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Research Article

MONITORING OF CONTRAST AGENT-INDUCED TOXICITY IN A TERTIARY HEALTH-CARE CENTER

MANTASHA REHMANI[1], IRFAN AHMAD KHAN[2]*

[1]MBBS Student, J.N.M.C.H., AMU, Aligarh, Uttar Pradesh, India. [2]Department of Pharmacology, J.N.M.C.H., AMU, Aligarh, Uttar Pradesh, India.
*Corresponding author: Irfan Ahmad Khan; Email: irfan1308@gmail.com

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ABSTRACT

Objective: The objective of the study is to monitor radiological contrast agent-induced toxicity in patients and compare the toxicity and safety profiles of different radiological contrast agents.

Methods: This is an open-label, prospective, observational study conducted in a tertiary care hospital in April 2021 and September 2021. The study assessed the incidence of contrast-induced adverse events in different radiological procedures, i.e., contrast-enhanced computerized tomography (CECT) scans and contrast-enhanced magnetic resonance imaging (CEMRI). Adverse drug reactions (ADRs) were recorded using the standard central drug standard control organization ADR reporting form. Causality assessment of the ADRs was done using Naranjo's scale while severity assessment was measured using the Modified Hartwig and Siegel scale.

Results: The baseline characteristics of patients were almost similar in both groups. The mean age and gender distribution of the patients were not significantly different among both groups. For the adverse reaction in CECT, the male-to-female ratio was 1.88, and for CEMRI, it was 1.61. The ADRs due to CEMRI and CECT were mild in severity. The results showed that ADRs between contrast-enhanced MRI and contrast-enhanced CT were not significantly different.

Conclusion: Based on the results obtained, we concluded that the contrast agents used in the radio-diagnostic procedures are safe, and further research in this field is of fundamental importance.

Keywords: Contrast agent, Contrast-enhanced magnetic resonance imaging, Contrast-enhanced computed tomography, Contrast-induced nephropathy, Gadolinium, Iohexol.

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INTRODUCTION

Adverse drug reactions (ADRs) have been reported to be associated with the use of contrast agents. They can be a mild inconvenience, like itching along with hives, to a life-threatening condition. The administration of contrast media during angiographic procedures can result in severe complications such as contrast-induced nephropathy (CIN) [1].

The most severe adverse reactions related to contrast agents are allergic reactions, CIN, and thyroid dysfunction [2].

Acute kidney injury (AKI) is one of the major complications of intravascular iodinated contrast media administration during radiographic procedures [1]. Due to the increasing number of contrast-using procedures, the number of adverse reactions is also increasing. Contrast medium-induced renal failure is reported to be a major adverse effect accounting for up to 70%. However, it mostly goes undetected [3]. CIN is the third most common cause of hospital-acquired acute renal injury. It represents about 12% of cases. With normal renal function, the chances of CIN are low (0.5%). However, several prospective controlled trials have demonstrated that in patients with pre-existing renal impairment, the incidence is 12–27%.

When iodinated contrast is administered into the arterial circuit, there is vasodilation due to endothelium-mediated release of nitric oxide. After this, there is a period of sustained vasoconstriction lasting for several seconds to minutes in the periphery. This results in a transient reduction in renal blood flow. The ongoing damage is further enhanced by direct iodine/osmolar toxicity to renal tubular cells due to the contrast agent. The free radicals attack the adjacent cells. This results in increased damage markers decreased tubuloglomerular feedback filtration rate and ultimately increased serum creatinine [4].

Iodine and barium are the most common types of contrast agents for radiography based on X-rays. Gadolinium contrast agents are used in contrast-enhanced magnetic resonance imaging (CEMRI). It improves the quality of MRI images [5,6]. Allergic reactions to gadolinium-based contrast agents occur rarely in about 0.04–0.3% of patients. More than 90% of these reactions are mild in severity. The adverse reactions can be acute or chronic [7]. Studies have shown that gadolinium-based contrast agents are very safe. Only rare incidences of deaths are reported [8].

