Print ISSN 2319-2003 | Online ISSN 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

doi: 10.18203/2319-2003.ijbcp20150016

Research Article

Role of nephrotoxic drugs in contrast-induced nephropathy

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Received: 22 March 2015
Accepted: 24 April 2015

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ABSTRACT

Background: Elevation of serum creatinine (SCr) more than 0.5 mg/dl or 25% or more of the baseline value in 3 days after contrast administration is considered as contrast-induced nephropathy (CIN). Contrast material (CM) used in the radiological studies like contrast-enhanced computed tomography (CECT) and intravenous urogram (IVU) are nephrotoxic and their ability to cause renal damage is increased when other potential nephrotoxic drugs are given simultaneously. The present study aimed to demonstrate the effects of CM on patients who are on nephrotoxic drugs by studying the incidence of CIN in patients who are on nephrotoxic drugs and need a CECT or IVU (cases presenting with an emergency). The study compares the incidence of CIN in patients on nephrotoxic drugs with that in those not on nephrotoxic drugs and evaluates the importance of withdrawal of nephrotoxic drugs (3 days) in non-emergency contrast studies.
Methods: The study population is divided into three groups. Group A consists of 40 cases undergoing emergency CECT or IVU, who are on nephrotoxic drugs. 40 cases undergoing CECT or IVU after 3 days of holding of nephrotoxic drugs are included in Group B. Group C consists of 40 cases undergoing CECT or IVU who are not on any nephrotoxic drugs. Patients with parenchymal renal disease, renal injury, and renal mass are excluded from the study. All cases having SCr <1.4 mg/dl are included in the study. SCr investigation is repeated 3 days after the contrast study.
Results: The incidence of CIN is more in the patients who are on nephrotoxic drugs (15%) than in those who are not on nephrotoxic drugs (5%). There is no significant difference in the incidence of CIN between Groups B and C. p=0.045 between Groups A and B was noted showing the significance of waiting period in reducing the incidence of CIN.
Conclusions: The incidence of CIN is more in patients who underwent contrast studies without stopping nephrotoxic drugs and stoppage of nephrotoxic drugs for 3 days prior to the procedure is beneficial by reducing the incidence of CIN among them.

Keywords: Contrast-induced nephropathy, Nephrotoxic drugs, Prevention

INTRODUCTION

The use of radiological procedures with intravascular iodinated contrast media injections is widely increasing for both diagnostic and therapeutic purposes. This has resulted in an increasing incidence of procedure-related contrast-induced nephropathy (CIN). Contrast media can have serious toxic effects on renal tubular cells, resulting in a condition known as CIN. CIN is the third most common cause of hospital-acquired acute renal failure, after impaired renal perfusion and nephrotoxic medications, and is associated with extended length of stay.[1]

CIN is an acute decline in renal function that occurs 48-72 hrs[2] after intravascular injection of iodinated contrast material (CM). The most common definition in use is an increase in serum creatinine (SCr) of 0.5 mg/dl or >25% of baseline value occurring following the intravascular administration of CM without an alternative explanation.[3]

The pathophysiological mechanisms leading to CIN are generally thought to be, alone or in combination, a decrease in renal perfusion, direct CM tubular cell toxicity and free radical formation.

The commonly used CM are low-osmolar, non-ionic, monomer, iohexol (omnipaque) and iso-osmolar, non-ionic, dimer, iodixanol (visipaque) most common drugs with nephrotoxicity as side effect include non-steroidal anti-inflammatory drugs (NSAIDS), diuretics, aminoglycosides like amikacin.

The present study aims to demonstrate the effects of CM on patients who are on nephrotoxic drugs by studying the incidence of CIN in patients who are on nephrotoxic drugs and need a contrast-enhanced computed tomography (CECT) or intravenous urogram (IVU) (cases presenting with an emergency). The study compares the incidence of CIN in patients on nephrotoxic drugs with that in those not on nephrotoxic drugs and evaluates the importance of withdrawal of nephrotoxic drugs (3 days) in non-emergency contrast studies.

METHODS

The study is an observational, prospective, randomized study done by the department of pharmacology, and radiology in a tertiary care hospital for a duration of 6 months from January 2014 to July 2014. The approval of institutional ethics committee was taken before start of the study. Informed consent is taken from all the patients. The CM used in the study is iohexol (omnipaque - 350 mg/ml). Enrollment, grouping and follow up of the subjects is given in Figure 1.

