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Prevalence of contrast nephropathy following the administration of N-acetyl cysteine; a systematic review and meta-analysis

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Abstract

Introduction: Nephropathy is a serious complication in patients receiving contrast during imaging. N-acetyl cysteine (NAC) can reduce the contrast nephropathy. This review evaluates the prevalence of contrast-induced nephropathy (CIN) following the administration of NAC.
Methods: A systematic literature search and meta-analysis was conducted in Scopus, Web of Science and PubMed for articles published by December 30, 2019 including the keywords of "N-acetyl cysteine ", "Acute kidney injury", "Nephrotoxicity", "Contrast media", "Contrast-induced AKI" and "Contrast nephropathy".
Results: A total of 29 articles of 537 studies examining 5,980 individuals were incorporated in this systematic review and meta-analysis. Pooled estimation of a meta-analysis of prevalence studies reported a prevalence of 9% (0.09), i.e. nine out of every 100 patients undergoing contrast media resulted in CIN but a prevalence of 14% (0.14) was observed in the placebo group. In addition, 41 out of every 100 patients with hypertension undergoing contrast media resulted in CIN (prevalence: 41%) and 64 out of every 100 patients with diabetes undergoing contrast media resulted in CIN (prevalence: 64%).
Conclusion: The prevalence of CIN in the group receiving NAC is lower than those who did not receive this drug. Additionally, in patients suffering from diabetes and hypertension, CIN is more prevalent compared to healthy people.

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Introduction

The use of contrast agents in imaging exposes the kidneys to damage, which is called contrast-induced nephropathy (CIN). The term is used when serum creatinine more than 25% of baseline or more than 0.5 mg/dL increases within 2-3 days after contrast administration, without the presence of other kidney diseases. The incidence of CIN in the adult population undergoing cardiac angiography is about 30% (1). Occurrence of CIN is of great importance because of its high mortality rate that is reported to be as high as 34% (2). Contrast agents are one of the most important causes of damage to renal tubules and acute tubular necrosis. Risk factors for nephropathy due to contrast agents include diabetes, chronic renal failure, severe congestive heart failure, fluid loss, hypotension, type and volume of contrast medium (3). Nephropathy due to contrast agents is the third most common cause of acute renal failure followed by low blood pressure and surgery in the hospital (4). People with a history of kidney failure, especially kidney damage due to diabetes, congestive heart failure, low blood pressure, high levels of contrast agents and concomitant use of drugs that impair kidney function, are at higher risk (5). Various substances have been tested in various studies to prevent harmful effects of contrast agents on the kidney including N-acetyl cysteine (NAC), theophylline, sodium bicarbonate, ascorbic acid, and diuretics (6). There are some meta-analyses regarding the effectiveness of NAC to prevent CIN. For example, a study by Sharp et al in 2019 (7), but another meta-analysis conducted by Li et al in 2017 showed that NAC therapy is not effective to prevent CIN in patients following angioplasty as a preventive treatment (8).

Key point

In a systematic literature search and meta-analysis, we found the prevalence of contrast nephropathy in the group receiving N-acetyl cysteine is lower than those who did not receive this drug. Additionally, in the patients suffering from diabetes and hypertension, contrast nephropathy is more prevalent compared to healthy people.

Methods

This systematic review and meta-analysis was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines (9).

Search strategy

Scopus, Web of Science, and PubMed were considered for papers published by December 30, 2019. The keywords searched were "N-acetyl cysteine", "Acute kidney injury", "Nephrotoxicity", "Contrast media", "Contrast-induced AKI" and "Contrast nephropathy" or a combination of them in the titles or abstracts. The references of the published articles were manually reviewed for additional relevant articles. The duplicate studies were removed by EndNote. The search strategy for PubMed is a sample of syntax done for this review.