The most widely and successfully used contrast agents presently are iodinated contrast agents. They have a similar function group – a tri-iodinated benzene ring. Adverse reactions are more common with high-osmolarity agents. The reactions are approximately 15% with a high-osmolarity agent as compared to 3% with a low-osmolarity contrast agent. Therefore, the high-osmolarity agents are not used now [9,10].

Iodinated contrast media are nephrotoxic [11]. AKI secondary to contrast agent administration is termed CIN or contrast-induced AKI, which is an iatrogenic AKI [12].

In a study, it was reported that the adverse reaction rate to gadolinium contrast material was 0.06% [6]. The occurrence of acute adverse reactions due to contrast administration was 0.17%. All reactions were classified as mild. The most common complaints following contrast agent administration were rashes and hives (9 of 30), nausea (7 of 30), and anxiety (6 of 30) [13,14].

The World Health Organization issued a restriction on the use of several gadolinium contrast agents in November 2009, stating that "High-risk gadolinium-containing contrast agents are contraindicated in patients with severe kidney problems, patients who have recently received a liver transplant, and 36% of new-born babies up to 4 weeks of age".

Studies have been done to evaluate the role of gender in contrast agent-induced ADRs. The incidence of ADRs between male and female patients was compared. It has been found that there is no significant difference in the occurrence of contrast-induced ADRs between male and female patients [14,15].

To our knowledge, none of the studies have statistically analyzed and enlisted the adverse effects due to contrast agents. Keeping all this in mind, we aim to explore better opportunities for contrast agents by comparing the toxicity and safety profiles of different radiological contrast agents.

Aims and objectives

1. To monitor radiological contrast agent-induced toxicity in patients
2. To evaluate and compare the toxicity and safety profiles of different radiological contrast agents.

METHODS

The study was conducted on patients undergoing radiological investigations using contrast agents in a tertiary health-care center in north India. It was an open-label, prospective, observational study. Approval for the study was obtained from the Institutional Ethics Committee. Written and informed consent was obtained from all the patients before they were enrolled in the study.

Description of methods used in the study

All adverse events experienced by the patients were noted on standard ADR reporting forms of the Central Drug Standard Control Organization (CDSCO). The causality assessment of ADRs was done using Naranjo's Scale [16] and severity assessment by the Modified Hartwig and Siegel Scale [17]. A physical examination, including vital signs, was performed at the start of the study and as required. Additional routine laboratory safety tests such as liver function tests, renal function tests, and electrocardiograms were performed wherever needed.

Inclusion criteria

1. Patients admitted to the wards undergo radiological investigations using a contrast agent
2. Age between 20 and 60 years
3. Either sex will be included in the study.

Exclusion criteria

1. Patients with renal impairment
2. Immunocompromised patients
3. Patients with chronic illnesses
4. Patients with any systemic condition related to peripheral neuropathy (malnutrition, alcoholic neuropathy, renal failure) or with neuropathies associated with exogenous toxins, metals, and drugs
5. Psychotic patients
6. Uncooperative patients refuse to give informed consent.

Data collection

The patient's general information, such as age, gender, height, weight, previous history of any debilitating disease, drug usage, etc., was obtained through a proper history using a predesigned pro forma. ADR was recorded using the standard CDSCO ADR reporting form.

Data analysis

The statistical analysis of the data and the correlation was done using Fisher's exact test.

Ethical consideration

Ethical clearance from the Institutional Ethical Committee was obtained before the study (D. No. 144/FM/JEC). The nature of the study was fully explained to the participants, and written informed consent was obtained from them.

