Prevention of Contrast-induced Nephropathy in Patients with Chronic Kidney Disease Undergoing Elective Coronary Angioplasty or Angiography with Sodium Potassium Citrate Solution, a Double Blind Randomized Clinical Trial

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Introduction. Contrast-induced nephropathy (CIN) is a frequent complication of contrast exposure. A recent study suggested that Na/K citrate might have a preventive role. We investigated the efficacy of Na/K citrate to prevent CIN in patients with renal dysfunction undergoing coronary intervention.
Methods. The randomized, double–blind, placebo–controlled trial included 201 patients with estimated creatinine clearance < 90 mL/min, randomized to receive oral Na/K citrate plus saline infusion (treatment group, 104 patients) or oral water plus saline infusion (placebo group, 97 patients). CIN was defined as an absolute increase of serum creatinine ≥ 0.5 mg/dL or a relative increase ≥ 25% or a relative decrease of estimated GFR ≥ 25% within 5 days.
Results. CIN occurred in 22 patients (12.29%); 10 (11%) in treatment group and 12 (13.6%) in placebo group ($P > .05$). Post-exposure Cr values were not significantly different between the two groups (1.18 ± 0.28 mg/dL in the placebo vs. 1.15 ± 0.29 mg/dL in the treatment group, $P > .05$). CIN-negative patients in the treatment group showed a significantly higher increase in urine pH than that of CIN-positive patients (1.642 ± 0.577 vs. 1.20 ± 0.422, $P < .05$).
Conclusion. Na/K citrate solution is not effective for prophylaxis of CIN in patients with renal dysfunction. However, a probable preventive effect might exist in a subgroup of patients with at least 1.6 units increase in urine pH values following Na/K citrate administration.

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INTRODUCTION

Contrast-induced nephropathy (CIN) is an acute kidney injury (AKI) caused by parenteral administration of a contrast medium. It is one of the leading causes of AKI.[1-3] Up to 12% of patients with CIN may require dialysis and longer hospital stay and show persistent deterioration of kidney function, which then possibly progress toward end-stage renal disease (ESRD).[4-7] It is a significant health issue, as the number of contrast-medium-based procedures has been increased rapidly.[8] Two possible pathogenic mechanisms have been proposed for the development of CIN: firstly, contrast-induced renal vasoconstriction that leads

to medullary hypoxia and secondly, direct tubular injury.[9] Both of the proposed theories involve the reactive oxygen species (ROS)-mediated tissue injury.[10-12] Different protocols have been studied for the prevention of CIN,[13,14] including hydration with isotonic saline, antioxidant agents,[15-19] use of iso-osmolar contrast media[20,21] and several others.[22-26] The results have been controversial except for intravenous volume expansion with isotonic saline, which remains the only measure of undisputed efficacy to date.[8,13,14,27] Several studies have tested the CIN-preventive effect of sodium bicarbonate[28-33] and the results vary from very good results[28-31] to ineffectiveness or even toxicity.[32,33] Alkalinization of urine is the rationale for the use of bicarbonate as it has been shown that production of ROS are mainly potentiated in acidic medium and suppressed by alkaline pH.[34-36] It is assumed that bicarbonate is preventive only when sufficient urine alkalinization has been achieved.[28,37,38] Several recent meta-analyses have shown that the use of bicarbonates can significantly reduce the occurrence of CIN.[37-39] Na/K citrate is a well known urine alkalinizing agent.[40-42] Recently, one randomized study has shown a possible CIN-preventive effect of oral Na/K citrate in patients underwent coronary angiography.[36] The objective of the present study was to compare the efficacy of oral Na/K citrate plus isotonic saline versus isotonic saline for prevention of CIN in patients with chronic kidney disease (CKD) undergoing elective coronary angiography or angioplasty.

