Adverse Reactions to Non-ionic, low-osmolar contrast media: A study of a Nigerian Population

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Abstract

Background: The use of iodinated contrast media is associated with adverse reactions, in which prevalence and pattern are understudied in Nigerian.

Objective: To determine the adverse reactions due to nonionic low-osmolar contrast media (CM) in a Nigerian population.

Method: This was a prospective observational study of 459 patients injected with CM and monitored for 7 days, each. Patients were randomly selected from a pool of patients booked for contrast-enhanced procedures by simple toss of a coin. Those who answered 'yes' and consented were issued consent form for inclusion. The study which was conducted at The EKO Hospital PLC and Mecure Healthcare Ltd, both in Lagos State, lasted from 20th November, 2016 to 25th November, 2017. Ethical approval was obtained from the HREC of Lagos University Teaching Hospital Idi-Araba. Immediate, and delayed reactions were documented.

Results: A total of 118 (25.7%) anaphylactic adverse reactions were recorded. The most prevalent adverse reaction was nausea/vomiting, occurring in 31 (6.8%) patients. Other adverse reactions were urticaria, (17, 3.7%), facial hyperemia (15, 3.3%), sneezing (8, 1.7%) and laryngeal edema/choking sensation (9, 2.0%). Cardiac arrhythmia and transient hypotension were noted in three patients each.

Conclusion: The incidence of anaphylactic, immediate and delayed adverse reaction to low osmolar contrast agent was high in a cohort of Nigerians residing in Lagos State. Low osmolar contrast agents, were therefore, seemingly not as safe in a Nigerian population as previously believed.

Keywords: Adverse reactions, contrast media, Medical Imaging

Introduction

The use of iodinated contrast media in medical imaging is associated with adverse reactions [1, 2] These adverse reactions according to Modi *et al.* can broadly be classified into general and organ specific effects [3]. The general adverse reactions are further sub-divided into acute and delayed reactions [3, 5]. Acute reactions are usually of immediate onset and are defined as reactions that occur within 1 hour of intravenous contrast injection [2, 6]. These reactions may further be classified into mild, moderate or severe; depending on the effect on the administered subject. Most immediate reactions are 'anaphylactoid' in nature [7], since the reactions are not immunoglobulin E (IgE) mediated [8, 9]. The tendency to manifest these reactions is unpredictable, partly idiosyncratic or acquired, as in concomitant medication or co-morbidity.

Many researchers have tried to document the different symptoms associated with these classifications of adverse reactions [1, 2, 10, 11]. Equally of interest is that these symptoms are not distinctly exclusive of each other in degree and form; and can sometimes be subjectively affected by the personal judgment of the researcher. This has resulted in the lack of consensus on the classification and determination of the prevalence of adverse reactions due to iodinated contrast media.

The overall incidence of early onset adverse reactions is dependent on the type of contrast media and the spectrum of adverse reactions evaluated by the researcher [6]. The incidence of acute adverse

reaction is therefore difficult to determine with precision [5]. This lack of precision may be due to the presentation of similar symptoms and signs from concomitant medical conditions, medication and anxiety-induced symptoms among other factors.

In a comprehensive review by American College of Radiology, a historical incidence of 5% to 15% of adverse events had been established in patients exposed to high osmolar contrast media (HOCM) [5]. Due to this degree of adverse reactions, HOCM are currently rarely in use for intravascular radiographic procedures. Low osmolar contrast media (LOCM) has gradually taken its position despite the adjudged high cost. LOCM are associated with low incidence of acute adverse reactions [5, 12], though the severity remains unpredictable. Cochran *et al.,* reported an overall incidence of 0.2% for non-ionic LOCM in a study in which both allergic-like and physiologic signs and symptoms were included [9].

The advent of new Computed Tomography (CT) technology with multi-detector array and multi-slice imaging protocol has led to increase in the use of iodinated contrast media [13], for many diagnostic procedures, such as CT angiography, urography and brain CT perfusion studies among others. This is in addition to the conventional intravenous urography procedures and routine brain CT series. The likely implication of this scenario is higher prevalence of adverse reactions among patients due to increased exposure to contrast-enhanced radiographic procedures.

