

## **Iodinated Contrast Media: Adverse Reactions in Radiography practice**

Article Review by Abonyi Livinus Chibuzo  
*Ph.D in Clinical Research, Texila American University*  
Email:- [chibuzoabonyi@yahoo.com](mailto:chibuzoabonyi@yahoo.com)

### **Abstract**

*This is an article review based on a research work on 'Adverse reactions to iodinated contrast media, prevalence, risk factors and outcome – the results of a 3-year period' by Panitan, et al., published in the Asian Pac J Allergy Immunology; April 31 2013: 299 – 306. <http://apjai.digitaljournals.org>. The review will comprise a brief summary of the article and a critical analysis of the structure. The article's general content and scope will also be assessed for currency and relevance. The article's authority on the issues discussed and credibility in view of current knowledge will also be evaluated.*

### **Introduction**

This article review is on a research work on 'Adverse reactions to iodinated contrast media, prevalence, risk factors and outcome – the results of a 3-year period'. The review will start with a brief summary of the article. This will be followed by critical analysis of the article structure. Being a case control study, the article's background, set- out objectives and the methodology applied to realize these objectives will be evaluated for appropriateness and suitability. The article's general content will also be assessed. The third leg of this review will question and critique the authority of this article on the issues discussed. The currency of the cited literature and accuracy of the information canvassed will be evaluated. The article will also be subjected to proof of objectivity, while doubtful areas of bias will be analyzed. The overall credibility of the article in view of the current knowledge will also be evaluated.

The article is a case control study with clear set- out objective arising from an identified scientific background and challenge. The article was well written and presented in simple clear language which offered readers easy understanding.

### **Review of Related Literature**

The use of iodinated contrast media in medical imaging is common and presently on the increase (Dickson & Kam, 2008). However, the use of contrast media has not been without some drawbacks due to adverse reactions. Reactions to iodinated contrast media has been reported in about 5% to 8% of the patients administrated with the intervention (manouchehrs, 2012). Another study by Katayama, et al (1990) reported a prevalence rate of 0.2 to 12.7% depending on the type and nature of the contrast medium used. However, the American College of Radiology (2010) expressed doubt in the true incidence of adverse reactions. This, it attributed to the difficulty in excluding the similar signs and symptoms due to concomitant medications and morbidity from that due to contrast media reactions.

Intravascular iodinated contrast media is presently, broadly grouped into two -ionic high osmolality and non-ionic low osmolality contrast media. High osmolar contrast media are the first developed version of intravenous iodinated contrast media (Fischer, 1986). They possess single benzene ring and are monomers; dissociating in solutions to produce ions that has a valence of -1. They produce cat- ions of either sodium or meglumine. This quality makes them produce hypertonic solutions which attract more hydroxyl molecules onto themselves. This hyper-tonicity in relation to the internal body fluid is one of the bases for its adverse reactions contrary to the non-ionic forms.

Advancement over the ionic osmolality contrast media is the non-ionic compounds. They are also monomers and dissolve in water but do not dissociate readily to form complexes. They form fewer particles in solution and are referred to as low-osmolar contrast media. The most recent class of iodinated

contrast media is the dimmers which are characterized by a molecule with two benzene rings. Each ring has three iodine atoms. They do not dissociate in water (similar to the non-ionic monomers) and are of near-osmolality with the human body serum; iso-osmolar. The toxicity of contrast media decreases as the osmolality approaches that of the body serum. The non-ionic monomers have twice the osmolality of the body serum, while the non-ionic dimmers are of same osmolality with that of the body serum.

The non-ionic low osmolality contrast media are safer and less toxic than the ionic high osmolality group. That informs the recommendation for the use of non-ionic low osmolality media for high risk cases; including breast feeding mothers (manouchehr, 2012).

Some radiographic procedures cannot use ionic contrast media due to the severity of adverse reactions that may occur (Meth & Maibach, 2006). Such procedures are myelography, and most angiographic or intra-arterial radiological procedures.

