Journal of Health and Medical Sciences

Karim, Nadiya Abdul, Shahzad, Kashif, Ibrar, Rafia, Sahar, Umeed E., Khalid, Sara, Maryam, Sarah, Farooq, Muhammad Yousaf. (2019), Frequency and Severity of Acute Adverse Effects of Low Osmolar Iodinated Contrast Media in Contrast-Enhanced Computed Tomography. In: *Journal of Health and Medical Sciences*, Vol.2, No.1, 89-96.

ISSN 2622-7258

DOI: 10.31014/aior.1994.02.01.24

The online version of this article can be found at:
https://www.asianinstituteofresearch.org/

Published by:
The Asian Institute of Research

The Asian Institute of Research *Journal of Health and Medical Sciences* is a peer-reviewed International Journal. The journal covers scholarly articles in the fields of Medicine and Public Health, including medicine, surgery, ophthalmology, gynecology and obstetrics, psychiatry, anesthesia, pediatrics, orthopedics, microbiology, pathology and laboratory medicine, medical education, research methodology, forensic medicine, medical ethics, community medicine, public health, community health, behavioral health, health policy, health service, health education, health economics, medical ethics, health protection, environmental health, and equity in health. As the journal is Open Access, it ensures high visibility and the increase of citations for all research articles published. The *Journal of Health and Medical Sciences* aims to facilitate scholarly work on recent theoretical and practical aspects of Health and Medical Sciences.

ASIAN INSTITUTE OF RESEARCH
Connecting Scholars Worldwide

ASIAN INSTITUTE OF RESEARCH
Connecting Scholars Worldwide

The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.2, No.1, 2019: 89-96
ISSN 2622-7258

DOI: 10.31014/aior.1994.02.01.24

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

Nadiya Abdul Karim[1], Kashif Shahzad[1], Rafia Ibrar[1], Umeed e Sahar[1], Sara Khalid[1], Dr. Sarah Maryam[1], Muhammad Yousaf Farooq[1]

[1] University Institute of Radiological Sciences & Medical Imaging Technology, The University of Lahore, Lahore, Pakistan

Corresponding Author: Nadiya Abdul Karim, University Institute of Radiological Sciences and Medical Imaging Technology, University of Lahore, Lahore-Pakistan. Mobile: +923344789800 E-mail: k.nadiya5102@yahoo.com

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 worldwide[1] 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 based[2]. 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 toxicity[3]. 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 tract[4]. A standard contrast-enhanced CT uses ~40 grams of iodine chemically enchained to an organic molecule that is injected into the vascular system[5]. 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 ring[6]. 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/L[2]. In clinical practice, classification based on osmolarity is mostly used[6]. 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:

Contrast agent ratio = Number of iodine atoms/ Number of particles in solution

The high osmolar contrast substances have a greater number of subatomic constituents for each iodine atom and thus lower ratios[4]. High osmolar agents can disintegrate in an aqueous solution significantly , in contrast to low osmolar agents which usually own an osmolarity marginally higher than blood[7] 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 body[8]. High-osmolar iodinated contrast media paved the way for low-osmolar agents, as they are related to adverse reactions to a lesser extent[7]. The hyperosmolarity of contrast agents is considered to be responsible for several adverse effects in patients injected with contrast media coming for computed tomography scanning[9]. 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 encountered[10]. It is necessary to be aware of the possibility of adverse reactions against these compounds ranging from mild aggravations to life-threatening crisis[11]. The immediate/acute reaction occurs up to one-hour post injection and is related to the osmotic load or contrast media chemotoxicity[12]. 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 reactions[7]. 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[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[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[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).