Some earlier researchers had also identified racial differences in these reactions among other factors [14]. Ansell *et al.,* in a 12-month prospective survey involving 272 hospitals in the United Kingdom, found a significantly increased risk (eight fold of severe reactions) for development of contrast media induced reactions in patients of Indian origin, compared with the native Britons [14]. Regrettably, literature on adverse reactions due to iodinated contrast media among the Nigerian population is limited. An inclusive intercontinental study to establish the incidences of adverse reactions to iodinated contrast media involving 300,000 case reports from European countries, the United States of America, Canada and Australia [14], did not include Africa. Though no significant difference was noted in the incidences among those regions, Africa was not included or evaluated. Most of the reported studies are therefore among the Caucasian population and cannot be generalized for the African population. Reports of adverse reactions to iodinated contrast media are therefore limited among the Nigeria population and same for many African countries.

It is equally observed that most of the studies on adverse reactions to iodinated contrast media were retrospective in design [16 – 18] and therefore lacked encompassing details required to provide enough facts for effective evaluation of confounding risk factors and peculiar circumstances. Retrospective studies lack the ability to investigate variables that are often missed in data retrieved from medical records [16]. This research was prospectively prosecuted. However, due to the increasing utilization of contrast medium in radio-diagnostic services in Nigeria, the need to establish the incidence and pattern of these reactions among Nigerians cannot be over-emphasized.

Methodology

This was a prospective observational study on the adverse reactions due to administration of iodinated contrast media. This study was carried out in two busy radio-diagnostic departments of Eko Hospitals, Ikeja and MeCure Healthcare Ltd, Oshodi, Nigeria. Patients were recruited from normal departmental bookings for contrast-enhanced radiographic procedures. The scheduling Senior Radiographers employed a next-available scheduling template in booking for the investigations [20]. Patients were randomly selected from the daily imaging sessions of the department by simple toss of a coin for participation or not. Those who answered 'yes', had the study fully explained to them. Upon indication of consent; a consent form was issued to the person for inclusion. The inclusion criteria were patients referred for any type of intravascular contrast media-related procedures, fully conscious; well orientated in time and space and not on renal dialysis. Pregnant or lactating mothers and patients on Radio or chemotherapy treatments were excluded from the study. The contrast medium used in both centres is iopamidol.

A contrast media incident data form was specifically designed to document subject demography, suspected risk factors, clinical history and observed adverse reactions following

contrast injection; including changes in vital signs such as temperature, blood pressure and heart rate in line with previous similar studies [2, 3, 19].

The surveillance for adverse reactions started from the onset of injection to about an hour post contrast administration for immediate reactions and the next 7 days for delayed reactions. Classification of the severity of the observed anaphylactoid reactions was based on a mild modification of the classifications previously carried out by Modi *et al.* [3].

Ethical approval was obtained from the Health Research and Ethics Committee (HREC) of the Lagos University Teaching Hospital (LUTH), ***[Appendix 1].*** An approved informed consent form was also obtained and administered to each patient as a condition for inclusion into the study sample.

Statistical Tools for Data Analysis: Descriptive statistics was used to characterize and categorize the patients' baseline demographic data. Analysis was carried out using SPSS, version 19 (IBM Corp., New York, NY), formerly SPSS Inc., Chicago, Illinois, USA.

Results

The Prevalence of Immediate Adverse Reactions

A total of 118 (25.7%) patients manifested one form of anaphylactic adverse reaction or the other (Table 1), including sudden increase or decrease in patients' blood pressure, which accounted for 30 (25.4%) cases of the reactions and 6.5% of the study population. Immediate reactions occurred in 96(20.9%) patients, while delayed reactions manifested in 22(4.8%). The most prevalent adverse reaction noted in this study was nausea/vomiting which occurred in 31 (6.8%) patients, out of the 459 subjects enrolled for this study (Table 1). Elevation of a minimum of 10mmHg was noted in both systolic and diastolic pressures of 27 (5.9%) patients, following contrast media injection. Those with either only systolic or diastolic elevation of 10mmHg or less were considered too transient and were excluded. However, the overall mean pre-contrast systolic/diastolic blood pressure was 131/82_±40/37mmHg, while the post contrast-enhanced examination measurement was 130/81 -± 25/16 mmHg (Table 2). There was therefore no significant statistical difference, with P- value = 0.471.