((N-Acetyl Cysteine [Title/Abstract] OR NAC [Title/Abstract])) AND ((acute kidney injury [MeSH Terms] OR acute kidney injury [Title/Abstract] OR AKI [Title/Abstract] OR kidney injury [Title/Abstract] OR nephropathy [Title/Abstract] OR acute tubular necrosis [Title/Abstract] OR renal injury [Title/Abstract])) AND ((Contrast media [MeSH Terms] OR Contrast media [Title/Abstract] OR Contrast-induced [Title/Abstract] OR Contrast nephropathy [Title/Abstract]))

Eligibility criteria

Two of the authors independently evaluated the eligibility of the papers according to the PRISMA guidelines. Inclusion criteria were studies in English about nephropathy after contrast medium receiving in patients who received NAC as intervention in original studies, case series or case reports, but only original and case series were added in the meta-analysis. Exclusion criteria were studies done on animals.

Data extraction

A structured checklist was used for the data extraction including, type of study, patients numbers, age, nephropathy (number, %), comorbidity, gender, NAC dose and complications. The data were retrieved by two independent investigators. The differences observed in this process were corrected by a third investigator independent from the other two. The Newcastle Ottawa Quality Assessment Scale (NOS) was used for qualitative assessment of studies (10).

Statistical analysis

The main measure of effect/effect size was prevalence (ratio of case to total population). Cochran's test (Q-test) (showing significant heterogeneity in the meta-analysis) and I2 (showing the amount of heterogeneity ranged from 0% to 100 %.) were used to assess the heterogeneity among the studies. The random-effects model was used for the continuous and frequency outcome under study. Additionally, a random effects meta-analysis was applied for estimating the main index, which was the pooled prevalence, at 95% confidence interval. A forest plot was used to present the pooled prevalence. Publication bias was assessed using Begg's tests. The analysis was performed using Stats version 13.

Results

A total of 29 articles of 537 studies examining 5980 patients were included in this systematic review and meta-analysis (Figure 1). Study characteristics of the patients included in the meta-analysis are presented in Table 1.

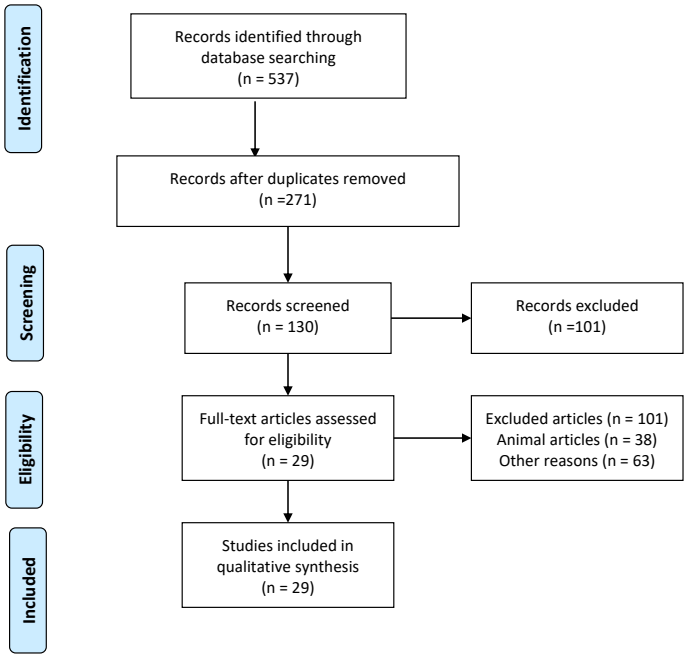

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart.