The use of ionic high osmolality contrast media has been associated with higher incidence of adverse reactions with a historical incidence of 5 to 15% among those administered with the media (Katayama et al, 1990, ACR, 2010). The discovery of non-ionic media (metrizamide) in 1974 (Meth & Maibach, 2006) was a crown of efforts in research that has been on-going in order to mitigate these noted adverse reactions.

Non-Ionic contrast agents are safer, less toxic and therefore elicit far less adverse events.

Cochran et al, (2001) reported an overall incidence of 0.2% adverse reactions among a patient group administered with non-ionic contrast media in one institution. A similar study by Wang et al, (2008) reported an incidence of 0.6% upon a review of 84,925 patients who received iohexol, iopromide or iodixanol (all non ionic contrast media).

The precise pathogenesis of most adverse reactions to iodinated contrast media is still unclear (ACR, 2010). Some potential mechanisms such as activation, deactivations or inhibition of a variety of vaso-active substances or chemical mediators may be involved. The degrees of these mechanisms differ from on individual to the other and may account for the idiosyncratic nature of some of these adverse events. Other conditions associated with increased reaction to iodinated contrast media have been identified. These conditions, categorized as risk factors range from the type of iodinated contrast media to comorbidity such as renal insufficiency and diabetes (Rudnick et al, 1994). The identification of these risk factors by screening prior to administration of the contrast media has formed a useful tool for determining the type of premedication and plan for prompt response in the event of adverse reaction. One of the simplest of such tools is the recommended use of adequate hydration in which isotonic saline, dextrose solution and/or sodium carbonate are employed in mitigating radio-contrast –induced nephropathy (Mueller, 2006) prior and following iodinated radiographic procedures.

Other risk factors associated with iodinated contrast media are age, allergy/asthma, concomitant medication, gender, among others (Greenberger, et al, 1987, Thrall, 1990, Land, et al, 1991)

## **Article Summary**

The article was aimed at determining the prevalence of adverse reactions to iodinated contrast media in patients who were exposed to the intervention in the usual course of radiographic investigations in Thailand. The article was also set out to explore the possible risk factors to such reactions and document the outcome of such reactions.

The article therefore had a clear and well defined objective. The background to this study was well captured and this informed the locus for the study. The article identified the increasing use of iodinated contrast media in radiological procedures. It equally observed that the use of these agents have been associated with differing degrees of reactions which may be immediate or delayed. These reactions ranged from minor reactions requiring nil medication to severe ones that necessitated hospitalization. The article, in the search for risk factors identified the different classes of iodinated contrast media. These classes posed different degrees of severity in the exposed subjects. The class with the lowest degree of

adverse reactions – the non-ionic iodinated contrast media were recommended for use contrary to the ionic high osmolality brands.

Other risk factors identified included female gender, asthma,  $\beta$  – Blocker drugs, co-morbidity involving cardiovascular diseases, age, sea foods, among others were also reported. The article used a retrospective case control study design to determine the prevalence and from the documented adverse reactions and outcomes, the relevant data was accumulated for analysis and discussion. The determination of the risk factors in the study was established by further search through the case notes/medical records of those that manifested any type of adverse reactions during the study. The outcomes were determined from the medical records of documented actions taken on those that required medication and extra care.

The article established a prevalence of 1.05% (95% CI 0.96 – 1.14) with a total of 579 cases reporting one type of adverse reaction or the other while contrast media was administered 55, 286times during the study period.

Skin involvement was the most frequent adverse reaction noted in 75% of all the immediate reactions and 100% of all delayed reactions. Gastrointestinal reactions were noted in 16.7%, respiratory 10.7%, cardiovascular 5.7% and neurological 4.8%.

The article used a multi-variant analysis to determine the risk factors among the patients that manifested reactions. The following risk factors were identified: female gender, history of previous reaction to contrast media, co-morbid allergic diseases such as sea food allergy, chronic urticaria, asthma and drug allergy. Repeated reaction was strongly associated with patients with previous history of allergy to sea food. Serious adverse reactions were significantly associated with history of previous reaction to asthma.