In line with the ACR guideline, warm sensation and analgia were excluded as adverse reactions in this study. All the noted adverse reactions were immediate in nature except urticaria and pruritic papules which were delayed in onset, accounting for 18.6% of the adverse reactions in the study. Immediate reactions, excluding warm sensation and injection site analgia, therefore constituted 81.4% of the total anaphylactic-like reactions.

The respective incidences of other adverse reactions due to iodinated contrast media are equally illustrated in a Line graph of Figure. 1.

Pattern of Adverse Reactions according to Gender

The distribution of adverse reactions according to gender is shown in Tables 7. A total of 63 (26.9%) female patients manifested one form of adverse reaction or the other, contrary to 55 (24.4%) in males. Higher incidences of vomiting 18(3.9%), urticaria 10 (2.2%) and laryngeal edema or choking sensation were noted in males than in females. However, hypertension 18 (3.9%) [Observed as sudden increase in blood pressure], sneezing (6, 1.3%) and hypotension (3, 0.7%), were greater in females. Using a fisher's exact test, no statistical difference was noted in both males and females, with P- value = 0.263, 0.379. 0.531, 0.287 and 0.236, for nausea/vomiting, urticaria, pruritic papules, sneezing and hyperemia respectively.

Pattern of Adverse Reactions in order of Severity

The noted adverse reactions were classified into mild, moderate and severe in accordance with previous literature [3] and ACR recommendation [5]. In this study mild reactions occurred in 78 (17.0%) patients, while moderate reactions manifested in 27 (5.9%). Severe reactions occurred in three patients (0.7%), who manifested cardiac arrhythmia (Table 3). The mild adverse reactions documented were mostly nausea/vomiting, 31(22.9%), urticaria (17, 14.0%), facial hyperemia (15, 12.7%) and sneezing (8, 6.8%). Moderate adverse reactions were mainly hypertension (27, 22.9%) and laryngeal edema/choking sensation (9, 7.6%). The severe adverse reactions recorded involved three subjects who manifested severe cardiac arrhythmia. They were admitted and treated but recovered within hours and were subsequently discharged.

Adverse reactions in this study were equally categorized according to body systems (Table 4). The cardiovascular system due to transient changes in the blood pressure recorded the highest prevalence of 33 (7.3%) cases. Gastrointestinal system had 31 (6.8%) cases while Respiratory system recorded 17 (3.6%) cases. Cutaneous (skin) manifestations accounted for 22 cases (4.8%). In the cardiovascular system, the most prevalent adverse reaction was hypertension (27, 5.7%), while nausea/vomiting (31, 6.8%) dominated in the gastrointestinal system. The cutaneous system was mainly dominated by urticaria (17, 3.7%).

In terms of onset of adverse reactions, 81.4% (96 of 118) of all recorded adverse reactions were immediate. Delayed adverse reactions were urticaria and pruritic papules, which accounted for 18.6% of the adverse reactions.

Table 1 Common Adverse Reaction (Immediate and Delayed) due to Iodinated Contrast Media

ADVERSE REACTIONS	FREQUENCY	% INCIDENCE
Nausea/Vomiting	31	6.8
Urticaria	17	3.7
Pruritic Papules	5	1.1
Sneezing	8	1.7
Hyperemia	15	3.3
Hypotension	3	.7
Laryngeal edema/Choking sensation	9	2.0
Cardiac arrhythmia	3	.7
Hypertension	27	5.9

Nausea/Vomiting is the most common adverse reaction, closely followed by hypertension, while hypotension and cardiac arrhythmia were the least in this study.