MATERIALS AND METHODS

Population and Study Protocol

From October 2014 to May 2015, 400 patients underwent planned coronary intervention in our medical center; 201 patients with pre-angiographic GFR less than 90 mL/min, based on MDRD formula, were selected. Exclusion criteria were: GFR less than 15 mL/min, AKI, exposure to contrast medium within the last 10 days, history of sensitivity to contrast media, pulmonary edema, multiple myeloma, history of 'diarrhea, vomiting, dehydration, bleeding', pregnancy, current use of NAC, theophylline, dopamine, fenoldopam, manitol, and NaHCO3, current consumption of nephrotoxic medications, clinically important electrolyte disturbances, and refusal to participate. Figure 1 illustrates the enrollment criteria and the trial flow. An external independent data-coordinating center monitored the study. Randomization was performed using blocked randomization with a block size of 4 and an allocation ratio of 1:1. Randomization sequences were computer generated at the coordinating center. Participants and investigators and outcome assessors, all were unaware of group assignment. The allocation process was concealed using sealed opaque envelopes that had been prepared in advance. All envelopes were sequentially numbered and locked in the data-coordinating center, and the investigator opened the envelope only at the time of patient's allocation. One hundred and four Patients assigned to the treatment group received the Na/K citrate solution (Uralyt U, Madaus granulat, Germany, with the formulation of hexakalium– hexanatrium–trihydrogen–pentacitrat), a dose of 7.5 g of granules diluted in 200 mL of water that was administrated before and after the angioplasty/graphy. Patients assigned to placebo group received 200 mL of water. Both drug and placebo are liquid and bottled in 200 cc black bottles and administered to patients by a nurse who was unaware of intervention assignment. All patients received 1 mL/kg/h 0.9% sodium chloride for 12-hour before and after the procedure. Echocardiographic assessment was performed in all participants on admission and hydration rate was reduced to 0.5 mL/kg/h for patients with LV ejection fraction less than 40% or New York Heart Association functional class (NYHA) III or IV. In all patients, iodixanol (Visipaque, GE Healthcare Ltd., Amersham, UK) an iso-osmolar contrast medium was used. Serum creatinine (Cr), blood urea nitrogen (BUN), sodium, potassium, albumin, hemoglobin, venous blood pH and urine pH were obtained for all patients at baseline. A well-trained laboratory technician, unaware of treatment assignment, measured urine pH by dipstick once before administration of oral solution and then 3-4 hours after consumption of the medication.

Sodium, potassium and blood pH were checked again. During the angiographic procedure, arterial blood samples were obtained from all patients for assessing acid-base status at the time of contrast exposure. The amount of the contrast medium administered during coronary intervention was measured for each patient. High-contrast load was defined as contrast agent volume ≥ 140 mL.[43]

