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Incidence of Iodinated Contrast Media Reaction: A Multi-centre Study in Computed Tomography

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Contrast enhanced Computed Tomography (CECT) plays a great role in investigating any clinical condition, because of its high sensitivity. But with this comes the problem of contrast reactions have risen over last years, representing an important concern. To find the incidence of iodinated contrast media reactions on Computed Tomography in different centers in a particular region. This was descriptive multicenter study conducted in radiology departments of University of Lahore Teaching hospital, Services hospital and Sheikh Zayed hospital, Lahore. This study included the entire in and out patients advised CT with contrast and both genders of all age. The collected data was entered and analyzed with the help of SSPS version 24 and Microsoft Excel. In our study, total 227 patients were included out of which 105 were females and 122 were males. 9.7% experienced mild reaction with no cases of moderate and severe reaction. Mild reactions were more common in females (12.4%) than males (7.4%). Most common symptoms observed were nausea (4.8%), vomiting (3.1%), and shivering (1.8%). Contrast reactions resulted is mostly mild and more proportion of mild reactions are found among females than males. No cases of severe reactions are identified in the patients.

Keywords: Hypersentivity Reactions, Iodinated Contrast Media, Adverse Reactions, Low Osmolality Contrast Media, High Osmolality Contrast Media ,Immediate Reactions, Non-Immediate Reactions, Acute Adverse Reactions.

INTRODUCTION

By computing attenuation data from an x-ray, clinicians can view pathology from multiple perspectives, unobstructed by anatomical structures, and adjust contrast to isolate soft tissue and hard tissue pathologies. Three-dimensional visualizations of pathology and anatomy are already possible with the advancement of computer software (Kobayashi et al. 2013) The first modern slice-imaging modalities, Computed Tomography (CT), was introduced into medical imaging in 1972 (Sohn et al. 2019)

The discovery of computed tomography (CT) has completely transformed radiology. Modern CT systems, which began as head-only scanners, can now perform whole-body scans in uniform resolution in a matter of seconds (Lell et al. 2015).

Intravenous contrast media are a crucial part for both imaging and diagnosing pathologies. The presence of contrast media can significantly contribute to the sensitivity and specificity of radiological diagnostics. Different tissues are more easily visible when they are contrasted. Consequently, contrast media can improve radiologists' accuracy and reliability (Zhang et al. 2016). Further more, contrast administration improves patient safety and lowers costs by reducing the need for additional imaging tests. The use of contrast enhanced CT is a gold standard for the diagnosis of acute abdomen, which is vital

In most conditions Lesion can be easily detected from normal surrounding organs with the help of contrast administration and tissues as well as the diagnosis of diseases affecting the parenchyma and the vascular system (Shehadi, 1975). The most common way to administer ICM into the body is through intravascular injection. This method is widely used because it allows the contrast media to enter the bloodstream quickly and efficiently (Park et al. 2019). The injection speed of ICM varies depending on the imaging purpose. For slow manual injection, the speed is usually around 3-5 mL/s. In contrast, a power injector can inject ICM at a speed of up to 20 mL (Chiu et al. 2022).

ICM-Used

The chemical structure of ICM with different organic side chains attached to the central benzene ring shared by all ICMs play a crucial role in the properties and application of ICM compounds that are derivatives of tri-iodobenzoic acid. Based on their chemical structure, ICM scan be divided into four groups. The first group is the ionic tri-iodized monomer contrast media containing iodinated elements are generally classified by pH and osmolarity; iohexol is classified as ionic (high osmolarity) and iobitridol as non-ionic (low the second group is the ionic hexa-iodized dimers. The third group is the non-ionic tri-iodized monomers. Finally, the fourth group is the non-ionic hexaiodized dimers. Each group of ICMs has its own unique properties and is used for different imaging purposes. For example, ionic ICMs are often used in angiography and CT scans, while non-ionic ICIMs are preferred for MRI scans due to their lower risk of causing adverse reactions (Doña et al. 2020). Contrast media usually have a higher viscosity and osmolality (more molecules per kilogram of water) than blood, plasma, or cerebrospinal fluid due to their chemical properties. There are three types of contrast media: high-osmolality contrast media (HOCM), low osmolality contrast media (LOCM) and Iso-osmolar contrast media. It is estimated that low osmolarity contrast media (LOCM)has plasma protein less than 5-8 times than high osmolarity contrast media (HOCM), and low osmolality contrast media have a serum osmolality 2–3 times that of iso-osmolarity contrast media. Increasingly used, isosmolar contrast agent have the same osmolality as blood, plasma, and cerebrospinal fluid (Singh & Daftary, 2008).Contrast media containing iodinated elements are generally classified by pH and osmolarity; omprol, iopamidol, iopromide, and ioversol are iodinated such media. Reports have been submitted about mild and severe adverse reactions (ADRs), with the use of low-osmolar non-ionic contrast media. However, it is already known that iodinated contrast media are relatively safe. It is important to note that not all ICM are the same in terms of their chemical structures and properties. As a result, the incidence of immediate adverse drug reactions (ADRs) may vary depending on the specific ICM used. Furthermore, ADRs can be life-threatening but in some case scan range from mild to severe (Davenport et al. 2020)

