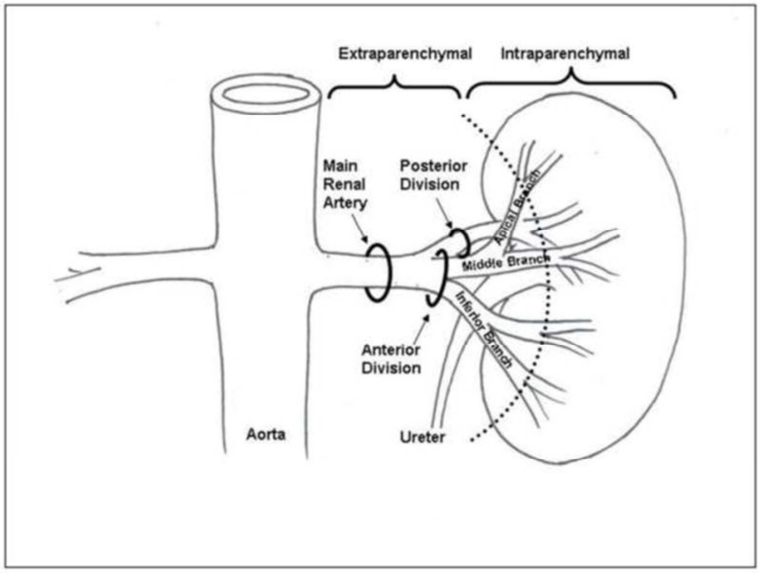


Venous system:

The "peritubular capillary venous plexus" empties into the arcuate veins via the venae rectae. Within the kidney, there are anastomotic longitudinal venous arcades. Because the primary branches of these veins are not terminal, they can be surgically ligated without causing a venous blockage. A retro pelvic vein, which drains sections of the kidney's posterior part, is present in two-thirds of cases.[21]

The right renal vein discharges straight into the IVC. In most cases, there are no tributaries; however, the right gonadal vein may occasionally leak into the right renal vein. Duplication is detected in 15–20 percent of cases. In contrast to the arterial system, isolated auxiliary polar veins are uncommon. The left renal vein enters the IVC anterior to the aorta and is two to three times longer than the right renal vein. It is extremely difficult to duplicate. In such cases, a retro aortic left renal vein may be found, which is commonly circumaortic to reflect branches anterior and posterior to the aorta. The inferior phrenic veins, adrenal vein, gonadal vein, first or second lumbar veins, and paravertebral veins are tributaries to the left renal vein in one-third of cases. The rich anastomotic anatomy facilitates closure of the left renal vein medially by IVC blockage for a right-sided IVC thrombus in the event of an IVC thrombosis.[21]

Figure 3: "The left renal artery's anatomy. There are two types of vascular sections: extra parenchymal and intraparenchymal".[22]



Physiology of kidney functioning:

The kidneys are essential for maintaining equilibrium. [25] They control BP, Haemoglobin, sodium, acidity, water, potassium, and bone minerals through fine sensory systems. However, the excretion of metabolic waste materials in urine is their primary function. The kidneys receive around 22% of cardiac output and filter about 20% of plasma, resulting in roughly 170 L of glomerular filtrate per day. Nearly 90% of reabsorption occurs in the nephrons, Ninety-nine percent of it is reabsorbed by the nephrons, leaving only 1.5 litres of urine every day. The glomerular filtration barrier filters the blood. There are five layers:

- "Holes (fenestrations) in glomerular endothelial cells."
- "The glomerular basement membrane."
- "The slit diaphragm between the podocyte foot-processes."
- "The sub-podocyte space between the slit diaphragm"
- "The podocyte cell body."

The structure, organization, and charge (electrical) of the protein collagen molecules that constitute the filtration barricade control the composition of glomerular filtrate. As a result, glomerular filtration is size- and charge-selective, preventing molecules that are too big or highly charged from passing. The barrier allows a large quantity of albumin to flow through, between 3.3 and 5.7 g each day. Transcytosis is the process through which a piece of the sub-podocyte space passes through the podocytes.[26] Angiotensin II helps albumin pass through the blood-brain barrier. Almost majority of the filtered albumin is reabsorbed via active absorption into the proximal tubular cells. The autoregulation process maintains glomerular filtration over a wide range of systemic and renal artery pressures. The afferent arteriole's constriction and dilation are controlled by the macula densa, which is positioned close

to the glomerulus. It is possible to detect sodium chloride flow through the tubule close to the macula densa. When this flow is increased, the macula densa promotes constriction of the afferent arteriole, lowering the glomerular filtration rate. When the blood pressure in the kidney falls, the resistance in the afferent arteriole falls in order to maintain the same pressure in the glomerulus. If the input pressure continues to decline, the efferent arteriole constricts under the effect of angiotensin II. This maintains a constant filtration pressure within the system.[27]

Risk factors:

In order to provide appropriate care, clinicians must be able to stratify patients based on their risk of CIN. People with pre-existing CKD and diabetes mellitus are more prone to develop CIN. CIN is increased by advanced age, cardiovascular disease, pre-procedural hemodynamic instability, and the administration of specific drugs at the same time. Some prevalent risk factors are summarised in [Table 1]. A short assessment of the risk variables could be very useful in determining whether people are at risk of developing CIN.[28]

Table 1: There are several significant risk factors that enhance the likelihood of developing CIN.[28]

- Diabetes with chronic kidney disease (at least stage III)
- Preexisting chronic kidney disease (at least stage III)
- Advanced age
- Intravascular volume depletion
- High volume of contrast and high-osmolarity agents
- Concomitant use of common medications
  - Diuretics
  - Angiotensin-converting enzyme inhibitors
  - Nonsteroidal anti-inflammatory drugs
  - Aminoglycosides
  - Calcineurin inhibitors

Renal dysfunction that has been present for some time:

The occurrence of pre-existing CKD is critical, as it puts subjects at a high risk of developing CIN. Davidson et al. studied 1144 patients having cardiac catheterization and found that subjects with normal renal function had a lower risk of CIN (Cr levels increasing by at least 0.5 mg/dL) than those with pre-existing CKD (Cr levels reaching 1.2 mg/dL).

When blood creatinine exceeded 2.0 mg/dL, the frequency of CIN increased dramatically (20%), according to these researchers.[29]

Diabetes mellitus co-existing with chronic kidney disease:

When compared to people who do not have diabetic nephropathy, diabetics with CKD have a four-fold increased chance of developing CIN.[30] Diabetes mellitus with renal insufficiency has been identified as a separate risk factor for contrast nephropathy, with up to 56% of those who get the disease developing permanent renal failure. Diabetics with severe CKD (serum creatinine >3.5 mg/dL) are at a higher risk of developing CIN.[31]

Age:

In many studies, patients with a higher age had a higher prevalence of CIN, probably reflecting the deterioration in a renal job with age. Increased arterial stiffness is linked to decreased endothelial function, which results in lower vasodilator responses and a reduced capacity for vascular repair with pluripotent stem cells as people get older. All of these factors work together to raise the risk of CIN in the older subjects and decrease the likelihood of a quick recovery.[32]

Contrast volume and timing of contrast administration:

The risk of AKI from contrast material is increased when high dosages and repeated injections are given within 72 hours. The first-generation contrast agents, which are hyperosmolar and ionic in comparison to plasma and carry a greater risk of nephrotoxicity, are rarely employed anymore.[33] Low osmolar (ioversol, iopamidol, and iohexol) or iso-osmolar ("iodixanol") medicines, on the other hand, are linked to a lower incidence of CIN. Iodixanol is a non-ionic dimeric iso-osmolar with a lower nephrotoxicity risk than low-osmolar contrast agents.[34]

Concomitant use of medications:

Diuretics produce intrarenal vasoconstriction and volume depletion. They raise the risk of contrast nephropathy in this situation. Other substances have the potential to produce direct nephrotoxicity. Among these are cisplatin, aminoglycosides, cyclosporine A and amphotericin. "Nonsteroidal anti-inflammatory drugs" (NSAIDs) reduce the effects of prostaglandins on local vasodilation, raising the risk of CIN.[28] Similarly, angiotensin receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACEI) may raise the risk of CN. Patients using an "ACE inhibitor/ARB" were more likely to develop CN AKI (OD (odds ratio): 1.43, 95 percent, CI: 1.06–1.94) in a large trial (n = 5299).[35] As a result, it's a good idea to go through the medicine list before getting the contrast. Nephrotoxic medications should be avoided if at all possible, during contrast injection.

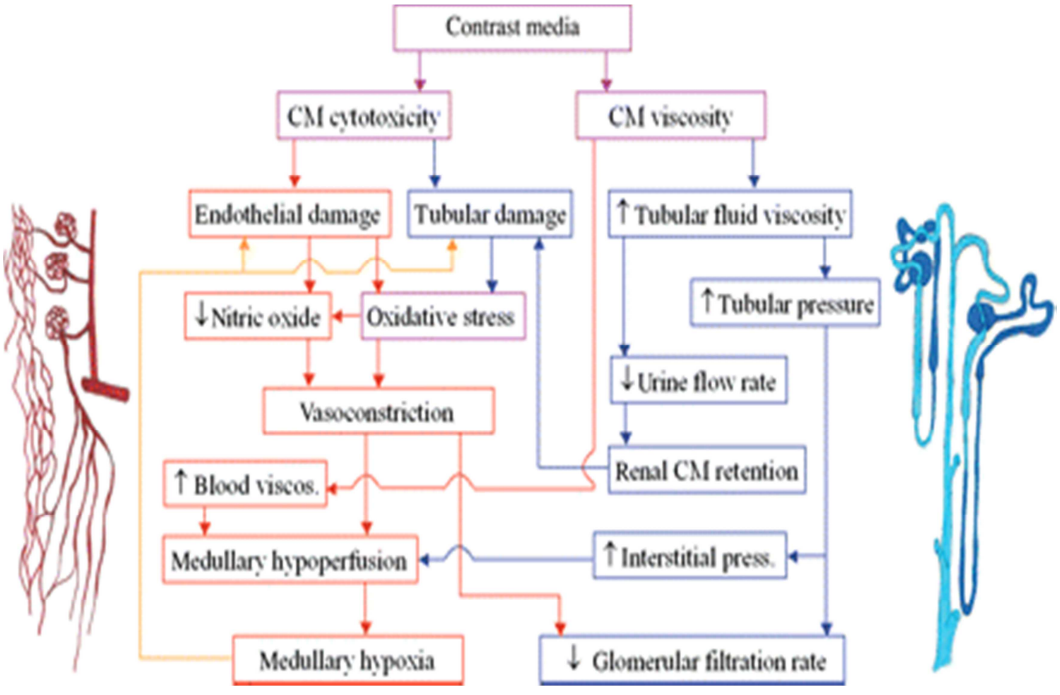
Pathophysiology:

Although the precise mechanism of CIN is unknown, various theories have been offered.[36]

Renal medullary hypoxia caused by an increase in vasoconstrictors or a reduction in vasodilators (nitric oxide or prostaglandins) ("adenosine and endothelin").

- "Direct toxicity of CM, which could be linked to free radical toxicity and oxidative stress." The main mechanism is assumed to be reactive free radicals activating cytokine-induced inflammatory mediators. Alkalinizing tubular cells, on the other hand, may minimize CIN by inhibiting or reducing free radical production.[37]
- Furthermore, apoptosis may have a role in the progression of CIN.[38]

Figure 4: "A simplified diagram is describing the pathogenesis of contrast media-induced acute kidney damage. Effects that primarily affect the nephron are depicted in blue (see stylized nephrons with glomeruli, tubules, and collecting duct at far left), effects that primarily affect blood perfusion and tissue oxygenation are depicted in red (see stylized vasculature including afferent and efferent arterioles, tufts of glomerular capillaries, peritubular capillaries, and descending vasa The orange arrows represent a feedback loop that could lead to a vicious cycle: Medullary hypoxia exacerbates cellular damage, which enhances vasoconstriction due to a variety of causes."[8]



Effect on the kidney:

The combination of hypoxic and toxic renal parenchymal damage caused by reactive oxygen species causes CIN (ROS). CM lowers renal oxygenation in medullary structures while having no effect on tubular reabsorption. This occurs as a result of NO inhibition and endothelin release from endothelial cells uncovered to CM, causing neurohumoral vasoconstrictive stimuli.[39]Under normal physiological conditions, tubular transport is connected to ROS production in the renal medullary thick ascending limb (mTAL). NADPH-oxidase produces superoxide anions and hydroxyl radicals, and the huge mitochondrial population seen in the mTAL is a major source of these radicals.[40]

CM treatment has been demonstrated to increase ROS generation and renal oxidative stress, which leads to cell membrane damage in a number of investigations, either directly[40], or indirectly.[41] This causes necrosis and cellular apoptosis, especially in the "mTALs" and segments of the outer medulla's proximal renal tubules. CM therapy has been linked to increased renal production of ROS metabolites such malondialdehyde and F2 isoprostane, which are markers of lipid peroxidation.[42] Clinical studies have demonstrated, for example, that urine elimination of "F2 isoprostane" was considerably enhanced in individuals receiving CM during coronary angiography.[43]

In addition, urine "3-nitrotyrosine, a biomarker of reactive nitrogen species like peroxynitrite", has increased by double. These occurrences happened immediately after coronary angiography, with varying degrees of intensity depending on the amount of CM administered. This was thought to be a process in which CM direction produces superoxide anions, which then cause the formation of peroxynitrite

via a chemical interaction with nitrogen, limiting NO-dependent vasodilation. Blood flow to renal is reduced as a result of this.[44]

Intravascular Contrast Administration:

The most prevalent usage of iodinated contrast media is intravascular delivery, which is further divided into "intra-arterial and intravenous injection." The intra-arterial injection is the most common method of contrast delivery used in investigative catheter angiography and catheter-directed arterial intervention, such as stent implantation and percutaneous angioplasty. Viscosity, iodine content, and osmolarity are all factors that influence the type and amount of contrast to be provided.[3,45]

Fluoroscopy is the most common imaging modality utilized for intra-arterial injections. In contrast to intravenous injections used for computed tomography (CT) scanning (usually 2-6 mL/s), this modality requires greater rates of contrast administration to opacify the target arteries (up to 30 mL/s).[46] As a result, viscosity plays an important role in the delivery of intra-arterial contrast media for angiography, and contrast agents are regularly warmed to 37°C before catheter injection to ensure appropriate flow rates. Furthermore, iodine concentration can be a key element in achieving appropriate opacification; therefore, using high-iodine contrast media can be beneficial, especially in larger patients.[47]

Finally, during extremities angiography, the osmolarity of intra-arterial contrast media has been demonstrated to alter patient comfort. As a result, upper- and lower-extremity runoff investigations usually use iso-osmolar contrast.[48]

The most common application of iodinated contrast media is intravenous contrast injection for CT scanning. Intravenous contrast injection is also used for studies of the genitourinary tract, such as intravenous pyelography, and the venous system, such as direct venography; however, these studies have declined in popularity over the last two decades, while the number of contrast-enhanced CT scans has increased dramatically.[49]

Anaphylactoid contrast response and contrast-induced nephropathy are two consequences of intravascular injection of iodinated contrast. Extravasation of contrast media is another concern of intravenous contrast injection. Contrast extravasation can cause local edema and erythema; however, it is unusual. Severe local consequences such as skin and subcutaneous ulcers, as well as tissue necrosis, can occur in rare cases.[47]

"Direct Contrast Injection:"

Direct injection of iodinated contrast can be done in two ways: via percutaneous needle access, as in direct arthrography, or via an indwelling catheter or tube, as in cystography or sonography (Yamaguchi et al., 2017).[45] This type of contrast injection varies from intravascular injection in that the contrast is not removed quickly by the kidneys after image collection but instead is emptied back through the catheter or by natural drainage. The contrast is absorbed slowly back into the body via the lymphatic system in some circumstances, such as articular injection and myelography (Han et al., 2018).[50] Contrast responses have been documented with intestinal contrast injection; however, they are extremely rare. Contrast-related problems are significantly more typically linked to negative local reactions in such

treatments (Barr et al., 2016).[48] As a result, the contrast preparation for each of these procedures must be tailored to the unique indication.