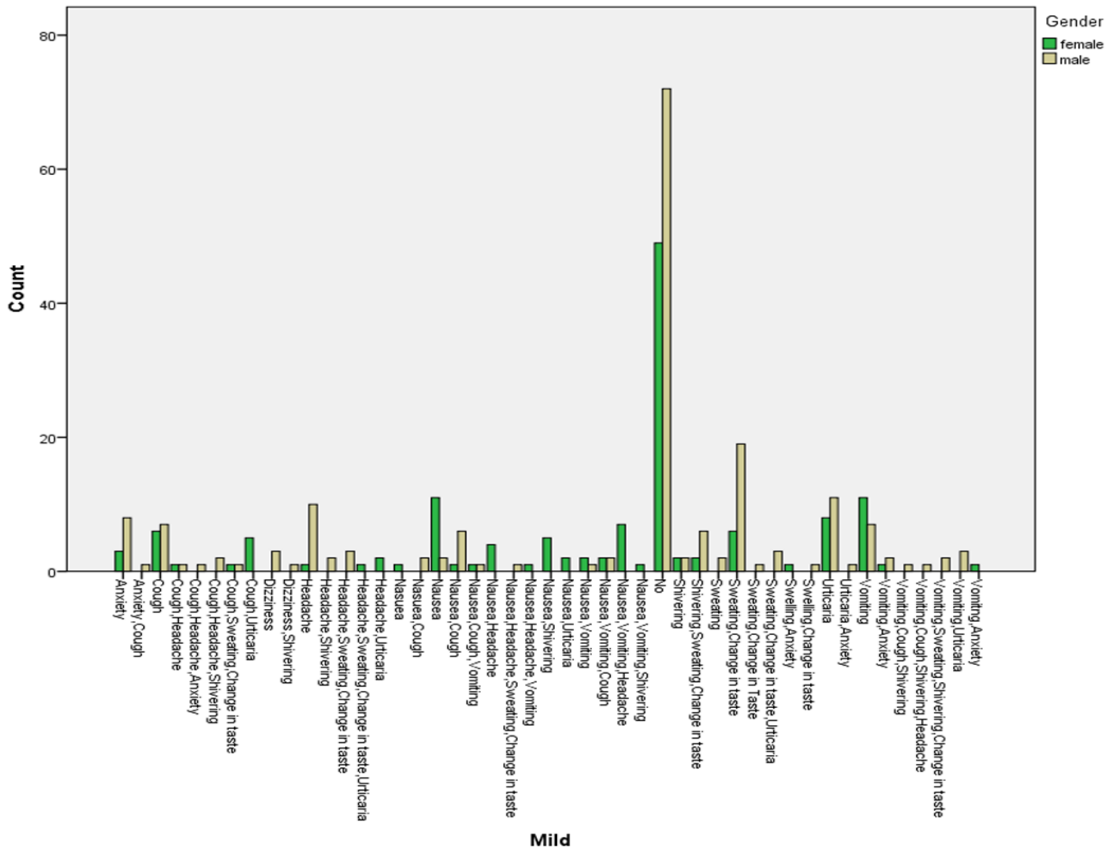

Figure 1. Graph representing the frequency of mild adverse reactions affecting females and males

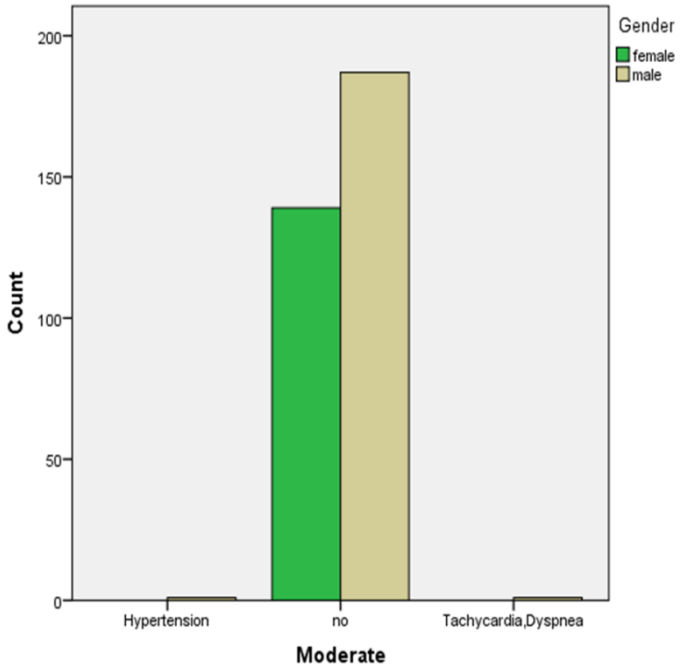

Figure 2. Graph representing the frequency of moderate adverse reactions affecting females and males