Table 1. Study characteristics of the patients included in the meta-analysis

Author	Design	Sample size	Age (year)	Gender	NAC dose (mg)	Duration of use (day)	CIN	Cr (mg/dL)	BUN (mg/dL)	GFR (ml/min)	Comorbidity	Case	Contrast (dose)
Ala et al (11)	RCT	100 In: 50 Co: 50	50-59	F:48 M: 52	600 twice daily	2	In: 11 Co:19	0.828	16.1	98.04	Diabetes: 5	Coronary artery angiography	Meglumine Compound 76% (120 ml)
Vallero et al (12)	RCT	100 In: 50 Co:50	-	-	600 twice daily	2	In: 6 Co:9	1.2	-	-	-	Coronary angiography and/or transluminal angioplasty	Iodixanol; Visipaque 320, Nycomed (203 mL/procedure)
Hoffmann et al (13)	Cohort	50	32.8	F:26 M: 24	600 twice daily	2	-	0.82	29.8	106	-	Coronary artery angiography	-
Oldemeyer et al (14)	RCT	96 In: 49 Co:47	In: 77 Co:74	F:22 M: 27	1500 twice daily	2	In: 4 Co:3	1.63	34.4	36.2 (Creatinine clearance)	Diabetes: 5 Myocardial infarction:6 Coronary revascularization: 10 Hypertension:23 Heart failure: 14 Hypercholesterolemia: 20	Coronary artery angiography	134 ml/ Gastrointestinal complication in 16% of receiving NAC
Balderramo et al (15)	RCT	61 In: 33 Co:28	-	-	1200 mg orally 3 h before and 3 after the procedure	1	In: 1 Co:2	-	-	-	-	-	-
Fung et al (16)	RCT	91 In: 46 Co:45	-	F:17 M: 64	400 mg, thrice daily	1	In: 6 Co:8	In: 2.27 Con: 2.4	-	In:28.1 Co: 27.5 (Creatinine clearance)	Nephrosclerosis:20 Diabetes:23	Elective coronary angiography	Nonionic low-osmolality contrast iopromide
Hobikoğlu et al (17)	RCT	81 In: 40 Co:41	62	F:23 M: 58	600 mg NAC before 3 h and after 6 h	1	In: 2 Co:4	-	-	-	-	Elective coronary angiography	-
Durham et al (18)	RCT	79 In: 39 Co:40	In: 69.8 Co:79.4	-	1200 mg NAC before 1 hr. and after 3 h	1	In: 3 Co:5	-	-	-	Diabetes:24	Cardiac angiography	Omnipaque
Allaqaband et al (6)	RCT	123 In: 45 Co:78	71	F:52 M: 71	600 mg twice daily	1	In:15 Co: 13	2.03	-	36.9 (Creatinine clearance)	Diabetes:38 CHF:43	Cardiac angiography	Low-osmolality nonionic contrast/1.54 ml/kg
Hsu et al (19)	RCT	20	-	-	600 mg orally twice a day	-	In: 0 Co: 5	-	-	24.5 (Creatinine clearance)	-	-	Omnipaque (iohexol)