Inclusion criteria

Patients who require CECT or IVU and having baseline SCr <1.4 mg/dl and who are on known nephrotoxic drugs like aminoglycoside antibiotics, NSAIDS and require a contrast study (CECT or IVU) are included in the study. Patients of both sexes of age between 18 and 60 are included.

Exclusion criteria

Cases with parenchymal renal disease (SCr >1.5 mg/dl), renal injury, renal mass or malignancy, dialysis are excluded.

Grouping of cases

The study population is divided into three groups. Group A consists of 40 cases undergoing emergency CECT or IVU, who are on nephrotoxic drugs. 40 cases undergoing CECT or IVU after 3 days of holding of nephrotoxic drugs are included in Group B. Group C consists of 40 cases undergoing CECT or IVU who are not on any nephrotoxic drugs.

Method of study

SCr of each patient is evaluated before the contrast study and 3 days after the contrast study. The criteria for diagnosing contrast-induced nephropathy (CIN) include more than 25% rise in the SCr level compared to baseline reading in 3 days[3] or rise in SCr >0.5 mg/dl from the baseline reading in 3 days.[3] Enrollment and follow-up of the subjects is explained in the Figure 1.

End points

The primary end point for the study included a raise in SCr by 0.5 mg/dl from the baseline value of the individual patient. The secondary end point was need of dialysis within 3 days of the study.

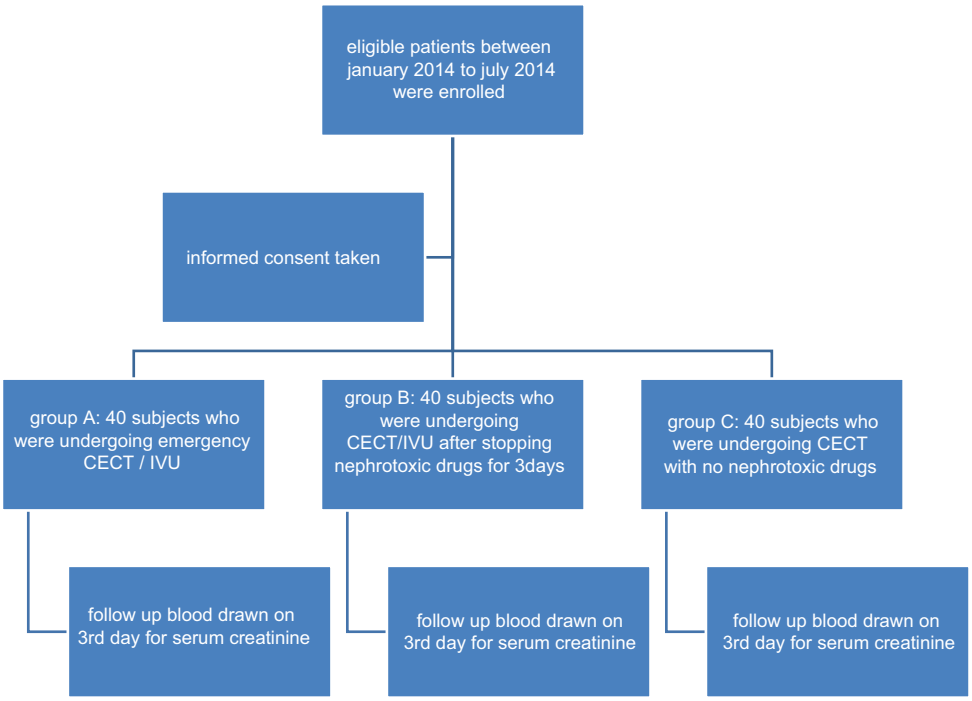

Figure 1: Enrollment, grouping, and follow-up of study participants.

Statistical analysis

One-way ANOVA test used to calculate the significance of waiting a period of 3 days in reducing the incidence of CIN.

RESULTS

Of the 120 people, there are 46 females and 74 males out of which 52 belong to the age group of 18-39 years and 68 belong to 40-60 years as given in Figures 2 and 3. Table 1 shows the comparison of the baseline characteristics between the patients who developed CIN and those without CIN shows that CIN is more common among females with 10.6% incidence and males with 5.4%. Table 2 shows the distribution of patients according to the anatomic part studied in CECT are head and neck 4%, chest 27%, abdomen pelvis 54%, other (including extremities) 15%.

