ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2024;(2): 178-187 // 10.5505/amj.2024.42385

DOES IODINATED CONTRAST AGENT AFFECT OXIDATIVE STRESS? OBSERVATIONAL STUDY

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Submitted: 19.12.2023 // Accepted: 05.06.2024

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Abstract

Objectives: Iodine in iodine-based contrast agents (ICM) is known as an antioxidant substance from the past to the present. Although some studies suggest that the use of ICM causes contrast-induced nephropathy (CIN) by causing an increase in reactive oxygen species, this is not yet fully understood.

Materials and Methods: Before scanning and 24 hours after ICA administration, blood samples were taken from 74 patients from a single center who had no known kidney disease, had Computed Tomography using ICA, and did not develop CIN within a 5-day follow-up period.

Results: The mean Total Oxidant Level (TOS) before ICA was 13.72 ± 9.40 and the mean TOS after ICA was 5.20 ± 2.06 ($p<0.001$). The mean TAS before ICA was 2.50 ± 0.27 and the mean Total Antioxidant Level (TAS) after ICA was 2.20 ± 0.24 ($p<0.001$). The mean OSI before ICA was 5.36 ± 3.39 and the mean Oxidative Stress Index (OSI) after ICA was 2.39 ± 0.98 ($p<0.001$).

Conclusion: Even while the pathophysiology of CIN is attributed in part to oxidative stress, we found that, on the contrary, it caused a decrease in oxidative stress in patients who did not develop CIN. We think this decrease in oxidative stress may be due to iodine, which is contained in ICA and known as a potent antioxidant.

Keywords: Contrast-induced nephropathy, iodinated contrast agent, oxidative stress index, total oxidant level, total antioxidant level.

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Introduction

After the widespread use of iodinated contrast agents (ICA) in computed tomography for various reasons, the incidence of acute kidney injury due to these agents is increasing.[1] The pathogenesis of contrast-induced nephropathy (CIN) is not known exactly and is thought that it may be due to many factors such as changes in renal hemodynamics, changes in renal parenchymal oxygenation, and direct tubular toxicity. It is thought that the hyperosmolar stress caused by the use of ICA triggers the increase in reactive oxygen species (ROS), and renal hypoxia and increased reactive oxygen species following ICA administration are involved in the development of CIN.[2]

ICA of 200 mL/dose contains approximately 7-10 times the iodine dose required in the daily diet. Iodine is known as an antioxidant from the past to the present. Oxidized iodine can function as an electron donor, hence counteracting reactive oxygen species. Molecular iodine functions as a scavenger of hydroiodic acid (HI) or hypoiodous acid (HIO), forming neutral compounds such as superoxide anions (O_2) or hydroxyl radicals (OH) of ROS.[3] Iodine has a protective effect against free radicals and peroxides. This phenomenon is shown in the decrease of hyaluronic acid depolymerization and the enhancement of the antioxidant status in human serum under laboratory conditions, as well as in the decrease of malondialdehyde and peroxides, which serve as markers for oxidative stress in living organisms.[4]

Oxidative stress refers to the state of imbalance between free radicals and antioxidants and has been observed to elevate in numerous disorders such as chronic renal failure, hypertension, atrial fibrillation, and contrast-induced nephropathy.[5,6] There are many measurement parameters for the assessment of oxidative stress. Since their measurements are variable, Utilizing Total Oxidant Level (TOS) to assess the overall oxidant status and Total Antioxidant Level (TAS) to evaluate the overall antioxidant status is a more pragmatic and beneficial approach. Additionally, the Oxidative Stress Index (OSI) can be determined by dividing TOS by TAS.[7,8]

Although some studies show that the use of ICA causes an elevation in reactive oxygen species levels,[2,5] no studies have evaluated whether there is an elevation in reactive oxygen species levels within the patient group who did not develop nephropathy after ICA exposure. In addition, it has not yet been clarified whether the increase in reactive oxygen species in patients who develop CIN is a factor in the pathogenesis or a result of the development of CIN. Therefore, in our study, we aimed to assess OSI, TOS, and TAS parameters and the oxidative stress within the patient group who received intravenous ICA during computed tomography and did not develop CIN.