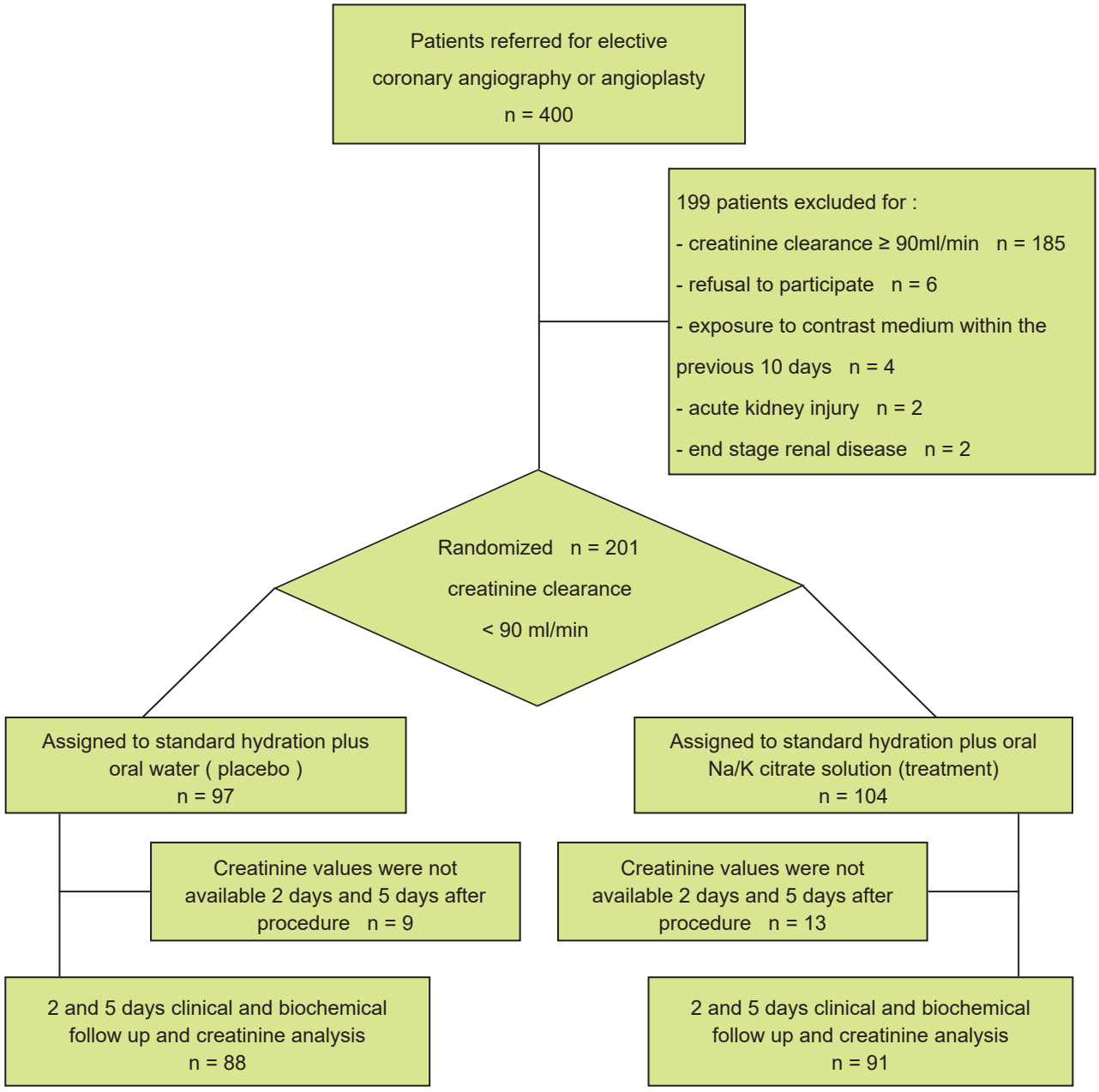

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) Diagram. CONSORT diagram depicting flow of study participants.

Three important time points were recorded for each patient: 1) The time of oral solution administration, 2) The time at which operation started, and 3) The time at which the operation ended. Based on these recorded times, two intervals calculated: 1) Solution administration time to initiation time interval, and 2) operation duration. Baseline procedural characteristics, including the procedure type and the involved coronary vessels name, were recorded for each patient. Serum creatinine and urea nitrogen was assessed again on the second and fifth day after the procedure. All laboratory tests were done in our hospital central lab with consistent methodology. The nephropathy risk score was calculated for all patients as specified by Mehran et al.[44] This was an independent investigator–initiated trial without any commercial interest. The ethics committee and the institutional review board of Ahvaz Jundishapur university of medical sciences (reference number AJUMS, REC.1393.260) approved the protocol and written informed consent obtained from all patients. This

trial complies with the Declaration of Helsinki. The trial was registered in Iranian Registry of Clinical Trials (Registration ID: IRCT2015050322065N1).

