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Nephrotoxicity of Iodinated Contrast Drugs: A comparative Analysis of Old Versus New, Ionic Versus Non Ionic Agents, Dose Effects, and the Impact of Relative Dehydration in Stroke Patients

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Introduction

Stroke is a type of cerebrovascular disease that impairs the functionality of the brain due to disturbance in the blood supply to the brain. There is approximately 1 stroke every 40 seconds, amounting to it being a leading cause of serious long-term disability [1]. It accounts for about 140,000 deaths annually with an incidence rate of 795,000 each year, necessitating need for prompt and accurate diagnosis and intervention. Stroke can either be hemorrhagic or ischemic in nature. Hemorrhagic stroke is when there is rupturing of blood vessels in the blood vessels in the brain and its majorly treated by reducing blood pressure in the brain or use of 'pro-hemostasis' medications. Ischemic stroke is when there is occlusion of the blood vessels supplying blood to the brain leading to shortage (hypoxemia) or no supply of blood supply (hypoxia) in the brain. It is majorly treated with thrombolytic medications that break down clots and must be administered early to prevent risk of dangerous bleeding or use of mechanical thrombectomy.

Neuroimaging technique such as computed tomography (CT) is important in stroke management due to its ability to provide accurate diagnosis, assessment of type and severity of stroke, etiology, as well as treatment selection and monitoring. Computed tomography angiography (CTA) enables evaluation of the major arteries providing blood to the brain and neck and it is administered via the peripheral line through the arm while computed tomography perfusion (CTP) enables evaluation of blood flow to the brain tissue at the capillary level when administered via the similar route [2]. Iodinated contrast media (ICM) produces image contrast due to differential photoelectric absorption between the media and the tissues in the body [3]. American Heart Association/ American Stroke Association Guideline 2018 recommends non-ionic contrast media (CM) for the evaluation of initial brain imaging and CTA for vessel evaluation if patients are suspected of having intracranial large-vessel occlusion [4]. However, Dzialowski et al reported increased risk in patients receiving intravenous iodinated contrast media (ICM) for CT angiography before intravenous (IV) thrombolysis which can be responsible for hemorrhagic transformation. Hemorrhagic transformation (HT) is a potential complication following an initial acute ischemic stroke worsening into hemorrhagic stroke [5]. This could be caused by loss of integrity of the blood-brain barrier due to vascular injury from ischemic stroke and can lead to leakage of blood and media transforming into hemorrhagic stroke [6]. Intravenous administration of iodinated contrast media is required for all computed tomography except NCCP (Non-contrasted computed tomography), buttressing the importance of these media in stroke management. Certain side effects are associated with these media such as nephrotoxicity in high risk patients, hemorrhage, cardiac side effects, and allergies, among others [7].

Contrast Induced Acute Kidney Injury (Ci-Aki)

After intravascular injection, the media is diluted in body fluids to enable visualization of organ then it is distributed to extracellular fluid. Due to poor binding to serum albumin, the contrast drug is filtered to be ultimately excreted by the kidneys. Contrast-induced acute kidney injury (CI-AKI) can be described as a rise in serum creatinine levels by≥0.3 mg/dl within 48 hrs of contrast administration. It can also be described as an absolute rise in serum creatinine of 0.5 mg/dl or more or a relative rise of 25% or more from baseline at 48 to 72 hrs after exposure to CM, in the absence of an alternative explanation for the rise [8]. It is also recommended by the Contrast-Induced Nephropathy Consensus Panel to measure relative creatinine level compared to absolute as the relative value is less sensitive to baseline renal function. Nephrotoxicity caused by contrast media is one of the major adverse events associated with administration of iodinated CM. It has been associated with progression to advanced stages of chronic kidney disease (CKD) and with increased risk for major adverse cardiac events (MACE) [9,10]. The incidence of CI-AKI varies from 2% in the general population to over 50% in high-risk groups [11]. Nephrotoxic effects of contrast media can be linked to three different mechanisms:

- **Interference With Vascular Hemodynamics:** after administration of these media there is increase in ROS (reactive oxygen specie) synthesis in particular O2-which induces an increase in tubule-glomerular feedback in the distal convoluted tubule, increasing renal hypo perfusion. The thick ascending loop located in the outer medulla is sensitive to hypoxia [12]. This superoxide also stimulates the reabsorption of sodium chloride in the nephrons which significantly increases oxygen demand that outweighs oxygen supply

which can lead to hypoxia [13]. There is also an increase in the synthesis of endothelin, angiotensin II, adenosine, and thromboxane A2, and a reduction in the synthesis of nitric oxide (NO) which makes it acquire a "vasoconstriction" phenotype.

