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ORIGINAL ARTICLE

EFFICACY OF SODIUM BICARBONATE VERSUS NORMAL SALINE IN THE PREVENTION OF CONTRAST-INDUCED NEPHROPATHY AMONG CARDIAC PATIENTS: A COHORT STUDY IN SAUDI ARABIA

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Summary

Background: Several alternative prevention strategies are being employed in various clinical settings to reduce Contrast-induced nephropathy (CIN). Despite the proposed theoretical advantage of these strategies, there is no agreement on their relative effectiveness in real practice. This study aimed to estimate the incidence of CIN and to report on the real effectiveness of sodium bicarbonate to protect the kidney from CIN in various cardiac patients undergoing cardiac catheterization.

Methods: This is a retrospective, single-center, cohort study. A total of 60 patients admitted between January 2016 and November 2021 who were undergoing coronary angiography at a single Saudi center were included. All patients received either intravenous sodium bicarbonate or normal saline hydration prior to, during, and after the implementation of CM. CIN was defined as serum creatinine (SCr) ≥ 25 % or ≥ 0.5 mg/dL compared to the baseline value within 48 h after CM exposure.

Results: Among all patients, the incidence of CIN at 24 and 48 h was 16.7 % and 15 %, respectively. Strikingly, the incidence of CIN at both time points was significantly higher among patients who received sodium bicarbonate than among those who received normal saline hydration only [30% vs. 3.6 % (P=0.012) and 38 % vs. 3.3 % (P=0.002), respectively]. Dyslipidemia status was the most positive predictor of CIN incidence at both time points.

Conclusions: The 16.7 % incidence of CIN in this sample is considered very high compared to the rates in previous national and international studies. This finding indicated that further preventive measures should be urgently initiated with strict protocols for the implementation of CM according to updated guidelines.

Key words: Contrast-induced nephropathy; Sodium bicarbonate; Normal saline

1 Introduction

Contrast-induced nephropathy (CIN) is a known complication of contrast media (CM) that leads to prolonged hospitalization and increased health care costs and is a major cause of morbidity and mortality [1]. Globally, CIN

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has become the third leading cause of acquired *de novo* acute kidney injury (AKI) among hospitalized patients in the United States of America (USA) and Europe (1). However, CIN is a type of reversible AKI. AKI is mostly described as an elevation in serum creatinine (SCr) by a factor of 1.5 or 0.3 mg/dL above the baseline within 48 hours (hrs) that was suspected to have occurred within 7 days or a urine output of < 0.5 mL/kg/hr for 6 hrs (2). According to most recent medical literature, CIN is defined as a relative increase in SCr of ≥ 25 % with respect to the baseline value within 24 to 72 hrs (3).

Due to the wide variety of CM-based diagnostic and intervention procedures, the epidemiological incidence of CIN has been reported as 0.6 % to 2.3 %, which is still significantly higher than the incidence rates of other diseases (4). According to a recent epidemiological review, CIN was reported to develop in approximately 2.5 % to 15 % of patients undergoing coronary angiography and in approximately 5 % to 25 % of patients who underwent percutaneous coronary intervention (PCI) (2, 4). This variability in incidence rate was mainly dependent on the prevalence of associated risk factors (2, 5).

Multiple risk factors may enhance the development of CIN; these factors are classified into two categories: patient- and procedure-related. Among the classic, patient-related risk factors for CIN are age> 75 years old, diabetes, uncontrolled hypertension, low blood pressure, congestive heart failure, preexisting renal insufficiency, anemia, and the use of some medications such as diuretics (4). However, procedure-related factors may include high contrast volume, osmolality or viscosity and repeated exposure to CM within 72 hrs (5).

