Caspian Journal of Neurological Sciences
"Caspian J Neurol Sci"

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Research Paper: Contrast Induced Nephropathy After Brain and Cervical CT Angiography in Stroke Patients: A Prospective Study

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Citation Poursadeghfard M, Torkaman A, Moazzam M, Aramesh A, Neydavoodi M. Contrast Induced Nephropathy After Brain and Cervical CT Angiography in Stroke Patients: A Prospective Study. Caspian J Neurol Sci. 2019; 5(3):140-146. https://doi.org/10.32598/CJNS.5.18. https://doi.org/10.32598/CJNS.5.18.140

Running Title Contrast Induced Nephropathy After CT Angiography

https://doi.org/10.32598/CJNS.5.18.140

Article info:
Received: 10 May 2019
First Revision: 30 May 2019
Accepted: 10 Jun 2019
Published: 01 Jul 2019

ABSTRACT

Background: Contrast-induced nephropathy (CIN) is a major side effect of intravenous iodinated contrast and causes both short- and long-term adverse effects. While diagnostic and interventional procedures of brain ischemia are recently advanced, it is necessary to be cautious about its major side effect.

Objectives: To evaluate CIN and its risk factors in neurology patients after brain and cervical CT angiography.

Materials & Methods: This prospective cross-sectional study was conducted on all patients who were admitted in stroke department of Nemazee hospital, affiliated to Shiraz University of Medical Sciences, Fars, Iran, and had undergone brain and cervical CT angiography from September 2014 to September 2016. Blood urea nitrogen (BUN) and creatinine (Cr) before contrast (BUN1, Cr1), 3 days after contrast (BUN2, Cr2), and 30 days after contrast (BUN3, Cr3) were recorded. t-test, paired t-test, Chi-squared test, repeated measurement-test and also SPSS V. 21 are used for statistical analysis.

Results: 5(2.7%) patients developed CIN after receiving contrast. However, repeated measurement of glomerular filtration rate (GFR) and Cr at the end of one month showed no significant changes between Cr3 and GFR3 in 2 groups of non-CIN and CIN patients, and all patients showed normal renal function at that time. Multiivariate logistic regression analysis demonstrated that hemoglobin (Hb) level is related to CIN (OR:0.5, CI: 0.28-0.90).

Conclusion: Our data showed that the rate of CIN in neurovascular evaluation was insignificant, but it is related to Hb level.

Keywords: Computed Tomography Angiography; Stroke; Kidney

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Highlights

- Contrast-Induced Nephropathy (CIN) is a major side effect of intravenous iodinated contrast after neurovascular intervention in neurology patients.

- CIN is related to Hb level and anemic patients have higher risk for CIN.

Introduction

Contrast-induced nephropathy (CIN) is a major side effect of intravenous iodinated contrast and causes both short- and long-term adverse effects. Both pre-existing renal dysfunction and diabetes mellitus could significantly increase the risk of this acute event. Therefore, these patients are called high-risk individuals [1]. It is diagnosed by transient serum creatinine (Cr) changes detected 48-72 hours after the contrast administration and usually depends on non-renal factors, such as age, hydration state, and previous renal state [2].

The renal failure caused by contrast tends to be nonoliguric and transient, and the maximum level of serum Cr usually occurs around the day 3 and returns to the normal rang in the majority of patients within 2 weeks. However, some cases may develop more severe renal damage; about 1% of them need dialysis. The morbidity and mortality rates in this group are relatively high [3]. There is no specific therapy for CIN. Therefore, all plans should be made to recognize the patients at risk for CIN and to prepare appropriate preventive approach [4].

Previous reports have shown that CIN occurs in 4 to 20% of patients after coronary angiography [5]. After coronary angioplasty, the degree of post-procedural renal failure is associated with in-hospital death [6]. In a large study on patients receiving cerebral computed tomography (CT) angiography and CT perfusion study, it was shown that the incidence of contrast nephropathy in neurovascular patients was low [7]. In another study carried out on patients with acute ischemic stroke, performing a contrast-enhanced CT protocol involving CT angiography/perfusion and conventional angiography in selected patients did not appear to increase the incidence of CIN [8].