- **Disruption of Intra Tubular Fluid Volume and Composition:**
  Hyper-viscosity of contrast media further impairs glomerular hemodynamics by reducing blood flow in both glomerular and tubular capillaries (filtration rate), thereby increasing contact time of ICM with nephrons and potentiating their cytotoxicity. In addition, owing to negligible tubular reabsorption, its concentration rises progressively as it passes through the tubular segments, to become highly concentrated in the medullary part of the distal nephron, increasing its fluid viscosity in an exponential manner [10]. In vitro, the osmolar power of ICM has been shown to exert a toxic effect on tight junction proteins [14].
- **Direct Nephrotoxic Effect on Nephrons:**
  ICM are tri-iodinated benzene derivatives. Iodine has three different forms that are: ionic (I-), molecular (I2), or hydrated H2OI+ (an antiseptic agent due to its oxidizing power). "The iodine contained in ICM has a direct toxic effect on human cells, and in particular on renal tubular epithelial cells (vacuolization of tubular cells and osmotic nephrosis) and on endothelial cells. Several mechanisms are involved but the exact pathophysiological mechanism of this cytotoxicity remains unknown. Direct activation of caspases-3 and -9 and the bcl2 pathway are involved in apoptosis, disrupting mitochondrial activity and physicochemical properties of ICM are also possible ways [9,15]. Furthermore, due to its strong oxidizing power, ICM stimulate the synthesis of reactive oxygen species (ROS) that are toxic to endothelial and tubular epithelial cells, which stimulate the JNK/p38 signaling pathway that is involved in the activation of apoptosis intrinsic pathway [16]. However, according to Liu et al, the increase in ROS synthesis appears to be 5 times more than a consequence of direct ICM toxicity on tubular cells than the cause of cellular damage [12].

Risk Factors for Contrast Induced Acute Kidney Injury

There are a number of factors that predisposes patients to this condition such as patients' related factors and CM related factors. Patients related factors include: chronic kidney disease (GFR < 60 mL/min per 1.73 m2), diabetes mellitus and diabetic nephropathy, are conditions that can worsen the state of kidney function due to the reduced efficacy of the kidney. Older age >65 years: higher risk associated with old age is multifactorial, which includes age related changes in renal function and the presence of old vessels of coronary artery disease. Other factors may include simultaneous use of nephrotoxic drugs such as aminoglycosides, colistin, as well as antifungals such as amphotericin B and states of reduced kidney perfusion (dehydration, congestive heart failure, and hemodynamic instability, etc). Contrast media related risk factors include: high volume of CM, as it is important to ensure that low but sufficient volume of CM is used. Lower doses of CM (definitions of low dose are variable: < 30-125 mL) is recommended when they are found to be less nephrotoxic. Use of hyperosmolal CM which is considered to be the first generation has been phased out due to the higher risk associated with it, as well as multiple exposures to CM in short term. Route of administration is also considered a factor due to the higher risk of CI-associated with intraarterial CM administration when compared to intravenous CM administration especially when given supra renally [17].

Historical Perspective

Contrast media are derived from 2, 4, 6-triiodinated benzene ring which is a toxic water insoluble liquid whose solubility can be altered by substituting the acidic group. ICM can either be water soluble or water insoluble compounds. The water soluble compounds are wildly used compared to the water insoluble ones. The only currently approved agent is ethiodinized poppy seed oil (lipiodol). For the water soluble media, ionic monomers ionize into an anion and cation components (increasing osmolality) and delivers 3 iodine atoms, whereas ionic dimers would deliver 2 ionic components per 6 iodine atoms (ratio, 1:3). Non-ionic monomers do not break up in solution; a single molecule delivers 3 iodine atoms (ratio, 1:3), whereas a single non ionic dimer delivers 6 iodine atoms (ratio, 1:6). Thus, non ionic dimers are the most ideal contrast agents as they deliver the most iodine with the least effect on osmolality [18].