The prevalence of CIN in studies conducted in the USA, ranged from 0% to 24 % (4-6). The wide range was attributed to differences in CIN definitions, historical risk factors, the form and dosage of the CM used, and the prevalence of other possible coexisting causes of acute renal failure (6). However, there are few studies in Saudi Arabia concerning CIN incidence (7-9). The incidence of CIN in these studies varied widely among 2013 (7.7 %) (7), 2015 (31.3 %) (8), and 2017 (4.9 %) (9). These variabilities in results may be attributed to heterogeneity in patient populations, differences in sample sizes, and discrepancies in CM preventive measures implemented in the three studies. However, the incidences of CIN in Saudi Arabia are considered comparable or relatively higher than those described in previous international reports (6). Additionally, the authors concluded that diabetes and hypertension are major risk factors for CIN in Saudi patients (7-9).

The sources of damage caused by CIN are unknown, but they appear to have a toxic effect on epithelial and renal cells and increase oxidative stress (10). The pathophysiology of CIN is complex and incomprehensible, and CIN has no definitive treatment (6, 11). Currently, prevention is the key strategy for reducing the incidence of CIN among susceptible patients (12). Various prevention strategies have been developed in an attempt to avoid CIN. These strategies involve volume expansion (with normal saline, sodium bicarbonate, or both), administration of N-acetylcysteine (NAC), withdrawal of some drugs (metformin, angiotensin-converting enzyme inhibitors, angiotensin II-receptor blockers, or nonsteroidal anti-inflammatory drugs), hemodialysis or statins (12). Despite the proposed theoretical advantage of these strategies, until now, there has been no agreement on their relative effectiveness in clinical practice (3, 5, 12). Therefore, alternative prevention strategies are being employed in various clinical settings to reduce CIN (7, 13-22). Specifically, the theory of prevention of nephropathy by continuous IV hydration either with sodium bicarbonate or normal saline was based on the concept of neutralizing free radicals generated by CM (23). Thus, decreasing acidity which is postulated to be the main cause of potentiating the induction of CIN due to oxygen free radicals (13, 14, 16, 20, 22). It was found that oxygen free radicals are released in acidic conditions, and their activity is prevented in alkaline settings due to neutralization. Therefore, urine alkalization was suggested as a preventive method for CIN (23). Sodium bicarbonate has been suggested for this purpose due to its antioxidant effect caused by the absorption of free radicals in the kidney (23). Therefore, sodium bicarbonate is expected to limit free radical synthesis and protect the kidney against oxidants by reducing acidity in the medulla and urine (22).

In the context of clinical studies, however, the impact of preventive hydration with sodium bicarbonate has been shown to be controversial and inconsistent (7, 13-22). Furthermore, a meta-analysis that included 22 randomized clinical trials revealed that sodium bicarbonate administration is not superior to the use of saline solution for preventing CIN, and neither sodium bicarbonate nor saline improved the mortality rate or the need for renal replacement in patients with risk factors (3).

In Saudi clinical settings, due to the scarcity of data regarding the effectiveness of preventive procedures for CIN in Saudi patients, various strategies have been implemented with no unified protocols for CM implementation or CM-associated CIN prevention (7-9).

Therefore, our study aims to estimate the incidence of CIN among patients undergoing coronary angiography who received CM in our setting, to report on the real effectiveness of sodium bicarbonate prophylaxis, and to identify the risk factors for CIN with the strongest predictive abilities among included patients.

2 Material and Methods

2.1 Study design and participants

This study was a retrospective, observational cohort study of hospital-based patients from Dr. Suliman Al-Habib Hospital in Riyadh, Saudi Arabia. All patients admitted between January 2015 and November 2021 who received CM during various procedures, including computed tomography (CT), intravenous pyelography, and percutaneous coronary intervention (PCI), were initially screened. However, only those who were admitted to the cardiac catheterization laboratory to receive diagnostic coronary angiography or PCI were included in this study.

The study population comprised 60 cardiac patients who received intravenous sodium bicarbonate or normal saline prior to and/or during the implementation of CM in the coronary care unit (for coronary angiography or PCI). All patients under 20 years old and those who had hypokalemia or hypernatremia were excluded. However, we did not exclude patients with any classic risk factors (diabetes mellitus, history of congestive heart failure, hypertension, chronic kidney disease (CKD), or age older than 75 years).