Materials and Methods

Study Group and Sampling

Our study is an observational study conducted with a total of 74 patients including men and women over the age of 18. The people enrolled were patients who did not have a known kidney disease, who underwent Computed Tomography using ICA, and who did not develop CIN within 5 days of follow-up. Patients with a history of drug use that would affect oxidative stress (glucocorticoid therapy, iron therapy acetylcysteine, etc.) were not included in the study. Patients' blood samples were collected before they underwent Computed Tomography using ICA. During scanning, all patients were given a single 80 cc of nonionic ICA administered as a bolus (The concentration of iodine is 350 milligrams per milliliter) at a low rate of 4 ml/s using an automatic injector with a dual syringe placed into the antecubital vein, and then a 20 ml saline solution is flushed at a rate of 2.5 ml per second. After 24 hours of ICA administration, the identical group of patients was summoned to the nephrology outpatient clinic and underwent another blood sampling.

The glomerular filtration rates (eGFR) were determined in our investigation by applying the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula both before and after ICA.

Total Oxidant Level and Total Antioxidant Level Measurement

Following an overnight fasting period, blood samples were obtained in the morning and collected into gel tubes. The tubes underwent centrifugation at a speed of 3500 revolutions per minute to collect serum samples. The serum samples were divided into smaller portions and kept at a temperature of -80 degrees Celsius until the day of analysis.

The spectrophotometric measurement of serum TAS level was conducted at a wavelength of 660 nm using a colorimetric approach. A commercially available kit from Rel Assay Diagnostics was used for this purpose. The results were quantified as millimoles of Trolox equivalent per liter (mmol Trolox equivalent/L). TAS levels were measured using commercially available kits (Rel Assay, Turkey).[9]

The spectrophotometric measurement of serum TOS level was conducted at a wavelength of 530 nm using a colorimetric approach. A commercially available kit from Rel Assay Diagnostics was used for this purpose. The results were quantified as micromoles of hydrogen peroxide equivalent per liter of solution. TOS levels were measured using commercially available kits (Rel Assay, Turkey).[10]

Statistical Analysis

Data analysis was conducted using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). The statistical analysis of the study involved the determination of mean, standard deviation, frequency, and percentage data. The distribution of the groups was examined using a one-sample Kolmogorov-Smirnov test. The groups' general features and demographics were assessed by frequency analysis, which is a descriptive method used to analyze a single variable. The Paired Sample t-test was employed to examine a single variable between two different conditions in paired comparisons. The chi-square test was employed to ascertain the association between categorical variables. In the entire investigation, a p-value of < 0.05 was deemed to be statistically significant.

Results

Out of the total number of individuals, 46 were female and 28 were male. The average age was 52.58 ± 13.49 years. The body mass index of the subjects was 29.31 ± 4.57. 11 (14.9%) of the subjects had diabetes mellitus (DM) and 18 (24.3%) had hypertension (HT). The individuals' demographic features are displayed in Table 1.

Table 1. Demographics of the Subjects

		n=74 *
Age	Total	52.58 ± 13.49 (22-81)
	≥65	17 (23.0)
	<65	57 (77.0)
Body Mass Index	Mean±SD	29.31 ± 4.57
Gender	Women	46 (62.2)
	Men	28 (37.8)
Diabetes Mellitus		11 (14.9)
Hypertension		18 (24.3)

* The values are given as Mean±SD (min-max) or n(%).

The mean eGFR before ICA was 97.15 ± 17.53 ml/min, and the mean eGFR after ICA was 98.82 ± 18.11 ml/min, and before and after eGFR did not show a statistically significant difference (p=0.210) (Table 2).

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Table 2. Laboratory Results Before and After ICA

	Before Contrast Agent	After Contrast Agent	*p*
	Mean±SD	Mean±SD	
Creatinine (mg/dL)	0.76 ± 0.19	0.73 ± 0.19	0.073
Glomerular Filtration Rate (ml/min)	97.15 ± 17.53	98.82 ± 18.11	0.210
Total Oxidant Level (µmol H202 Equiv. /L)	13.72 ± 9.40	5.20 ± 2.06	***<0.001****
Total Antioxidant Level (mmol Trolox Equiv. /L)	2.50 ± 0.27	2.20 ± 0.24	***<0.001****
Oxidative Stress Index	5.36 ± 3.39	2.39 ± 0.97	***<0.001****