End Points of the Study and Definitions

The primary outcome measure of the study was CIN development, defined as an absolute increase of serum creatinine ≥ 0.5 mg/dL or a relative increase ≥ 25% or a relative decrease of estimated GFR ≥ 25% within 5 days after contrast exposure. If a significant crescendo pattern, but not to the point signifying CIN, of serum Cr values was observed in the first 5 days, a further re-measurement was performed according to the consultation with a team of three nephrologists and if Cr values reached the aforementioned cut-points the patients were tagged on late CIN and considered as primary endpoint. Other end points were: 1) Mean peak increase in serum Cr and BUN concentration within 2 and 5 days after contrast exposure; 2) Mean decrease in GFR values within 2 and 5 days after contrast exposure; and 3) Adverse clinical events, including in-hospital mortality, need for dialysis, acute pulmonary edema and need for re-admission due to CIN development.

Statistical Analysis

The sample size was calculated by assuming a significant reduction of the incidence of CIN from 20% in the control group to 5% in the Na/K citrate group.[36] The analysis showed that the required sample size was 95 participants in each group to achieve a reduction of 20% with an 80% power and statistical significance of .05. Data were presented as mean ± standard deviation (SD), median (range) or number (percentage). Univariate analysis including chi-square or Fisher exact test for dichotomous variables and t test or Mann-Whitney U test for Continuous variables was used. Multivariate statistics including Multivariate logistic regression analysis was performed to assess the preventive effect of Na/K citrate administration on CIN development by adjusting potential confounders. Analysis was intention to treat. All analyses were computed with SPSS statistical software, version 11.5.

RESULTS

Patient Population and Baseline Characteristics

We assessed 400 patients for eligibility and after exclusion of 199 patients, 201 patients were randomly assigned to the treatment (104 patients) and placebo group (97 patients). Twenty-two patients were excluded because the creatinine values were not available after procedure. So, 179 patients were included for final analysis, with 91 patients in the treatment group and 88 patients in

Table 1. Numerical Baseline Characteristics

Numerical Characteristics	Placebo	Treatment	Normal Distribution	*P*
Age, y	62.31 ± 9.43 (40-80)	61.95 ± 10.1 (31-85)	Yes	> .05*
SBP (mmHg)	128.24 ± 18.29 (90-180)	131 ± 18.68 (100-180)	No	> .05**
DBP (mmHg)	77.21 ± 10.78 (50-100)	78.77 ± 10.40 (50-100)	No	> .05**
LV ejection fraction (%)	46.02 ± 9.21 (20-60)	46.88 ± 7.28 (23-60)	No	> .05**
Basal Serum Creatinine (mg/dL)	1.24 ± 0.24 (0.7-1.9)	1.20 ± 0.2 (0.8-1.8)	No	> .05**
Basal Serum Urea Nitrogen (mg/dL)	20.52 ± 6.69 (11-45)	20.23 ± 6.73 (10-55)	No	> .05**
Basal GFR (mL/min)	53.96 ± 10.30 (30-83)	54.98 ± 10.93 (30-84)	Yes	> .05*
Contrast Volume Administered (mL)	136.03 ± 55.59 (50-300)	139.38 ± 66.12 (45-315)	No	> .05**
Hemoglobin (g/dL)	12.02 ± 1.50 (8.90-16.40)	12.60 ± 1.63 (8.50-17.10)	No	< .05**
Serum Albumin (g/dL)	4.40 ± 0.52 (2.90-5.30)	4.35 ± 0.55 (2.40-5.30)	No	> .05**
Basal Serum K (mEq/L)	4.25 ± 0.37 (3.50-5.20)	4.13 ± 0.40 (2.90-4.90)	No	> .05**
Basal Serum Na (mEq/L)	138.14 ± 3.06 (131-146)	136.05 ± 17.48 (130-150)	No	> .05**
Basal Urine pH	5.66 ± 0.66 (5-7)	5.34 ± 0.53 (5-7)	No	< .001**
Basal Venous Blood pH	7.38 ± 0.048 (7.21-7.46)	7.38 ± 0.064 (7.13-7.56)	Yes	> .05*
Meal to Start Time (min)	174.95 ± 67.32 (60-420)	203.71 ± 87.03 (60.00-420.00)	No	> .05**
Procedure Duration (min)	34.47 ± 28.98 (10-199)	37.81 ± 21.64 (10.00 ± 165.00)	No	< .05**