2.2 CIN prevention protocol

In our setting, the CM agent employed for intra-arterial angiography is iodixanol, which is a nonionic dimer. Its iodine content is 320 mg I/ml, it has a low osmolality of 290 mOsm/kg H_2O, and its viscosity at 37 °C is 10.6 mPa.

According to our cardiac catheterization laboratory, the volume of CM used was determined by the procedure carried out on each patient and according to judgment of the cardiologists based on standard guidelines. In patients with glomerular filtration rate (eGFR) $\geq$ 60 ml/min/1.73 m^2, the maximum allowable volume of intravenous iodine CM is $\leq$ 300 mL (with a concentration of 300 mg I/ml). In patients with eGFR below 60 ml/min/1.73 m^2, the volume of CM must be calculated based on the formula: 5 × [kg body weight (maximum 300 mL)/SCr (in mg/dL)] (24).

The type of prevention therapy was chosen based on the discretion of the interventional cardiologist. The guidelines that were followed at the time of the study suggested one of the following two preventive methods:

1. Initial intravenous infusion of 3 mL/kg/h of 150 mEq/L sodium bicarbonate for 1 hr immediately before the injection of the CM, after which the patients received the same fluid at a rate of 1 mL/kg/h during the contrast exposure and for 6 h after the procedure. The sodium bicarbonate solution was prepared by adding 150 ml of sodium bicarbonate (8.4 %) to 850 ml of 5 % dextrose with water.

2. Intravenous administration of normal saline at a rate of 60-70 ml/hr for 6 hrs before the injection of the CM, after which the patients received the same fluid at the same rate during the contrast exposure and for 4 h after the procedure.

2.3 Study variables and outcomes

The primary outcome (independent variable) was the total incidence of CIN associated with CM despite the concurrent use of prophylactic treatment with either sodium bicarbonate or normal saline hydration. CIN was defined as a relative 25 % increase or an absolute increase of $\geq$ 0.5 mg/dL in the SCr value from the baseline reading within 48 hrs post-catheterization. The results of SCr and blood urea nitrogen (BUN) were recorded on a daily basis before and after injection of CM. For each patient, one value for each test (SCr and BUN) was obtained

before the procedure, and two values for each test within 72 hrs after the procedure were also recorded. The most recent SCr value before CM exposure was defined as the baseline SCr value and was used to calculate the baseline eGFR by the Modification of Diet in Renal Disease (MDRD4) method in mL/min per 1.73 m^2 [eGFR = 186 x (creatinine/88.4)-1.154 x (age)-0.203 x (0.742 if female) x (1.210 if black)] (25), and creatinine clearance (CrCl) was estimated by the Cockcroft-Gault Equation [CrCl in ml/min (male) = ([140-age] × weight in kg)/(SCr × 72)× 0.85 if female] (26). The second objective was to estimate the effectiveness of sodium bicarbonate in the prevention of CIN compared to normal saline and its correlation with patients' demographic and clinical criteria. Prior history of CKD was defined as a baseline eGFR ≥ 60 mL/min/1.73 m^2. Data concerning other associated clinical conditions were extracted by reviewing electronic medical records.

As a secondary purpose, we evaluated the changes in SCr, BUN, eGFR, and CrCl separately in each group and between groups at the beginning of the procedure and 24 and 48 hrs after exposure to the contrast agent.

2.4 Statistical analysis

Statistical analyses were conducted using STATA 12 (Stata Corp, USA) and IBM SPSS 26 (IBM Corp, USA) software. The study population (n = 60) was divided into two groups: Group A (patients who received normal saline, n = 30) and Group B (patients who received sodium bicarbonate, n = 488). The normal distribution of data was examined by the one-sample Kolmogorov-Smirnov test. Continuous variables are presented as the means and standard deviations (SDs). The intergroup differences were compared using a t-test, and correlations were assessed using a linear regression model. Paired numerical data were compared using the paired t-test. Categorical variables are presented as absolute values and percentages, and the differences between groups were compared using Pearson's chi-squared test or Fisher's exact test. Ordinal data were compared using the chi-squared test for trend. Paired binary data were compared using the McNemar test. To examine the crude and adjusted effects of intervention groups, baseline risk factors, and pre- and postintervention laboratory values on the study outcome (development of CIN), univariate (1 variable at a time) and multivariate (all variables together) logistic regression models were conducted. Statistical significance was set at an alpha level of 0.05.