Diagnosis:

After ruling out other possibilities, the major diagnostic criteria include an increase in Scr of more than 25% above baseline within 48 hours of CM administration. "Acidosis and/or hyperkalaemia" may also be observed in the lab. In terms of urine output, the subjects could be anuric or oliguric or can have a normal output. Urine examination results are frequently vague.[51]

The time between contrast exposure and the change in Scr is usually 24 to 48 hours. Because creatinine is a late indication of alterations in renal function,51 more sensitive indicators of renal damage are desired. In fact, multiple tubular injury biomarkers have been investigated.[52]

Human neutrophil lipocalin, commonly known as "plasma neutrophil gelatinase-associated lipocalin" (NGAL), is an early prognostic biomarker of AKI. It's a tiny lipocalin protein that was first isolated from the supernatant of activated human neutrophils in 1993. Tubularly secreted NGAL has now been established as a unique and specific biomarker for the early diagnosis of AKI after contrast agent administration and in critically ill patients in subsequent studies. NGAL is being examined more as an AKI marker since its serum and urinary levels rise well before Scr and have a higher sensitivity for AKI identification than Scr alone. After 2 hours, patients with CIN have a considerable rise.[53]

"Plasma cystatin-C" (CysC) is a low molecular weight protein that is produced at a consistent rate by all nucleated cells, filtered freely across the glomerular membrane, and not secreted or reabsorbed along the nephron. Its renal clearance

cannot be assessed because it is virtually fully catabolized in the proximal tubule, although its concentration in serum or plasma reflects GFR. After 8 hours, it is considerably higher in patients with CIN. However, the increase has been observed in other circumstances such as thyroid dysfunction, corticosteroids, neoplasia, systemic inflammation, aging, and an increase in muscular mass.[54]

"Urinary NGAL" ("uNGAL or lipocalin-2 (LCN2)") is an iron-transporting protein that rapidly accumulates in kidney tubules and urine following nephrotoxic and ischemic insults. It has been proposed as an early, sensitive, and non-invasive biomarker for AKI. Zappitelli et al. found that uNGAL is useful in predicting AKI before a rise in SCr become apparent, as well as people who will have persistent AKI, in a study of 150 patients with AKI. Despite a considerable increase in these urine indicators as early as 2 hours in patients with CIN, its usage is currently exploratory.[55]

- "Urinary interleukin-18" (IL-18) is a specific biomarker for proximal acute tubular necrosis. After 24 hours of exposure to CM, a value of more than 60 pg/ml is considered significant.[56]
- "Interleukin-18" (IL-18, interferon-gamma inducing factor) in the urine is a particular biomarker for proximal acute tubular necrosis. After 24-hour exposure to CM, a value of more than 60 pg/ml is considered substantial.[57]
- "Urinary kidney injury molecule-1" (KIM-1) is a transmembrane protein that is not found in normal kidney tissue but is highly expressed in differentiated proximal tubule epithelial cells in human and rodent kidneys following ischemia or toxic injury.[58]

Scoring systems

As a result, in 2015, the American College of Radiology's Committee on Drugs and Contrast Media approved new words to clarify the implicit causative association between contrast media and AKI.[59] In these consensus statements, the following terms are endorsed:

CA-AKI ("contrast-associated acute kidney injury"): Any AKI that occurs within 48 hours of CM treatment. The term "postcontrast acute kidney injury" (PC-AKI) is used interchangeably with "chronic, acute kidney injury" (CA-AKI) in radiology recommendations. Correlative diagnosis is implied by both phrases. Neither term implies a link between the delivery of contrast medium and the occurrence of AKI. CA-AKI and PC-AKI are terms for related AKI events that occur in clinical treatment and incidents documented in study protocols without a control group.[59]

"Contrast-induced acute kidney injury" (CI-AKI) is a subtype of CA-AKI that can be connected to the administration of contrast media. The term CI-AKI refers to a link between intravenous contrast media and the development of AKI (i.e., contrast-induced). Because of the high rate of false-positive occurrences, the term CI-AKI (previously called contrast-induced nephropathy) might be deceptive in clinical practice (i.e., AKI related to concurrent nephrotoxic exposure or insults in proximity to the time of contrast media administration).[60]

Figure 5: Use of intravenous iodinated contrast media in patients with kidney disease: consensus statements from the American college of radiology and the national kidney foundation.

KDIGO AKI Staging	
Stage	Serum Creatinine Criteria
1	1.5–1.9 times baseline serum creatinine
	OR
	Increase in serum Cr ≥ 0.3 mg/dL (≥26.5 μmol/l)
2	2.0–2.9 times baseline serum creatinine
3	3.0 times baseline serum creatinine
	OR
	Increase in serum Cr to ≥ 4.0 mg/dL (≥353.6 μmol/l)
	OR
	Initiation of kidney replacement therapy
	OR
	Decrease in eGFR to < 35 mL/min/1.73 m² (for patients < 18 years old)

Kidney Disease Improving Global Outcomes (KDIGO) staging criteria for acute kidney injury (AKI).

- The risk of contrast-induced acute kidney injury has been estimated to be near 0% at eGFR greater than or equal to 45, 0%–2% at eGFR of 30–44, and 0%–17% at eGFR less than 30 mL/min/1.73 m^2.
- Prophylaxis for contrast-induced acute kidney injury with IV normal saline is indicated for patients with an eGFR less than 30 mL/min/1.73 m^2 who are not undergoing maintenance dialysis, or in high-risk patients with an eGFR of 30–44 mL/min/1.73 m^2.

Treatment/ management:

There is no established treatment for AKI after radiocontrast injection at this time. But, deterrence remains the basis of this entity, necessitating a thorough examination of the risk factors as well as the adoption of the preventative interventions listed below.[61]

'Preservation of volume status:"

The single most critical method for avoiding contrast-induced kidney impairment is to avoid intravascular volume depletion. Maintaining proper hydration is essential in this situation. NSAIDs are commonly administered to patients. Stopping these medications 24–48 hours prior to the operation is recommended. Normal saline, delivered at 1 mL/kg/h for 6–12 h preprocedural, intraprocedural, and continuing for 6–12 h post-procedure, is recommended for volume replacement for hospitalized patients receiving contrast administration.[62] Fluids should be given to patients with compensated congestive heart failure at the discretion of the physician

and with frequent lung examinations. Normal saline has been shown to be superior to hypotonic solutions like 0.45 percent saline in terms of volume expansion.[63]

"N-acetylcysteine:"

"N-sulfhydryl acetylcysteine's" group is a good antioxidant and scavenger of free oxygen radicals. It has, however, failed to provide compelling evidence that it can protect against the development of CIN. This medication is widely included in the preventative plans of numerous medical centres against contrast nephropathy due to its inexpensive cost, absence of side effects, and potential beneficial effect. Despite this, we do not suggest this agent due to a lack of conclusive proof.[64,65]

"Prophylactic hemofiltration and haemodialysis:"

Clinicians frequently request dialysis treatment following the delivery of CM. However, there is no compelling evidence that preventive dialysis protects the kidneys from contrast-induced renal damage.[66] Prophylactic dialysis therapy is not currently recommended. Dialysis is not without risks and necessitates the insertion of a large-bore catheter, which is an intrusive process.

"Oral hydration and other measures:"

Oral hydration is a more appealing and realistic option than intravenous fluid replacement because of its ease of delivery and low cost. Oral hydration with water was found to be as effective as hydration with i.e. saline in a recent meta-analysis of randomized clinical studies. [67] Statins, oral sodium citrate, atrial natriuretic peptide, ascorbic acid, theophylline, and nifedipine have all been examined and shown to be ineffective in the prevention of CIN[66–68]

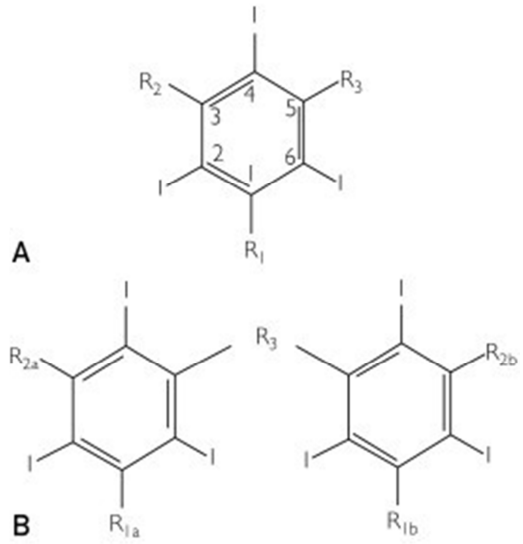
"Logistical barrier to CIN prevention:"

While it has been claimed that intravenous hydration is the single most essential factor in preventing CIN, there are a number of challenges that make this strategy difficult to apply in clinical practice. Procedures are frequently planned in an emergency and with simultaneous complicating circumstances (CHF, etc.) that limit the use of intravenous hydration. Furthermore, the scarcity of space in radiology suites for i.e. Hydration contributes to the difficulty of implementing CIN prevention techniques.[61]

"Effect on kidney function following contrast-enhanced CT using iso-osmolar/low osmolar iodinated contrast medium."

Chemical modifications of the 2, 4, 6 tri-iodinated benzene rings constitute the basis for all currently used ICM. The three iodine atoms added to the parent benzene ring side chains at locations 2, 4, and 6 make the ICM less poisonous and lipophilic. The substituent at position 5 has an impact on the elimination route as well. Chemical structure, osmolality, iodine concentration, and ionization are used to classify ICM.[47] The amount of iodine required to achieve radiographic attenuation relative to the particles in solution determines osmolality.[69]

Figure 6: "Iodinated contrast agents' basic molecular structure units. Monomeric form (A). B is the dimeric form". "Iodine atoms are trisubstituted at positions 2, 4, and 6 on benzene rings. Substitution of a carboxylate (-COO-)-containing functional group at site R1 in the monomeric form or R1a in the dimeric form results in "ionic" compounds; otherwise, substitution at this site with a non–carboxylate–containing functional group leads in "nonionic" compounds. Non–carboxylate–containing functional groups are found at sites R2, R2a, R2b, and R3".[70]



The presence of carboxyl side chains causes ionic inclination, which is reduced by hydroxylation of these side chains. Molecules in contrast media can take four different forms:[47]

- "Ionic monomer": "single tri-iodinated benzene ring with a carboxylate-containing benzene substituent."
- "Ionic dimer": "2 linked tri-iodinated benzene rings in which at least 1 carboxylate-containing group is substituted on at least 1 benzene ring".
- "Non-ionic monomer": "single tri-iodinated benzene ring without a carboxylate-containing benzene substituent."

- "Non-ionic dimer": "2 linked tri-iodinated benzene rings that do not contain a carboxylate functional group within any benzene substituent".

Figure 7: "Properties of the 4 classes of iodinated contrast agents".[70]

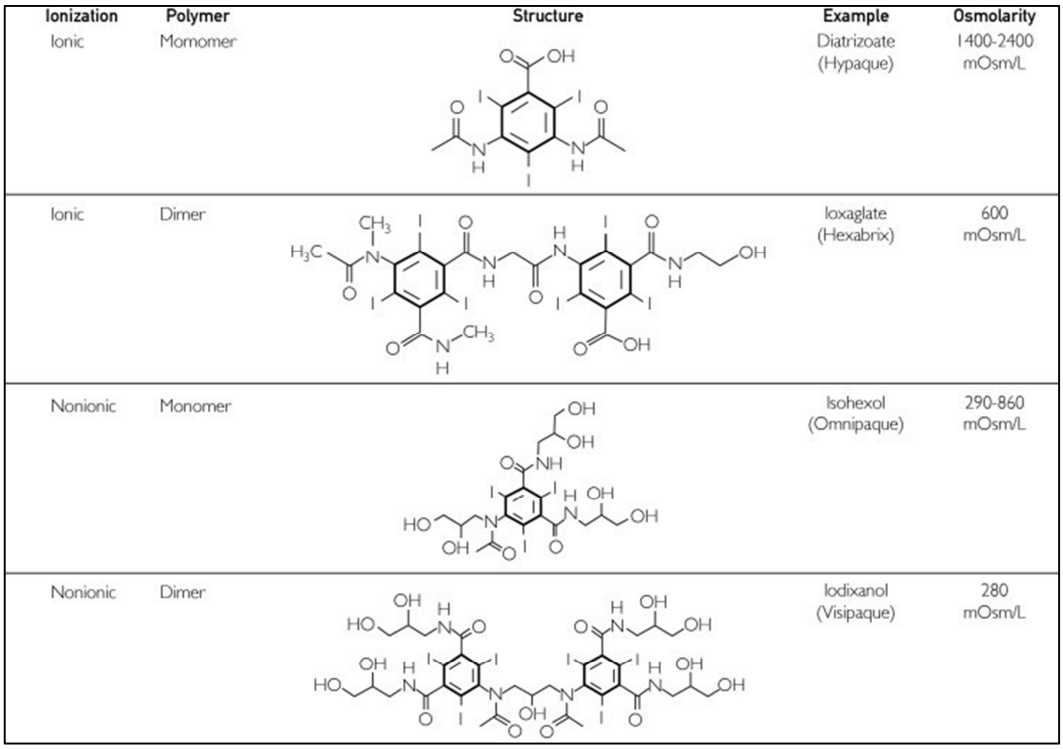


Table 2: Indications for the "Use of Iodinated Contrast Media".

Intravascular	Intra-arterial
CT (Computed tomography)	Angiocardiography
"Digital subtraction angiography"	Computed tomography
"Intravenous urography"	Coronary angiography
"Venography" ("phlebography")	Pulmonary angiography
"Inferior vena cava and its tributaries"	
"Superior vena cava and its tributaries"	
"Extremities"	
"Other venous sites"	
"Epidural venography"	

Contraindications:[71]

Absolute:

- Anaphylaxis, angioedema, and bronchospasm were documented past severe reactions to iodinated contrast media.
- Previous iodinated CM /excipient reactions were milder.
- Renal failure or impairment
- Factors that increase the risk of an allergic reaction to iodinated contrast media
- "Myasthenia gravis" is a disputed condition that is nonetheless mentioned in some product instructions and guidelines.

"Intravascular Contrast Administration"

The most prevalent usage of iodinated contrast media is intravascular delivery, which is further divided into intra-arterial and intravenous injection. The predominant method of contrast delivery in diagnostic catheter angiography and catheter-directed arterial intervention, such as percutaneous angioplasty and stent implantation, is intra-arterial injection. Viscosity, iodine content, and osmolarity are all factors that influence the type and amount of contrast to be provided.