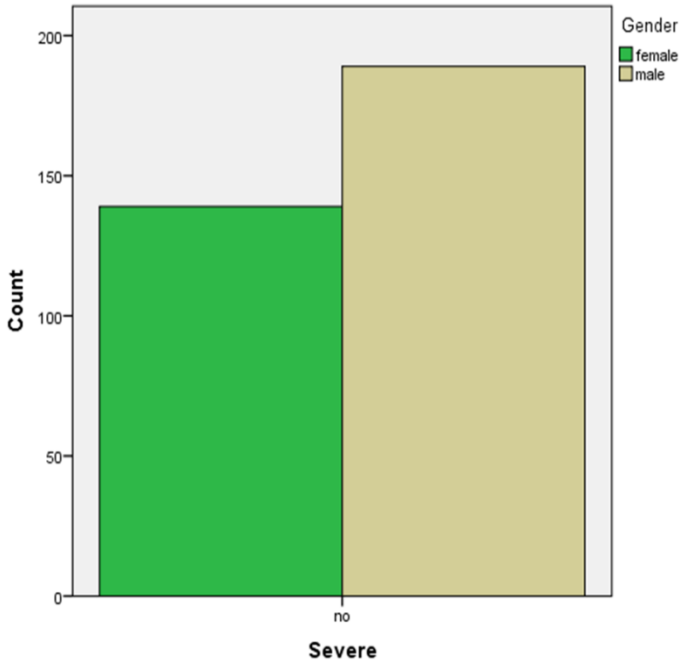

Figure 3. Graph representing the frequency of severe adverse reactions affecting females and males

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

		Moderate	303	0
		Severe	303	0
	yes	Mild	11	14
		Moderate	23	2
		Severe	25	0

Table 2: Frequency of adverse effects based on technical aspects of a CT examination

		Mild		Moderate		Severe
		no	yes	no	yes	no
		Count	Count	Count	Count	Count
Type of Contrast	Omnipaque	2	10	12	0	12
	Ultravist	119	197	314	2	316
Administration Site	Cubic Fossa	41	73	114	0	114
	Forearm	27	43	69	1	70
	Hand	53	91	143	1	144
Type of Exam	Abdomen	19	37	56	0	56
	Aorta Angiography	0	1	1	0	1
	Brain	33	41	74	0	74
	Brain Angiography	4	7	11	0	11
	Carotid Angiography	2	8	10	0	10
	Chest	40	47	87	0	87
	Chest+Abdomen+Pelvis	7	18	24	1	25
	Head+Neck	5	18	23	0	23
	Lower Limbs Angiography	0	11	11	0	11
	Pelvis	8	7	15	0	15
	Renal Angiography	1	7	7	1	8
	Upper Limbs Angiography	2	5	7	0	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[22]. 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[23]. 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[24], 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.