Mild reactions were associated with co-morbid cardiovascular diseases, male gender, history of sea food allergy and previous reaction to contrast media.

The outcome of the total adverse reactions noted, showed that 57.1% (331) were treated as outpatients, 7 patients (1.2%) were hospitalized while only one patient (0.2%) died as a result. A total of 240 (41.5%) did not require any medication.

The findings from this study were compared with the existing literature on the subject. The article's classification of history of sea food allergy as a risk factor is not supported by some other literature which rather identified atopy as the cause of the increased risk and not iodine specific reactivity. The article concluded that the prevalence of adverse reaction in the study was 1.02% while a previous history of CM reaction and female gender posed the highest risk of adverse reactions. The role of seafood allergy as a risk factor remained controversial and unresolved.

## Article Structure

The article was introduced with a summary, which provided a concise framework on which the article was built. The summary provided a short background to the study and clearly stated the objective. The research design used to achieve the set objective was briefly stated in the methodology section. A brief outline of the findings was stated in the result. The abstract was apt and, concisely set the stage for the direction of the article. The article was presented in the normal conventional reporting of a scientific research comprising the basic sections of abstract, introduction/background, methodology, results and discussion.

The introduction laid the foundation and justification for the study. This justification informed the choice of the research method employed to harness the required data for analysis and presentation. The information canvassed was delivered in short and clear sentences. The research design was succinctly stated and directly implemented which aided collection of relevant data collection with particular reference to the research objective. The data collection technique was comprehensive and meticulous.

The choice of the statistical instruments was appropriate for the nature of the raw data to be analyzed. That showed a fair knowledge of the application of the different statistical analytical tools employed in clinical research.

The result presentation was made as concise and unambiguous as possible. This aided easy perception of the key findings in the research and effective comparison with other related literature on the topic. The article structure was in overall logically developed with the use of defined sections which contained the body of information required in such a scientific study. The sentences are appropriate, short and clear for easy comprehension. There were several links to authors, other journals and citations which are instruments used for effective evaluation of the worth and authority of the article.

The article had no separate conclusion. What appeared as the conclusion was sandwiched within the discussion segment. This made the conclusion to be brief and excluded some highlights of the findings, especially those that were contrary to the existing literature on the subject.

### **Authority**

The journal in which this article was published is the Asian Pacific Journal of Allergy & Immunology. This journal is the official journal of the Asian Pacific Association of Allergology and Clinical Immunology; an academic and professional journal of international repute. It started publication in 1983 and is presently indexed for Medline. The authors' credibility lies firstly in their varied professional background involving, Nursing, Pharmacy, Allergy and Clinical immunology in tertiary establishments. Secondly, most of the authors are university-based which implies that they are academics involved in teaching and research. Though, their qualifications are not stated, their status as researchers and clinicians confers a possibility that some of them might be PhD holders or equivalents. Thirdly, the article's credibility also drives from the wealth of the different specialties of the authors which could be perceived in the meticulous implementation of the research strategy and documentation of the accessed data used for analysis.

The article was also a peer-reviewed paper in a well established journal. This implies that it must have passed through expert editorial evaluation and scrutiny before acceptance for publication. The study that led to the publication of this article also enjoyed the support of a research grant from the faculty of medicine, Siriraj Hospital, Mahidol, University of Bangkok, Thailand.

### **Accuracy**

This article was based on a current issue bordering on adverse reactions to iodinated contrast media. The information content of the article is current and relevant. This information is backed up by recent references which are known and verifiable. The cited references are with direct link to known authors with acclaimed credibility.

The article also passed through strict editorial review and processing which contributed to its accuracy and rating. The quality of cited sources in terms of research content and scope especially in the literature review and discussion enhanced the article's accuracy and contemporarity.