ICM-relatedHSRs

Several ADRs associated with the intravenous administration of ICM can be separated into two categories: hypersensitivity (allergic-like) reactions and chemo-toxic reactions. There are also three grades of ADR: “Mild” (signs and symptoms that are self-limiting and do not progress),“moderate”(signs and symptoms that require medical attention), and “severe”(if the symptoms and sign are not taken seriously then it can cause morbidity or death) (Faucon et al. 2019). ADRs associated with ICM t end to be immediate (acute) and often manifest within 1hour of intravenous administration. In most cases, non-immediate (delayed) cutaneous reactions occur between a few hours and one week after the ICM is received mild hypersensitivity reactions include: Limited urticaria or pruritis, cutaneous edema, “itchy or scratchy” throat, 16 nasal congestion, sneezing or conjunctivitis. Moderate hypersensitivity reactions includes: Diffuse urticaria or pruritis, diffuse erythema, facial edema without dyspnea, throat tightness without dyspnea, wheezing or broncho spasm, mild or no hypoxia. Severe hypersensitivity reactions include: Diffuse edema, or facial edema with dyspnea, diffuse erythema with hypotension, laryngeal edema with stridor and hypoxia, significant hypoxia, hypotension, tachycardia (Caimmi et al. 2010). ICM hypersensitivity is a serious condition that can pose a significant risk to patients. One of the most significant risk factors for ICM hypersensitivity is a history of ICM hypersensitivity. Patients who have experienced this type of hypersensitivity in the past are at a higher risk for experiencing it again in the future. While premedication can be effective in reducing the occurrence of hypersensitivityreactions.Forpatientswithahistoryofsever eICMhypersensitivity, the best policy is to avoid the same ICM. This can help to lessen the risk of hypersensitivity events and ensure the well-being of the patient. If an alternative ICM is needed, it is important to carefully consider the patient's history and risk factors before making a decision (Cha et al. 2019)

ICM-related AKI and CKD

The use of ICM can lead to acute kidney damage or induces CKD. A pre-existing kidney disease is the greatest risk factor of CKD. AKI can also be caused by other factors such as diabetes, age, dehydration, proteinuria, or kidney-damaging drugs. AKI is further exacerbated by intra-arterial administration, high osmolality, and high viscosity ICMs, as well as repeated injections within a short time interval (48-72 hours) (Cochran et al. 2001) When the ICM volume-to-creatinine clearance ratio exceeds 3.7, there is an independent predictive factor for increased serum creatinine following ICM injection in any population. A number of preventive measures have resulted in a reduction in the incidence of this disease over the last 10 years, from 15 to 7percent(Cohan et al. 1997) Treatment for ICM-induced acute tubular necrosis is not specific. But, to limit ICM-induced renal toxicity, prevention is still the best approach. 17 During the examination, nephrotoxic drugs must be stopped 48 hours prior, sufficient hydration must be maintained (stop diuretics 48 hours in advance), conditions that cause plasma osmolality to increase (hyper-glycaemia) should be removed, patients at risk should be screened, and last but not the least, avoid ICM injections if possible, or consider alternative imaging methods such as MRI or

ultrasound, especially when renal function is compromised (Dillman et al. 2018)

MATERIALS AND METHODS

This clinical research was approved by institutional ethics committee of University of Lahore. Duration of study was 7 months and data collected within 4months. We recruited patients from three hospitals of Lahore (University of Lahore Teaching Hospital, Services Hospital, and Sheikh Zayed Hospital). We recruited patients from three hospitals. This study included all patients who underwent contrast-enhanced CT examinations between March 2023 and June2023. In total, 227 patients who underwent ICM administration 105 were female and 122 males. In our study all Patients were administered with i.e., omnipaque, ultravist, Kopaq,and xenetix. For each patient who underwent ICM administration, a case report form was submitted that included the following information: (a) baseline characteristics of the patients, including age, sex, and underlying disease such as diabetes mellitus, heart failure, and hyperthyroidism; (b)previous individual history of ICM usage and ICM-related HSRs; (c) previous individual history of drug allergy, asthma, and other allergic diseases; (d) family history of ICM-related HSRs and allergic diseases, including asthma; (e) name of the administered ICM product; (f)regimen of premedication, if administered; and (g) in instances of HSR occurrence, the symptoms, severity (mild, moderate, and severe), and duration of the HSR, along with details on its management (Nucera et al. 2022).The characteristics of enrolled patients were listed in table1.