OBSERVATION AND RESULTS

The present study was conducted in the Department of Pharmacology and Department of Radiodiagnosis, J. N. Medical College and Hospital, A.M.U., Aligarh, in April 2021 and September 2021. The study assessed the incidence of contrast-induced adverse events in radiological procedures, i.e., contrast-enhanced computerized tomography (CECT) scans and CEMRI. In patients undergoing CECT, iohexol was used as a contrast agent, while in CEMRI, a gadolinium-based contrast agent was used.

Investigation	Contrast agent used
CECT	Iohexol
CEMRI	Gadolinium

CECT: Contrast-enhanced computerized tomography, CEMRI: Contrast-enhanced magnetic resonance imaging

A total of 200 patients were enrolled in the study who met the inclusion and exclusion criteria and gave valid consent. Among these 200 patients, 100 underwent CEMRI, and 100 underwent CECT. Out of 200 patients, 122 (61%) were males and 78 (39%) were females.

The observations made during the study were as follows:

1. Number of patients with ADR

Out of 100 patients who underwent CEMRI, ADR was observed in 26 patients, while in a CECT scan, 30 patients reported ADR. The occurrence of ADR in CEMRI and CECT patients is shown in Table 1.

2. Gender-wise ADR distribution of patients

The results showed that ADR occurrence was not significantly different between CEMRI and CECT patients. The gender-wise ADR occurrence in CEMRI and CECT patients and comparison are detailed in Table 2 and Fig. 1. As the data for ADRs are a categorical variable and the cells have an expected count of <5, even zero, Fisher's exact test was applied. There was no significant difference between the groups in respect to the occurrence of ADRs.

3. Age distribution of patients

The age-wise distribution of the patients in both groups was not significantly different. The maximum ADR was reported in the age group 41–50. The age-wise distribution of patients is shown in Table 3 and Figs. 2 and 3.

4. Causality assessment of individual ADR

On assessment with Naranjo's Scale, the ADRs were possible (Score = 1–4) in 58 cases (77.3%) and probable (Score = 5–8) in 17 cases (22.7%) with contrast-enhanced MRI whereas possible (Score = 1–4) in 54 cases (79.4%) and probable (Score = 5–8) in 14 cases (20.6%) with contrast-enhanced CT. There was no statistically significant difference between CEMRI and CECT ADRs. The causality assessment of individual ADR is shown in Table 4.

Table 1: Number of patients with adverse drug reaction

S. no.	Group	Patient	No. of patients with ADR	%
01	CEMRI	100	26	26
02	CECT	100	30	30

CECT: Contrast-enhanced computerized tomography, CEMRI: Contrast-enhanced magnetic resonance imaging, ADR: Adverse drug reaction

5. Severity assessment of ADRs

The majority of adverse reactions were mild in severity classification (no hospitalization, no change in therapy, and no additional treatment). In patients who had undergone CEMRI, 92% of cases were mild, 8% were moderate, and no severe cases were found, whereas in patients, who had undergone CECT, 92.6% of cases were mild, 7.4% were moderate, and no severe cases were found.