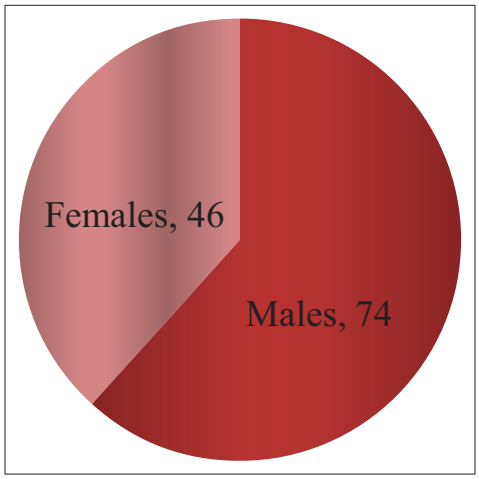

Figure 2: Sex distribution.

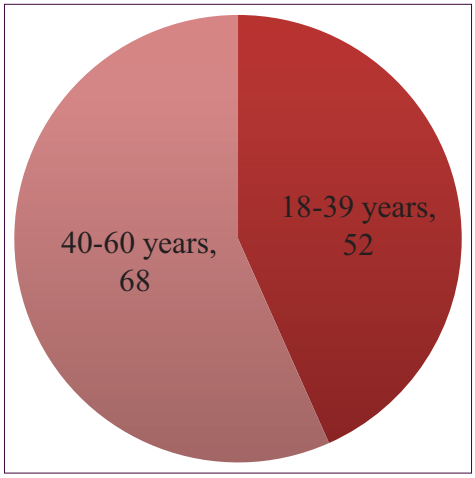

Figure 3: Age distribution.

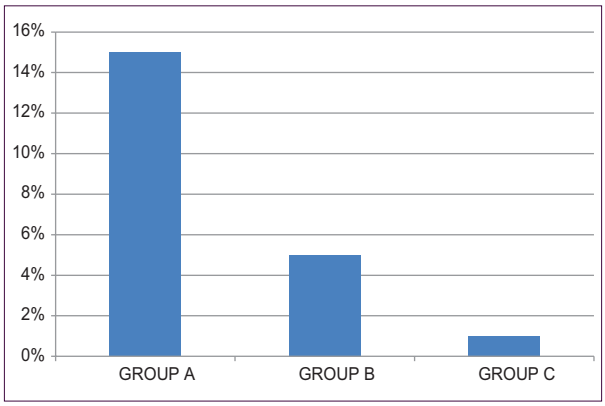

Figure 4: Incidence of contrast-induced nephropathy.

The incidence of CIN in Group A that is cases on nephrotoxic drugs while doing contrast studies is 15%. The incidence is 5% in patients for whom nephrotoxic drugs are withheld prior to the study and 1% in patients who are not on any nephrotoxic drugs Figure 4.

DISCUSSION

The present study is designed mainly to define the incidence of CIN in randomized, heterogenous population coming to the outpatient department for CECT/IVU of any anatomic region and the effect of nephrotoxic drugs on the acute kidney injury due to CM.

The major finding of our study is that the incidence of CIN is more in patients who underwent contrast studies without stopping nephrotoxic drugs and stoppage of nephrotoxic drugs for 3 days prior to the procedure is beneficial by reducing the incidence of CIN among them. Though the standard wash out period for any drug being 7 days, stoppage of the drug for 3 days is proved beneficial for prevention of CIN.

The first 24 hrs post-procedure is crucial in the development of CIN. A study of SCr levels in the randomized prevention of radio CIN clinical evaluation trial indicated that in 80% of CIN cases show increase in SCr levels within the first 24 hrs of post-contrast medium administration, and majority of the patients progressed to serious renal failure (one requiring

Table 1: Comparison of baseline features among patients who underwent contrast studies and developed CIN with those who did not develop CIN.

Characteristics	CIN positive	CIN negative
Age	49±9	52±5
Females	5	41
Males	4	70

CIN: Contrast-induced nephropathy

Table 2: Distribution of anatomic regions studied by CECT imaging.

Anatomic region	Proportion (in %)
Head and/or neck	4
Chest	27
Abdomen and/or pelvis	54
Other (including extremities)	15

CECT: Contrast-enhanced computed tomography

either nephrology consultation or dialysis).[4,5] The same study showed that patients with <0.5 mg/dl rise in SCr within the first 24 hrs were unlikely to have any clinically meaningful form of CIN. The SCr typically peaks 3-5 days after contrast administration and returns to baseline or near baseline within 1-3 weeks. The development of acute renal failure is a significant complication of the intravascular contrast medium.[6] The true incidence of CIN is difficult to assess because of difference in the clinical outcome of high-risk patients, types of contrast media used, and also because of preventive measures.