Fluoroscopy is the most common imaging modality utilized for intra-arterial injections. In contrast to intravenous injections used for computed tomography (CT) scanning (usually "2-6 mL/s"), this modality requires greater rates of contrast administration to opacify the target arteries (up to 30 mL/s). As a result, viscosity plays an important role in the delivery of intra-arterial contrast media for angiography, and contrast agents are regularly warmed to 37°C before catheter injection to ensure appropriate flow rates. Furthermore, iodine concentration can be a key element in achieving appropriate opacification; therefore, using high-iodine

contrast media can be beneficial, especially in larger patients. Finally, during extremities angiography, the osmolarity of intra-arterial contrast media has been demonstrated to alter patient comfort. As a result, upper- and lower-extremity runoff investigations usually use iso-osmolar contrast.[70]

The most common application of iodinated contrast media is intravenous contrast injection for CT scanning. Intravenous contrast injection is also used for studies of the genitourinary tract, such as intravenous pyelography, and the venous system, such as direct venography; however, these studies have declined in popularity over the last two decades, while the number of contrast-enhanced CT scans has increased dramatically.

CT uses an iodinated contrast medium for arterial opacification and parenchymal enhancement, just like catheter arteriography. The arterial contrast opacification is shown initially after intravenous injection, followed by parenchymal contrast enhancement. The amount and pace of contrast administration are directly proportional to the local iodine concentration; however, depending on the indication, the amount and rate of contrast administration may fluctuate dramatically.[72]

Arterial opacification is the basic goal of CT angiography. This opacification is proportionate to the iodine transfer rate, which is regulated by the iodine content in the CM and is determined chiefly by the rate of contrast injection.[73] Because the primary goal is arterial opacification, the total volume of CM employed is typically less of a concern than the speed with which the contrast may be delivered. As with catheter angiography, viscosity and iodine concentration influence the choice of contrast medium to inject, especially when IV access is limited. Warming more viscous contrast media, such as those with a high iodine concentration or iso-osmolar contrast agents, to 37°C ensures appropriate flow rates during intravenous injection.[70]

The scenario changes when the primary purpose of CT scanning is to evaluate a solid organ, such as the liver or pancreas. The overall amount of iodine provided has a greater impact on parenchymal organ augmentation than the iodine delivery rate. As a result, even if the contrast media cannot be supplied fast, lesion conspicuity within a solid organ may necessitate a larger volume of contrast media to be injected. As a result, viscosity is less of a concern in nonvascular CT, and contrast media selection is mostly focused on safety.[74]

Anaphylactoid contrast response and contrast-induced nephropathy are two consequences of intravascular injection of iodinated contrast. Extravasation of contrast media is another concern of intravenous contrast injection. Contrast extravasation can cause local edema and erythema; however, it is unusual. Severe local consequences such as skin and subcutaneous ulcers, as well as tissue necrosis, can occur in rare cases. For intravenous injection of iodinated contrast media for CT scanning, most published studies show an extravasation rate of less than 1%.[75] The majority of contrast extravasations are minor in size and can be treated conservatively. Unfortunately, the severity of the damage cannot be established at the time of the initial assessment. Although there is no consensus on how to treat contrast media extravasation, it is recommended that patients be closely monitored, with prolonged discomfort, skin blistering, or indications of altered tissue perfusion being considered signs of serious harm.[76]

To re-opacify the stomach and duodenum, 200 to 300 mL of "top-off" liquids are frequently administered at the time of the CT scan. To thoroughly opacify the colon, 200 to 300 mL of rectal contrast may be required in exceptional instances. Anaphylactoid-type Contrast responses have been recorded after the oral ingestion of iodinated contrast, albeit they are extremely rare. These responses usually occur at the

same time as intravascular contrast reactions, are similar in severity, and are treated with the same methods.

Because of the rarity of these events, corticosteroid premedication before oral contrast treatment is not recommended for patients who have had an intravenous contrast reaction. Furthermore, the potential negative effects of iodinated contrast media on the kidney are not thought to occur in a clinically relevant way when administered by nonvascular routes.

Direct injection of iodinated contrast can take two forms: injection using a percutaneous needle, as in direct arthrography, or injection through an indwelling catheter or tube, as in cystography or sinography. This type of contrast injection varies from intravascular injection in that the contrast is not removed quickly by the kidneys after image collection but instead is emptied back through the catheter or by natural drainage. The contrast is absorbed slowly back into the body via the lymphatic system in some circumstances, such as articular injection and myelography. Contrast responses have been documented with intestinal contrast injection; however, they are extremely rare. Contrast-related problems are significantly more typically linked to negative local reactions in such treatments.

As a result, the contrast preparation for each of these procedures must be tailored to the unique indication. The potential effects of iodinated contrast on the kidney, as with oral contrast treatment, are not thought to be significant with direct contrast injection.

"ADVERSE REACTIONS TO ICAs" (intravascular contrast administration):

Adverse responses are more likely after using high-osmolarity agents: 15% with a high-osmolarity agent vs. only 3% with a low-osmolarity ICA. As a result, in recent years, the use of high-osmolarity medicines has reduced dramatically. Most adverse

effects and reactions to ICAs are multifactorial and are most likely caused by a combination of direct chemotoxicity, ionic state (ionic versus non-ionic), and osmolarity of the injected ICA preparation.[70]

- **"Acute reaction"**

Within 1 hour of receiving an iodinated contrast agent, this happens. Osmotic or chemotoxicity are the most common mechanisms. Anaphylactic or anaphylactoid responses are the most common.

Signs and symptoms:

- Can be variable in presentation and severity Common signs and symptoms: Nausea, vomiting Pain on injection Hemodynamic change's Vagal reaction (bradycardia and hypotension)
- "Arrhythmia"
- Anaphylactoid reaction or Anaphylaxis
- Rash (pruritic urticaria)
- Flushing
- "Angioedema"
- "Bronchospasm"
- "Cardiovascular collapse."

Risk factors:

- Subjects with Asthma history.
- Previous reaction to contrast Atopy.
- Higher risk when using ionic monomers.

Delayed reaction:

- After administering an iodinated contrast agent, it occurs between 1h and 1wk.
- T-cell–mediated type IV hypersensitivity reactions are most commonly seen on the skin.

Chemotoxicity may be the cause of other symptoms.

Effect on kidney function following contrast-enhanced CT using low-osmolar iodinated contrast medium:

"Low osmolality contrast media:"

Low osmolality contrast media (LOCM) are favoured for intravascular and intrathecal delivery since their osmolality is less than three times that of human serum. Modern LOCMs are "non-ionic monomers" made up of "tri-iodinated benzene rings" with different side chains containing polar alcohol (-OH) groups that make them water-soluble 3. The following LOCM is currently in use:[71]

- "Iopamidol" ("Isovue")
- "Iohexol" ("Omnipaque")
- "Iopromide" ("Ultravist")
- "Ioversol" ("Optiray")
- "Ioxilan" ("Oxilan")

"Iso-osmolal contrast media" (IOCM), which have a similar osmolality to serum, are also included in the LOCM group. "A non-ionic dimer made up of two covalently bonded tri-iodinated benzene rings is the only IOCM currently in use":

Iodixanol (Visipaque)

Iodixanol's dimer structure allows for a larger concentration of iodine atoms per osmole, allowing for diagnostic contrast opacification at lower osmolality. Non-ionic LOCM comes in a variety of concentrations ranging from 240 to 400 mg iodine per mL. The peak of enhancement ("measured in Hounsfield units") is higher in higher concentration formulations, but they are also more viscous.

Comparison of Prevalence of CIN following contrast-enhanced CT using iso-osmolar versus low-osmolar iodinated contrast medium

Feldkamp, T et al.78 2006, conducted a prospective, double-blind study to compare the nephrotoxicity of iso-osmotic contrast media iodixanol vs. low-osmotic contrast media iopromid in patients receiving contrast media during coronary angiography. As evaluated by impaired creatinine clearance, the incidence of CIN was 22.2 percent in the iopromid group and 19.7 percent in the iodixanol group. As evaluated by elevated blood creatinine, CIN was 6.9% in the iopromid group and 8.6% in the iodixanol group. Between these two groups, there was no discernible difference. In a subgroup examination of diabetic persons or patients who had a high dosage of contrast media, there was no significant difference in the incidence of CIN between the two-contrast media. Both iso-osmolar and low-osmolar contrast mediums had the same rate of CIN in our study sample. Iopromid or iodixanol administration has no influence on the risk of CIN in patients.[77]

Contrast-associated AKI. — For intravenous applications, there are no clinically relevant variations in CA-AKI risk between LOCM and IOCM. Although this has yet to be established, indirect data suggests that the LOCM iohexol is connected with a

higher risk than other LOCM. The outcomes of randomized studies comparing LOCM with IOCM mostly looked at intra-arterial administrations and were mixed. According to the findings of a comprehensive review and meta-analysis published in 2015, any difference in CA-AKI risk between LOCM and IOCM is unlikely to be clinically significant.[78]

Contrast-induced AKI. — There have been no studies that directly compare the risk of CI-AKI in LOCM vs. IOCM. Randomized trials comparing CM with CA-AKI as an endpoint, on the other hand, provide information on the risk of CI-AKI because the groups are balanced aside from CM exposure (i.e., the outcome is a combination of CA-AKI unrelated to contrast media and CI-AKI, with the primary difference being the CI-AKI fraction). The risk of CI-AKI between LOCM and IOCM is regarded to be clinically insignificant.[78]

LOCM are "hyperosmolar" (about 600 mOsm/kg) in comparison to IOCM (roughly 290 mOsm/kg) and serum (approximately 290 mOsm/kg), despite the abbreviation. The dimeric structure of IOCM, on the other hand, makes them more viscous than LOCM. LOCM refers to the majority of current iodinated contrast media. Despite the fact that high-osmolality iodinated contrast media have a higher osmolality than LOCM and IOCM, they have been replaced by LOCM and IOCM for intravenous administration in modern clinical practise.[59]

MOST RELEVANT STUDIES:

A study by Werner, S et al.[79] 2020 sought after contrast-enhanced CT (CECT) with intravenous application of a reduced dose of the iso-osmolar contrast agent iodixanol to determine the incidence of post-contrast acute kidney injury (PC-AKI) and presumed contrast-induced acute kidney injury (CI-AKI) in cancer patients with

chronic kidney disease. They included 237 CECTs were done on 198 oncology patients with an estimated glomerular filtration rate (eGFR) of less than 60ml/min/1.73m^2 using a lower dose of 60ml iodixanol. The overall incidence of PC-AKI was 6.3 percent. The CI-AKI incidence was estimated to be 3.8 percent after excluding individuals with concurrent medical diseases known to have a direct and independent impact on kidney function, as well as subjects who had AKI prior to the CT scan. There was no lasting post-contrast deterioration of renal function or the need for AKI treatment. PC-AKI occurrences were 4.6 percent and 7.4 percent in subgroups based on baseline eGFR.

Zhao, F et al.[80] 2019 conducted a systematic study to see if there is a difference in CI-AKI incidence between iso-osmolar (IOCM) and low-osmolar (LOCM) contrast medium in diabetic individuals. A total of 2190 individuals were included in the study, with 1122 receiving IOCM and 1068 receiving LOCM. When compared to LOCM, IOCM had no significant effect in preventing CI-AKI (OR = 1.66, P = 0.06, I2 = 54 percent). The distinction between IOCM and LOCM was observed when CI-AKI was defined as an absolute SCr rise (0.5 mg/dl) rather than a percentage increase (0.5 mg/dl).

A meta-analysis by Han, X et al.[50] 2018 studied 12 RCTs. They found Iodixanol found no significant reduction in the risk of CIN. When compared to the LOCM drug iohexol, the risk of CIN was much lower with iodixanol (RR: 0.32, 95 percent CI [0.12, 0.89]). There were no differences between iodixanol and the other non-iohexol LOCMs. In diabetics, iodixanol is not linked to a significant reduction in the risk of CIN. Iodixanol had a decreased risk of CIN than iohexol, but no significant difference was found between iodixanol and other LOCM.

McDonald et al.[81] 2017 aimed to equate the rates of acute kidney injury (AKI), emergent dialysis, and short-term mortality in patients who received an intravenous injection of the iso-osmolar contrast material (IOCM) iodixanol 320 versus patients who received a non-contrast computed tomography (CT) examination. A total of 5758 individuals were included in the study (1538 with stage 1–2 CKD, 2899 with stage 3 CKD, and 1321 with stage 4–5 CKD). After propensity score adjustment, rates of AKI, dialysis, and death in the IOCM group were not significantly higher than in the non-contrast group for all CKD subgroups. Sensitivity analyses yielded similar results. In patients with the highest perceived risk of postcontrast AKI, intravenous iodixanol for contrast material enhanced CT was not an independent risk factor for AKI, dialysis, or mortality.

A systematic analysis by Eng, J et al.[82] 2016 conducted a comprehensive review to examine the risk of CIN for CM within and within osmolality classes in subjects undergoing diagnostic or therapeutic imaging procedures. There was no statistically significant or clinically meaningful difference between research groups in any of the five trials that evaluated kinds of LOCM; however, the level of evidence was low. In a meta-analysis of twenty-five randomized, controlled trials, the IOCM agent iodixanol was found to have a small reduction in CIN risk when compared to a broad set of LOCM ($P = 0.045$). The strength of evidence in this comparison was moderate.

In a meta-analysis, Nguyen, S et al.[83] 2009 looked at the effects of iso-osmolality contrast medium versus low-osmolality contrast medium on renal function in high-risk subjects undergoing IV contrast material-enhanced CT. At the 30- or 90-day follow-up, no patient-reported an adverse event due to the contrast material. The use of intravenous CM in high-risk individuals is unlikely to result in long-term

negative consequences. Iodixanol groups have lower SCr levels after contrast material administration than iopromide groups.

The goal of a study by Davenport, M et al.[84] 2013 was to see how IV low-osmolality iodinated contrast material (LOCM) affected the development of the post-CT syndrome. In subjects with a steady eGFR less than 30 mL/min/1.73 m (2), IV LOCM is a nephrotoxic risk factor, with a trend toward significance at 30-44 mL/min/1.73 m (2). In subjects with a pre-CT eGFR of 45 mL/min/1.73 m (2) or more, IV LOCM does not appear to be a nephrotoxic risk factor.

A systematic analysis by Reed, M et al.[85] 2009 compared the nephrotoxicity of the IOCM, iodixanol, to LOCM. A total of 16 trials with a total of 2,763 participants were combined. Overall, there was no significant variance between the iodixanol and LOCM groups in terms of the occurrence of CI-AKI. The rates of haemodialysis or mortality after the procedure were not significantly different. Depending on the kind of LOCM, the relative renal safety of LOCM versus iodixanol may differ.

A prospective study by Rudnick, M et al.[86] 2008 examined the renal side effects of Ioversol and iodixanol in CKD subjects on coronary angiography. This study involved 337 subjects with constant CKD and was randomly grouped to the IOCM "iodixanol" or the LOCM "ioversol." In the 299 subjects, the incidence of CIN was 21.8 percent in iodixanol subjects and 23.8 percent in ioversol subjects. The renal side effects in both groups showed no significant difference.

McCullough, P et al.[87] 2006 compared the renal function of IOCM iodixanol to LOCM and identified determinants of CIN. The authors retrieved 2727 patients from 16 RCT, which were double-blinded where every subject (n=1382) was injected with intra-arterial iodixanol IOCM and intra-arterial LOCM (n = 1345). Subjects were divided into groups based on whether they had CKD, DM, or both.

The intra-arterial IOCM found to show a small rise in the serum creatinine levels with a lesser rate of CIN compared to LOCM, in particular with CKD subjects or DM +CKD subjects.