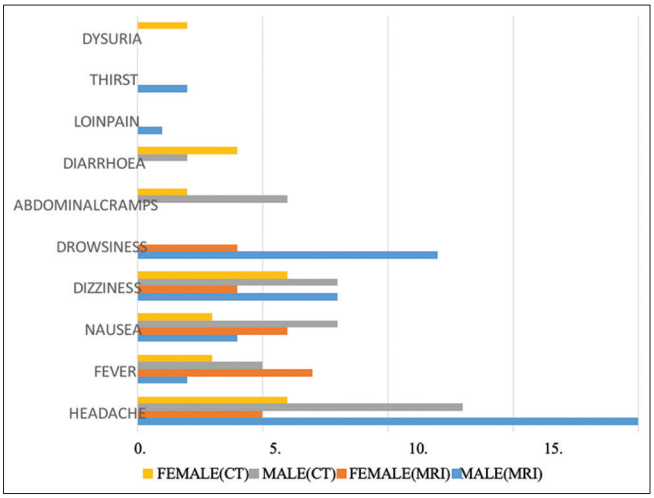

Figure 1: Gender-wise ADR distribution of patients

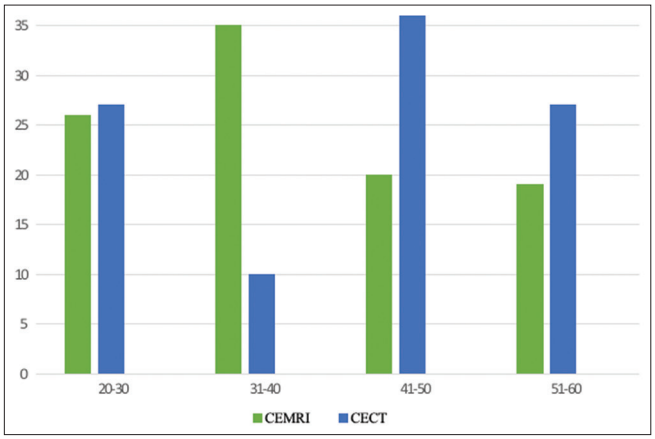

Figure 2: Age distribution of patients

Table 2: Gender-wise ADR distribution of patients

ADRs	CEMRI			CECT			Significance (2-tailed)
	Male	Female	Total	Male	Female	Total	
Headache	20	05	25	13	06	19	0.290
Fever	02	07	09	05	03	08	0.153
Nausea	04	06	10	08	03	11	0.198
Dizziness	08	04	12	08	06	14	0.701
Drowsiness	12	04	16	-	-	-	1.000
Abdominal cramps	-	-	-	06	02	08	1.000
Diarrhea	-	-	-	02	04	06	1.000
Loin pain	01	-	01	-	-	-	1.000
Thirst	02	-	02	-	-	-	1.000
Dysuria	-	-	-	-	02	02	1.000
Total	49	26	75	42	26	68	0.728

CECT: Contrast-enhanced computerized tomography, CEMRI: Contrast-enhanced magnetic resonance imaging, ADR: Adverse drug reaction

Table 3: Age distribution of patients

Age group (in years)	CEMRI	No. of patients with ADRs	CECT	No. of patients with ADRs	Total % of patients with ADRs (%)
20–30	26	04	27	03	13.2
31–40	35	11	10	06	37.7
41–50	20	10	36	16	46.4
51–60	19	01	27	05	13.0

CECT: Contrast-enhanced computerized tomography, CEMRI: Contrast-enhanced magnetic resonance imaging, ADR: Adverse drug reaction

Table 4: Causality assessment of individual ADR

ADRs	CEMRI			CECT		
	Possible	Probable	Definite	Possible	Probable	Definite
Headache	20	5	-	16	3	-
Fever	7	2	-	5	3	-
Nausea	8	2	-	11	-	-
Dizziness	8	4	-	12	2	-
Drowsiness	12	4		-	-	-
Abdominal cramps	-	-	-	6	2	-
Diarrhea	-	-	-	2	4	-
Loin pain	1	-	-	-	-	-
Thirst	2	-	-	-	-	-
Dysuria	-	-	-	2	-	-
Total	58 (77.3%)	17 (22.7%)	-	54 (79.4%)	14 (20.6%)	-

CECT: Contrast-enhanced computerized tomography, CEMRI: Contrast-enhanced magnetic resonance imaging, ADR: Adverse drug reaction

