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Frequency and Severity of Acute Adverse Effects of Low Osmolar Iodinated Contrast Media in Contrast-Enhanced Computed Tomography

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Abstract

Background: Nonionic, low osmolar agents are now used nearly universally for intravenous (IV) contrast administration in computed tomography. The osmolarity of a contrast agent is considered to be responsible for adverse effects in patients injected with contrast media. With the increase in its utilization, acute adverse reactions are suspected to rise substantially. Regardless of the usage of low osmolar non-ionic agents to reduce adverse effects, a large number of reactions are still experienced by patients. However, the frequency of immediate adverse contrast reactions to various low osmolar non-ionic iodinated contrast media is not well studied. A basic understanding of the occurrence, risk factors and clinical features of these reactions is important as it can help in ensuring optimal patient care. Objective: To determine the frequency and severity of acute adverse reactions related to administration of low osmolar iodinated contrast media to patients during contrast-enhanced computed tomography scans. Methods: A cross-sectional study of intravascular doses of low osmolar non-ionic iodinated contrast media administered from October 2018 to February 2018 was conducted on patients undergoing CT examinations at Combined Military Hospital, Lahore. Acute adverse effects were characterized by using the data collected. These effects were investigated for determining the frequency and severity of reactions. Results: A total of 328 low osmolar iodinated contrast doses were administered to patients coming for CT examinations. 209 cases of acute adverse effects (63.72%) were identified. 90 out of 139 (64.75%) females, 117 out of 189 (61.90%) males were affected. Mild reactions were in the majority with the most common being nausea, sweating, and change in taste. Two cases of moderate reactions and no severe/fatal reactions were found over the study period. One case necessitated transfer to the emergency for urgent care. Female patients were affected more than males. Conclusion: Acute adverse reactions to the administration of low-osmolar non-ionic iodinated contrast agents are rare. The severity of these reactions is governed by multiple aspects of an examination, but the majority of them are mild. Moderate and severe reactions occur infrequently. Ideal patient care can be very helpful to combat these reactions.

Keywords: Non-Ionic Iodinated Contrast, Osmolarity, Anaphylactic Reaction, Vasovagal Reaction
Introduction

Contrast media are the most common pharmacological agents injected into the human body, used in approximately 75 million procedures per year worldwide¹ and have been utilized for imaging of structural anatomy and investigate typical and atypical physiological findings. With the introduction of advanced discriminational radiographic imaging procedures, the requirement for radiation rarefying contrast agents used in conventional radiographic techniques or recently, in image subtraction, has increased. Markedly, the most efficient and extensively administered contrast agents are iodine based². Iodine-containing contrast media were initially used in the clinical setting with the development of sodium iodide in the 1920s, but their usage was limited by low-quality radiographic contrast and patient toxicity³. Iodinated contrast agents that are water-soluble extend all over the extracellular space. They can be injected straight into the body cavity, for instance, in the gastrointestinal and the urinary tract⁴. A standard contrast-enhanced CT uses ~40 grams of iodine chemically enchained to an organic molecule that is injected into the vascular system⁵. All presently used iodinated contrast media are categorized on the grounds of their chemical and physical traits, involving chemical composition, iodine content, osmolarity and ionization in solution. They are usually chemical variations of a 2, 4, 6-tri-iodinated benzene ring⁶. Compounds are either monomers (1 tri-iodinated benzene ring) or dimers (2 tri-iodinated benzene rings joined together by an organic functional group). Besides, the presence (i.e., ionic) or absence (i.e., non-ionic) of a carboxylate (-COO-) functional group on an organic side chain controls the ionic tendency. Generally, these agents are available as sodium, calcium salts or cations of methylglucamine, for the reason that (-COO-) component gives the molecule a net negative charge. The different characteristics, clinical uses, and toxicity levels of contrast media impact which type of agents are used by the imaging sector for particular indicated treatments. The charged ionic agents contribute to derange the electrical potentiality of the cytoplasmic membranes, justifying their enhanced toxicity, unlike non-ionic agents, that are uncharged. Ionic monomers have a weak capability for attenuation of X-rays and require to be applied in high concentration that is hyperosmolar compared to blood. They are known as high osmolar agents. Low osmolar agents constitute ionic dimers and nonionic monomers with a range of osmolarities from 290 to 860 mOsm/L⁷. In clinical practice, classification based on osmolarity is mostly used⁸. An implication of the osmolarity of an agent is defined by a ratio, obtained by dividing the number of iodine atoms in a solution with the number of particles in solution:

\[
\text{Contrast agent ratio} = \frac{\text{Number of iodine atoms}}{\text{Number of particles in solution}}
\]