Following administration of ICA, TOS decreased in 88.6% of patients and both TAS and OSI were decreased in 78.3%. The mean TOS before ICA was 13.72 ± 9.40 and the mean TOS after ICA was 5.20 ± 2.06 (p<0.001) (Figure 1) (Table 2). The mean TAS before ICA was 2.50 ± 0.27 and the mean TAS after ICA was 2.20 ± 0.24 (p<0.001) (Figure 2) (Table 2). The mean OSI before ICA was 5.36 ± 3.39 and the mean OSI after ICA was 2.39 ± 0.98 (p<0.001) (Figure 3) (Table 2).

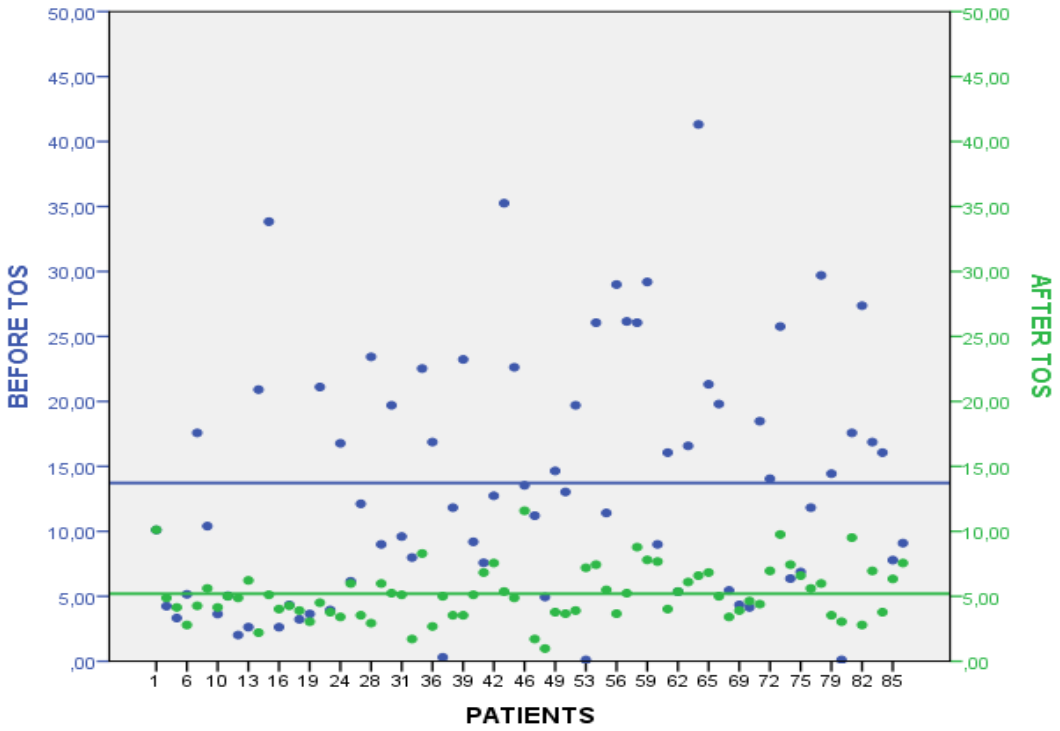

Figure 1. TOS Values of Patients Before and After ICA

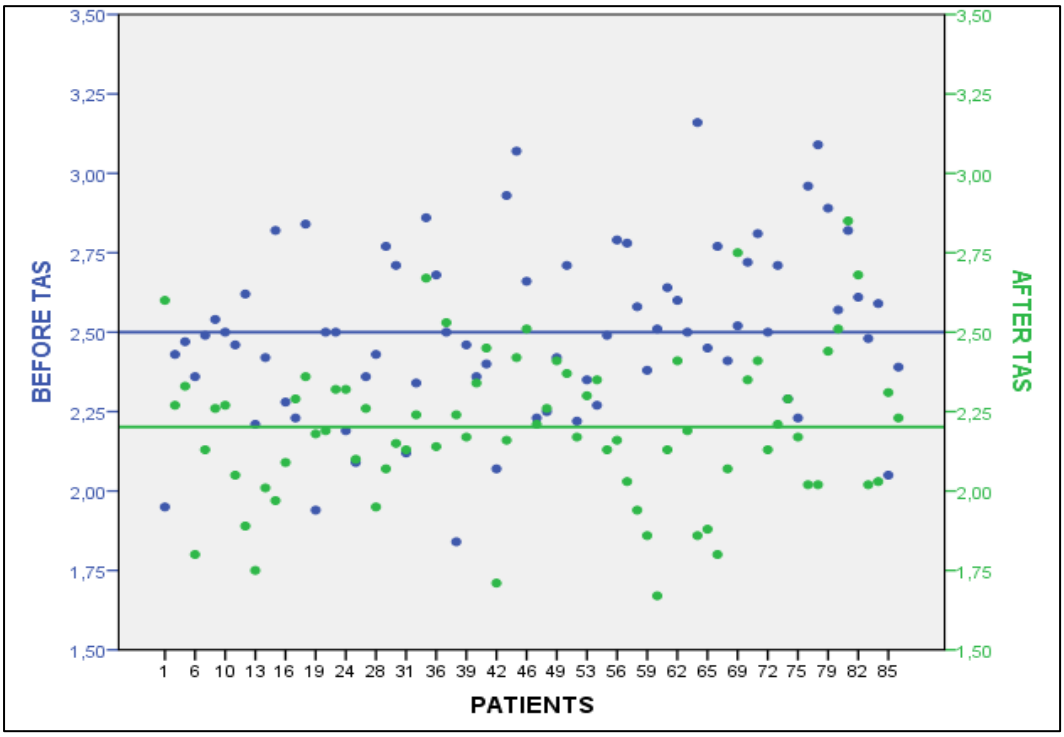

Figure 2. TAS Values of Patients Before and After ICA

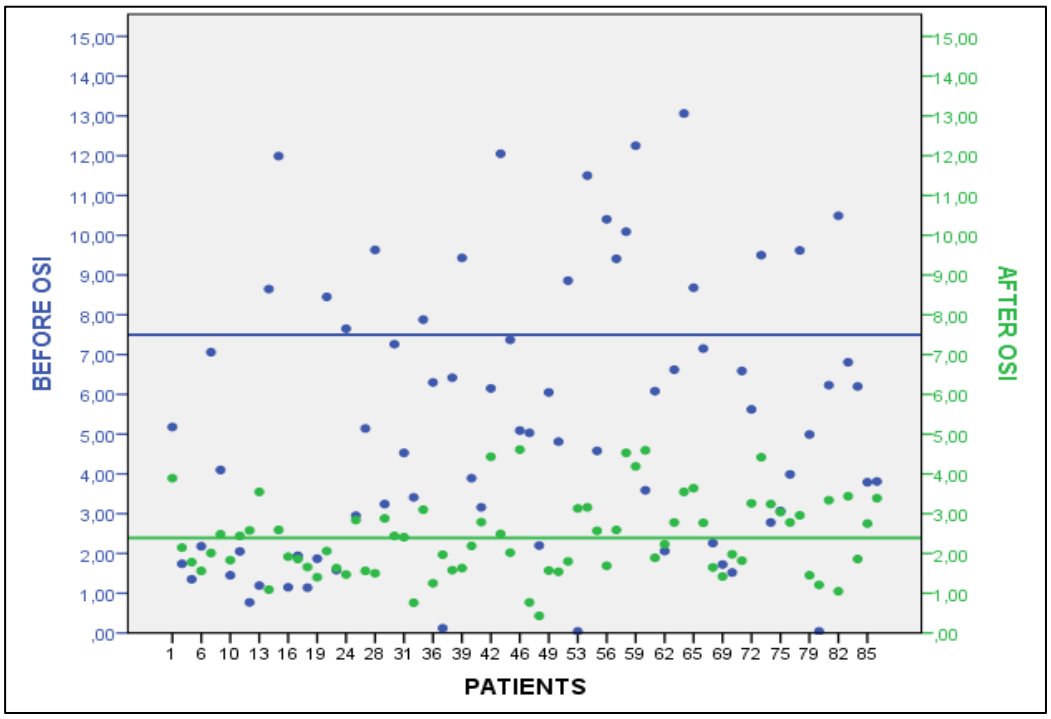

Figure 3. OSI Values of Patients Before and After ICA

Discussion

The objective of this study is to evaluate TOS, TAS, and OSI status in patients who received ICA and did not develop CIN. ICMs are designed to be polar and have high osmolality to provide better imaging and better water solubility. Evidence demonstrates that the elevated osmolality of intravenous contrast agents (ICAs) is a significant factor in the development of contrast-induced nephropathy (CIN), either through direct or indirect mechanisms, by imposing an excessive osmotic burden on the kidneys. CIN is a significant contributor to the development of acute renal injury in patients who are admitted to the hospital. It is also linked to increased morbidity. The etiology of CIN remains incompletely elucidated, with a dearth of information regarding the underlying biological pathways. Oxidative stress is identified as a causative element in the progression of CIN.[11]

In two prospective studies on patients diagnosed with myocardial infarction who received primary percutaneous coronary intervention, including patients with and without CIN development, they found that OSI and the group with CIN exhibited significantly elevated TOS levels and significantly reduced TAS levels compared to the group without CIN. They identified OSI as a risk factor for the development of CIN.[5,12]