Development of contrast media from ionic monomers through non-ionic monomers to non ionic dimers increase the number of iodine atoms associated to each molecules molecule from 1.5 to 6.0. These changes resulted in less number of molecules to deliver sufficient amount of iodine for imagining that is lower osmolality. The reduced osmolality in non-ionic contrast media makes it more similar to blood plasma and are less likely to interfere with vascular hemodynamics or disrupt intra-tubular fluid volume [19].

The water soluble contrast media are majorly classified based on their osmolality which indicates the concentration of all particles dissolved in body fluids. High osmolality contrast media (HOCM) also known as the ionic contrast media are the first generation contrast media with osmolality approximately five to eight times of serum (1,500–1,800 mOsm/kg), for example, iothalamate and diatrizoate. Newer generations have lower osmolality and they are: non-ionic low-OCM (LOCM, example being iohexol) and non-ionic iso-OCM (IOCM, example being iodixanol) having osmolalites of 600–850 mOsm/ kg (two to three times plasma osmolality) and ~290 mOsm/kg (similar to that of plasma) respectively [18,20]. Molecular size and number of the organic component binding the iodine are the primary determinant of the osmolality and viscosity of these media. McCollough et al conducted a meta-analysis of 16 randomized controlled trials and discovered that CI-AKI occurred less in patients administered iodixanol when compared with the LOCM [21]. In addition, recent meta-analysis also concluded that iodixanol use is associated with less incidence of nephrotoxicity compared with LOCM [17]. Also, a study conducted to compare Major Adverse Renal and Cardiac Events (MARCE) shows a relative reduction of risk by 9.32% when IOCM are used when compared with LOCM [22].

Comparison between old and new Contrast Agent

A study carried out by The Interventional Management of Stroke III trial assessed 5 efficacy and safety end points, including asymptomatic and symptomatic intracranial hemorrhage, as well as mortality between iodixanol and LOCM among patients with stroke treated with endovascular therapy, discovered that both the unadjusted and adjusted results for efficacy and safety end points assessed favored the use of iodixanol (IOCM) over LOCM and can be attributed to less endothelial cytotoxic effect in the thrombotic process [5]. An in vitro study carried out in rats by Morales et al also confirmed previous hypothesis that the development of hemorrhagic transformations (HT) can be a direct/indirect effect of radiographic CM in the brain parenchyma, with less complication associated with IOCM iodixanol when compared with LOCM iopamidol [23]. Intracarotid arterial infusion of iohexol has been associated with increased intracranial hemorrhage in a rat middle

cerebral artery occlusion model compared with saline infusion. Also, when is osmolar iodixanol infusion was compared with low-osmolal iopamidol, it demonstrated smaller infarcts and less intracranial hemorrhage, thus giving the hypothesis that low osmolal contrast media may be associated with worse outcomes when compared with iodixanol in the Interventional Management of Stroke III Trial (IMS III).

Another study using real world hospital data was conducted to evaluate the correlation of types of contrast media and hemorrhagic transformation. There was less incidence of hemorrhagic transformation in patients placed on IOCM when compared to patients placed on LOCM with a relative risk reduction of 12.5%. Several explanations were suggested but the mechanism is not well understood [24]. A study also found out that patients who received IOCM were sicker (had higher rates of diabetes and renal disease), suggesting that physicians may preferentially administer IOCM to higher risk patients. Additionally, operators may select IOCM for perceived lower risks of major allergic complications or more tolerable symptoms during injection. Despite their higher baseline risk after adjusting for hospital fixed effects, patient demographics, and co-morbid conditions of the cohort, the use of IOCM was associated with fewer adverse events [22].