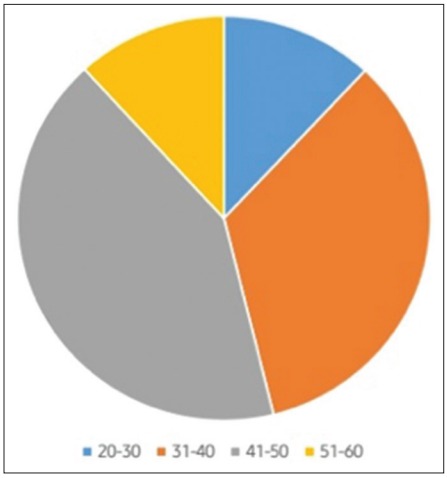

Figure 3: Age distribution of patients with ADRs

DISCUSSION

Radio-diagnostic investigations have become an important diagnostic approach nowadays. Contrast agents are used during such procedures. Due to the use of contrast agents during computed tomography and magnetic resonance imaging, a safety assessment of contrast agents is very necessary. Contrast agents help to appreciate the differences between body tissues on imaging. Contrast agents that do not produce any adverse effects and reach a very high concentration in tissues are considered ideal contrast agents [18].

All available contrast agents are associated with some side effects. The widespread use of contrast agents in radiological procedures has given rise to unavoidable reactions. Therefore, the need to find appropriate contrast agents that have good efficacy and safety is need of hour. Furthermore, there is a need to evaluate the effect of contrast on patients with underlying conditions and emergencies [19].

Adverse reactions that present early are termed acute adverse reactions and late as delayed reactions. The acute adverse reactions are allergic and physiologic reactions. Allergic reactions include nausea, vomiting, itching, bronchospasm, and anaphylactoid reactions, while pulmonary edema, arrhythmia, and decreased cardiac activity are physiologic reactions [20]. Delayed reactions are more commonly caused by the nonionic dimeric contrast agent. The majority of delayed reactions are cutaneous reactions. They present after 12–48 h of injecting contrast as an erythematous, maculopapular rash. These are mild in severity and self-limited but may involve the entire body and increase the discomfort [21].

CIN is classified as an allergic-like reaction and a physiologic reaction in many studies. Earlier, in about 15% of patients being administered high-osmolar agents, adverse reactions were seen. The use of newer low-osmolar agents has further reduced it significantly to 0.2–0.7%. CIN is an iatrogenic toxicity resulting in AKI. Within 24–48 h of contrast agent administration, there occurs deterioration of renal function. The gadolinium-based contrast agents during MRI are the most studied. There was no impairment in renal function with its use even in patients with renal insufficiency [20].

Hinson *et al*., found no correlation between the incidence of AKI and the administration of contrast agents. CIN criteria odds ratio (OR) was 0.96, 95% confidence interval (CI) was 0.85–1.08, and AKI Network/ Kidney Disease Improving Global Outcomes criteria OR=1.00, 95% CI 0.87–1.16. These results were the same even in patients with baseline renal function. The increased incidence of chronic kidney disease was not associated with the use of contrast agents. The doctors avoided prescribing contrast to patients with deranged renal function and mostly administered intravenous fluids along with contrast. Therefore, intravenous contrast was not associated with an increased occurrence of AKI [22]. In our study, renal dysfunction was not found to be significant.

Table 5: Severity assessment of ADRs by Modified Hartwig and Siegel scale

Severity	CEMRI	%	CECT	%
Mild	69	92	63	92.6
Moderate	06	8	05	7.4
Severe	-	-	-	-

CECT: Contrast-enhanced computerized tomography, CEMRI: Contrast-enhanced magnetic resonance imaging, ADR: Adverse drug reaction

In another study, Aycock *et al*., demonstrated that both noncontrast CT and contrast-enhanced CT were not significantly associated with either AKI (OR 0.94; 95% CI 0.83–1.07), need for renal replacement therapy (OR 0.83; 95% CI 0.59–1.16), or cause mortality (OR 1.0; 95% CI 0.73–1.36) [23].

At present, triiodobenzoic acid compounds are used as contrast agents [24]. Iohexol is one of a group of such compounds used as a contrast agent for computed tomography.

According to Cochran *et al*., mild and moderate adverse reactions occur more commonly with ionic contrast agents as compared to nonionic which are allergic-like. Severe reactions are common with both types of contrast agents. Allergic-like adverse reactions were associated with the ionic group while nonionic contrasts were associated with cardiopulmonary decompensation [7].