The high osmolar contrast substances have a greater number of subatomic constituents for each iodine atom and thus lower ratios⁹. High osmolar agents can disintegrate in an aqueous solution significantly, in contrast to low osmolar agents which usually own an osmolarity marginally higher than blood¹⁰ and have arms with a strong affinity to water consisting amido linkages and hydroxyl substituents. The success of these molecules mainly dwells in some diacritic physico-chemical properties that conjoin low osmolarity with low viscosity to a high concentration in water and in the stability of iodine substitution and the high concentration of iodine per molecule. The side chains are valuable not only for increasing the aqueous solubility but also because they lessen the toxicity and escalate the expulsion of substances from the patient body⁵. High-osmolar iodinated contrast media paved the way for low-osmolar agents, as they are related to adverse reactions to a lesser extent¹. The hyperosmolarity of contrast agents is considered to be responsible for several adverse effects in patients injected with contrast media coming for computed tomography scanning⁹. Despite the efforts to minimize the rate of unfavorable reactions to iodinated contrast media by using low osmolar nonionic agents, a large number of reactions are still encountered¹⁰. It is necessary to be aware of the possibility of adverse reactions against these compounds ranging from mild aggravations to life-threatening crisis¹¹. The immediate/acute reaction occurs up to one-hour post injection and is related to the osmotic load or contrast media chemotoxicity¹². These acute adverse reactions are of clinical concern because they are uncertain and cause discomfort to patients. The American College of Radiology (ACR) guidelines classify acute adverse reactions as allergic-like or physiologic and organize in terms of severity as follows: mild, moderate, or severe. The symptoms of allergic-like reactions resemble those of true allergic/anaphylactic reactions because an antigen-antibody response is sometimes unidentifiable and include skin and respiratory tract symptoms. The use of an iodinated contrast agent contributes to an adverse reaction by the emancipation of histamine from white blood cells (basophils, eosinophils), which is considered to be a vital process in the physiopathology of anaphylactoid reactions⁵. The
second type, physiologic reactions, include cardiovascular effects, especially problematic in patients with latent cardiac disease. These vasovagal reactions are characterized by hypotension with bradycardia and gastrointestinal signs (e.g., vomiting and nausea). Others include flushing, sweating, shivering, headache, dizziness, anxiety, and alteration of taste may also occur\textsuperscript{13}. Overall, physiologic reactions are anticipated to be an outcome from a disruption in homeostasis. Additionally, the dose injected, and route of administration may control the prevalence of adverse reactions. Large intra-arterial doses (>100 ml) are correlated to increased risk\textsuperscript{7}. Deaths prompted by iodine-based contrast are extremely uncommon attributing to renal failure, anaphylaxis or allergic reaction. Nearly all lethal reactions occur within minutes after injection and patients need to be under surveillance in this period. A fatal reaction may occur prior to inconsequential events, such as nausea and vomiting, or without warning. The majority of deaths occur in patients in older patients, above 50 years of age and can be caused by cardiac arrest, pulmonary edema, respiratory arrest, consumption coagulopathy, bronchospasm, laryngeal edema, and angioneurotic edema\textsuperscript{14}.

Methods

A cross-sectional study was conducted using the Toshiba Aquilion 64-slice CT scanner at Combined Military Hospital, Lahore. Data were collected from patients indicated with contrast-enhanced computed tomography including male and female patients of age 16 years or older having acute reactions to the low osmolar contrast agent used. Patients were reviewed for pertinent medical history of undergoing a CT examination, previous allergy from contrast material, intake of medication for diabetes and history of asthma. Before administration of contrast, patients were checked for the type of CT scan, serum creatinine/eGFR, type of contrast agents used, amount of contrast to be given and administration site. The severity of reactions to the contrast agent was classified into mild, moderate or severe as per the guidelines are given by the American College of Radiology. Patients who had delayed reactions or serum creatinine concentration >1.5mg/dL and eGFR <60mL/min/1 were excluded from this study.

Results

From October 2018 to February 2018, a total of 328 patients (ages between 16 and 80 years old; 189 males, 139 females) were administered low-osmolar iodinated contrast doses over the study period. Among these doses, 316 were of Ultravist, and 12 were of Omnipaque. A total of 209 (63.72%) of acute adverse reactions were identified and affected 90 out of 139 (64.75%) females, 117 out of 189 (61.90%) males (Figure 1,2,3).
Figure 1. Graph representing the frequency of mild adverse reactions affecting females and males

Figure 2. Graph representing the frequency of moderate adverse reactions affecting females and males
The frequency and severity of these adverse effects were as follows: 207 (63.11%) mild reactions represented by nausea, sweating, change in taste in an overwhelming majority, two (0.61%) moderate reactions represented by hypertension, tachycardia, and dyspnea. Only one patient who suffered both mild and moderate reactions in combination required to transfer to the urgent care unit. No patients were recorded to have a severe reaction, and none died as a result of an adverse effect. Out of the 209 patients who suffered reactions, 52 had undergone contrast media examination before, 17 patients self-reported prior allergy to contrast media and were affected again, 30 were taking metformin, and 14 were asthmatic (Table 1). Age, EGFR and contrast amount did not show to have any significant impact on the occurring reactions. Table 2 depicts the frequency of acute adverse reactions based on the type of contrast used, administration site and type of examination.