### **Currency**

The article was published in March 2013 while the paper was accepted for publication in December 2012, following the article's 1<sup>st</sup> submission in September 2012. The article and the research carried out, is current and relevant. The article cited up-to-date references which spanned from 1977 to 2012. Most of the references (> 50%) are within the last decade of the article's publication. The older citations/ references were based on their relevance and currency of the information contained. The article is therefore current in knowledge and professional application.

### **Relevance**

This article was published in an academic per-reviewed journal with high credibility. Its content is meant to inform and contribute to knowledge and not for entertainment. It is meant for academics, researchers and healthcare providers especially in the Radiological imaging community. The article was based on a regular imaging product with expanding application and daunting adverse effects. The article

is a wakeup call for greater efforts in identifying adverse reactions, predicting its occurrence by way of risk factor identification and subsequent prevention, so as to bring the prevalence to the barest minimum.

The article is mostly suitable for medical imaging scientists; comprising Radiologists, Radiology Residents, Radiographers, Radiography Interns and Radiology Nursing Assistants who are directly involved in radiographic procedures that require the use of iodinated contrast media. The article was aimed at improving general patient care and welfare and is therefore very relevant.

### **Objectivity**

The article was based on a scientific research on an identified challenge in medical imaging. The challenge is universal and global; differing only in severity and frequency, depending on the type of products available and departmental screening and preventive measures in place. There is therefore no bias in developing the title, content and research design.

The authors' review of literature on the topic was based on credible and verifiable citations which were well referenced. The study was retrospective and case-controlled. There was no room for bias in the selection of study participants. The criteria for data collection were well developed with clear inclusion criteria. This informed an objective and factual build-up of the data used for analysis and conclusion.

The objectivity of this article is also demonstrated in the seeking and obtaining of approval for the study from the Institutional review Board for access to the patients records. This implied compliance to ethical issues and practices required for absolute protection of patients privacy. The authors were equally frank enough to acknowledge where their findings differed from the existing literature, such as the case of sea food being a risk factor for adverse reactions to iodinated contrast media. The authors applied known statistical methods for analysis of their data and consequential deduction of their findings. The research objective, design and data presentation and analysis therefore followed the required rigorous research processes which are demanded of such a study. The support received by the authors for the research was duly acknowledged.

### **Stability**

The article was published in Asian Pac J of allergy & Immunology, an academic journal in an academic data base. It is a peer-reviewed journal with expert editorial team, through which an article must pass its scrutiny before publication. The stability of this article also lies in the authors and their academic background in an academic institution involved in translational medicine; being in the clinical services arm of the university. Their research work which led to the publication was both didactic and empirical.

The article is therefore stable as all citations were well referenced and verifiable.

### **Analysis of Tables**

The article utilized six (6) tables to summarize and highlight the utilization of the data collected during the study period. The tables were well organized and designed to address specific subject matter. There were such tables as prevalence of contrast media adverse reactions, co-morbid diseases in contrast media reaction, clinical manifestation of immediate reactions and some others. Each table had an assigned and specific role of displaying and highlighting the required data at a glance for the information seeking reader of the article. The data separation into tables was appropriately done such that each of the tables contained the relevant information for addressing a specific research question.

The tables were explicit, simple and easy to comprehend. They provided the shortest summary of what could have been a long and complex analysis of the data collated during the research. The tables were therefore self explanatory and helped in highlighting the detailed findings of the study

### **Recent Advances Related to the Topic**

Adverse reaction to iodinated contrast media is attributed to two major broad factors, chemotoxicity and idiosyncrasy (Dawson, 1987). Chemotoxic reactions are due to the chemical structure components of the contrast molecules and have been subject of research and consequent modifications. These have

resulted in the progressive development of iodinated materials from the ionic high osmolality to non-ionic low osmolality species. The ionic nature of the earlier contrast materials has been reported to affect transiently the extracellular fluid components of the human body and could alter the cell membrane potentials (Swanson, 1988). Some other authors cited calcium-binding characteristics associated with ionic contrast materials and the contrast media packaging chelating agents as progenitors of adverse reaction (Swanson, 1988). Chemotoxic adverse reactions therefore produce such effects as red blood cell damage, interference with coagulation and clotting factors, myocardial depression, cardiac arrhythmia, renal toxicity, and bronchospasm (Rao et al, 1985, Dawson, 1987, Swanson, 1988). These effects are less in non-ionic contrast media than in the ionic counterpart.