However, in another prospective study on patients with normal renal function and with low risk for the development of CIN, there was no statistically significant disparity in the baseline serum levels of antioxidant substances between individuals with and without renal failure following cardiac catheterization.[13]

In a separate study that included individuals diagnosed with Diabetes Mellitus, both with and without nephropathy, there was no notable change in TOS, TAS, and OSI levels between the two groups.[14]

In our study, we evaluated patients who did not develop CIN in the check on the 5th day. Our literature review did not reveal any comparison for TOS, TAS, and OSI before and after the use of ICA for the patient group who did not develop CIN. Oxidative stress is considered a contributing component in the development of CIN but we found that, on the contrary, it caused a decrease in oxidative stress in patients who did not develop CIN. Our study found a significant decrease in TAS, TOS, and OSI values 24 hours after ICM administration, compared to the values before ICM administration. This suggests that nephropathy development may be the cause of oxidative stress, rather than that oxidative stress causes CIN development. Studies are showing that oxidative stress increases in case of acute kidney injury.[15,16] Considering the studies with different results in the literature, more comprehensive studies are needed on this subject.

There are publications of various studies reporting that some minerals and vitamins reduce oxidative stress. One of these minerals is iodine.[17,18] ICAs contain high doses of iodine. 200 mL/dose contains approximately 7-10 times the iodine dose required in the daily diet.[3] In our study, 28 grams of iodine was given to patients using