The main results of post-procedural renal failure were derived from studies on peripheral angiography or coronary angioplasty. To the best of our knowledge, there are few studies conducted on renal failure after brain or cervical CT angiography, especially in stroke patients. While diagnostic and interventional procedures of brain ischemia are recently advanced, it is necessary to be cautious about its major side effects. Most studies done on stroke patients are retrospective based on the patients' chart regarding the baseline and up to 7 days of the contrast administration. The aim of this study was to evaluate the in-hospital incidence and predictors of contrast-induced nephropathy after cervical and/or brain CT angiography in patients who developed ischemic stroke or transient ischemic attack (TIA) in a large center of stroke in Shiraz (Nemazee Hospital) and also to analyze the factors that may contribute to prevention or early diagnosis of acute renal failure. In contrast to others, our study was done prospectively and we followed the patients for 1 month to evaluate the probable delayed renal dysfunction.

Materials and Methods

This prospective cross-sectional study was done on all patients admitted in stroke department of Nemazee hospital, an academic center affiliated to Shiraz University of Medical Sciences, for ischemic stroke or TIA; and had undergone brain and cervical CTA according to the local protocol from September 2014 to September 2016 in Shiraz, south of Iran. Demographic data including gender, age, weight, height, past medical history like diabetes mellitus (DM), hypertension (HTN), cardiovascular disease (CVD), peripheral-vascular disease (PVD), chronic renal disease (CRD), drugs history, and personal history (smoking) were obtained from the patients' charts. Hospital laboratory tests including sodium (NA+), potassium (K+), hemoglobin (Hb), blood urea nitrogen (BUN) and Cr before contrast (BUN1, Cr1), 3 days after contrast (BUN2, Cr2), and 30 days after contrast (BUN3, Cr3) were recorded as well.

In this hospital, for all patients who are planned to receive iodine contrast, an obligatory local protocol is done to prevent CIN as follows: 1cc for each kilogram of body weight of Ultravist 370 is used as contrast. Some medications like metformin are discontinued 48 hours before until 24 hours after the study to prevent the kidney damage. Hydration with 500cc normal sa-

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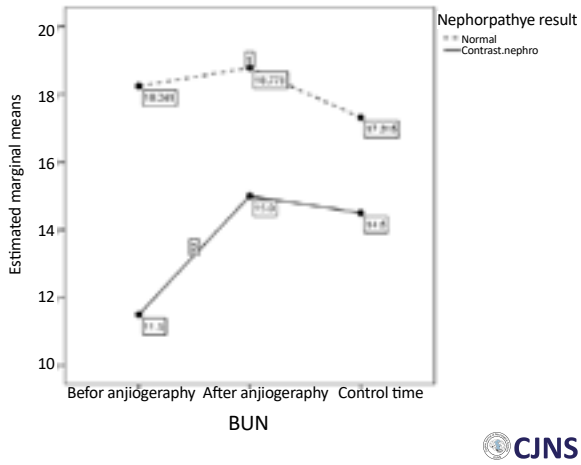

Figure 1. Change of BUN in non-CIN and CIN patientss

line (0.9%) before and after indeed 600 milligrams oral tablet of N-Acetyl Cysteine (NAC) for 4 separated doses before and after contras administration with the interval of 12 hours is prescribed. GFR between 30 to 60% needs more closed observation and GFR under 30% is a contraindication for receiving of the contrast. We defined CIN by at least 25% decrease in GFR or a 25% increase in serum creatinine or absolute increase ≥0.5mg/dL in serum creatinine [9].

Statistical analysis

For statistical analysis, SPSS V. 21, (SPSS Inc, Chicago, Illinois) was used. For continuous and categorical variables, mean and standard deviation (SD) and numbers and percentage are used. t-test, paired t-test, Chi-squared test and repeated measurement-test are used for statistical analysis.