3 Results

3.1 Baseline population criteria

A total of 60 patients met the eligibility criteria for inclusion in our sample, with a mean age of 61 ± 12 years old (range, 21-88 years). The majority of patients (n=40, 66.7 %) were males. Overall, the most common comorbidities in the sample were hypertension (n=38, 63.3 %), followed by CKD (n=37, 61.7 %), dyslipidemia (n=36, 60 %), diabetes (n=31, 51.7 %), and other cardiovascular diseases (n=23, 38.3 %). The mean SCr, eGFR, and CrCl at baseline were 142 ± 144 (μmol/L), 73.6 ± 41.1 ml/min/1.73 m^2, and 68.6 ± 41.8 ml/min, respectively.

Table 1. Baseline demographics and laboratory data by intervention group.

Item	Group A (normal saline) n = 30		Group B (sodium bicarbonate) n = 30		P value
	Mean	SD	Mean	SD	
Age (years)	59.9	10	62.2	13.8	0.45
Weight (kg)	79.6	14	78.6	18.2	0.8
Height (cm)	166.2	9.2	163	9.3	0.2
Sodium (mmol/L)	138.4	2.3	138.7	6	0.8
Potassium (mmol/L)	4.2	0.4	4.4	0.9	0.36
BUN (mmol/L)	6.8	4.7	15.3	9.1	0.0001
SCr (umol/L)	93.3	88	194.2	173.6	0.006
GFR (ml/min/1.73 m^2)	90.2	29.2	55.7	45	0.001
CrCl (ml/min)	82.9	33.5	53.3	44.9	0.006
Infusion rate (ml/hr)	61.5	10	83.5	42.3	0.008

Table 2. Comparison between intervention groups with regard to sex and comorbidity distribution.

Item	Group A (normal saline) n = 30		Group B (sodium bicarbonate) n = 30		P value
	N	%	N	%	
Sex					
Male	21	70	19	63.3	0.5
Female	9	30	11	36.7	
Comorbidities					
Hypertension	17	56.7	21	70	0.2
Diabetes	12	40	19	63.3	0.07
Dyslipidemia	29	96.7	7	23.3	0.0001
CKD	17	56.7	20	66.7	0.4
Obesity	17	56.7	17	56.7	0.87
Smoking	9	30	4	13.3	0.11

Tables 1 and 2 show comparisons between different management strategies with respect to baseline continuous data (demographics and laboratory tests) and categorical data (comorbidities and gender distribution), respectively.

Regarding baseline demographics, there was no significant difference between the groups. However, with respect to the baseline laboratory test, there was a statistically significant difference between the two groups in terms of all renal function tests (Table 1). The BUN, SCr, eGFR and CrCl were significantly worse in the sodium bicarbonate group (with P values of 0.0001, 0.006, 0.001 and 0.006, respectively).

Regarding comorbidities (Table 2), the percentage of patients suffering from dyslipidemia was significantly higher in the normal saline group (P=0.0001). In contrast, the prevalence of patients with prior diagnosis of cardiovascular diseases were significantly higher in the sodium bicarbonate group (P=0.0001).

3.2 Comparison of laboratory data between intervention groups after CM injection

Comparison between the two intervention groups again showed significant differences in post-CM laboratory results (Table 3), particularly in all renal function tests at both time points (after 24 hrs and 48 hrs), BUN (P=0.0001 and 0.0001, respectively), SCr (P=0.0008 and 0.0008, respectively), eGFR (P=0.00001 and 0.00001, respectively), and CrCl (P=0.0001 and 0.0001, respectively). Closer inspection of these new values indicated further worsening of kidney function in the sodium bicarbonate intervention group compared to the saline treatment group (Table 3).

Table 3. Comparison of laboratory results after CM injection between intervention groups.