Table 2. Variations in patients' vital signs: Temperature, Heart rate and Blood pressure

	Mean ± SD	P- value
Temperature before	35.8 ± 2.7	.104
Temperature after	36.7 ± 3.7	
Blood pressure before	131/82 ± 40/37	.471
Blood pressure after	130/81 ± 25/16	
Heart rate before	84 ± 14.4 (b/min)	.504
Heart rate after	83 ± 14.1 (b/min)	

Test of significance on Temperature, Blood Pressure and Heart Rate Change, before and after contrast injection, using t-test analysis showed no significant increase between the variables

Table 3 Percentage (%) Incidence of Adverse Reaction according to Gender

Adverse Reactions	Male	% incidence	Female	% incidence
Nausea/Vomiting	18	3.9	13	2.8
Urticaria	10	2.2	7	1.5
Pruritic Papules	2	0.4	3	0.7
Sneezing	2	0.4	6	1.3
Hyperemia	5	1.1	10	2.2
Hypotension	0	0.0	3	0.7
Laryngeal edema/Choking sensation	6	1.3	3	0.7
Cardiac arrhythmia	3	0.7	0	0.0
Hypertension	9	2.0	18	3.9

Nausea/ vomiting 18 (3.9%), urticaria 10 (2.2%) and laryngeal edema or choking sensation were more in males, while hypertension 18 (3.9%), sneezing (6, 1.3%) and hypotension (3, 0.7%), were greater in females.

Table: 4. Distribution Pattern of Adverse Reactions in order of Severity

Reactions		No.	%Incidence
Mild:	Nausea, Limited urticaria, Mild palor, mild vomiting Sneezing, Increased & Decreased Blood pressure	78	17.0
Moderate:	Severe vomiting, extensive urticaria, laryngeal edema, rigors, facial hyperemia, hypertension	27	5.9
Severe:	Pulmonaryedema,Cardiac arrhythmia, hypotension, seizures, syncope, bronchospasm	3	0.7

Most (17%, 78) of the anaphylactic adverse reactions were mild in nature, while 5.8% (27) and 0.7%(3) were moderate and severe.

Table: 5. Incidence of Adverse Reactions according to the affected Body System

Systems Affected	No of Patients affected	% of Patients affected
Gastro Intestinal (Total)		
Nausea/Vomiting	31	6.8
Abdominal Pain	0	0
Cardiovascular (Total)		
Hypertension	27	5.9
Hypotension	3	0.7
Cardiac arrhythmia	3	0.7
Cardiac arrest	0	0
Respiratory (Total)		
Sneezing	8	1.7
Bronchospasm	0	0
Nasal cold/irritation	0	0
Respiratory Distress/failure	0	0
Laryngeal edema	9	1.9
Cutaneous/Skin (Total)		
Urticaria	17	3.7
Pruritc Papules	5	1.1

According to body systems, the highest incidence of adverse reactions occurred in the cardiovascular system (33, 7.3%), followed by the gastrointestinal (31, 6.8%).