LACUNAE IN LITERATURE:

India is largely populated, and CT is largely recommended in various serious illness such as cancer, injuries, etc. The contrast media popularly used is iodinated contrast media. LOCM has been used in most subjects, but most recommended is iso-osmolar contrast media due to its least adverse effects. Till date, there has been literature on a randomized controlled trial comparing the LOCM and IOCM, but in India, there has been a lack of concrete evidence of the incidence of CIN among these 2 CM. There is a paucity of procedural specifics about contrast administration that have not been reported consistently. Clinical indications and the severity of baseline renal impairment were only mentioned in a few studies.

MATERIALS AND METHODS

Study site: This research was conducted in the "Department of Radiodiagnosis at Jawaharlal Nehru Medical College K.L.E. University, Belgaum."

Study population: All the eligible patients undergoing CECT requiring IV contrast media, above the age of 18 years in the Department of Radiodiagnosis at Jawaharlal Nehru Medical College were considered as the study population.

Study design: The current study was an observational study.

Sample size:

Cases above 18 years presenting to "Department of Radio-diagnosis at the KLE'S Dr. Prabhakar Kore Hospital and MRC, Belgaum requiring IV CECT." As per the study by Moos SI et. Al.,[88] the prevalence of developed a rise in SCR>25% of baseline was 4.96% and the other parameters considered for the sample size was 7% precision 95% confidence interval.

Using the formula.[89]

n=4pq/d2

Where p is the prevalence of subjects developed a rise in Scr >25% of baseline (6.5%)

q is (l-p)

d is absolute precision of 7

As per the above formula, the sample size was calculated to be 38. After considering the lost to follow up of 5%, 2 cases were added up and the total subjects considered into the final study was 40.

Sampling method: Universal Sampling.

Study duration: The study's data was collected during a one-year period, from January 2020 to December 2020.

Inclusion Criteria:

Patient aged above 18 years.

Exclusion criteria:

- Any previously diagnosed with known allergy to contrast media.
- Any other absolute contraindication to the use of contrast media.
- Patients who are clinically advised not to undergo CECT due to their deranged kidney function.

Ethical considerations: The human ethics commission at the university approved the study. All study participants were asked to sign an informed consent form, and only those who agreed to do so were included in the study. Before the agreement was obtained, participants were informed about the study's risks and benefits, as well as the voluntary nature of participation. The study participants' confidentiality was protected.

Data collection tools: All the relevant parameters were documented in a structured study proforma.

Methodology:

All patients were evaluated clinically and then undergo a CECT performed using GE EVOLUTION 128 SLICE CT. Once the CECT is done, the SCr level was measured after 48-96 hours of the study was noted and analyzed. (As serum creatinine levels are seen to peak 2 to 5 days post CECT.)

Equipment: GE EVOLUTION 128 SLICE CT SCANNER MACHINE

CT sequences that were obtained:

- Scout image
- Plain image

- Contrast image

Investigations: Serum creatinine level was observed 48-96 hours after CECT.

STATISTICAL METHODS:

Serum creatinine was considered as the primary outcome variable. IV contrast agent was considered as a primary explanatory variable.

For quantitative variables, mean and standard deviation were used, whereas, for categorical variables, frequency and proportion were used. The median and interquartile ranges were used to summaries non-normally distributed quantitative values (IQR). Data was also shown using relevant diagrams such as bar graphs and pie graphs.

Visual inspection of histograms and normality Q-Q plots were used to assess all quantitative variables for normal distribution within each category of the explanatory variable. To determine normal distribution, the Shapiro-Wilk test was used. Normal distribution was defined as a p-value of >0.05 in the Shapiro-Wilk test. The mean values of normally distributed quantitative variables were compared between study groups using an independent sample t-test (2 groups). A paired t-test (in the event of two time periods) was used to analyze the change in quantitative parameters before and after the intervention. A P value of 0.05 was considered statistically significant. SPSS software, version 22, was used to analyze the data.[90]

RESULTS

A total of 40 subjects were analyzed.

Table 3: Descriptive analysis of age distribution in the study population (N=40)

Age Group	Frequency	Percentage
Up to 30	5	12.50%
31 to 45	7	17.50%
46 to 60	15	37.50%
>60	13	32.50%
	Mean ± SD	**Range**
Age (in years)	53.85 ± 17.17	19 to 85

Among the study population, 5 (12.50%) were aged up to 30 years, 7 (17.50%) were aged between 31 - 45 years, 15 (37.50%) were aged between 46 - 60 years, and 13 (32.50%) participants were >60 years. (Table 3 & Figure 8)

Figure 8: "Bar chart of age distribution in the study population" (N=40)

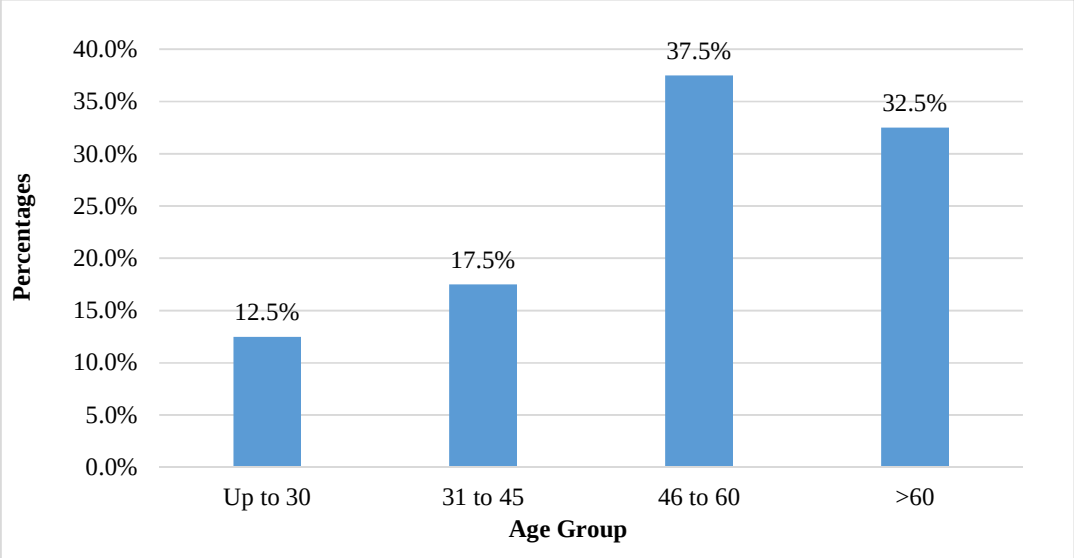


Table 4: Gender descriptive analysis in the research population (N=40)

Gender	Frequency	Percentages
Male	25	62.50%
Female	15	37.50%

In the study population, 25 (62.50%) were male, and 15 (37.50%) participants were women. (Table 4 & Figure 9)

Figure 9: "Pie chart of gender in the study population" (N=40)

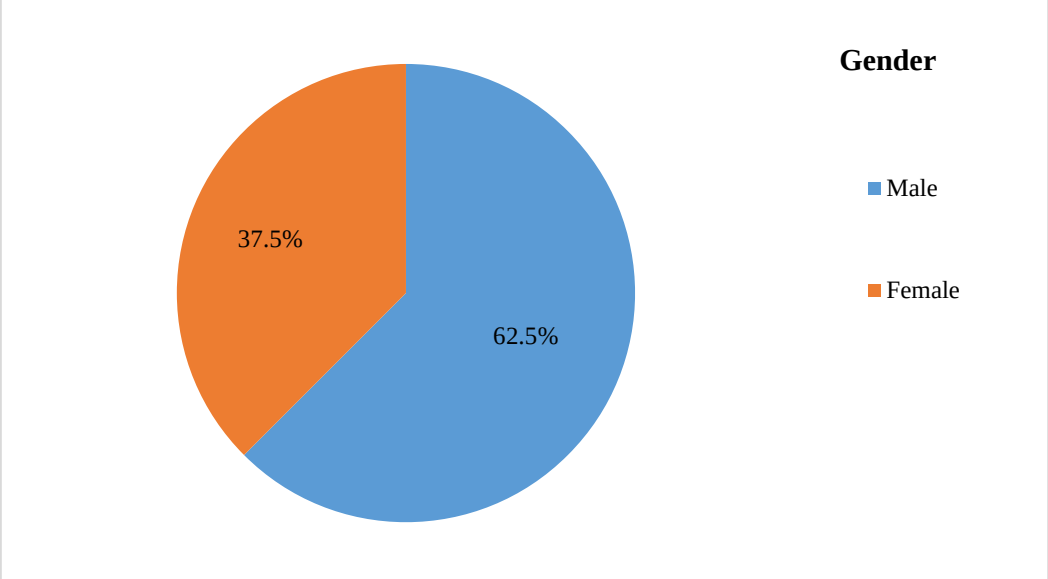


Table 5: Scanning in the study population: a descriptive analysis (N=40)

Scan Done	Frequency	%
CECT ABDOMEN + PELVIS	9	22.50%
CECT BRAIN	4	10.00%
CECT ABDOMEN	3	7.50%
CECT NECK	3	7.50%
CECT THORAX	3	7.50%
CT PULMONARY ANGIO	3	7.50%
CECT NECK + THORAX	2	5.00%
PULMONARY ANGIO	2	5.00%
CAROTID ANGIO	1	2.50%
CECT KUB	1	2.50%
CECT PELVIS	1	2.50%
CECT THORAX+ ABDOMEN	1	2.50%
CORONARY ANGIO	1	2.50%
CT AORTIC ANGIO	1	2.50%
CT NECK	1	2.50%
CT RENAL ANGIO	1	2.50%
Lower limb ANGIO	1	2.50%
Upper limb ANGIO	1	2.50%
Urography	1	2.50%

Out of 40 participants, majority 22.50% were done CECT abdomen+ pelvis and 10% participants were done CECT brain. (Table 5)

Table 6: Descriptive analysis of IV contrast agent in the study population (N=40)

IV Contrast Agent	Frequency	%
Iodixanol	15	37.50%
Iohexol	25	62.50%

Among the study population, 15 (37.50%) took iodixanol, and 25 (62.50%) were taken iohexol. (Table 6 & Figure 10)

Figure 10: "Bar chart of iv contrast agent in the study population" (N=40)

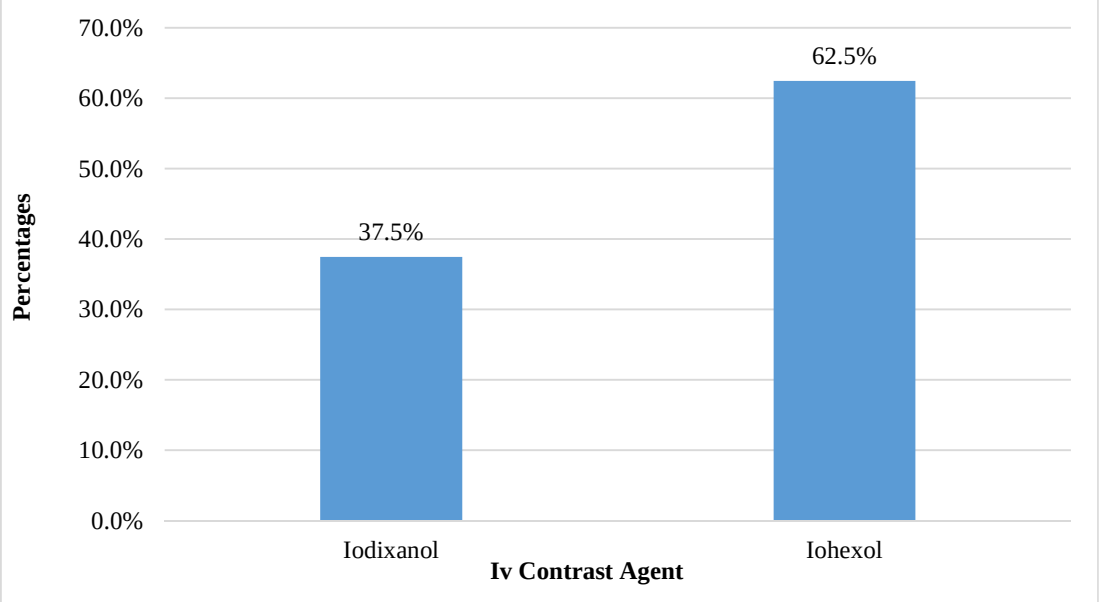


Table 7: "Descriptive analysis of the type of contrast agent in the study population" (N=40)

Type of contrast agent	Frequency	%
Iso osmolar	15	37.50%
Low osmolar	25	62.50%

Among the study population, 15 (37.50%) took Iso osmolar, and 25 (62.50%) were taken low osmolar. (Table 7 & Figure 11)

Figure 11: "Pie chart of type of contrast agent in the study population" (N=40)

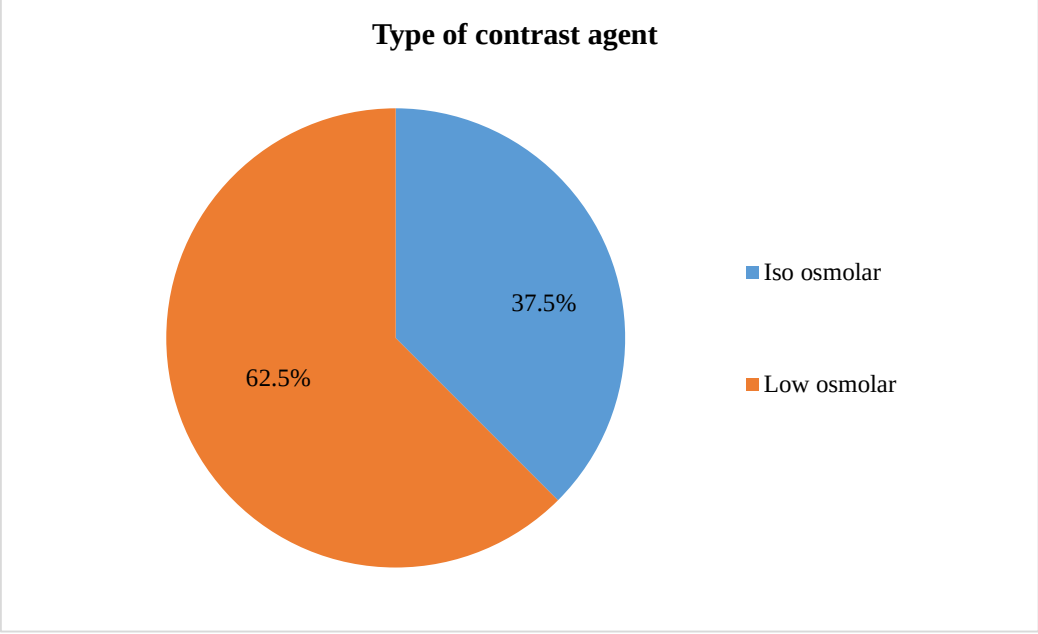


Table 8: "Descriptive analysis of patient weight in study population" (N=40)

Parameter	Mean ± SD	Median	Minimum	Maximum
Patient Weight (in kg)	70.23 ± 17.64	65.50	43.00	120.00

The mean patient weight was 70.23 ± 17.64 (in kg), ranged between 43 to 120 kg in the study population. (Table 8)

Table 9: Descriptive analysis of serum creatine in study population (N=40)

Parameter	Mean ± SD	Median	Minimum	Maximum
Baseline Serum Creatine (mg/dl)	1.03 ± 0.28	1.00	0.50	1.80
Serum creatinine after 48 - 96 Hours (mg/dl)	1.03 ± 0.28	1.00	0.50	1.80
Baseline creatinine clearance (ml/min)	83.17±33.62	81.25	34.10	183.30
Creatinine clearance after 48 - 96 hours (ml/min)	83.11 ± 33.54	80.95	34.20	183.30