Item	Group A (normal saline) n = 30		Group B (sodium bicarbonate) n = 30		P value
	Mean	SD	Mean	SD	
Sodium $_{24\ hrs}$	138.1	0.4	140.5	1.4	0.13
Sodium $_{48\ hrs}$	138.2	0.5	140	1.8	0.29
Potassium $_{24\ hrs}$	4	0.05	4.1	0.15	0.59
Potassium $_{48\ hrs}$	4.14	0.06	4.1	0.14	0.78
BUN $_{24\ hrs}$	6.5	0.6	16.4	2.02	0.0001*
BUN $_{48\ hrs}$	6.8	0.66	18.9	2.6	0.0001*
SCr $_{24\ hrs}$	91.9	11.3	241.8	39.3	0.0008*
SCr $_{48\ hrs}$	95.5	13.8	273.5	56	0.0008*
eGFR $_{24\ hrs}$	84.6	4.5	45	5.8	0.00001*
eGFR $_{48\ hrs}$	83.9	4.8	40.5	6.6	0.00001*
CrCl $_{24\ hrs}$	78.9	5.8	43.4	5.8	0.0001*
CrCl $_{48\ hrs}$	77.2	6.2	38.2	6.7	0.0001*

*Significant

Further comparisons of laboratory changes within each intervention group at 24 and 48 hrs post CM injection are displayed in Table 4. Specifically, potassium level $_{24\ hrs}$, eGFR $_{24\ and\ 48\ hrs}$, and CrCl $_{48\ hrs}$ were observed to be significantly decreased in group A, which received normal saline, compared to the respective baseline levels (p-value < 0.05). However, other tests displayed no significant statistical changes compared to the baseline values in either intervention group (normal saline or sodium bicarbonate).

Table 4. Comparison of laboratory changes within intervention groups.

Item	Group A (normal saline) n = 30		Group B (sodium bicarbonate) n = 30	
	Test	P value	Test	P value
Sodium Baseline VS. 24 hrs	0	1	-1.5	0.14
Sodium Baseline VS. 48 hrs	0.5	0.6	-1.25	0.22
Potassium Baseline VS. 24 hrs	2.6	0.01*	1.76	0.08
Potassium Baseline VS. 48 hrs	1.23	0.22	0.87	0.4
BUN Baseline VS. 24 hrs	0.89	0.3	-0.7	0.48
BUN Baseline VS. 48 hrs	0.009	0.9	-1.18	0.25
SCr Baseline VS. 24 hrs	0.46	0.64	-1	0.32
SCr Baseline VS. 48 hrs	-0.8	0.4	-1.32	0.2
eGFR Baseline VS. 24 hrs	2.32	0.02*	1.09	0.28
eGFR Baseline VS. 48 hrs	2.9	0.006*	1.11	0.27
CrCl Baseline VS. 24 hrs	1.4	0.16	1.08	0.28
CrCl Baseline VS. 48 hrs	2.38	0.02*	1.18	0.25

*Significant

3.3 The incidence of CIN

Among all patients, the incidence of CIN at 24 and 48 hrs was 16.7 % (10 out of 60 patients) and 15 % (9 out of 60 patients), respectively. Strikingly, the incidence of CIN at both time points was significantly higher among patients who received sodium bicarbonate than among those who received normal saline hydration only: CIN incidence at 24 hrs was 30 % vs. 3.6 % (P=0.012, by Fisher's exact test), and CIN incidence at 48 hrs was 38 % vs. 3.3 % (P=0.002, by Fisher's exact test).

Table 5. Multivariate logistic regression models* for potential predictors of CIN among the study population 24 hrs after CM injection.