Results

184 patients received iodine contrast for brain and cervical CT angiography after an attack of ischemic stroke or TIA. The mean age of the patients was 62.7 years with SD of 16.33. The youngest patient was 20 and the oldest was 90 years old. 105(57.1%) were male and 79(42.9%) were female. The mean age of the females was 61.04 years (SD=15.71) and that of males was 64.91 years (SD=16.97) which was not statistically significant (P=0.11).

There was a significant difference in hemoglobin level between men and women (13.79±1.96 versus 12.81±1.5329; P<0.001). Also Hypertension (P=0.03) and smoking (P<0.001) were more common in the male subjects. The range of Cr before contrast was higher in men as well (P=0.002). Other historical (DM, CVD, PVD, CRD) and laboratory data like Na+, K+, BUN were not different between males and females. 5(2.7%) patients developed CIN after receiving the contrast. Difference in BUN1, 2, 3 was not significant in all patients, but there were significant changes in Cr2 and GFR2 in 5 patients, which was defined as CIN.

Figure 1 shows no difference between BUN before and after contrast (BUN1, 2, 3) in 2 groups of non-CIN and CIN (P=0.72). Figure 2 shows repeated measure analysis of GFR1, 2, 3 in both groups. There were no significant changes between GFR3 in 2 groups of non-CIN and CIN patients and all patients showed normal GFR at the end of one month (P=0.33). Actually, patients with CIN returned to normal kidney function. Figure 3 also demonstrates no significant difference among Cr3 in the 2 groups compared after one month and all patients had normal Cr (P=0.128) as was shown in both Figures 2

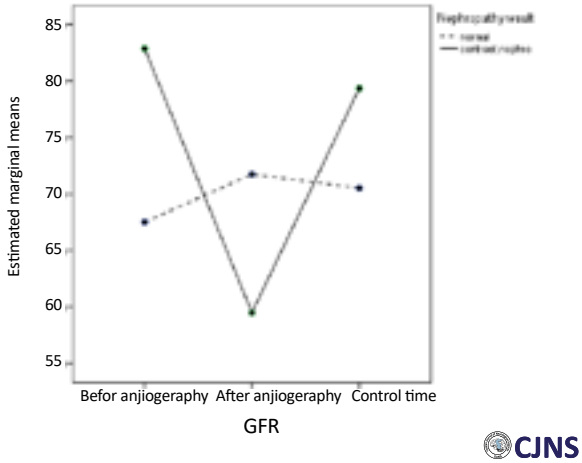

Figure 2. Changes of GFR in non-CIN and CIN patient (P=0.014 for GFR2)

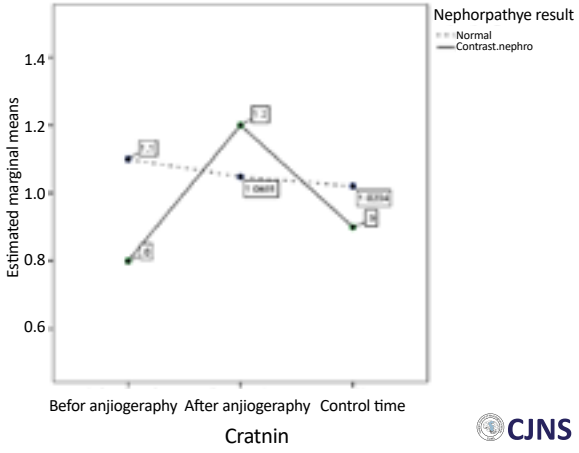

Figure 3. Changes of Cr in non-CIN and CIN patients (P=0.01 for Cr2)