The mean baseline serum creatinine was 1.03 ± 0.28 (mg/dl) and serum creatinine after 48 - 96 hours was 1.03 ± 0.28 (mg/dl). The mean baseline creatinine clearance was 83.17 ± 33.62 (ml/min), and creatinine clearance after 48 - 96 hours was 83.11 ± 33.54 (ml/min) in the study population. (Table 9)

Table 10: "Descriptive analysis of comorbidities in the study population" (N=40)

Comorbidities	Frequency	%
DM	7	17.50%
DM and HTN	6	15.00%
HTN	5	12.50%
No	22	55.00%

Among the study population, 7 (17.50%) participants had diabetes, 6 (15%) participants had diabetes & hypertension 5 (12.50%) participants had hypertension. (Table 10 & Figure 12)

Figure 12: "Bar chart of comorbidities in the study population" (N=40)

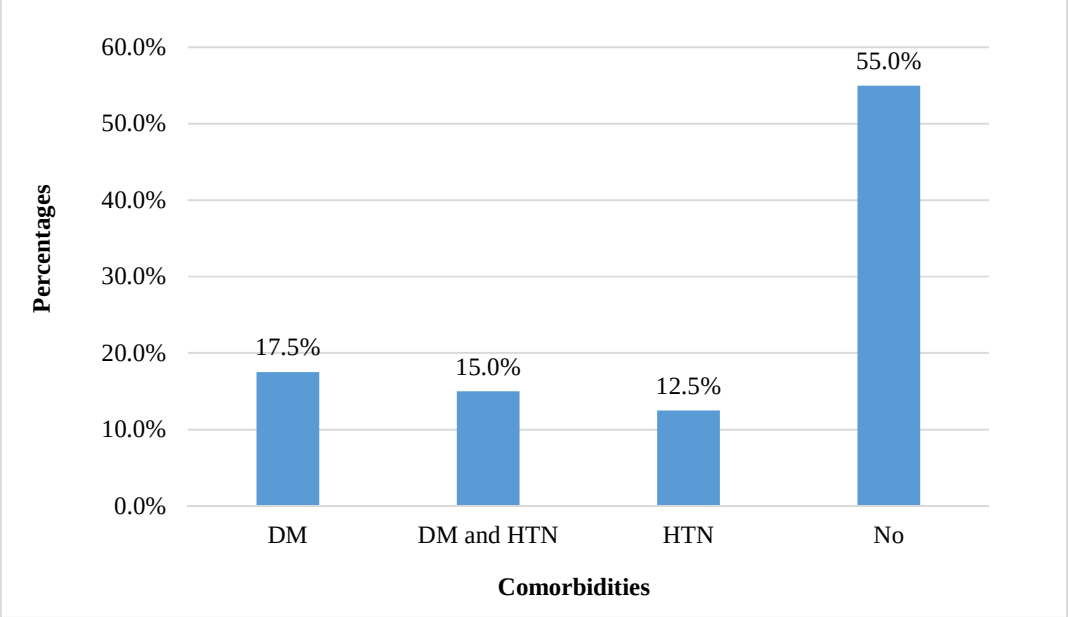


Table 11: Comparison of mean of baseline and after 48 to 96 hours serum creatine between IV contrast agent (N=40)

Parameter	IV contrast agent (Mean± SD)		P value
	Iodixanol (N=15)	Iohexol (N=25)	
Baseline serum Creatine (mg/dl)	1.07 ± 0.33	1.01 ± 0.25	0.527
Serum creatinine after 48 - 96 hours (mg/dl)	1.09 ± 0.33	1 ± 0.25	0.302

The mean of baseline serum creatine was 1.07 ± 0.33 (mg/dl) in the iodixanol group, and it was 1.01 ± 0.25 in the Iohexol group. The difference between the two groups was statistically insignificant. (p-value 0.527). The mean of serum creatine after 48 - 96 hours was 1.09 ± 0.33 (mg/dl) in the iodixanol group, and it was 1 ± 0.25 in the Iohexol group; the difference between the two groups was statistically insignificant. (p-value 0.302). (Table 11)

Table 12: Comparison of mean serum creatinine in pre-operative and after 48 to 96 hours among the Iodixanol (N= 15)

Follow-up periods	Mean± SD	"Mean Difference"	"95% CI of mean difference"		P-value
			Lower	Upper	
Baseline serum Creatine	1.07 ± 0.33				
Serum creatinine after 48 - 96 hours	1.09 ± 0.33	0.03	0.03	0.08	0.301

Among the iodixanol group, the mean serum creatinine of baseline was 1.07 ± 0.33 and after 48 to 96 hours was 1.09 ± 0.33. The difference between baseline and after 48 to 96 hours was statistically insignificant (P value 0.301). (Table 12 & Figure 13)

Figure 13: Bar chart of serum creatinine in pre-operative and after 48 to 96 hours among the Iodixanol (N= 15)

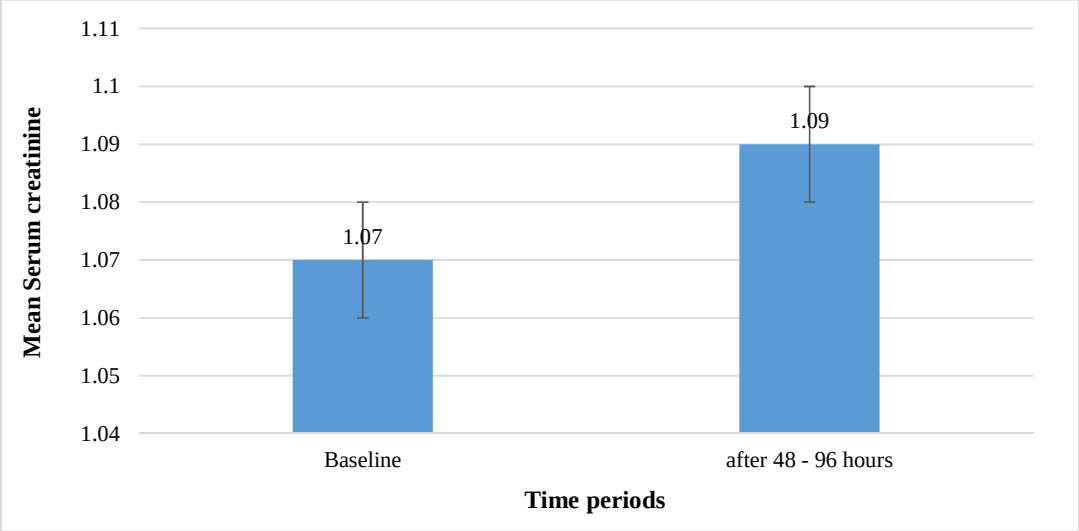


Table 13: Comparison of mean serum creatinine in pre-operative and after 48 to 96 hours among the Iohexol (N= 25)

Serum Creatine Follow-up periods	(Mean± SD)	"Mean Difference"	"95% CI of mean difference"		P-value
			Lower	Upper	
Baseline	1.01 ± 0.25				
Serum creatinine after 48 - 96 hours	1 ± 0.25	0.01	0.06	0.08	0.722

Among the iohexol group, the mean serum creatinine of baseline was 1.01 ± 0.25 and after 48 to 96 hours was 1 ± 0.25. The difference between baseline and after 48 to 96 hours was statistically insignificant (P value 0.722). (Table 13 & Figure 14)

Figure 14: Bar chart of mean serum creatinine in pre-operative and after 48 to 96 hours among the iohexol (N= 25)

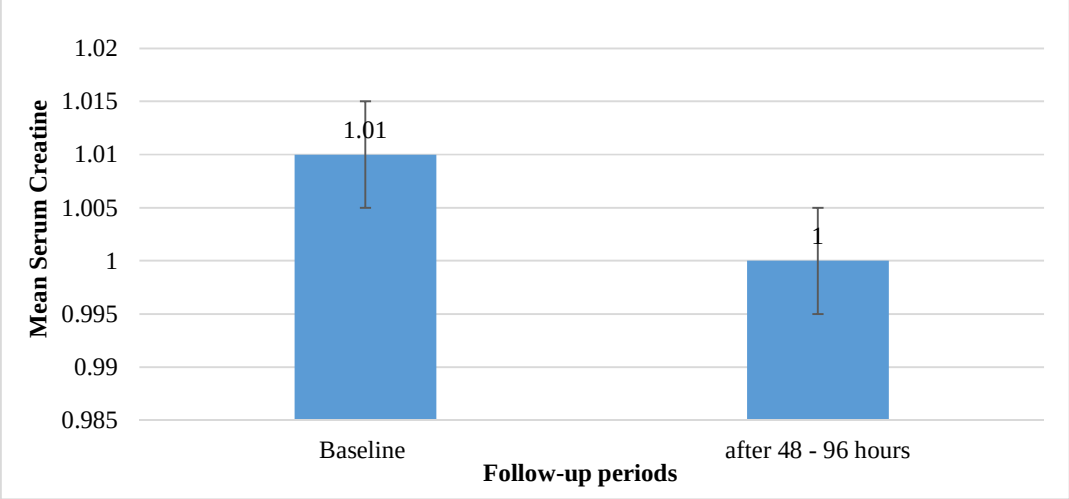


Table 14: Comparison of median change serum creatinine between the IV contrast group (N=40)

Parameter	Iv Contrast Agent		Mann Whitney U test (P-value)
	Iodixanol Median (IQR)	Iohexol Median (IQR)	
Change serum creatinine (N=40)	0 (0, 10)	0 (-10, 10.56)	0.525

Among the people with iodixanol group, the median serum creatinine change was 0 (IQR 0 to 10) and it was 0 (IQR -10 to 10.56) in people with iohexol group. The difference in the serum creatinine change between IV contrast agent was statistically not significant (P Value 0.525). (Table 14)

Table 15: Comparison of gender between iv contrast agent (N=40)

Gender	Iv Contrast Agent		Chi square	P value
	Iodixanol (N=15)	Iohexol (N=25)		
Male	9 (60%)	16 (64%)	0.064	0.800
Female	6 (40%)	9 (36%)		

In the Iodixanol group, 9 (60%) were male participants, and 6 (40%) were female participants. In the Iohexol group, 16 (64%) were male participants, and 9 (36%) were female participants. The association between gender and Iv Contrast Agent was statistically insignificant (P value 0.800). (Table 15 & Figure 15)

Figure 15: "Cluster bar chart of comparison of gender between iv contrast agent" (N=40)

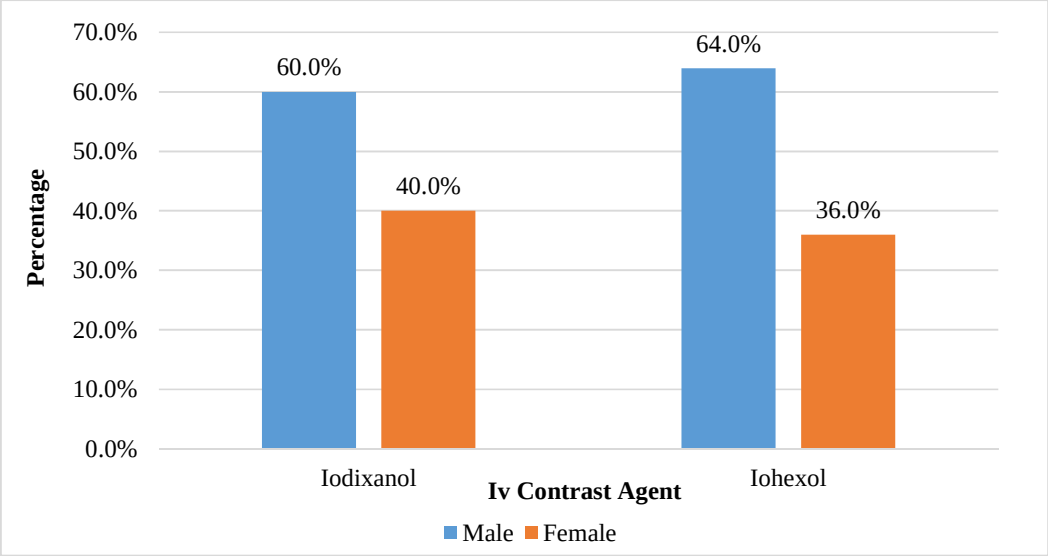


Table 16: Comparison of comorbidities between iv contrast agent (N=40)

Comorbidities	Iv Contrast Agent		Chi square	P value
	Iodixanol (N=15)	Iohexol (N=25)		
Yes	8 (53.33%)	10 (40%)	0.673	0.412
No	7 (46.67%)	15 (60%)		

In the Iodixanol group, 8 (53.33%) had comorbidities. In the Iohexol group, 10 (40%) had comorbidities. The association between comorbidities and Iv Contrast Agent was statistically insignificant (P value 0.412). (Table 16 & Figure 16)

Figure 16: "Cluster bar chart of comparison of comorbidities between iv contrast agent" (N=40)

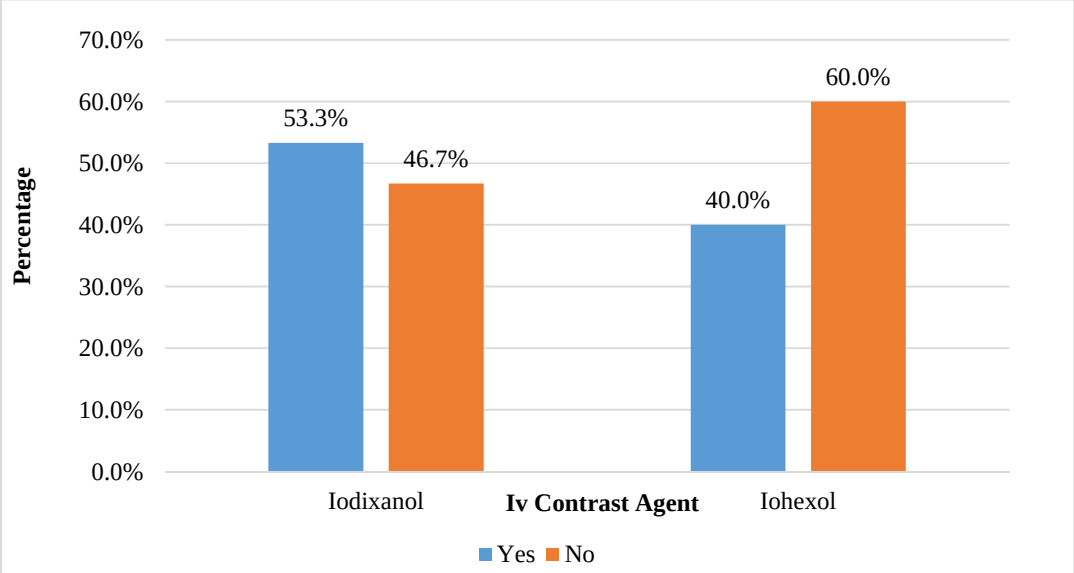


Table 17: "Descriptive analysis of baseline creatinine value in the study population" (N=40)

Baseline Creatinine Value	Frequency	Percentages
High (>1.4)	3	7.50%
Low (<=1.4)	37	92.50%

Among the study population, 3 (7.50%) participants were high (>1.4) creatinine, and 37 (92.50%) participants were low (<=1.4) creatinine. (Table 17 & Figure 17)

Figure 17: Bar chart of baseline creatinine value in the study population (N=40)