	B	S.E.	Sig.	Exp(B)	95% CI for EXP(B)	
					Lower	Upper
Sex (male)	3.509	1.432	0.014*	33.402	2.016	553.337
Hypertension	2.089	1.290	0.105	8.079	0.645	101.171
Diabetes mellitus	-1.311	1.280	0.306	0.270	0.022	3.317
Dyslipidemia	1.509	0.756	0.046*	4.521	1.028	19.879
CKD	-0.361	1.012	0.721	0.697	0.096	5.061
Obesity	-2.289	1.193	0.055	0.101	0.010	1.050
Age	-0.057	0.051	0.259	0.944	0.855	1.043
Constant	0.827	0.453	0.068	2.286	-	-

*Significant

3.4 Predictors of CIN incidence

Univariate analysis followed by multiple logistic regression models (after adjustment for baseline eGFR and prophylactic management) revealed that the incidence of CIN at 24 hrs (Table 5) was significantly predicted

by male gender (OR, 33.4; 95 % CI, 2.02–553.34; P=0.014) and concomitant dyslipidemia (OR, 4.52; 95 % CI, 1.03–19.9; P=0.04). Further application of conditional backward stepwise elimination of variables with a P-value >0.10 and retaining variables with a P-value <0.05 revealed that dyslipidemia status was the most positive predictor of CIN incidence at both time points: after 24 hrs (R^2 0.017, P=0.04) and after 48 hrs (R^2 0.17 and P=0.04). The correlation of other variables with CIN incidences at both time points are displayed in Tables 5 and 6. It is important to note that none of the pre- (baseline) or postprocedure laboratory tests (BUN, SCr, eGFR and CrCl) were significant independent predictors of CIN (P-value >0.05).

Table 6. Multivariate logistic regression models* for potential predictors of CIN among the study population at 48 hrs post CM injection.

	B	S.E.	Sig.	Exp(B)	95% CI for EXP(B)	
					Lower	Upper
Sex (male)	2.647	1.451	0.068	14.113	0.822	242.375
Hypertension	-0.569	1.484	0.702	0.566	0.031	10.374
Diabetes mellitus	-0.959	1.168	0.412	0.383	0.039	3.783
Dyslipidemia	2.169	0.872	0.013*	8.750	1.586	48.288
CKD	-0.455	1.105	0.681	0.635	0.073	5.537
Obesity	-4.116	2.122	0.052	0.016	0.000	1.044
Age	-0.071	0.072	0.324	0.932	0.810	1.072
Constant	0.539	0.476	0.257	1.714	-	-

*Significant

4 Discussion

Several international studies have been conducted to explore the prevention of CIN after cardiac catherization using alternative prophylactic therapies (13-22). However, only one local randomized trial was conducted to examine the relative efficacy of three preventive measures (excluding sodium bicarbonate) among patients undergoing coronary angiography (7). These studies were mostly based on an original study finding of Merten et al. (27), which demonstrated that water with sodium bicarbonate was more effective than normal saline in patients undergoing radiographic imaging procedures. Another previous trial by Mueller et al. (28) showed that normal saline is more effective in the prevention of CIN than half normal saline. However, despite the postulated theoretical benefits of sodium bicarbonate or normal saline in preventing or reducing CIN, a review of recent medical literature revealed that data on the effectiveness of sodium bicarbonate therapy in the prevention of CIN are inconclusive (3, 12). Moreover, on an international level, data concerning the incidence of and risk factors for CIN in numerous patients receiving CM are scarce, reporting wide variability in range, depending on various settings (ICU, CCU, in-hospital, etc.) and various populations' associated risk factors (2, 4-6). Given this background, the current study was conducted to investigate the effectiveness of sodium bicarbonate prophylaxis and the incidence of and risk factors for CIN in a Saudi sample of heterogeneous patients undergoing cardiac catheterization in our center.

Preliminary, with regard to CIN incidence, our cohort study involving 60 patients in the coronary care unit (for catheterization) and in the critical care area reported both an early and delayed total incidence of CIN at 24 and 48 hrs of 16.7 % and 15 %, respectively. In comparison to local data, these estimates were higher than those previously reported in two studies, both involving 243 (7.7 %) (7) and 1117 (4.9 %) (9) patients who were similar to the patients in the current population undergoing coronary angiography. However, our results were somewhat lower than the incidences reported in a similar large-scale Saudi setting (31.3 %) (8).