Though CIN is rare in general population, several risk factors predispose to this condition. Underlying renal dysfunction, diabetes, anemia, age all form risk factors. All these act synergistically to cause CIN. A careful risk-benefit analysis must always be performed prior to the administration of CM to patients at risk for CIN. Given the volume of CM is one of the strongest risk factor. The increasing use of CM, an ageing population and an increase in chronic kidney disease will result in an increased incidence of CIN.

The nephrotoxicity of CM is multifactorial and the experimental studies suggest pathogenesis of CIN due to direct toxic injury to nephron and renal tubular epithelial cell damage by renal vasoconstriction, reduced blood flow leading to hypoxia.[7,8] The possible mechanism for vasoconstriction and direct injury is high osmolality of the CM, which results in increased resistance in renal vessels. Although the exact mechanisms of CIN have yet to be fully elucidated, several causes have been described. Increased adenosine, endothelin, and free radical-induced vasoconstriction and reduced nitric oxide and prostaglandin-induced vasodilatation have been reported. Oxygen free radicals are produced during intrarenal adenosine catabolism to xanthine. These mechanisms cause ischemia in the deeper portion of the outer medulla, an area with high oxygen requirements and remote from the vasa recta supplying the renal medulla with blood. Contrast agents also have direct toxic effects on renal tubular cells causing vacuolization, altered mitochondrial function and apoptosis.[7]

The nephrotoxicity of NSAIDS is explained by interstitial inflammation[9] and decreased production of vasodilatory prostaglandins. Analgesic nephropathy is a condition of slowly progressive renal failure, decreased concentrating capacity of the renal tubule, and sterile pyuria. Risk factors are the chronic use of high doses of combinations of NSAIDs and frequent urinary tract infections. If recognized early, discontinuation of NSAIDs permits recovery of renal function.

Approximately 8-26% of patients who are an aminoglycoside for several days develop mild renal impairment that is almost always reversible. Aminoglycosides cause the release of lysosomal acid hydrolases thus resulting in mitochondrial degeneration and cellular death.[10] The toxicity results from accumulation and retention of an aminoglycoside in the proximal tubular cells. The initial manifestation of damage at this site is the excretion of enzymes of the renal tubular brush border. After several days, there is a defect in renal concentrating ability, mild proteinuria, and the appearance of hyaline and granular casts and the glomerular filtration rate (GFR) is reduced.

When GFR is <60 mL/mins preventive measures should be instituted. The risk of CIN is greatest in patients with GFR <30 mL/mins.[11,12]

The diagnostic criteria for CIN include[13] exposure to contrast agent, increase in serum level of creatinine of 0.5 mg/dL or 25%> baseline, increase in serum level of creatinine occurs 48-72 hrs after administration of contrast agent and persists for 2-5 days with other alternative major injuries ruled out.

The preventive measures for CIN are stopping nephrotoxic drugs like NSAIDS 3 days prior to the study and replacing them with non-nephrotoxic drugs, assessment of comorbid conditions like diabetes, chronic renal failure which add to the nephrotoxicity of contrast medium, providing proper hydration to the patient prior to the contrast administration.[14]

Though many drugs like theophylline are used no drug is proved efficient in treating CIN. The best treatment strategy for CIN include hydration with normal saline for 12 hrs prior and post study at 1 ml/kg/hrs if it is an emergency procedure[15] and 1 ml/kg/hr 12 hrs pre and post contrast administration.[5,16]

The complications of CIN may progress up to requirement of hemodialysis and death.[17] The patients who already have preclinical renal failure or renal compromise due to various conditions carry poor prognosis.[18,19]

The present study is mainly aimed at finding the incidence of CIN in various patients undergoing contrast studies irrespective of the comorbidity. Despite this limitation, it is noteworthy that the incidence is higher for patients who are on nephrotoxic drugs.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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doi: 10.18203/2319-2003.ijbcp20150016
Cite this article as: Annavarapu S, Kota KK. Role of nephrotoxic drugs in contrast-induced nephropathy. Int J Basic Clin Pharmacol 2015;4:458-62.