Instrumentation and Methods

The CT machine of Toshiba Aquillion cxl 128 slice was used in this study. A written informed consent from each patient, data collection commenced for individuals undergoing contrast-enhanced computed tomography at UOL Teaching Hospital, Lahore, Services Hospital, Lahore, and Sheikh Zayed Hospital, Lahore. This was done utilizing a customized questionnaire and transferred onto data collection sheets, focusing on variables such as age, scan type, serum creatinine, hydration status, weight, contrast agent details (type and quantity), and presence of reactions categorized as mild, moderate, or severe. Patient was given 10cc saline before and after the contrast administration. The flow rate of ICM was 2.5 or 3ml/s. The accumulated data was organized in Microsoft Excel.

Table1: Clinical characteristics of patients with Contrast CT scan

Clinical Characteristics Data (n=227)	Change
Overall reaction and Severity **Female** **Male**	22/227(9.7%) 13/105 (12.4%) 9/122 (7.4%)
Age	
Mean	43.49±19.76.years
Weight Mean **Contrast quantity Mean**	64.68±18.23 82.14±23.08
Different Contrast Reactions	
Kopaq	3/19 (15.8%)
Omnipaque	4/70 (5.7%)
Ultravist	6/94 (6.4%)
Xenetix	9/44 (20.5%)

RESULTS

Complete analysis of the descriptive radiological examinations of 227 patients was carried out for the evaluation of incidence of iodinated contrast media reaction in CT in a population subset. The study included 122 males and 105 females with mean age of 43.9 years. Among the study population, 9.7% had mild contrast reactions with no moderate and severe reaction. The most common symptoms appear nausea (4.8%) and vomiting (3.1%).The least common symptom was shivering with 1.8%. With respect to gender female had more reaction than male which makes up 12.4% and7.4%respectively.

Table 2: Out of total 227 (100%) patients, n=205(90.3%) with no contrast reaction and n=22(9.7%) have contrast reaction. The highest reaction rate was observed in xenetix n=22(20.5%).The least no reaction rate was observed in omnipaque n =66(94.3%) and ultravist n=88(93.6%)

	Reaction		Total
	no	yes	
Kopaq	16	3	19
	84.2%	15.8%	100.0%
Omni paque	66	4	70
Contrast	94.3%	5.7%	100.0%
ultravist	88	6	94
	93.6%	6.4%	100.0%
xenetix	35	9	44
	79.5%	20.5%	100.0%
	205	22	227
Total	90.3%	9.7%	100.0%

Contrast*Reaction Cross tabulation

Table 3: This table shows the symptoms of different contrast media. Omnipaque and Ultra vistgive less symptoms as compared to Xenetix and Kopaq contrast media

	Symptoms				Total
	Nausea	no	Shivering	Vomiting	
kopaq	1	16	1	1	19
	5.3%	84.2%	5.3%	5.3%	100.0%
omnipaque	2	66	1	1	70
Contrast	2.9%	94.3%	1.4%	1.4%	100.0%
ultravist	4	88	1	1	94
	4.3%	93.6%	1.1%	1.1%	100.0%
xenetix	4	35	1	4	44
	9.1%	79.5%	2.3%	9.1%	100.0%
Total	11	205	4	7	227
	4.8%	90.3%	1.8%	3.1%	100.0%

Table 4: Out of total 227 patients, n=22(9.7%) got mild reaction and the remaining =205(90.3) got no reaction. The highest mild reaction rate was seen in Xenetix contrast n=9 (20.5%) out of total n=44(100%). The least no severity was observed in Omnipaque contrast n=66(94.3%) and ultravist n=88(93.6%).