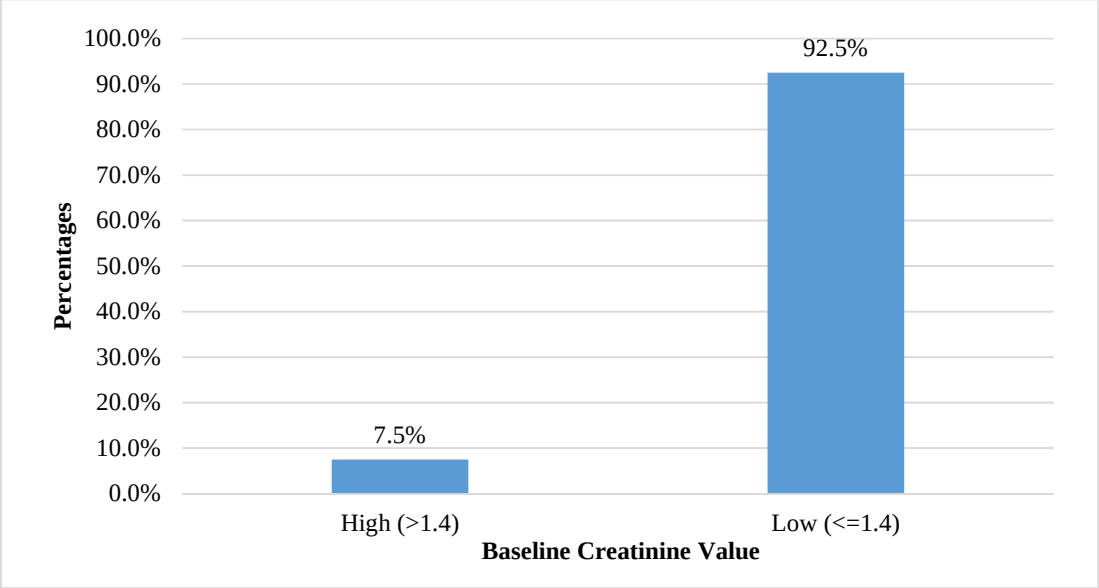


Table 18: Comparison of baseline creatinine value between iv contrast agent among comorbidities present population (N=18)

Baseline creatinine value	Iv Contrast Agent		Fisher exact P-value
	Iodixanol (N=8)	Iohexol (N=10)	
High (>1.4)	2 (25%)	1 (10%)	0.559
Low (<=1.4)	6 (75%)	9 (90%)	

The difference in IV contrast agents between the baseline creatinine is found to be insignificant, with a P-value of 0.559. (Table 18 & Figure 18)

Figure 18: Cluster bar chart of comparison of baseline creatinine value between iv contrast agent (N=18)

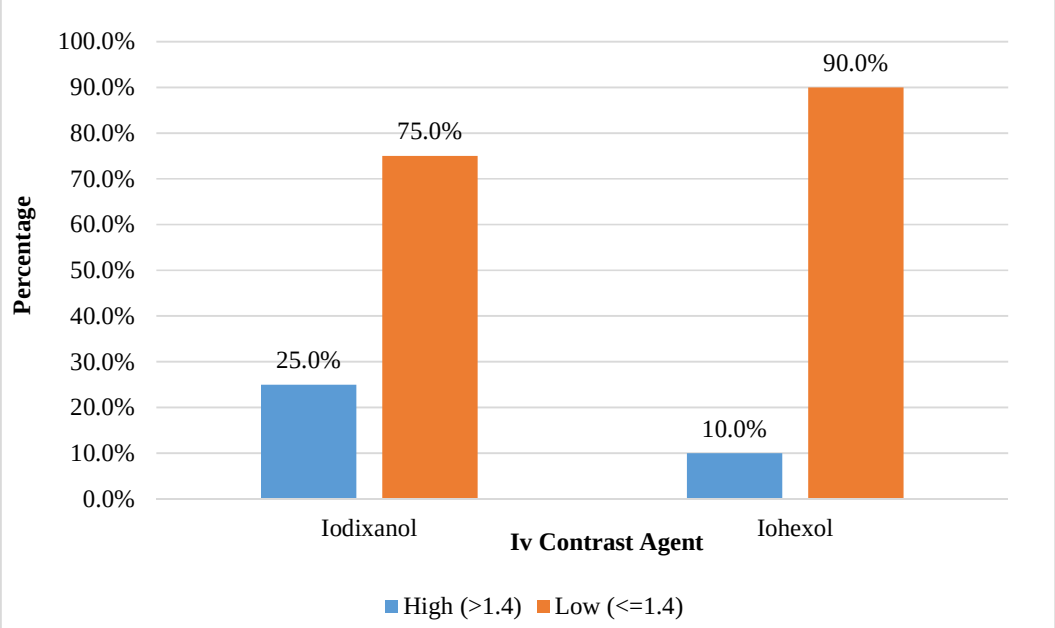


Table 19: "Descriptive analysis of CIN in the study population" (N=40)

Contrast induced nephropathy (CIN)	Frequency	Percentages
Positive (> 0.5 or > 25 % increase from baseline)	3	7.50%
Negative	37	92.50%

Among the study population, 3 (7.50%) were contrast-induced nephropathy (CIN). (Table 19 & Figure 19)

Figure 19: "Pie chart of CIN in the study population" (N=40)

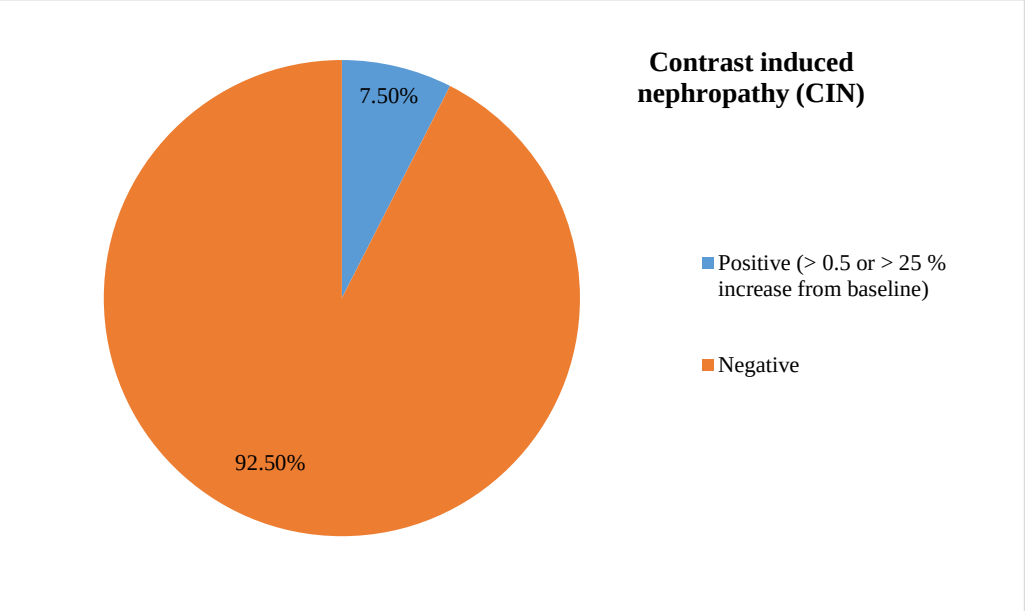


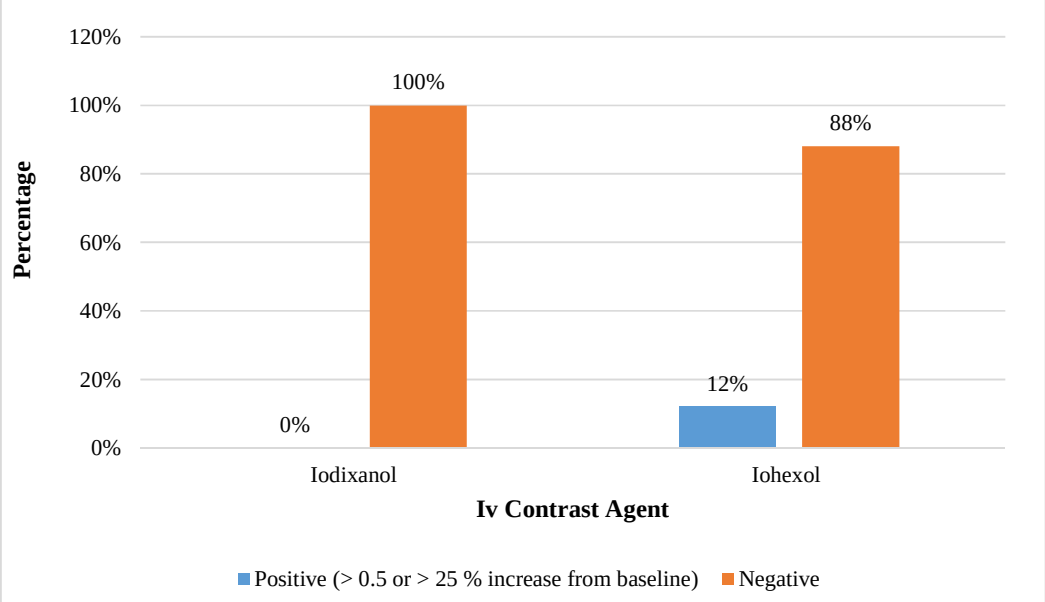
Table 20: Comparison of Contrast-induced nephropathy (CIN) between IV contrast agent (N=40)

CIN	Iv Contrast Agent		P value
	Iodixanol (N=15)	Iohexol (N=25)	
Positive (>0.5)	0 (0%)	3 (12%)	*
Negative	15 (100%)	22 (88%)	

**** Because there were no volunteers in the cells, no statistical test was performed.***

Out of 25 participants with Iohexol IV contrast agent, 3 (12%) participants had positive CIN. (Table 20 & Figure 20)

Figure 20: Cluster bar chart Contrast-induced nephropathy (CIN) between IV contrast agent (N=40)



DISCUSSION

CIN is a major concern among the general population and especially in subjects with comorbidities, especially when iodinated contrast material is used.[81] ICAs, which were first used in clinical practice in the 1950s, are by far the most effective and commonly used contrast materials in use today. Every year, it is projected that 75 million doses of ICAs are delivered around the world.[91] The ICAs are divided into four classes, each with its own set of physical, chemical, and biologic features. These ICAs are required to meet the requirements of a wide range of imaging modalities.

The most prevalent usage of iodinated contrast media is intravascular delivery, which is further divided into "intra-arterial and intravenous injection."

The chief method of contrast delivery in investigative catheter angiography and "catheter-directed arterial intervention," such as "percutaneous angioplasty" and stent implantation, is intra-arterial injection. The most frequent application of ICA is IV contrast injection for CT scanning.[91]

The type and amount of contrast to be produced are influenced by viscosity, iodine content, and osmolarity. Adverse responses to ICAs are prevalent, but severe ones are uncommon. High-osmolarity ionic monomeric ICAs cause the most severe acute responses and CIN. After nonionic dimers, late reactions are the most common. The best way to handle all unpleasant reactions is to avoid them in the first place. Documentation of subjects at risk for adverse responses and mitigation of risk through precautionary measures or the use of substitute (i.e., "ICA autonomous") diagnostic procedures can help to reduce the incidence of adverse effects. Furthermore, given the potential for negative outcomes related with this class of medications, clinicians

accountable for prescribing imaging tests that necessitate the use of ICAs must discuss the benefits, risks, and substitutes with their subjects.[70]

The actual process that causes CIN is unknown but lethal, and ischemia damage to tubular cells has been proposed as contributing factor. One of the causes for CIN is augmented fluid viscosity due to the contrast agent concentration in the medullar hyperosmolar environment, which primes to reduced flow in the medullary tubules and arteries.[92] One of the methods hypothesized to produce tubular cell injury is the direct cytotoxic impact of CM on tubular cells. Kidney damage is expected to increase as a result of the risk factors.[93]

There is still debate on whether certain CM types with different osmolarities are linked to a lower incidence of CI-AKI. Despite significant advances in improving the quality of contrast media, doctors continue to be concerned about acute kidney impairment following intravascular contrast injection.[80] Hence the present study aimed to find the incidence of CIN among the IOCM group and LOCM group in the general population.

The present study involved 40 subjects with male predominance (62.50%), and female was 37.50%. The mean patient weight was 70.23 ± 17.64 (in kg), ranged between 43 to 120 kg in the study population. The mean baseline S Cr was 1.03 ± 0.28 (mg/dl) and serum creatinine after 48 - 96 hours was 1.03 ± 0.28 (mg/dl). The mean baseline creatinine clearance was 83.17 ± 33.62 (ml/min), and creatinine clearance after 48 - 96 hours was 83.11 ± 33.54 (ml/min) in the study population. A meta-analysis by Zhao, F et al.[80] 2019, involved 2190 diabetic subjects with or without chronic renal disease, where the proportion of IOCM was 51.23% and in LOCM was 48.76%. A large institutional review by McDonald et al.[81] involved 5758 subjects with male predominance (40.77% women, 59.22% men).

Out of the study population, 5 (12.50%) were aged up to 30 years, 7 (17.50%) were aged between 31 to 45 years, 15 (37.50%) were aged between 46 to 60 years, and 13 (32.50%) participants was >60 years.

The group iodixanol (iso-osmolar) involved 37.50%, and iohexol (LOCM) involved 62.50%. In our study population, the comorbidities recorded were diabetes in 17.50%, diabetes and hypertension in 15%, and hypertension in 12.50%. The mean baseline serum creatinine among the 2 groups showed insignificant difference (p-value 0.527) (iodixanol group -1.07 ± 0.33 (mg/dl) vs 1.01 ± 0.25 in Iohexol group). There was an insignificant difference in the mean serum creatinine between the 2 groups (1.09 ± 0.33 (mg/dl) in the iodixanol group VS 1 ± 0.25 in the Iohexol group, p-value 0.302). Further, the difference between baseline means serum creatinine and post-48-96hrs was insignificant in both the iodixanol group and the iohexol group. (P-value 0.30, P-value 0.722). A study by Nguyen S et al.[83] found the baseline serum creatine in the Iodixanol group had decreased from 1.77 mg/dL +/- 0.24 to 1.65 mg/dL +/- 0.35 (P = .046) at day 1; however, the change was insignificant at 3rd day. In the Iopromide group, there was an increased SCr from 1.75 mg/dL +/- 0.32 at baseline to 1.8 mg/dL +/- 0.42 at the first day and at day 3, the serum creatine levels were insignificant. Similar results were found in our study.

The association of gender and IV contrast agents across the groups was insignificant and found male predominance in both the groups. (P-value 0.800). Although the relation between comorbidities and IV contrast agent was insignificant (P value 0.412), the iodixanol group found a greater proportion (53.33%) compared to the Iohexol group (40%). Univariate analysis by Sonhaye, L et al.[94] found renal failure, diabetes, age greater than 55 years, and intravenous contrast doses > 150 mL were all risk factors for CIN. Similar outcomes were found in Colling et al.[95] and thus

former study showed that only diabetes found to be autonomously associated with an augmented risk for CIN in multivariate analysis. However, these studies found these correlations in contrast media with low osmolarity non-ionic form.