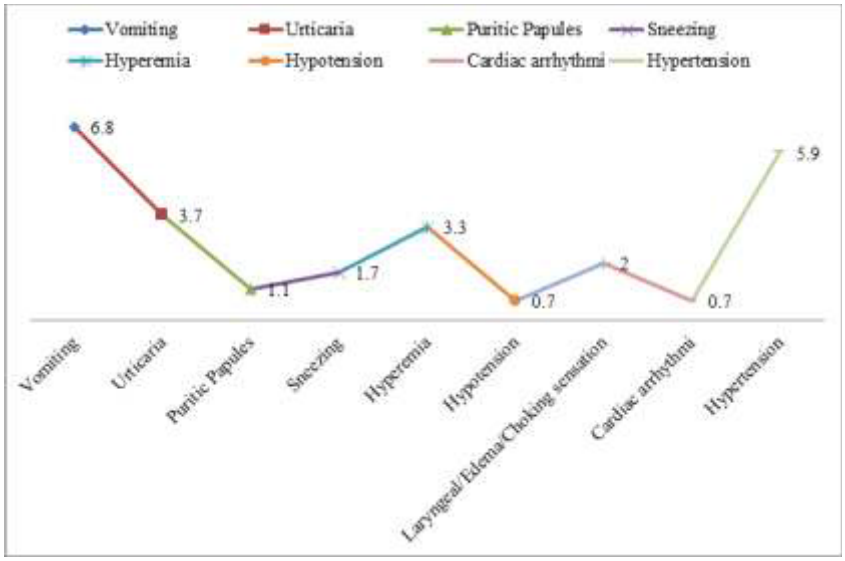

Figure 1. Line graph showing % incidence of common adverse reactions due to iodinated radiological contrast media

Discussion

Prevalence of immediate adverse reactions

A total of 118 (25.7%) adverse reactions were noted in this study, (Table 1). This finding is considered very high, especially in relation to more recent studies [6, 20] in which the prevalence in nonionic contrast media ranged from 0.04 to 3%. The finding here could be due to poor screening and pre-selection of patients referred for contrast-enhanced radiographic procedures in this study. Most of the subjects were referred from other hospitals and healthcare centres with different pre-screening criteria for radiocontrast examinations. Some of the referrals were also from non-specialists and young clinicians who were unaware of the need for pre-selection of patients based on risk factors for contrast-enhanced procedures. Another factor may be the disparities in the study [2] and changes in vital signs [17] as adverse reactions, others had excluded such [21].

In this study, individual reactions were documented. Adverse reactions noted include drastic changes in blood pressure following contrast media injection. A total of 30 (25.48%) participants had a change of at least 10mHg in both their diastolic and systolic blood pressure values. While 27 had elevation in their blood pressures, only three experienced a significant drop. This finding is in line with a study by Panitan *et al.,* [17] in which incidence of cardiovascular reactions due to iodinated contrast media in form of hypertension and hypotension occurred in 26 patients or 4.7% of the study population [17]. While hypertension occurred in 11 patients, hypotension was documented in 15 patients. It is therefore established that one of the adverse reactions to iodinated contrast media is possible change is patient's blood pressure. The direction of this change could not be established but are suspected to be influenced by underlying risk factors and/or idiosyncratic reasons.

The most prevalent adverse reaction in this study was nausea/vomiting. This occurred in 31 (6.8%) participants and constitutes 26.3% of the total reactions in this study. The finding here is higher than that of Panitan *et al.* [17] in which Nausea/vomiting accounted for (92) 16.4% of the adverse reactions. The disparity in these findings could be attributed to the subjective classifications of patients' urge to vomit and actual vomiting. In this study, patients were implored ahead of time to indicate any feeling of urge to vomit, while in the Panitan *et al.*'s study, records were only extracted from previous documentation as it was a retrospective study [17].

However, the incidence of nausea/vomiting in this study is in line with findings of a review by Pasternak and Williamson on 'Clinical Pharmacology, uses and adverse reactions to Iodinated contrast media [6] in which they concluded that nausea and vomiting can occur in up to 6 -7% of patients that had been exposed to iodinated contrast media.

Other reactions such as Urticaria 17 (3.7%), Hyperemia 15 (3.3%), laryngeal edema and choking sensation 9(2.0%) showed different degrees of variability with literature [17]. The underlying factors for these variabilities are possible areas for further research.