Table 1. Continued

Author	Design	Sample size	Age (year)	Gender	NAC dose (mg)	Duration of use (day)	CIN	Cr (mg/dL)	BUN (mg/dL)	GFR (ml/min)	Comorbidity	Case	Contrast (dose)
Ozcan et al (20)	RCT	264, Three groups of 88	69	F:67 M: 197	600 mg orally twice a day	2	Sodium bicarbonate: 6 Sodium chloride:16, NAC:15	-	-	45.3 (Creatinine clearance)	Diabetes:52 CHF:33	Cardiac angiography	110 ml of ioxaglate
Shavit et al (21)	Retrospective	140 In: 83 Co:57	-	-	-	-	In: 6 Co:11	-	-	-	-	Cardiac catheterization	-
Negita et al (22)	Retrospective	168 In: 82 Co:86	-	-	-	-	In: 3 Co:15	-	-	-	-	Cardiac catheterization	-
Amini et al (23)	RCT	87 In: 45 Co:42	In:63.25 Co:65.09	F:36 M: 54	-	-	In:5 Co:6	-	-	-	-	Elective diagnostic coronary angiography	Iohexol (100 mL) and Iodixanol (6 mL)
Jo et al (24)	RCT	212 In: 106 Co:106	In:64.3 Co:65.6	F:47 M: 165	1200 mg orally twice a day	-	In:2 Co:5	1.41	-	-	Diabetes: 43	Cardiac catheterization	Iodixanol
Buyukhatipoglu et al (25)	RCT	60 In: 30 Co:30	In:58.9 Co:61.8	F:18 M: 42	600 mg NAC intravenously	2	In: 1 Co:1	1	42.3	-	-	Cardiac catheterization	-
Calabro et al (26)	RCT	597 In: 342 Co:255	>65	-	600 mg before and after	1	In: 15 Co:25	-	-	-	-	Coronary artery angiography	-
Kinbara et al (27)	RCT	45 In: 15 Co 1:15 Con2:15	70	F:17 M: 28	704 mg orally twice daily	2	0	0.67	-	46.1 (Creatinine clearance)	Diabetes: 43 Hypertension: 13	Coronary artery angiography	147 ml
Calabro et al (28)	RCT	322 In: 152 Co:170	54	-	-	-	In: 4 Co:19	-	-	-	-	-	-
Chong et al (29)	RCT	548 In: 185 Co 1:182 Con2:181	68	F:195 M: 353	1.2 g BID	3	In: 4 Co1:7 Con2:6	134 µmol/L		48.3 (Creatinine clearance)	-	Elective cardiac catheterisation	Iohexol, iopamidol, ioversol and iopromide

Table 1. Continued

Author	Design	Sample size	Age (year)	Gender	NAC dose (mg)	Duration of use (day)	CIN	Cr (mg/dL)	BUN (mg/dL)	GFR (ml/min)	Comorbidity	Case	Contrast (dose)
Aslanger et al (30)	RCT	312 In : 104 Co 1:104 Con2:104	56	F:112 M: 241	1200 mg orally twice a day	2	In: 27 Co1:24 Con2:23	0.9	-	107	Diabetes: 27 Hypertension: 55	Primary angioplasty	Low-osmolality contrast agent, ioxaglate
Hsu et al (31)	RCT	209 In: 106 Co:103	79.6	F:106 M: 103	600 mg intravenous	1	In: 7 Co:14	1.4	-	36.7 (Creatinine clearance)	Diabetes: 31 Hypertension: 70 Chronic kidney disease: 32	Elective cardiac catheterisation	Iobitridol, Iohexol and Iopromide
Jaffery et al (32)	RCT	398 In: 206 Co:192	65.4	F:252 M: 146	1200 mg bolus followed by 200 mg/h for 24 h	1	In: 33 Co:25	1.09	-	87.4 (Creatinine clearance)	Diabetes: 73 Hypertension: 152	Elective cardiac catheterisation	Iodixanol
Albabtain et al (33)	RCT	243 In: 62 Co1:57 Co2:58	61.1	F:66 M: 177	600 mg twice daily	2	In: 11 Co1:7 Co2:10	1.48	-	61.5 (Creatinine clearance)	Diabetes: 52 Hypertension: 38	Elective cardiac catheterisation	Ioxaglate
Alessandri et al (34)	RCT	296 In: 138 Co:158	65	F:97 M: 199	1200 mg daily	2	In: 7 Co:8	-	-	-	-	-	-
Alioglu et al (35)	RCT	113 In: 49 Co:64	In: 62.73 Co:60.84	-	600 mg twice a day	2	In: 6 Co:11	0.99	-	78.31	Diabetes: 11	Elective cardiac catheterisation	Iomeron
Heguilén et al (36)	RCT	123 In: 81 Co:42	-	-	1200 mg daily	2	In: 9 Co:15	-	-	-	-	Elective cardiac catheterisation	Ioxaglate
Thayssen et al (337)	RCT	715 In:176 Con: 539	65	F:165 M: 550	600 mg BID	2	In: 32 Co:109	0.84	-	94.3	Diabetes: 15 Hypertension: 58	Angiography and coronary revascularisation	Visipaque, omnipaque
Habib et al (38)	RCT	105 In: 30 Co:75	62.3	F:44 M: 61	1200 mg orally BID	2	In: 2 Co:13	0.96	-	-	-	-	-
Biernacka-Fiałkowska et al (39)	RCT	222 In: 108 Co:114	In: 66 Co:64.3	F:53 M: 171	600 mg intravenously	1	In: 9 Co:21	-	-	76.2	Diabetes: 34 Hypertension: 98	-	-