In a study by Cha *et al*., the prevalence of allergic reactions to iodinated contrast agents was 0.73% and severe reactions 0.01% [25].

In another study, Pelagatti *et al*., demonstrated that after injecting an iodinated contrast agent into 1480 patients, only five ADRs (0.34%) were noted. The ADRs were found more in patients with a history of allergy (1.5%), compared to our study. 30% of patients experienced ADRs of mild severity who have undergone contrast-enhanced CT (Table 1) [26].

Regarding the discussion on gender distribution in patients undergoing contrast-enhanced CT, Lee *et al*. did not find any significant difference in the incidence of ADRs between males and females [15].

It was reported that 9,056,566 (60.1%) were females and 6,012,804 (39.9%) were males. ADRs were reported more in females. In our study, the male-to-female ratio of ADRs was found to be 1.6:1.

The number of studies and scientific papers on iodinated contrast media are decreasing [14]. The search for safer and more effective iodinated contrast agents remains an ongoing challenge and an important research topic [24].

Allergic reactions are rare due to gadolinium-based contrast agents. It occurs in 0.04–0.3% of administrations, out of which more than 90% are mild.

There is a 30% chance of a recurrence of hypersensitivity in patients with a history of a similar episode of adverse reaction. The risk is even higher in patients with bronchial asthma, an allergy to iodine-based contrast media, etc. [8].

The highest rates of adverse events are related to abdominal MRI. Adverse events were more likely in women, with a ratio of 3.3 (female: male), and patients with a previous history of allergic reactions (<0.001) [27]. In our study, the occurrence of ADRs among males and females undergoing CEMRI was at a ratio of 1.884 (male: female).

Data demonstrate that gadolinium-based contrast agents are very safe. Only rare incidences of deaths are reported [8]. In our study, 26 patients

out of 100 who had undergone contrast-enhanced MRI experienced adverse reactions of mild severity (Tables 1 and 5).

In the study by Hunt *et al*., the most common adverse effects were hives (274, 52.5%) and nausea (92, 17.6%). Of all adverse effects, 79 were due to iodinated contrast agents, and 15 of gadolinium contrast were managed in the radiology unit. Only 16 cases of adverse events required further treatment. Compared to our study, there was no significant difference between the adverse reactions due to iodinated and gadolinium contrast agents [28].

On causality assessment, both in CEMRI and CECT patients, none of the ADRs were definite, and mostly (77.3%) CEMRI and (79.4%) CECT were in the possible category. Hence, the causal relationship is poor, and these ADRs can be because of the underlying disease for which the patients underwent these investigative procedures.

Hence, the study suggests that the use of these contrast agents in MRI and CT is safe in radiological investigations.

CONCLUSION

Contrast agents, which are being used in radiological procedures, i.e., iodinated contrast (nonionic, low-osmolality) in computed tomography and gadolinium-based contrast in magnetic resonance imaging, are safest to date, with the majority of adverse reactions being mild in severity and a rare instance of severe anaphylactoid reactions.

In the current study, the most commonly found adverse reactions were headache, nausea, fever, drowsiness, and dizziness.

Due to the extensive use of contrast media, further research in this field to find better contrast agents by employing a large multicentric approach is of fundamental importance. Patient screening and prophylaxis before administration of contrast agents are another topic of concern. Furthermore, in cases of adverse events, radiologists must be trained to manage and treat the patient.

AUTHORS CONTRIBUTION

The authors confirm their contribution to the paper as follows: Mantasha Rehmani: study conception and design; data collection; draft manuscript preparation. Both authors reviewed the results and approved the final version of the manuscript. Irfan Ahmad Khan: study conception and design; draft manuscript preparation; analysis and interpretation of results; draft manuscript preparation. Both authors reviewed the results and approved the final version of the manuscript.

CONFLICT OF INTEREST

Nil.

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