References

1. Kyung E, Ryu J, Kim E. Evaluation of adverse reactions to contrast media in the hospital. The British journal of radiology. 2013;86(1032):20130418.
2. Pasternak JJ, Williamson EE, editors. Clinical pharmacology, uses, and adverse reactions of iodinated contrast agents: a primer for the non-radiologist. Mayo Clinic Proceedings; 2012: Elsevier.
3. Bottinor W, Polkampally P, Jovin I. Adverse reactions to iodinated contrast media. The International journal of angiology: official publication of the International College of Angiology, Inc. 2013;22(3):149.
4. Thompsen H, Jaw W. Contrast media. Safety issues and ESUR guidelines Heidelberg: Springer. 2013.
5. Solomon R. Contrast media: are there differences in nephrotoxicity among contrast media? BioMed research international. 2014;2014.
6. Siddiqi N. Medscape reference [Internet]. New York: WebMD; Jul 22, 2017.[cited 2018 Apr 8]. Contrast medium reactions. c1994.
7. Morzycki A, Bhatia A, Murphy KJ. Adverse reactions to contrast material: a Canadian update. Canadian Association of Radiologists Journal. 2017;68(2):187-93.
8. Giannini G, Cuppo F, Fontanive L, D'Amelio N, Cesàro A, Maiocchi A, et al. Interactions in iodinated contrast media solutions. Journal of thermal analysis and calorimetry. 2011;103(1):89-94.
9. Iyer RS, Schopp JG, Swanson JO, Thapa MM, Phillips GS. Safety essentials: acute reactions to iodinated contrast media. Canadian Association of Radiologists Journal. 2013;64(3):193-9.
10. Prakkamakul S, Lerdlum S. Incidence and severity of acute adverse reactions to intravenous iodinated contrast media: 8-year experience in King Chulalongkorn Memorial Hospital. Asian Biomedicine. 2013;7(2):203-9.
11. Rossi C, Reginelli A, D'Amora M, Di GG, Mandato Y, D'Andrea A, et al. Safety profile and protocol prevention of adverse reactions to uroangiographic contrast media in diagnostic imaging. Journal of biological regulators and homeostatic agents. 2014;28(1):155-65.
12. Gharekhanloo F, Torabian S. Comparison of allergic adverse effects and contrast enhancement between iodixanol and iopromide. Iranian Journal of Radiology. 2012;9(2):63.
13. Motosugi U, Ichikawa T, Sano K, Onishi H. Acute Adverse Reactions to Nonionic Iodinated Contrast Media for CT: Prospective Randomized Evaluation of the Effects of Dehydration, Oral Rehydration, and Patient Risk Factors. American Journal of Roentgenology. 2016;207(5):931-8.
14. Watson N. Chapman & Nakielny's Guide to Radiological Procedures. 6th ed: Saunders Ltd; 2013 21 November. 428 p.
15. Kim S, Lee J, Park K, Park H, Park J. Varied incidence of immediate adverse reactions to low-osmolar non-ionic iodide radiocontrast media used in computed tomography. Clinical & Experimental Allergy. 2017;47(1):106-12.
16. Zhang B, Dong Y, Liang L, Lian Z, Liu J, Luo X, et al. The incidence, classification, and management of acute adverse reactions to the low-osmolar iodinated contrast media Isovue and Ultravist in contrast-enhanced computed tomography scanning. Medicine. 2016;95(12).
17. Li X, Chen J, Zhang L, Liu H, Wang S, Chen X, et al. Clinical observation of the adverse drug reactions caused by non-ionic iodinated contrast media: results from 109,255 cases who underwent enhanced CT examination in Chongqing, China. The British journal of radiology. 2015;88(1047):20140491.
18. Callahan MJ, Poznauskis L, Zurakowski D, Taylor GA. Nonionic iodinated intravenous contrast material–related reactions: incidence in large urban children's hospital—retrospective analysis of data in 12 494 patients. Radiology. 2009;250(3):674-81.
19. Wang CL, Cohan RH, Ellis JH, Caoili EM, Wang G, Francis IR. Frequency, outcome, and appropriateness of treatment of nonionic iodinated contrast media reactions. American Journal of Roentgenology. 2008;191(2):409-15.

20. Dillman JR, Strouse PJ, Ellis JH, Cohan RH, Jan SC. Incidence and severity of acute allergic-like reactions to iv nonionic iodinated contrast material in children. American journal of roentgenology. 2007;188(6):1643-7.
21. Mortelé KJ, Oliva M-R, Ondategui S, Ros PR, Silverman SG. Universal use of nonionic iodinated contrast medium for CT: evaluation of safety in a large urban teaching hospital. American Journal of Roentgenology. 2005;184(1):31-4.
22. Thomsen HS, Dorph S. High-osmolar and low-osmolar contrast media: an update on frequency of adverse drug reactions. Acta Radiologica. 1993;34(3):205-9.
23. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiology. 1990;175(3):621-8.
24. McDonald JS, McDonald RJ, Carter RE, Katzberg RW, Kallmes DF, Williamson EE. Risk of intravenous contrast material–mediated acute kidney injury: a propensity score–matched study stratified by baseline-estimated glomerular filtration rate. Radiology. 2014;271(1):65-73.