In the overall study population majority of them (92.50%) had ≤ 1.4 creatine levels, and 7.50% had >1.4 creatine levels. The difference in IV contrast agents between the baseline creatinine is found to be insignificant, with a P-value of 0.559. The intravascular delivery of iodinated contrast media causes CI-AKI, which is a serious side effect. In a meta-analysis by Zhoa F et al. of 15 RCTs involving 2190 patients compared the effect of IOCM and LOCM on the prevalence of CI-AKI in diabetic subjects. They found that the use of IOCM had an insignificant benefit over LOCM in preventing CI-AKI in diabetic subjects with or without chronic kidney disease (CKD) when CI-AKI was defined as an absolute SCr increase (0.5 mg/dl) or a When CI-AKI was defined as an absolute elevation in SCr (0.5 mg/dl), the incidence of IOCM was lower than that of LOCM. More importantly, IOCM was connected to a decreased likelihood of negative outcomes when compared to LOCM.[80]

More than 130 patients with CKD and diabetes mellitus who underwent angiography were randomized to receive either "iodixanol or iohexol" in the NEPHRIC trial. "Iodixanol was a safer agent, at least in those at higher risk of CI-AKI ("defined by an initial increase in SCr level of 0.5 mg/dl"), such as those with chronic renal failure due to diabetes mellitus." [34] Other studies, on the other hand, found an insignificant difference in CI- AKI incidence among IOCM and LOCM in high-risk patients (defined as an initial elevation in SCr level 0.5 mg/dl).[15] The results of studies comparing the nephrotoxicity of IOCM and LOCM were mixed.[78,87,96] However, in our study, the association of comorbidities and SCr levels in either group was insignificant.

The overall incidence of contrast-induced nephropathy (CIN) was 7.50%. In 25 subjects in Iohexol IV contrast agent,12% showed positive for CIN. When IOCM was compared to iopromide, iopamidol, iomeprol, or ioversol, Reed et al.[85] discovered that iodixanol had a lower CI-AKI incidence than iohexol or ioxaglate. However, similar results were not achieved when IOCM was compared to iopromide, iopamidol. In a prospective study of 299 patients conducted by Rudnick, M et al.[86] the incidence of CIN was found to be 21.8 percent in the iodixanol group and 23.8 percent in the ioversol group (P = 0.78). Another meta-analysis by Eng, J et al.[82] found that the iso-osmolar contrast media agent iodixanol had a slight reduction in CIN risk when compared to a diverse group of LOCM that had just reached statistical significance in a meta-analysis (P = 0.045).

However, this proof for this evidence was moderate. In another meta-analysis by Han, X et al.[50] found numerous outcomes were discovered after incorporating 12 prospective RCTs to relate iso-osmolar CM, iodixanol, with LOCM for measuring the occurrence of CIN solely in subjects with DM: 1) Iodixanol is not superior to LOCM in terms of dropping the risk of CIN; 2) If CIN is well-defined as a comparative rise in SCr of at least 25% from the reference point, iodixanol exhibited a non-significantly lower CIN incidence. However, the outcome does not appear to be very solid; 3) Iodixanol outperforms iohexol in terms of reducing the risk of CIN; 5) The difference between iodixanol and other non-iohexol LOCMs was not evident. Our research yielded similar results.

CONCLUSION

- The present study involved 40 subjects with male predominance (62.50%), and female was 37.50%. The mean patient weight was 70.23 ± 17.64 (in kg), ranged between 43 to 120 kg in the study population. The mean baseline SCr was 1.03 ± 0.28 (mg/dl) and SCr after 48 - 96 hours was 1.03 ± 0.28 (mg/dl). The mean baseline creatinine clearance was 83.17 ± 33.62 (ml/min), and creatinine clearance after 48 - 96 hours was 83.11 ± 33.54 (ml/min) in the study population.
- The group iodixanol (iso-osmolar) involved 37.50%, and iohexol (LOCM) involved 62.50%.
- The comorbidities recorded were diabetes in 17.50%, diabetes and hypertension in 15%, and hypertension in 12.50%. The mean baseline serum creatinine among the 2 groups showed insignificant difference (p-value 0.527) (iodixanol group -1.07 ± 0.33 (mg/dl) vs 1.01 ± 0.25 in Iohexol group). There was an insignificant difference in the mean serum creatinine between the 2 groups (1.09 ± 0.33 (mg/dl) in the iodixanol group VS 1 ± 0.25 in the Iohexol group, p-value 0.302).
- Further, the difference between baseline mean serum creatinine and post 48-96 hrs was insignificant in both the iodixanol group and iohexol group. (P-value 0.30, P-value 0.722).
- The association of gender and IV contrast agents across the groups was insignificant and found male predominance in both the groups. (P-value 0.800). Although the association between comorbidities and IV contrast agent was insignificant (P value 0.412), the iodixanol group found a greater proportion (53.33%) compared to the Iohexol group (40%).

- In the overall study population majority of them (92.50%) had ≤ 1.4 serum creatinine levels, and 7.50% had >1.4 creatinine levels.
- The difference in IV contrast agents between the baseline creatinine is found to be insignificant, with a P-value of 0.559.
- The overall incidence of contrast-induced nephropathy (CIN) was 7.50%. In 25 subjects in Iohexol IV contrast agent,12% showed positive for CIN.

The results of our study show that iodixanol to have no risk of CIN, but Iohexol found a 12% incidence of CIN.

LIMITATIONS AND RECOMMENDATIONS

- Small sample size and research restricted to a single centre limits our results to be generalized
- There was an inequal distribution of cases for the 2 types of contrast medium limiting our results.
- Other possible causes of deranged renal function can limit our results.
- Further multicentric, randomized controlled trials are necessary to see the potential of these two iodized contrast dyes in CT imaging as India holds a large number of subjects who are subjected to CT consultation.

SUMMARY

This study was a hospital-based observational study with subjects aged greater than 18 years. This study aimed to assess the incidence of CIN among the iso-osmolar (IOCM) group and low-osmolar contrast media (LOCM) group in the general population.

A total of 40 subjects were included in the final analysis. The group iodixanol (iso-osmolar) involved 37.50%, and iohexol (LOCM) involved 62.50%. The comorbidities recorded were diabetes in 17.50%, diabetes and hypertension in 15%, and hypertension in 12.50%. The mean baseline serum creatinine among the 2 groups showed insignificant difference (p-value 0.527) (iodixanol group -1.07 ± 0.33 (mg/dl) vs 1.01 ± 0.25 in Iohexol group). There was an insignificant difference in the mean serum creatinine between the 2 groups (1.09 ± 0.33 (mg/dl) in the iodixanol group VS 1 ± 0.25 in the Iohexol group, p-value 0.302). The association between comorbidities and IV contrast agents was insignificant (P value 0.412). The iodixanol group found a greater proportion (53.33%) compared to the Iohexol group (40%). In the overall study population majority of them (92.50%) had ≤ 1.4 creatine levels, and 7.50% had >1.4 creatine levels. The overall incidence of contrast-induced nephropathy (CIN) was 7.50%. In 25 subjects in Iohexol IV contrast agent, 12% showed positive for CIN. The results of our study show that iodixanol to have no risk of CIN, but Iohexol found a 12% incidence of CIN.

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ANNEXURE I-CONSENT FORM

TITLE OF THE STUDY: "EFFECT ON KIDNEY FUNCTION OF INTRAVENOUS CONTRAST-ENHANCED CT USING ISO-OSMOLAR AND LOW-OSMOLAR IODINATED CONTRAST MEDIUM"

INVESTIGATOR: REG. NO. BS0119008

GUIDE: DR. SANTOSH PATIL

INTRODUCTION AND PURPOSE:

The purpose of this study was to to find the incidence of CI-AKI using iso-osmolar (IOCM) and low-osmolar contrast media (LOCM) in the general population. The use of contrast medium (CM) in diagnostic and interventional procedures is becoming more common. As a result, the frequency of iatrogenic renal function impairment due by CM exposure, also known as contrast-induced nephropathy, is increasing (CIN).

PROCEDURE:

I request you to kindly participate in the study titled **"EFFECT ON KIDNEY FUNCTION OF INTRAVENOUS CONTRAST-ENHANCED CT USING ISO-OSMOLAR AND LOW-OSMOLAR IODINATED CONTRAST MEDIUM"** at Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi is being conducted by **REG. NO. BS0119008**, Postgraduate in Radio diagnosis at J.N. Medical College, Belagavi, Karnataka, under the guidance of Dr. _____, Dept. of Radio-diagnosis, J. N. Medical College, Belagavi. We request you to participate in this study as you are eligible to be included. During the study, you will be asked questions regarding your present and past medical history, and you

will be required to answer to the best of your knowledge. You will also be clinically examined as per the protocol drawn.

If you agree to participate in the study, please furnish the details pertaining to the study.

BENEFITS:

- No use of surgical equipment/ risk associated with it.

COMPLICATIONS:

- Minimal Exposure to Radiation. A single exposure to radiation during a CT scan usually does not cause any adverse effects.

ALTERNATIVES:

If you are not willing to take part in the study, your treatment, or any other further investigations the patient wants to undergo, in future, in KLE will not be affected by your decision.

VOLUNTARY PARTICIPATION/ WITHDRAWAL:

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part, you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or the sponsor may stop your participation in this study. Any important new findings may change your willingness to continue to take part in the study. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

COSTS:

NIL (The study is to be conducted on the participants who are advised CONTRAST ENHANCED COMPUTED TOMOGRAPHY as an investigation by the referring consultant, and the participants will bear the charges for it.)

Payment for Participation: No incentive will be paid to you for participating in this study.

COMPENSATION:

In the event that you become injured as a result of taking part in this study, treatment, whatever available at KLE Charitable hospital, Belagavi, will be offered to you. No reimbursement, compensation, or free medical care is given.

CONFIDENTIALITY:

All information collected about you during the course of the study will be kept confidential to the extent permitted by the law. The code numbers will identify you in this research record. Information from this study may be published, but your identity will be kept confidential in any publication/ presentation.

QUESTION:

If you have any enquiries in the future or in case of research-related injury illness, you may contact the following persons:

Name: Dr. Nitish Makhija

Mobile No: 8095691282

Email ID: nitish_makhija@yahoo.in

REG. NO. BS0119008	**Dr. _____**	**Dr. ROOPA BELLAD**
Post-Graduate, Department of Radio-Diagnosis, J.N. Medical College, Belagavi.	Guide, Professor, Department of Radio-Diagnosis, J.N. Medical College, Belagavi.	Professor, Chairman, J.N. Medical College Institutional Ethical Committee for Human Subjects Research.
Ph.0831-2473777, Ext. 1163 Mob-8095691282	Ph. No. 0831-2473777, Ext. 1163	Ph. No: 0831-2473777, Ext. 1529

CONSENT TO PARTICIPATE IN RESEARCH STUDY:

1. "I understand that I am participating in the study, which includes contrast enhanced computed tomography using IV contrast agent.

2. I confirm that I have read and understood the information in the patient information sheet. The procedure is explained to me in detail along with information about the advantages and disadvantages of taking part in the study. I have been given the opportunity to discuss all aspects of the trial, to ask questions, and hereby consent to participation in the trial outlined above.

3. I understand that the decision to take part in this study is completely voluntary, and I am aware that I can choose to withdraw from the study at any point of time.

4. I consent to the photographing or recording of the procedure to be performed, including appropriate portions of my body, for medical, scientific, or educational purposes, provided my identity is not revealed in the pictures or by the descriptive texts accompanying them.

5. I understand that there is no significant risk involved in the test that would be done in this study.

6. No guarantee or assurance has given by anyone as to the results that may be obtained.

7. My signature on this form signifies that I have willingly decided to participate after understanding the above information".

Participant's Name/ legally authorized representative _____

Signature _____

Name and signature of witness _____

Name and signature of interviewer _____

Date: _____

Place: _____

ANNEXURE-II

ETHICAL CLEARANCE

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed - to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
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Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 313 Date: 24/12/2019

To,

REG. NO. BS0119008
PG student in Radio-diagnosis,
J. N. Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"EFFECT ON KIDNEY FUNCTION OF INTRAVENOUS CONTRAST- ENHANCED CT USING ISO- OSMOLAR AND LOW-OSMOLAR IODINATED CONTRAST MEDIUM"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Anita Dalal)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research.
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research.
J.N.Medical College, Belagavi.

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ANNEXURE-III

STUDY PROFORMA

KAHER

J. N. MEDICAL COLLEGE, BELAGAVI.

DEPARTMENT OF RADIODIAGNOSIS

TITLE: "EFFECT ON KIDNEY FUNCTION OF INTRAVENOUS CONTRAST-ENHANCED CT USING ISO-OSMOLAR AND LOW-OSMOLAR IODINATED CONTRAST MEDIUM"

RESEARCH INVESTIGATOR: REG. NO. BS0119008

GUIDE: _____

PROFORMA FOR DATA COLLECTION

DATE OF INTERVIEW: _____

NAME OF THE PATIENT: _____

AGE (in years): _____ SEX: OP/IP NO _____

WEIGHT (in Kg):

MOBILE NUMBER: _____

CT STUDY: _____

CT NUMBER: _____

CHIEF COMPLAINTS **DURATION**

1.		
2.		
3.		

HISTORY OF PRESENTING ILLNESS

1.		
2.		
3.		

PAST HISTORY

1.		
2.		
3.		

CLINICAL EXAMINATION:

CVS:

RS:

BASELINE SERUM CREATININE:

SERUM CREATININE AFTER 48 TO 96 HOURS:

CT FINDINGS:

FINAL DIAGNOSIS:

ANNEXURE-IV

FIGURE 21: PHOTOGRAPH OF GE EVOLUTION 128 SLICE CT MACHINE AT KLES PRABHAKAR KORE HOSPITAL

PHOTOGRAPH OF CASES

FIGURE 22: PATIENT UNDERGOING RENAL ANGIOGRAPHY

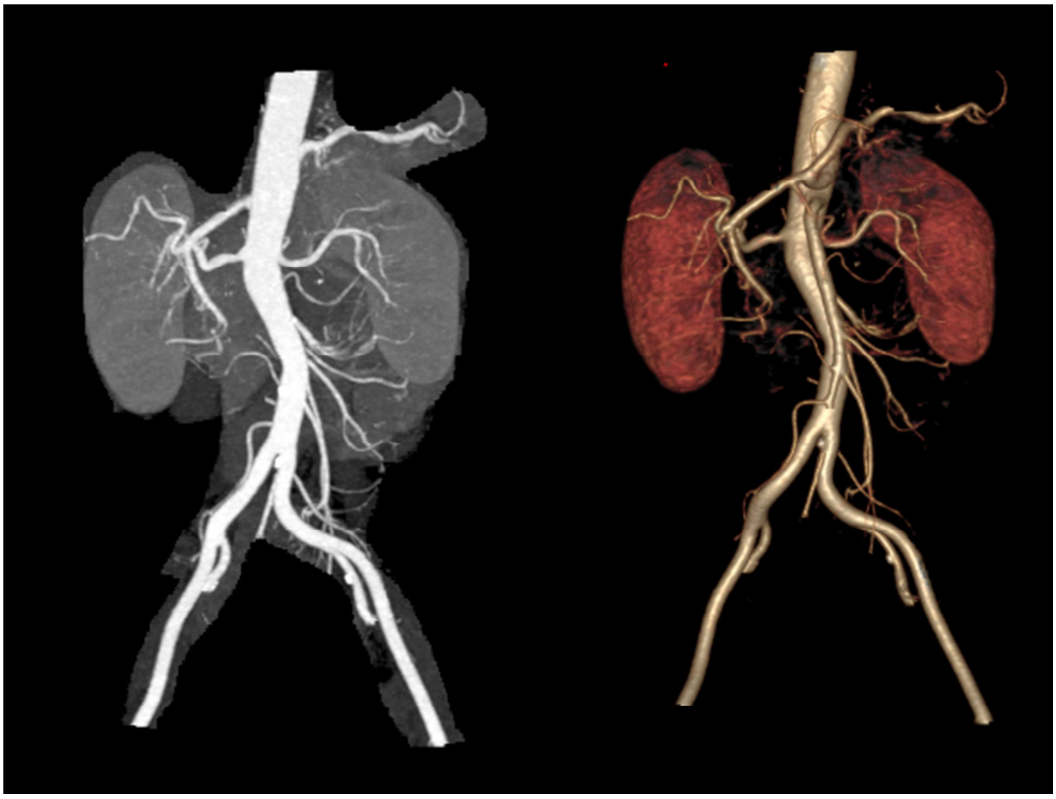


FIGURE 23: PATIENT UNDERGOING CECT ABDOMEN

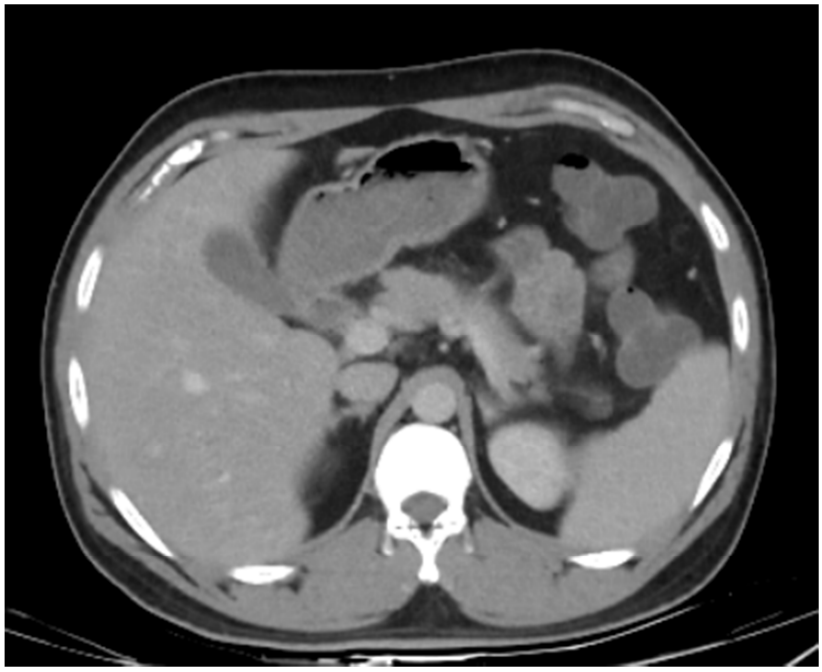


FIGURE 24: PATIENT UNDERGOING CT PULMONARY ANGIOGRAPHY

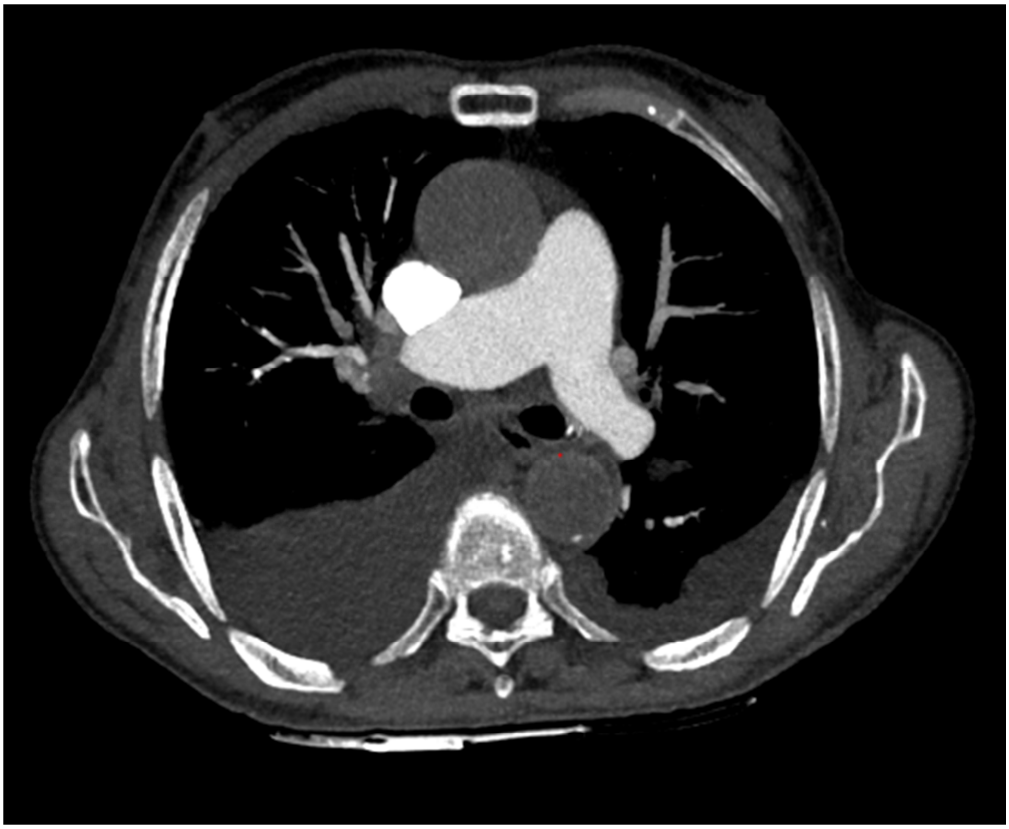


FIGURE 25: PATIENT UNDERGOING CECT NECK

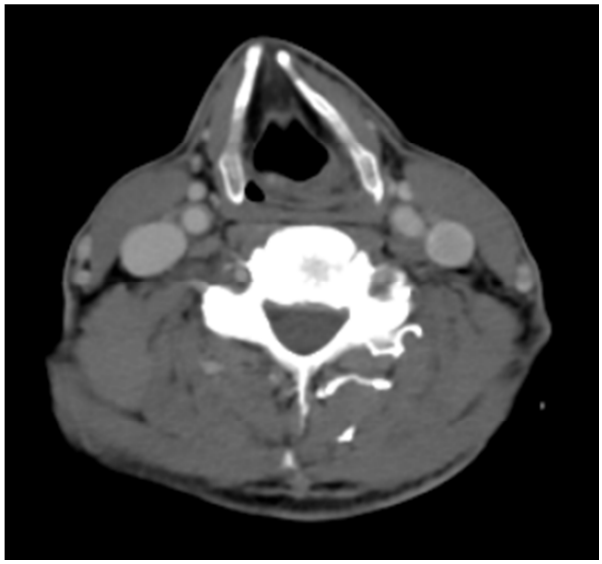
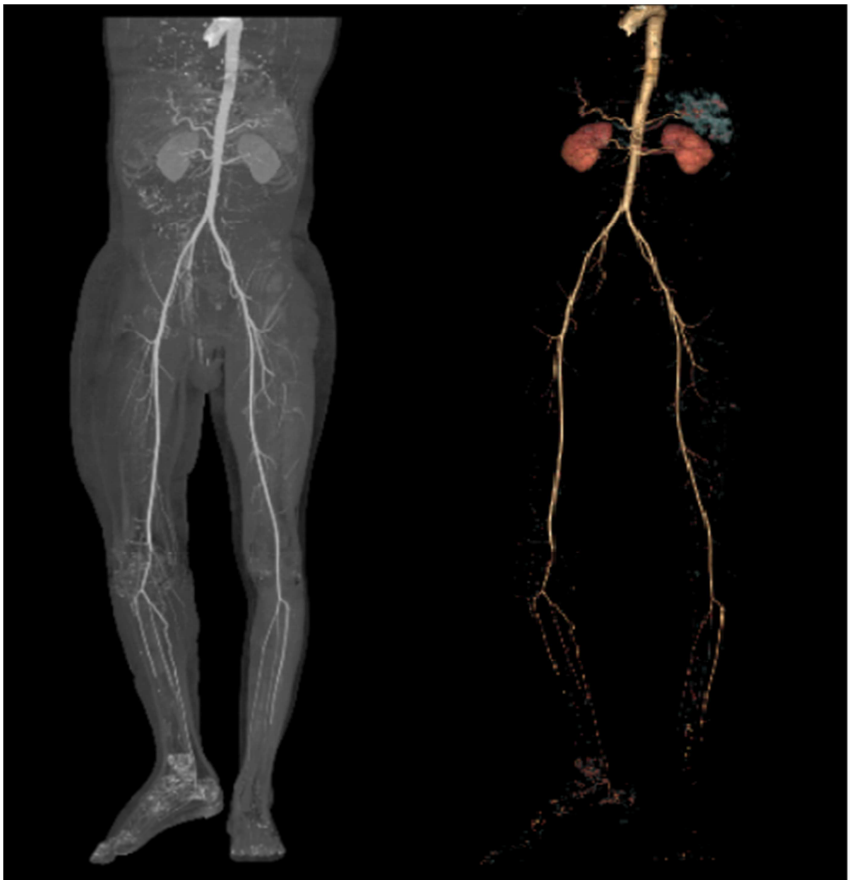


FIGURE 26: PATIENT UNDERGOING LOWER LIMB ANGIOGRAPGY



MASTER SHEET

S. No	CT Number	Age (In years)	Sex	Scan done	Date	IV contrast agent	Type of contrast agent	Patient weight	Baseline serum Creatine	Serum creatinine after 48 to 96 hours	Baseline Creatinine clearance (mL/min)	Creatinine clearance after 48 - 96 hours (mL/min)	COMORBITIES (DM/HTN)
1	C19970	42	Male	Cect abdomen + pelvis	17-Aug-2020	Iohexol	Low osmolar	76	1.1	0.8	94.0	129.3	No
2	C18868	51	Male	Cect thorax+ abdomen	30-Jul-2020	Iodixanol	Iso osmolar	54	0.8	0.9	83.4	74.2	No
3	C18315	24	Male	Ct pulmonary angio	21-Jul-2020	Iohexol	Low osmolar	68	0.7	0.8	156.5	136.9	No
4	C18042	85	Male	Cect neck	14-Jul-2021	Iohexol	Low osmolar	58	1.3	1.2	34.1	36.9	HTN
5	C 18015	70	Female	Cect abdomen + pelvis	14-Jul-2021	Iodixanol	Iso osmolar	45	0.9	1.0	41.3	37.2	DM and HTN
6	C17712	60	Female	Cect pelvis	03-Jul-2020	Iohexol	Low osmolar	61	1.1	1.2	52.4	48.0	DM
7	C17661	67	Female	Pulmonary angio	01-Jul-2020	Iodixanol	Iso osmolar	94	1.0	1.1	81.0	73.6	No
8	C17073	24	Female	Cect neck+ thorax	15-Jun-2020	Iohexol	Low osmolar	85	1.0	0.9	116.4	129.3	DM
9	C17085	26	Male	Cect brain	15-Jun-2020	Iohexol	Low osmolar	60	1.4	1.4	67.9	67.9	No
10	C17036	47	Male	Cect abdomen + pelvis	13-Jun-2020	Iohexol	Low osmolar	55	1.0	1.1	71.0	64.6	HTN
11	C15989	53	Male	Cect neck thorax	06-May-2020	Iohexol	Low osmolar	63	1.2	0.8	63.4	95.2	No
12	C 15581	55	Female	Cect abdomen	01-May-2020	Iodixanol	Iso osmolar	100	1.6	1.8	62.7	55.7	HTN
13	C15825	75	Female	Cect brain	28-Apr-2020	Iohexol	Low osmolar	85	0.9	0.8	72.5	81.5	No
14	C15725	82	Male	Pulmonary angio	20-Apr-2020	Iodixanol	Iso osmolar	51	1.2	1.2	34.2	34.2	DM and HTN
15	C15114	47	Male	Coronary angio	13-Mar-2020	Iohexol	Low osmolar	90	1.0	1.0	116.3	116.3	No
16	C15058	59	Male	Carotid angio	12-Mar-2020	Iodixanol	Iso osmolar	60	0.9	0.8	75.0	84.4	No
17	C15036	80	Female	Cect brain	12-Mar-2020	Iohexol	Low osmolar	62	1.1	1.0	39.9	43.9	DM and HTN
18	C15034	45	Male	Cect abdomen + pelvis	11-Mar-2020	Iohexol	Low osmolar	75	0.9	1.0	110.0	99.0	HTN
19	C15005	72	Female	Cect abdomen	10-Mar-2020	Iohexol	Low osmolar	65	0.6	0.8	87.0	65.2	No
20	C14939	27	Female	Urography	08-Mar-2020	Iohexol	Low osmolar	43	1.1	1.2	52.1	47.8	DM
21	C14930	60	Female	Ct neck	07-Mar-2020	Iodixanol	Iso osmolar	76	1.2	1.2	59.8	59.8	No
22	C14893	65	Male	Upper limb angio	07-Mar-2020	Iohexol	Low osmolar	71	1.6	1.6	39.3	39.3	DM
23	C14709	54	Male	Ct aortic angio	02-Mar-2020	Iodixanol	Iso osmolar	67	0.5	0.5	160.1	160.1	No
24	C14673	75	Male	Cect thorax	01-Mar-2020	Iohexol	Low osmolar	49	0.8	0.9	118.5	105.3	No
25	C14598	50	Female	Ct pulmonary angio	27-Feb-2020	Iodixanol	Iso osmolar	65	1.0	1.0	69.1	69.1	DM and HTN
26	C145382	40	Male	Cect brain	26-Feb-2020	Iohexol	Low osmolar	46	0.6	0.6	106.5	106.5	No
27	C14535	50	Male	Cect abdomen + pelvis	26-Feb-2020	Iodixanol	Iso osmolar	66	0.8	0.8	103.7	103.7	DM
28	C14503	31	Male	Lower limb angio	25-Feb-2020	Iohexol	Low osmolar	59	1.0	0.9	89.3	99.2	No
29	C14500	42	Female	Cect thorax	25-Feb-2020	Iohexol	Low osmolar	56	1.0	0.8	64.8	81.0	No
30	C14448	19	Male	Cect kub	24-Feb-2020	Iodixanol	Iso osmolar	120	1.1	1.1	183.3	183.3	HTN
31	C14449	43	Male	Cect abdomen + pelvis	24-Feb-2020	Iohexol	Low osmolar	80	1.3	1.2	82.9	89.8	No
32	C14380	42	Female	Cect abdomen + pelvis	21-Feb-2020	Iohexol	Low osmolar	75	1.0	1.3	86.8	66.7	DM
33	C14375	63	Female	Cect abdomen + pelvis	21-Feb-2020	Iohexol	Low osmolar	48	0.5	0.5	87.3	87.3	No
34	C14004	52	Male	Cect neck	09-Feb-2020	Iodixanol	Iso osmolar	80	1.2	1.3	81.5	75.2	No
35	C13951	71	Male	Cect thorax	07-Feb-2020	Iodixanol	Iso osmolar	100	1.8	1.6	53.2	59.9	DM and HTN
36	C13922	64	Male	Ct pulmonary angio	06-Feb-2020	Iohexol	Low osmolar	92	0.9	1.2	107.9	80.9	No
37	C13702	58	Male	Cect abdomen + pelvis	31-Jan-2020	Iohexol	Low osmolar	85	1.1	1.1	88.0	88.0	No
38	C13681	55	Male	Ct renal angio	30-Jan-2020	Iohexol	Low osmolar	63	1.0	0.8	74.4	93.0	DM
39	C13635	80	Female	Cect abdomen	29-Jan-2020	Iodixanol	Iso osmolar	96	1.2	1.3	56.7	52.3	DM and HTN
40	C13623	49	Male	Cect neck	29-Jan-2020	Iodixanol	Iso osmolar	65	0.8	0.8	102.7	102.7	No