80 ml of nonionic ICA. Iodine has been known as an antioxidant from the past to the present.[3] In their study assessing pregnant women, Vidal et al. discovered a significant decrease in superoxide dismutase and total antioxidant status activity among women with mild iodine deficiency compared to those with optimal iodine levels. This finding indicates that individuals with iodine deficiency experience significantly higher levels of oxidative stress.[19] In our study, in patients who did not develop CIN, there was a statistically significant decrease in TAS, TOS, and OSI values measured 24 hours after ICM administration, compared to the values before ICM administration. We think that this decrease in oxidative stress may be due to iodine, which is contained in ICM and known as a potent antioxidant[3,4]. The finding of Vidal et al. that oxidative stress levels were elevated in pregnant women with iodine deficiency may support our suggestion on this matter.

In our literature review, the role of oxidative stress in the pathogenesis of CIN has not been fully elucidated. Considering that iodine in ICA is an antioxidant and that patients who develop CIN have increased oxidative stress, more comprehensive further research is required to evaluate The function of oxidative stress in the pathogenesis of CIN or whether it is increased by different mechanisms. Within our research, the decreased OSI, TOS, and TAS after ICA suggest that ICA does not increase oxidative stress.

Ethical Considerations: All subjects provided informed consent and the study received approval from the local institutional ethics committee (Atatürk University Local Ethics Committee. on December 30, 2021, with resolution number 9, session number 15 and No: B.30.2.ATA.0.01.00/72).

Conflict of Interest: Atatürk University Scientific Research Projects Unit covered the financial fees required for the study. (TAB-2022-10405) The authors declare no conflict of interest.

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