Descriptive characteristics

The mean age of the participated individuals was 63.57 ± 9.18 years. The mean serum creatinine, BUN and creatinine clearance and additionally glomerular filtration rate (GFR) levels in the patients undergoing contrast media were 1.23 mg/dL, 30.65 mg/dL, 45.10 mL/min and 93.30 ml/min (Table 2). Regarding the dose of NAC administered in the prevention of CIN, the most common dose was 600 mg twice daily by two days (Figure 2).

Prevalence of CIN in the intervention groups

Pooled estimation of a meta-analysis of prevalence studies reported a prevalence of 9% (0.09), i.e. nine out of every 100 patients undergoing contrast media with NAC resulted in CIN (Figure 3).

Prevalence of CIN in the placebo groups

Pooled estimation of a meta-analysis of prevalence studies reported a prevalence of 14% (0.14), i.e. 14 out of every 100 patients undergoing contrast media without NAC resulted in CIN (Figure 4).

Prevalence of diabetes in the patients who developed CIN

Pooled estimation of a meta-analysis of prevalence studies reported a prevalence of 64% (0.64), i.e. 64 out of every 100 patients with diabetes undergoing contrast media resulted in CIN (Figure 5).

Table 2. Descriptive characteristics of the individuals who underwent contract media

Variable	Minimum	Maximum	Mean	SD
Age (y)	32.80	79.60	63.5730	9.18938
Creatinine (mg/dL)	0.67	2.27	1.2397	0.44884
BUN (mg/dL)	16.10	42.30	30.6500	10.98802
Creatinine clearance (mL/min)	24.50	87.40	45.1000	18.25711
GFR* (ml/min)	76.20	107.00	93.3083	13.33835

GFR, glomerular filtration rate.

Prevalence of hypertension in the patients who developed CIN

Pooled estimation of a meta-analysis of prevalence studies reported a prevalence of 41% (0.41), i.e. 41 out of every 100 patients with hypertension undergoing contrast media resulted in CIN (Figure 6).

Publication bias

The results of the analysis showed that bias publication did not have an influence on the creation of negative results, which is shown as symmetry in the funnel plot. Meanwhile, no evidence of publication bias was detected using Egger's test (Egger's test t = 2.84, $P = 0.014$, 95% CI: 2.207 to 16.206).

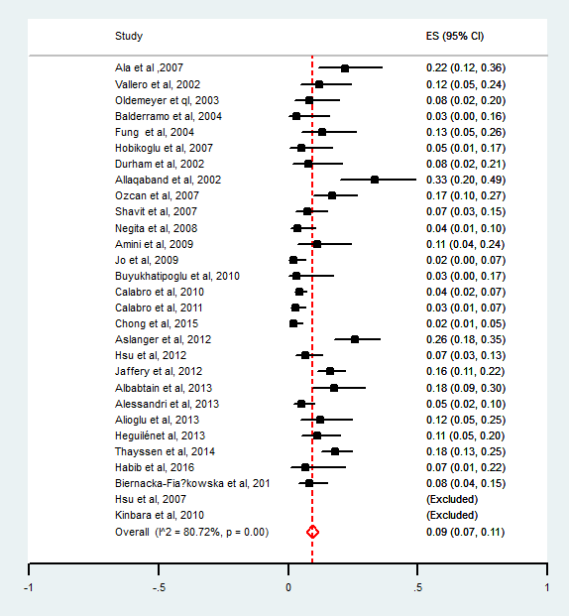

Figure 3. Forest plot showing the prevalence of CIN following NAC administration.