	Severity		Total
	mild	no	
kopaq	3	16	19
	15.8%	84.2%	100.0%
omnipaque	4	66	70
Contrast	5.7%	94.3%	100.0%
ultravist	6	88	94
	6.4%	93.6%	100.0%
xenetix	9	35	44
	20.5%	79.5%	100.0%
Total	22	205	227
	9.7%	90.3%	100.0%

DISCUSSION

Nowadays, iodinated contrast is one of the most used agents in radiology. Almost any part of the body can be benefitted from them. It is most administered intravenously, but can also be administered through arteries, rectum, or abdomen. They are most commonly safe, and usually give mild reactions. However, severe reactions can also occur. Radiologists and other medical personnel must be understood the risk factor of reactions to iodinated contrast agents. They should have strategies in place to recognize and minimize adverse reactions. In previous studies, it has been estimated that there is a low rate of reactions to contrast agents of low osmolarity. Hypotension, pruritus, and flushing are some of the common side effects resulting from an adverse reaction to contrast agents. More severe reactions include broncho spasm and airway obstruction, which can be fatal. Daiki Kobayashi1 et al. performed a study in 2013, in which CT imaging with contrast agent was done on 36,472 patients in the period of 7 years. 9 cases (0.0005%) observed some severe reactions, e.g., low blood pressure, airway obstruction andshock16. In our study n nausea or vomiting were the commonly occurring reactions with 241cases (31.8%). Non-ionic and low-osmolar contrast agents (iopamidol, iohexol, ioversol oriomeprol) were given to all patients. Sohn, K. H. et al in 2019 during his observation period,714 patients were enrolled, 26 (which makes up 3.6%) experienced Immediate reaction17. In our finding, all patients were administered with iodinated contrast media that is low-osmolar, non-ionic. The overall reaction rate was 9.7%. No severe reaction was observed in our finding. The most common symptoms in our study were nausea (4.8%) and vomiting (3.1%). The least occurring symptom in our study was shivering (1.8%). Bin Zhang et.al conducted a study in2016, in which contrast enhanced computed tomography was done on 137,473 patients.Ultravist-370 was used on 67, 923 patients and Isovue-370 was used on 69, 550 patients. 39% patients were women and 61% were men. 0.31% (n=428) was the total incidence of adverse reactions. The number of mild AARs was 330 (0.24%), the number of moderate AARs was 82(0.06%), and the number of severe AARs was 16. Moderate and severe reactions were rare but most common AARs were mild18.Our study revealed that 9.7% (n=22) got mild reaction out of total 227 patients. Among these 13 (12.4%) were female and 9 (7.4%) were male. In our study no moderate and severe reaction was observed. Lang et al. 2004 carried outcross-sectional research to find the reaction rate with respect to gender. 47 Out of 5191 patients who were given intravenous contrast media, 22 males and 51 females experienced reactions19.In our research of 227 patients 22 got reaction out of which female n= 13 (12.4%) and male n=9 (7.4%). Park et al. (2019) conducted a retrospective study of 2 years. He

concluded that the speed of injection and the quantity of contrast material dose were linked with less frequent mild reactions and a lower rate of moderate and severe reactions20 whereas, in our study all the patients underwent low-osmolar contrast media administration, and we observe90% of the patients were given injection speed of 2.5 or 3 ml/sec which is low, due to which we got 9.7% mild reactions, with no moderate or severe reaction. Although non-ionic contrast media adverse reactions are rare, but they could still occur occasionally. Since serious reactions are rarely observed, treatment protocols should be reviewed regularly.

CONCLUSIONS

Reactions resulted from iodinated contrast agents are primarily mild among the group of studied patients. Notably, there was a greater proportion of mild reactions among females than among males. Instances of moderate or severe reactions are not identified within this patient population. However, further research studies are required to better understand the causes of mild reactions and to devise suitable strategies for ensuring patient safety and well-being.

Author contributions

Conceptualization, Areej Amir and Wajeeha Tariq; methodology, Areej Amir, Rimsha Ajmal, Aitezaz Hussain, and Maham Nazir; software, Syed Muhammad Yousaf Farooq; validation and formal analysis Syed Muhammad Yousaf Farooq and Muhammad Zakir; data curation, Rimsha Ajmal and Khadija Rasool; resources, Babar Ali and Saqib Mehmood; writing-original draft preparation, Wajeeha Tariq; writing-review and editing, Areej Amir and Wajeeha Tariq; supervision, Syed Muhammad Yousaf Farooq and Muhammad Zakir; project administration, Syed Muhammad Yousaf Farooq. All authors have read and agreed to the published version of the manuscript.

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The Research Ethical Committee, The University of Lahore, approved the study.

Informed Consent Statement

The authors declare no conflict of interest.

Data Availability Statement

All of the data is included in the article/Supplementary Material.

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Conflict of interest

The authors declare no conflict of interest.

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