At the international level, our CIN estimate was comparable to incidence data reported in two American studies (range, 13.9-19 %) (14, 19). However, our CIN incidence was higher than those reported in Indian (2.4 %) (29)

and Iranian (10 %) studies (20). In contrast, it was lower than the incidences reported in some other Arabic populations (range, 22-29 %) (30, 31) of patients from the cardiology unit.

With regard to the absolute effectiveness of sodium bicarbonate (short-term protocol), our study revealed its inadequacy in protecting the kidney from CIN, with a high global incidence of 38 % among the high-risk group (based on renal indexes) of patients undergoing cardiac angiography. In agreement, previous randomized clinical trials (14, 20, 22), prospective (21), and retrospective (17) cohort studies that implemented similar bicarbonate prophylaxis guidelines, this study demonstrated significant incidence rates of CIN but with a variable range (5 % to 51.5 %). In contrast, a randomized study (13) revealed that the long-term sodium bicarbonate regimen (6 hrs before and after CM injection) was a more effective strategy to prevent CIN than the short regimen, which was employed in our cohort and all other studies.

Furthermore, the relative effectiveness of sodium bicarbonate compared to that of the normal saline regimen revealed much lower kidney protection, with significantly higher CIN incidence among current cohort patients who received sodium bicarbonate than among those who received normal saline hydration only (relative risk of 12.2 (95 % CI, 1.4-103.8; P=0.023)). Furthermore, closer inspection indicated further worsening of the kidney function parameters in the sodium bicarbonate intervention group compared to those in their counterparts in the saline treatment group. Similar to our study, previous trials demonstrated the nonsuperiority of sodium bicarbonate compared to standard hydration with normal saline in patients with moderate to severe CKD who were undergoing coronary angiography (14, 17, 18, 20-22). The previous trials included a prospective randomized trial comparing sodium bicarbonate to isotonic saline with NAC in patients undergoing coronary angiography with creatinine clearance (CrCl) <60 ml/min (18). In addition, one large-scale, retrospective cohort study organized at the Mayo Clinic revealed that the incidence of CIN increased with intravenous sodium bicarbonate administration (15). In contrast, a previous meta-analysis found a preventive effect of the use of sodium bicarbonate on the risk for CIN, but the statistical significance was borderline. Therefore, it was concluded that only a restricted endorsement can be made in support of the use of sodium bicarbonate, particularly in light of existing evidence of the relatively low quality of the individual studies, heterogeneity and possible publication bias (32). These findings were similar to another Iranian study that suggested that sodium bicarbonate may be the treatment of choice in the prevention of CIN in patients with volume overload and urgent procedures because of a smaller fluid volume and the reduced time requirement (one hour before procedure until six hours after) compared to normal saline (22).

As previously mentioned, the synergistic interaction of complex risk factors may enhance the development of CIN (2, 4-6). Interestingly, our study identified the risk factor for CIN incidence with the strongest predictive ability among the included patients to be hyperlipidemia, followed by male gender. However, a study in a similar Saudi population reported that high C-reactive protein (> 3 mg/dL), obesity (BMI > 30), age < 65 years, and CKD were independent risk factors for CIN (7). Two other retrospective, national Saudi cohorts reported that hypertension was the only independent predictor for CIN (8, 9).

In agreement with these results, an Indian study reported that hypertension is the only observed risk factor for CIN incidence (29). In several studies involving various Arabic (30, 31) or non-Arabic populations (14, 17, 21), the concomitance of hypertension was reported among other known comorbidities (diabetes, CRF, obesity, heart failure, and anemia) to be a significant determinant of CIN following angiography. In this study, we found minimal or no impact of these conditions on the incidence of CIN. This finding could be due to the adequate control and proper management of all these diseases before the performance of the CM procedure in this cohort. Additionally, few studies have demonstrated that abnormal baseline values of SCr (20, 30, 31) or eGFR (8, 19) are predictors of CIN. However, the findings in this study and many other trials (14, 17, 21, 22) did not support this similar prognostic impact. In fact, an Egyptian study reported that diabetic patients with normal baseline SCr were at an increased risk of developing CIN (31).