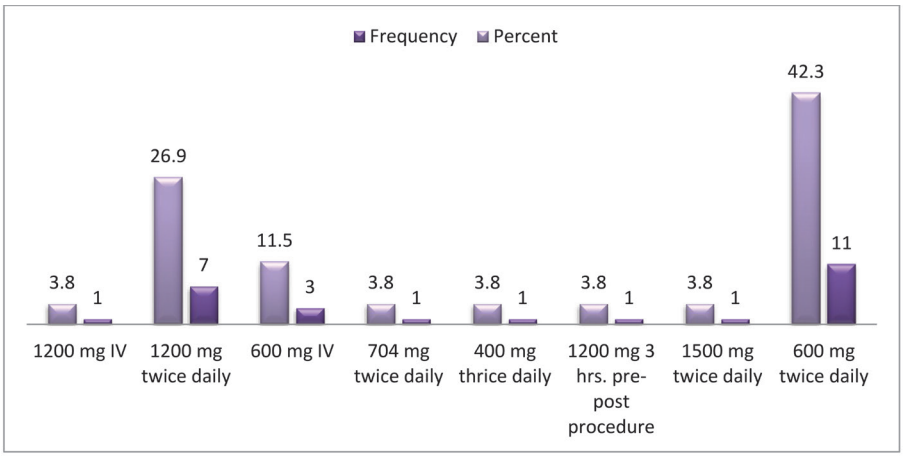

Figure 2. NAC used doses according to reports of studies.

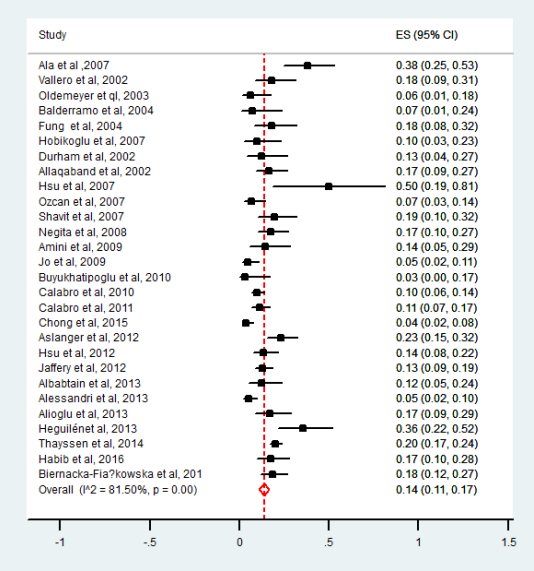

Figure 4. Forest plot showing the prevalence of CIN following placebo administration.

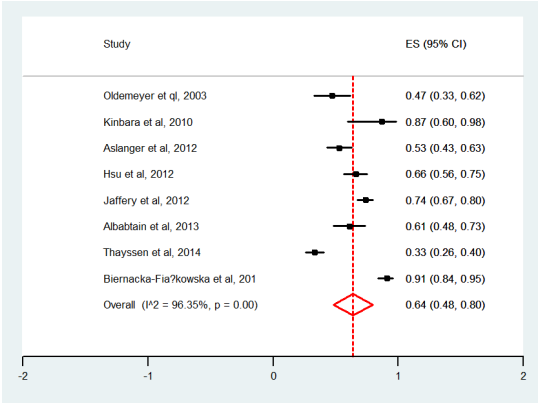

Figure 5. Forest plot showing the prevalence of diabetes in the patients who developed CIN.