Ionic vs Non Ionic Contrast Agents in Stroke Patients

Osmotic diuresis with HOCM could result to stimulation of the intra renal renin angiotensin aldosterone axis, and release vasoconstrictor hormones such as endothelin or adenosine that can exacerbate ischemia [26,26]. HOCM is more cytotoxic in vitro on proximal tubular cells than LOCM or IOCM suggesting higher nephrotoxicity of HOCM, therefore, HOCM are used less frequently [27]. HOCM are used less frequently due to its more cytotoxic effect on proximal tubular cells when compared to LOCM or IOCM [20]. In contrast to this, it has been suggested that ionic contrast media may be advantageous in patients whom have undergone coronary angioplasty, because they can act as anticoagulants and inhibitors of platelet aggregation, whereas non-ionic contrast media have less of these effects [28].

There are other several risk factors associated with contrast-induced nephropathy (CIN), such as pre-existing chronic renal insufficiency, diabetes, and hypertension, etc., have been identified, and a risk scoring has been proposed. The properties of iodinated contrast media (CM) might contribute to the incidence of CIN. When non-ionic low-osmolar contrast media (LOCM) are compared to ionic high osmolar CM, there is less deterioration of renal function after angiography in patients with chronic renal impairment. The only available agent in the class of non-ionic iso osmolar contrast media (IOCM), iodixanol (with reference to VisipaqueTM, Nycomed, Amersham, Princeton, and New Jersey), is favorable compared with non-ionic LOCM for renal protection. Also, in the NEPHRIC (Nephrotoxicity in High Risk Patients Study of Iso Osmolar and Low Osmolar Non Ionic Contrast Media) study carried on 129 patients with diabetes and baseline renal insufficiency, iodixanol was associated with significant lower rates of CIN than iohexol [29].

Although preclinical findings suggested that LOCMs would be less nephrotoxic than HOCMs, the clinical relevance of this was disputed for at least a decade. Several studies found no statistically or clinically significant differences in nephrotoxicity between HOCMs and LOCMs. However, a meta-analysis reported by Barrett and Carlisle demonstrated that LOCMs were associated with a significantly lower incidence of CIN than HOCMs ($P = 0.02$, using data from 5146 patients in 31 trials; results from 22 of the 31 trials in which these data were available favoured LOCMs) [30]. The OR for CIN (defined as a mean increase in SCr of 44 mmol/l) with LOCMs was found to be 0.61 (95% CI 0.48–0.77; data were available for >4000 patients in 25 trials). Therefore, further research is needed to investigate the extent to which IOCM and LOCM differ in nephrotoxic potential.

Dose Effect of Contrast Media in Nephrotoxicity

Larger volume of contrast media increases the amount of contrast media exposed to the nephrons and also the exposure time, thus exacerbating cellular damage. Also, due to the changes in renal hemodynamics as discussed beforehand, there is a reduction in renal blood flow to the cortex and medulla which can result to ischemia. A retrospective study by Taliercio of 139 patients with renal impairment (SCr 2.0 mg/dl) undergoing coronary angiography found that administration of 125 ml CM was a significant risk factor for CIN (defined as increase in SCr >1.0 mg/dl at any point between days 1 and 5) compared with the use of <125ml ($P = 0.05$) particularly in patients without additional risk factors [31]. In addition, contrast media are also hyper-osmolar (HOCM and LOCM) when compared to the blood plasma which can increase the osmotic load in the kidney, this in return can damage the renal medullary gradient impairing the kidney's ability to concentrate urine and maintain electrolyte balance. In a study in a diabetic population, each 100 ml increment in contrast volume resulted in a 30% increase in the risk of CIN (odds ratio 1.30, 95% confidence interval 1.16–1.46), and there was a significant ($P<0.0001$) relationship between risk of CIN and volume of CM. A proposed dosing strategy is the use of maximal acceptable contrast dose (MACD) to guide the safe dose of contrast media in patients. It is calculated by 5 ml of contrast body weight (kg)/ baseline serum creatinine (mg/dl). It was stated that a maximum of 300 mL of contrast should be used regardless of the tailored threshold for each patient. Cigarroa found that only 2% of patients who had contrast exposure under the calculated threshold (MACD principle) developed CI-AKI, but 38% of patients receiving contrast over the MACD developed nephrotoxicity [32]. Also, Freeman showed that there is a 6-times increase in risk when volume of contrast media is exceeded [33].