Table 1. Demographic andprimary laboratory data of non-CIN and CIN patients

Variables	No. %		P
	CIN	Non-CIN	
Sex (men)	1(1)	104(99)	0.1
BMI	25.43±3.53	23.96±2.33	0.34
D.M	2(3.30)	58(96.70)	0.52
HTN	2(1.9)	106(98.1)	0.33
CVD	1(1.5)	64(98.5)	0.42
CRD	0	7(100)	0.82
Smoking	0	43(100)	0.26
PVD	0	2(100)	0.94
Hb	11.42±0.90	13.4±1.84	0.017
Hct	34.06±4.59	40.58±7.54	0.056
K+	4.260±.397	4.267±.93	0.98
Na+	139.4±3.91	138.6±10.6	0.86
Cr1	1.042±0.266	0.8±0.28	0.047
BUN1	14.6±6.26	16.74±6.36	0.45
GFR1	97.71±49.89	74.85±31.45	0.36

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BMI: Body mass index; DM: Diabetes mellitus; HTN: Hypertension; CVD: Cardio-vascular disease; CRD: Chronic renal disease; Hb: Hemoglobin; Hct: Hematocrit; K+: Potassium; Na+: Sodium; Cr: Creatinin; BUN: Blood urea nitrogen

and 3 , the means of Cr 2 and GFR2 were different significantly between 2 groups.

None of our patients needed hospital admission or dialysis because of CIN. Table 1 compares detailed information before contrast between the non-CIN and CIN patients, showing a meaningful diferrence in Hb beween patients who developed CIN and those who did not before receiving contrast (P=0.017). Other items show no significant relationship. Multiivariate logistic regression analysis of the variables which have P-value less than 0.2 demonstrares that Hb level is related to CIN (OR=0.5, CI=0.28-0.90 and P=0.02). Other items show no significant relationship (Table 2).

Discussion

Our study showed not only the low rate of nephropathy in stroke patients who received contrast in the first 72 hours (2.7%), but also its transient time which recoverd after one month. Indeed, none of our patients needed hospital admission or dialysis because of CIN. These results are in line with those of many other studeis. Dittrich et al. (2007) did a survey on strocke patients who had undergone CT perfusion and angiography with the pre-contrast fluid substitution. Like our result, only 2% of their patients developped CIN and no subject was hemodialyzed [10].

In another study done after CT angiography and CT perfusion brain imaging in 2005, from 1075 patients 4.8% were diagnosed with CIN and only 0.19% needed temporary hemodialysis during hospilazation [11].

We followed the patients for one month to evaluate them for probable delayed renal failure despite the many studies which were designed retrospectively. At the end of the first month, nobody had abnormal BUN, Cr or GFR. Even the patients who progressed to CIN, 3 days after the modality, returned to their baseline value. Thus, the morbidity in our study had low frequency and was temporary without any

Table 2. Multiivariate logistic regression analysis of the baseline patients' data related to CIN

Variables	Odds Ratio	95% CI (Lower-Upper)	P
Age	1.004	0.95-1.061	0.888
Gender (men)	0.18	0.02-1.66	0.13
BMI	0.88	0.68-1.14	0.35
D.M	0.72	0.11-4.45	0.72
HTN	2.15	0.35-13.23	0.40
CVD	2.24	0.24-20.52	0.47
Hb	0.50	0.28-0.90	0.02
Hct	0.92	0.85-1.009	0.08
K+	0.98	0.36-2.69	0.98
Na+	1.014	0.85-1.20	0.87
Cr1	0.001	0-0.30	0.018
BUN1	0.92	0.76-1.12	0.44
GFR1	1.02	0.99-1.04	0.11

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BMI: Body mass index; DM: Diabetes mellitus; HTN: Hypertension; CVD: Cardio-vascular disease; Hb: Hemoglobin; Hct: Hematocrit; K+: Potassium; Na+: Sodium; Cr: Creatinine; BUN: Blood urea nitrogen; GFR: Glomerular infiltration rate; OR: Odds ratio; CI: Confidence interval

mortality. It was parallel to the results of other studies. In one retrospective study on 735 patients with 90 days outcome, the rate of the CIN was said to be 2.6% and none of the subjects had chronic renal disease or needed hemodialysis; also, there was no any negative impact on 90-day (by modified Rankin scale) [12]. However, some reports have indicated a late rise in Cr value in a few patients due to hemodynamic disturbance, dehydration or medication effects [13].