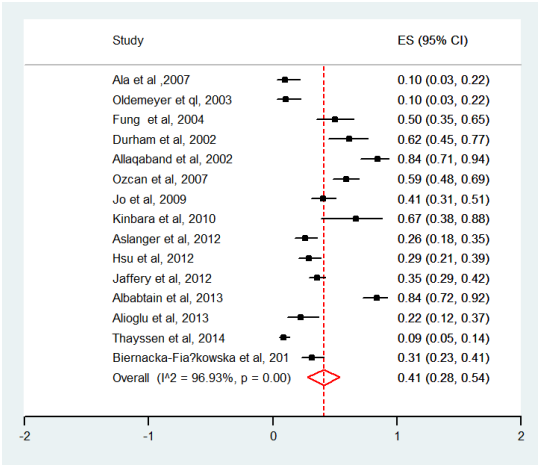

Figure 6. Forest plot showing the prevalence of hypertension in the patients who developed CIN.

Discussion

This review showed that the prevalence of CIN in the group receiving NAC is lower than those did not receive NAC (placebo). In addition, CIN in the patients suffering from diabetes (64%) and hypertension (41%) is prevalent compared to healthy people. In a study by Ala et al, investigated the effects of N-acetylcysteine in preventing CIN due to coronary angiography in patients with normal renal function. They showed in the first group, fluids with oral NAC 600 mg twice daily for 2 days (the day before and the day of administration of contrast agent) and in the second group (control group), only fluids were prescribed. CIN was observed in 30 patients, 11 patients (22%) in the NAC group and 19 patients (38%) in the control group, and there was no significant difference. In the control group, the mean serum creatinine of patients increased significantly after 48 hours, but in the NAC group, no significant increase was observed in the mean serum creatinine of patients. These results suggest that AC has been able to reduce contrast-induced renal impairment (11). In a study conducted by Vallero et al in 2002 in Italy on 100 patients undergoing angiography with an iodixanol with a volume of 203 ml from 1-2 hours before to 24 hours after angiography and the NAC group received 600 mg twice daily before and immediately after angiography. Vallero et al showed no potential advantage of NAC in the prevention of acute nephropathy, induced by high volumes of contrast agent (12). The study by Hoffmann et al conducted on 50 patients with healthy renal function under contrast-enhanced angiography. In their investigation, serum creatinine was measured 48 hours after angiography, which showed a significant decrease in the group that received NAC. This study confirmed the effect of NAC in preventing renal impairment of contrast agents in patients with healthy renal function undergoing angiography (14). There is strong controversy about the effectiveness of the NAC. In this regard, Loomba et al showed that NAC may not have any significant effect on clinical outcomes after cardiac catheterization (40). According to the results of a meta-analysis performed by Ali-Hassan-Sayegh et al in 2017, many procedures can be considered to prevent CIN in the patients undergoing angiography such as enough hydration, use of NAC and ascorbic acid (41). Our review approved the effect of NAC in preventing CIN compared to the placebo group in which in patients receiving NAC, the prevalence of CIN was 9% while it was 14% in the control groups. It should be noted that comorbidities can affect the prevalence of CIN, which our review indicated more frequency of hypertension and diabetes among patients with CIN. We showed, 41 out of every 100 patients with hypertension undergoing contrast media resulted in CIN (prevalence: 41%) and 64 out of every 100 patients with diabetes undergoing contrast media resulted in CIN (prevalence: 64%). These values are threatening the life of patients and it is recommended

to perform larger randomized clinical trials with different groups to find better prophylactic treatment.

Conclusion

The prevalence of CIN in the group receiving NAC is lower than those did not receive NAC (placebo). In addition, CIN in the patients suffering from diabetes (64%) and hypertension (41%) is prevalent compared to healthy people

Authors' contribution

Primary draft by MKM and HN. First edit by HN. Manuscript finalized by MKM and HN both equally. All authors read and signed the final paper.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues

This study was approved by ethic committee of Isfahan University of Medical Sciences (#IR.MUI.MED.REC.1399.693) and was extracted from the medical thesis of Marzieh Khosravani Moghadam at this university (Thesis #399660). Additionally, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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