Another proposed dosing scale is the use CV/CVV (Contrast volume to calculated creatinine clearance volume) where a ratio under 2 is associated with a low incidence of CIN, whereas a ratio exceeds 3 is associated with high risk of CIN. Contrast volume can be based on imaging procedure and the creatinine volume is calculated with the use of serum creatinine and other relevant factors such as weight and sex, etc. Depending on the result the ratio is adjusted within the threshold to ensure safety of patient and diagnostic efficacy. This ensures personalization of dosing to patients renal function and reduces risk of nephrotoxicity.

Role/Impact of Relative Dehydration in Stroke Patients

Dehydration has been noticed to be present in a large percentage of stroke patients who mostly encounter poor functional outcomes. This is also dependent on stroke severity, infarction volume and comorbidities. Dehydration can be associated with diminished thirst mechanisms, altered mental status, language impairment, inaccurate assessment (especially in geriatric patients). Hence, biochemical parameters like plasma osmolality, BUN/creatinine ratio can be considered. A common marker used for the assessment of dehydration is the blood urea nitrogen to creatinine ratio (BUN/Cr). Studies also suggest that dehydration after stroke is a prevalent phenomenon, with a frequency of around 60% as measured with the BUN/Cr ratio associated with a poor outcome. Dehydration has a significant impact by being both a contributing factor to

initial stroke and also a complicating factor to previous stroke during recovery. Dehydration has been proposed to contribute to stroke occurrence by increasing the viscosity and flow of blood. This thereby increases the risk of clot formation which can result in ischemic stroke. Another mechanism is electrolyte disruption which affects the heart functions causing arrhythmias. Arrhythmias, being a risk factor for stroke, increase the chances. Lastly, changes in blood volume reduce the blood supply to the brain ultimately which can initiate transient ischemic stroke. Changes in hemodynamics due to dehydration complicate contrast-induced nephropathy based on the proposed pathways as discussed above. It is also a complicating factor due to the negative effect it can have on cognitive function and impairment of healing, among others [34].

Prevention and Management of Contrast Induced Nephropathy

- Prevention of unnecessary contrast administration: they should be administered when the indication emerges, in order to avoid unnecessary contrast administration and its related complications. Certain cases such as intracranial hemorrhages, cervical trauma, simple bone fractures, and interstitial lung diseases, etc., do not require administration of these media. Clinicians should be informed about the medical imaging techniques alternative to contrast enhanced medical imaging by the radiologist. If contrast use is inevitable, every patient should be properly evaluated for the risk factors for CI-AKI before the procedure.

- Re-Evaluation of Concomitant Use of Other Nephrotoxic Drugs:
  due to the additive or synergistic effect of these medications on the kidney, it is important to re-evaluate the use of these drugs, having in mind of the risk – benefit ratio of the procedure.

- Intravenous Hydration and Protective Procedures:
  Prophylactic intravenous saline hydration, 1 mL/kg per h for 12 hrs before and 12 hrs after exposure to contrast media has been shown to reduce the incidence of CIN by the expansion of the plasma volume, suppression of the renin angiotensin-aldosterone cascade system, down regulation of the tubule glomerular feedback mechanism, and dilution and expedition of excretion of contrast media, thereby reducing the length of time that tubular cells are exposed to the toxic effects of contrast media. This, in the long-run, protects patients from renal vasoconstriction and tubular obstruction; it also reduces the workload and level of oxygen consumption (oxygen demand) in the renal medulla [30]. Eisenberg also claimed that contrast-induced nephropathy could be avoided with adequate hydration given at a sufficient duration as prophylaxis [35].