With regard to the gender-impact, in contrast to our results, studies in the USA (14, 19) and one study in Iraq (30) found that male gender was associated with a lower risk of CIN. Collectively, the discrepancies identified in the relevance of risk factors may be partially attributed to the small sample size, type of CM used, and genetic make-up of the cohort in this study.

4.1 Study limitations

Despite the novelty of the current study in reporting the first Saudi experience of sodium bicarbonate as a prophylactic therapy for CIN prior to CM implementation in angiography, some limitations should be illustrated. Perhaps the major limitation is that the findings obtained currently are from a single medical center. This could limit the extrapolation of the findings to all Saudi practices in this area. Second, the small sample size could have led to inaccurate (under- or over-) estimations of the incidence of CIN and the prevalence of predictive risk factors. However, the significant impact of dyslipidemia revealed in the current population has confirmed the scientific fact postulated recently that not all post-PCI AKI is directly linked to CIN; nonrenal and procedure-related factors (e.g., embolization of atheromatous cholesterol material from the aorta during catheter manipulation) that are independently associated with the development of AKI could be confounding factors in CIN epidemiological studies (2). Future collaboration in multicenter studies with more data on renal biopsies is mandatory to confirm the causal association between exposure to CM and the observed clinical outcome in our patients. This result may also explain the limited efficacy of sodium bicarbonate prophylactic therapy in the prevention of CIN. Third, this study implemented only one type of CM (iodixanol), which is mostly due its safety, but variable volumes were used. Further analysis of this factor may shed light on the national CM protocol. Additionally, future trials should be performed to evaluate the long regimen of bicarbonate supplementation to determine whether it would be a better and more efficient strategy to prevent CIN than the short regimen. While awaiting further studies to verify these solutions, in light of current data, it would be imperative to consider other potential preventive measures such as combination therapy (NAC) and withdrawal of nephrotoxic drugs prior CM.

Last, another possible limitation is that this study was performed during an in-hospital short-term observation period (only 48 hrs postprocedure). However, CIN was also reported to be associated with poor long-term outcomes, including the need for renal replacement therapy (RRT), a longer length of stay in the ICU, and a higher mortality rate (17).

5 Conclusions

The overall incidence of CIN of 16.7 %, with a much greater tendency to be observed in the sodium bicarbonate group (38%) in this cohort study, is considered very high compared to the incidence rates reported in previous national and international studies. Implementation of the short-term protocol of sodium bicarbonate therapy in our setting was not adequately effective for the prevention of CIN after angiography. In addition, in agreement with other prospective and retrospective studies, this study did not show any beneficial effect over standard normal saline hydration. This finding highlights the importance of re-evaluating further preventive measures that may be urgently initiated with strict protocols for the implementation of CM according to updated guidelines. Based on current data, the strongest independent predictive risk factor for CIN was hyperlipidemia, an additional confounding factor that could limit the efficacy of prophylaxis for CIN. Therefore, a large prospective randomized multicenter trial is needed to clarify whether preprocedural risk stratification based on this factor in addition to the type of preventive treatment and other known clinical risk factors may be a valuable means to identify patients early who are at high risk of CIN and to resolve other questions concerning CM type and volume. In conclusion, the impact of long-term sodium bicarbonate on the prevention of CIN has yet to be determined, and the decision to use sodium bicarbonate for the prevention of CIN should be made on an individual basis.

List of abbreviations

AKI: Acute kidney injury
BUN: Blood urea nitrogen
CIN: Contrast-induced nephropathy
CKD: Chronic kidney disease
CM: Contrast media
CrCl: Creatinine clearance
CT: Computed tomography
eGFR: Glomerular filtration rate
MDRD4 method: The Modification of Diet in Renal Disease 4-variables method

NAC: N-acetylcysteine
PCI: Percutaneous coronary intervention
RRT: Renal replacement therapy
SCr: Serum creatinine

Adherence to Ethical Standards

The local institutional research ethics committee approved the study protocol (HAP-01-R-082); however, obtainment of informed consent before inclusion was not required by the board because of the retrospective study design.

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Declarations of interest

No conflict of interest has been declared by the author.

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