After exposure to a iodine contrast media, many factors would induce the likelihood of nephropathy [14]. Among the factors we considered in our survey, Hb was shown to be the risk factors. Patients with the lower Hb level had more probability of the CIN. This was in the same line with the findings of other studies which showed the relationship between the low hemoglobin level or anemia with the risk of developing nephropathy, especially in patients suffering from chronic kidney disease [15-17]. It is hypothesized that anemia has a negative impact on oxygen delivery to some parts of the kidney such as cortical part which may have developed vasoconstriction and hypoperfusion after contrast media. Thus, hypoxic damage will be aggravated and it causes more damage to the renal function.

We did not find any association between DM, HTN, smoking, BMI with CIN. 32.6% of our patients were diabetic, but only 3.3% of them developed CIN. Also, from 58.7% of hypertensive subjects 1.9% and from 35.32% persons with CVD 1.5% were diagnosed with CIN. Although all of these underlying diseases are potential negative prognostic values, we think careful selection of patients and management besides enough fluid substitution before contrast administration would be the main factors for prevention of the CIN. Sufficient hydration is demonstrated as the principle way of avoiding CIN. Actually, the benefits of extracellular volume expansion by intravenous fluid administration in previous reports were highlighted [18, 19].

The fluid infused or recommended for this purpose is mostly saline 0.9% followed by sodium bicarbonate. It is believed that the infusion of the crystalloid enhances the renal tubular flow and glomerular filtration that consequently decreases the contact time of the contrast and susceptible renal structures [19].

As a local protocol, all of our patients received 600 milligrams oral tablet of NAC before and after the pro-

cedure. According to the published data, the benefit of NAC to protect from CIN is very controversial. Some reports have stressed its value to some extent, especially in high-risk patients. Moreover, the drug is safe and inexpensive and is usually easily tolerated; also, no important side effects were reported [20, 21]. NAC induces glutathione synthesis which has a prominent role against oxidative stress. It is believed that NAC could enhance the renal glutathione level after exposure to the contrast and oxidative injury [22]. In contrast, some others do not confirm the effectiveness of NAC. For example, in one meta-analysis published in 2017 done on 19 randomized placebo-controlled clinical trials and 4514 patients, oral NAC therapy was not recognized as an efficient alternative agent to prevent CIN in persons who had undergone cardiac angioplasty. In this meta-analysis, most included trials used low dose of NAC (600mg twice a day) for 48 hours [23].

Conclusion

As a conclusion, our data showed the rate of CIN in neurovascular evaluation would be insignificant. But anemic patients have higher risk for CIN. We also think in case careful selection of patients, standard hydration and risk management are done well. It is recommended that all neurology patients who need contrast for neurovascular survey should receive enough volume expander before and during the procedure, discontinuing medications which damage the kidney function. High risk patients also need closer observation and more intensive management. We recommended good hydration and preventive care for all neurology patients who are candidate for CTA as the crucial way to protect the patients from kidney damage. The main limitation of our study included only neurologic patients with limited number of the patients.

Ethical Considerations

Compliance with ethical guidelines

All the study procedures were in compliance with the ethical guidelines of the Declaration of Helsinki 2013.

Funding

The cost of this study (No. 94-01-01-10014) was taken by Shiraz University of Medical Sciences, Shiraz, Iran.

Authors contributions

Preparing the proposal, primary draft of the article, critical revision of the analysis and results: Maryam Poursadeghfard; Patients' selection and follow-up during the next month for their laboratory data, Revision of the article: Amir Torkaman; Data gathering and analysis and preparing the results: Mahshad Moazzam and Aida Aramesh: Data analysis, critical revising the article: Mojtaba Neydavoodi.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgements

The authors would like to thank Shiraz University of Medical Sciences and also Center for Development of Clinical Research of Nemazee Hospital and Dr. Nasrin Shokrpour for editorial assistance.

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