Idiosyncratic reactions due to iodinated contrast media are similar to anaphylactic reactions which could be precipitated by other causes of allergic reactions such as drugs, nuts, certain food products, insect venom, latex materials, co-morbidity ( e.g. asthma), among many other triggers. Anaphylaxis; which is a severe life-threatening, generalized or systemic hypersensitivity reaction (NICE clinical guide, 2011) is characterized by rapidly developing life-threatening symptoms such as airways, breathing and circulatory problems. These symptoms may be due to allergic response to immunologically mediated or non immunologically mediated response or idiopathic in origin (Solensky & Khan, 2010). The etiology of these idiosyncratic reactions due to iodinated contrast media is not yet established. However, certain mechanisms have been cited. Such mechanisms involve histamine release, complement cascade activation and nervous system effect (Dawson, 1987). Contrast induced anaphylactic reactions are therefore not immunologically mediated as no circulating immunoglobulin E antibodies could be isolated in patients that manifested these reactions. The reactions are therefore classified as anaphylactoid (Solensky & Khan, 2010). Anaphylactoid reactions are reported to occur in about 1% to 3% of patients administered with ionic high osmolality contrast media while the prevalence is less than 0.5% in nonionic low osmolality brand (Wolf, 1991). Severe life threatening reactions are uncommon and according to Katayama (1990), occur in 0.22% of patients exposed to ionic high osmolality contrast media and 0.04% in patients that received non ionic low osmolality t type.

Predisposing risk factors for anaphylactoid reactions have been identified to include female gender, asthma, previous history of allergy,  $\beta$ -blocker exposure/concomitant medication, concomitant morbidity( e.g. cardiovascular), severe hydration, age, etc(Schatz, et al, 1975, Enricht, et al, 1989, Land et al, 1995) Anaphylactoid reactions to iodinated contrast media are classified according to severity into mild, moderate and severe reactions. These reactions require attention, ranging from mere observation and reassurance to hospitalization. However, the following have been advocated by different researchers as management steps to reduce contrast media reactions among patients administered with the product (Greenberger & Patterson, 1991, Mashall & Lieberman, 1991, Lasser et al, 1994)

- i. There should be justification for the procedure while it's inevitability (no alternative diagnostic modality) should be ensured.
- ii. The patients should be screened for risk factors.
- iii. The procedure should be well explained to the patient; including associated possible risk factors for informed consent.
- iv. Non- ionic low osmolality or iso-osmolality contrast media should be used, especially for high risk patients.
- v. Adequate hydration of the patient should be maintained, before and following the procedure.
- vi. Utilization of premedication regimen according to the empirically proven departmental protocol or as previously documented in literature should be ensured.

## **Conclusion**

The article on 'Adverse reactions to iodinated contrast media; prevalence, risk factors and outcome – the result of a 3-year period' by Panitan et al had been reviewed.

The review had summarized the article, critically evaluated the structure and examined the associated literature. The review also critiqued the article's authority and accuracy of the study design, methodology and analysis, including data presentation. The article was also assessed for currency of the issues discussed and relevance of the article to the scientific community.

The authors were scrutinized for bias and interest in carrying out the research which none was found. The article used well-designed and simplified tables for easy appreciation of the relevant findings which were also reviewed. The article was found to be based on sound scientific protocol and experimental design. The background and associated literature were well reviewed which set the objective for the study. The research design and employed statistical analysis methods were appropriate for the research questions and this ensured credibility of the article. The article was on a current and relevant challenging issue in radiographic imaging procedures; globally. It therefore contributed to knowledge and will impact positively in improving patient care, especially among those referred for radiographic procedures involving iodinated contrast media.

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