Table 1: Frequency of adverse reactions according to medical history

|                                      | no | yes |
|--------------------------------------|----|-----|
|                                      | Count | Count |
| Patients that had contrast media before |     |     |
| no                                    | Mild  | 72   | 155  |
|                                       | Moderate | 226  | 1    |
|                                       | Severe  | 227  | 0    |
| yes                                   | Mild  | 49   | 52   |
|                                       | Moderate | 100  | 1    |
|                                       | Severe  | 101  | 0    |
| Patients with a history of contrast media allergy |     |     |
| no                                    | Mild  | 102  | 190  |
|                                       | Moderate | 291  | 1    |
|                                       | Severe  | 292  | 0    |
| yes                                   | Mild  | 19   | 17   |
|                                       | Moderate | 35   | 1    |
|                                       | Severe  | 36   | 0    |
|Patients that take Metformin           |     |     |
| no                                    | Mild  | 102  | 177  |
|                                       | Moderate | 277  | 2    |
|                                       | Severe  | 279  | 0    |
| yes                                   | Mild  | 18   | 30   |
|                                       | Moderate | 48   | 0    |
|                                       | Severe  | 48   | 0    |
| Yes                                   | Mild  | 1    | 0    |
|                                       | Moderate | 1    | 0    |
|                                       | Severe  | 1    | 0    |
| Patients that are asthmatic           |     |     |
| no                                    | Mild  | 110  | 193  |
Table 2: Frequency of adverse effects based on technical aspects of a CT examination

| Type of Contrast       | Mild no | Moderate yes | Severe no |
|------------------------|---------|--------------|-----------|
| Omnipaque               | 2       | 10           | 12        |
| Ultravist               | 119     | 197          | 314       |
| Administration Site    |         |              |           |
| Cubic Fossa             | 41      | 73           | 114       |
| Forearm                 | 27      | 43           | 69        |
| Hand                    | 53      | 91           | 143       |
| Type of Exam            |         |              |           |
| Abdomen                 | 19      | 37           | 56        |
| Aorta Angiography       | 0       | 1            | 0         |
| Brain                   | 33      | 41           | 74        |
| Brain Angiography       | 4       | 7            | 11        |
| Carotid Angiography     | 2       | 8            | 10        |
| Chest                   | 40      | 47           | 87        |
| Chest+Abdomen+Pelvis    | 7       | 18           | 24        |
| Head+Neck               | 5       | 18           | 23        |
| Lower Limbs Angiography | 0       | 11           | 11        |
| Pelvis                  | 8       | 7            | 15        |
| Renal Angiography       | 1       | 7            | 7         |
| Upper Limbs Angiography | 2       | 5            | 7         |

Discussion

The rate of acute adverse reactions in our study with low-osmolar iodinated contrast media was 63.72 % amongst 328 doses, a substantial drop from the proportion registered with high-osmolar iodinated contrast media. Although less in number, females were affected at a higher percentage than men. There were no severe reactions recorded. In our study, the rate of mortality for the use of low osmolar iodinated contrast agents was 0% which is in accordance with the mortality rate affiliated with the administration of contrast media, reported hitherto. In spite of the fact that no deaths occurred, the possibility of risk should not be ignored, even in patients lacking a medical background of contrast reactions.

It has been proposed that particular characteristics, such as age, EGFR and contrast amount are associated with the rising probability of adverse effects, our work did not reaffirm the assumption. The registration of EGFR and amount of contrast administered are a part of our standard screening, but the usefulness of the record remains restricted.

Almost all the adverse effects that took place were mild, though moderate effects occurred at a rate adequate to assert patient assistance and constant monitoring.

This study was limited by certain aspects. Firstly, this study was a cross-sectional one that mandatorily required constant reporting by the imaging technologist. While departmental actions were implemented to promote consciousness about the occurrence of these adverse effects, there was an innate inclination towards precise reporting of more severe episodes. In addition, because this study was conducted in a single center, the generalization of the results is confined. These limitations, though not significant, influenced the results of the study minimally.

The emergence of low-osmolar iodinated contrast media and utilization of pre-treatment regimes have declined the frequency of contrast-associated adverse effects as a whole, but they still persist. While adverse reactions can
be effectively manipulated in the health facility, most of them with observations only, severe effects can constrain immediate treatment and shift to emergency care. Cautious investigations and treatment conventions are needed to avoid morbidity and mortality.

Conclusion

Acute adverse reactions caused by low osmolar non-ionic iodinated contrast agents are primarily mild and transient. In the adult population, moderate reactions are seldom occurring. Females have a higher frequency of acute reactions occurring from low osmolar contrast media than males. In our study, no severe reactions were found, but they do occur rarely and can be life endangering. However, adverse reactions should be accurately documented, treated and managed.

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