Hydration with isotonic (0.9% saline) and half isotonic (0.45% sodium chloride plus 5% glucose) solution was compared in a prospective randomized study in terms of efficiency in prevention of contrast induced acute kidney injury (CI-AKI) in patients undergoing coronary angioplasty. A total volume of 2000 mL was approximately given before, during, and after the procedure. In this study, isotonic hydration was found to be superior to half isotonic hydration in the prevention of CI-AKI. Hypervolemia should be avoided during hydration of the patients, and monitoring of left ventricular end diastolic pressure was found to be a useful and effective way of guiding fluid replacement in a randomized controlled trial. Remote ischemic preconditioning (RIP) is a procedure that has been evaluated as a potential protective mechanism of CI-AKI. It depends on a hypothesis that a transient ischemia of an organ may protect against an ischemic injury of another distant organ. In preliminary studies, RIP has been found to decrease the risk of CI-AKI [36,37]. However further randomized clinical trials are needed before a recommendation can be made.

● N-acetylcysteine and Sodium Bicarbonate:

Kidney Disease Improving Global Outcomes (KDIGO) suggested N-Acetylcysteine (NAC) for patients with high risk of CI-AKI. It is usually used at a dose of 600-1200 mg orally twice daily. Combination of N-acetylcysteine and sodium bicarbonate are also preventive measures since they are oxygen derived free radical scavengers and therefore block injury to the renal tubules. N-acetylcysteine also increases production of nitric oxide (which has vasodilatory capabilities) and the concentration of glutathione, which acts as a free radical scavenger. Isotonic sodium bicarbonate acts through the alkalinisation of renal tubular fluid and subsequent reduction in free oxygen radicals has shown beneficial results in reducing contrast-induced AKI. It has been proposed that a direct causal relationship exists between low pH of tubular fluid and enhanced activity of generated reactive oxygen species (ROS, formed by incomplete reduction of molecular oxygen) to damage renal tubular cells. Merten (2004) reported patients receiving isotonic (154 mEq/L) infusion of sodium bicarbonate before and after contrast administration (370 mg iodine/mL) had an 89% reduction in contrast-induced AKI compared with patients that received hydration with isotonic sodium chloride. Unfortunately, N-acetylcysteine might cause an artificial transient decline in serum creatinine without changing renal function and therefore additional markers of renal function should be incorporated to confirm these effects [38-42].

Conclusion

The comparative analysis of nephrotoxicity induced by iodinated contrast drugs reveals significant advancements and enduring challenges within the realm of diagnostic imaging. Prior research and investigations have highlighted that newer contrast agents, particularly non ionic formulations, exhibit a reduced nephrotoxic potential compared to older, ionic counterparts. These advancements have contributed to a lower incidence of contrast induced nephropathy (CIN), particularly benefiting high risk groups such as stroke patients.

Despite these advancements, the nephrotoxicity risk remains intricately linked to the administered dosage and the patient's hydration status. Higher doses of contrast agents are consistently associated with an elevated risk of nephrotoxicity, underscoring the need for precise dosage management and individual risk assessment. More so, relative dehydration in stroke patients has been identified as a critical exacerbating factor for CIN, emphasizing the importance of rigorous pre-procedural hydration protocols and vigilant monitoring.

Innovative approaches, such as the development of personalized contrast regimens tailored to individual patient profiles, hold promise for further reducing the nephrotoxic risk. This personalization would involve considering variables such as baseline renal function, hydration status, and the specific characteristics of stroke. Furthermore, the exploration of novel biomarkers for early CIN detection could facilitate timely intervention and improved outcomes.

The role of emerging therapeutic interventions, including pharmacological agents designed to mitigate nephrotoxic effects, represents a promising avenue for future research. Additionally, advances in imaging technology that reduce the required contrast dose or employ alternative imaging modalities could further enhance patient safety.

In conclusion, integrating these findings into clinical practice necessitates a multifaceted approach that combines technological advancements with individualized patient care strategies. By doing so, these may help enhance patient outcomes, minimize the burden of nephrotoxicity, and ensure safer diagnostic imaging for stroke patients. The continued evolution of contrast agent technology and patient management protocols will be instrumental in achieving these goals, ultimately leading to improved healthcare delivery and patient safety.

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