Pattern of adverse reactions in order of severity

Majority of the reactions in this study were mild, accounting for 66% (78 of 118) of all the reactions noted and 17.0% of the study population. The adverse events in this study were classified into mild, moderate and severe reactions, according to the American College of Radiology guideline [4]. A reaction was rated mild when it was self-limiting, and could not progress further for any intervention. The prevalence of mild reactions in this study is in line with previous studies that noted that acute allergy-like reactions due to contrast media are mostly mild in nature [15, 18]. However, the prevalence is higher than the 0.7% to 3.1% reported by Panitan *et al.,* in patients administered with non-ionic contrast media [17]. A total of 27(22.9%) patients had moderate reactions; manifesting mainly as facial hyperemia, laryngeal edema or hypertension. Adverse reactions that necessitated immediate medical intervention and were kept for observation till full recovery in the radio-diagnostic department were categorized as moderate. Severe reactions in this study only occurred among 3(2.5% of all adverse reactions) patients and 0.7% of the study sample. This finding is higher than the reported prevalence of 0.02% to 0.04% [7,17]. The wide disparity in this finding from the previous literature is due to differences in the criteria for classification of adverse reactions. The three cardiac arrhythmia cases in this study were not actually life threatening but by classification [5], severe adverse reactions. Dillman *et al.,* had posited that a life-threatening adverse reaction is one which necessitated hospital admission or transfer of an emergency department patient into the hospital ward due to exacerbation of adverse reactions [15]. In this study the three severe adverse reaction patients were observed, treated and discharged within 12hours of the contrast media injection.

Gender and Demographic Pattern of Adverse Reactions

The prevalence of adverse reactions was higher in females (63; 26.9%) than in males (55; 24.4%). This finding is similar to a previous work by Mortele *et al.*, in which the prevalence was significantly more in females [22]. In another study that evaluated the incidence and severity of acute allergy-like reactions in children administered with low-osmolar, non-ionic contrast media, fourteen (70%) of the patients that had reactions were girls, while six (30%) were boys [16]. In this study,

increase in blood pressure, sneezing and hypotension were noted to be more prevalent in the females. Similar researches did not observe the distribution of these individual adverse reactions along gender lines. Vomiting, urticaria, and laryngeal edema or choking sensation were more in males. The underlying mechanism and bases for this finding is still unclear. However, the biochemical composition and physiology of the female gender is quite different from that of males, especially in water content and requirements of the body. This could account for these findings. However, the statistical evaluation of the distribution of these adverse reactions, using Fisher's exact test, with P= 0.263, 0.379 and 0.531, among other values, for the different adverse reactions, showed that gender is not a predisposing factor for adverse reactions in this study. The reason for gender dominance of some specific adverse reactions in this study is for further investigation.

The mean age of the study participants was 51.2years $\pm$ 16.18. The youngest participant was 15years old while the oldest was 94years.

This study therefore shares participant age-range with that of Mortele *et al.*,[22] in which the mean age was 50.5years and Panitan *et al.* [17], with mean age of 51.5 $\pm$ 16.5 and female to male ratio of 1.4:1

Most of the adverse reactions noted in this study occurred within ages 40-79yrs; mainly within the middle age groups. This could be attributed to the composition of the study participants who were mainly within working class age range.

The effect of age on the incidence of immediate adverse reactions has been subject of controversy [2, 5]. In this study, adverse reactions were noted less at the extremes of ages (highest incidence within 40 – 79yrs), in line with Dillman *et al.,* [15] who maintained that paediatrics and elderly patients have lower incidents of adverse reactions. However, this is contrary to Dickinson and Kam [1], who classified extremes of ages as a risk factor for adverse reactions. In a study by Roh and Larola [23], increased incidence of adverse reactions among younger patients was noted. However, no statistical difference was established among the different age groups.

Conclusion

'The incidence of anaphylactic, immediate and delayed adverse reactions to low osmolar contrast media was high in a cohort of Nigerians residing in Lagos State'. Low osmolar contrast agents, were therefore, seemingly not as safe in a Nigerian population as previously believed. Underlying risk factors and patient's prescreening criteria for contrast-enhanced procedures may be possible justification for this finding. In view of the daily high volume of contrast media deployed in current diagnostic medical imaging practice, screening and pre-selection of patients for contrast-enhanced procedures should be enforced. A standardized protocol for patients' screening and preparation for contrast-enhanced radiographic procedures should be developed and incorporated into routine radiography practice in Nigeria.

Limitations of the Study

The sample size for this study cannot be assumed to be a true representation of the overall population of Nigerians in Lagos State, not to extrapolate to that of all Nigerians. This is a limitation.

The delayed adverse reactions were monitored for only 7days due to cost of logistics and time constraints.

Conflict of interest. None.

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