Data are presented as mean value ± SD (min-max).
*The values were compared using the Independent t test.
**The values were compared using the Mann-Whitney U test.
# *P* < .05.
SBP = systolic blood pressure; DBP = diastolic blood pressure; LV = left ventricular;
GFR = glomerular filtration rate based on MDRD equation.

the placebo group (Figure 1). All baseline numerical variables were evenly distributed between the 2 groups except for the hemoglobin (12.60 ± 1.63 mg/dL vs. 12.02 ± 1.50 mg/dL; $P < .05$), the procedure duration time (37.81 ± 21.64 min vs. 34.47 ± 28.98 min; $P < .05$) and the urine pH values (5.34 ± 0.53 vs. 5.66 ± 0.66; $P < .001$) that the two formers were higher and the latter was lower in the treatment group (Table 1). Patient with DM (47.1% vs. 30.9%; $P < .05$) and low EF% (9.6% vs. 19.6%; $P < .05$) were more frequent in the treatment and placebo groups, respectively; but other baseline categorical variables were similarly distributed between the 2 groups. In particular, patients with high contrast nephropathy risk score (i.e. ≥ 11), high NYHA functional class (i.e. III–IV) and high- contrast exposure were evenly distributed (Table 2). Contrast nephropathy risk scores were not significantly different between patients who were excluded from the final analysis due to lack of follow-up creatinine measurements.

Biochemical Follow-up

Na/K citrate significantly increased urine and venous blood pH in the treatment group. Mean Cr values were not significantly different in the 2 groups within 5 days. The same pattern was observed for BUN and eGFR values within 5 days (Table 3).

Contrast-induced Nephropathy (CIN)

The incidence of primary endpoint was 13.6% (12/88) in the placebo and 11% (10/91) in the treatment group ($P > .05$). By limiting the analysis to the first 48 hours, no significant trend favoring the treatment group was observed (5.5% vs. 9.1%, $P > .05$). Different definition of CIN would lead to different event rates but no significant trend favoring the treatment group was observed (Supplemental Table 1). By adjusting potential confounders, Multivariate logistic regression analysis failed to reveal any significant CIN -preventing role for Na/K citrate (odds ratio [OR] = 0.54, 95% confidence interval [CI] = 0.13 to 2.34; $P > .05$). According to our expectation, the incidence of CIN significantly increased in high-risk patients: 9.2% in low and moderate nephropathy risk scores versus 43.8% in high and very high risk scores ($P < 0.05$). The incidence of CIN in high-risk patients was shown in Table 4. By considering 6 as nephroprotective

Table 2. Categorical Baseline Characteristics

	Placebo	Treatment	*P*
Gender			
Female	45 (46.4%)	52 (50%)	> .05
Male	52 (53.6%)	52 (50%)	
Smoking			
Yes	28 (28.9%)	31 (29.8%)	> .05
No	69 (71.1%)	73 (70.2%)	
Diabetes Mellitus			
Negative	67 (69.1%)	55 (52.9%)	< .05
Positive	30 (30.9%)	49 (47.1%)	
Hypertension			
Negative	32 (33%)	38 (36.5%)	> .05
Positive	65 (67%)	66 (63.5%)	
Hyperlipidemia			
Negative	56 (57.7%)	48 (46.2%)	> .05
Positive	41 (42.3%)	56 (53.8%)	
Myocardial Infarction			
Negative	74 (76.3%)	76 (73.1%)	> .05
Positive	23 (23.7%)	28 (26.9%)	
Aspirin			
Negative	5 (5.2%)	2 (1.9%)	> .05
Positive	92 (94.8%)	102 (98.1%)	
ARB or ACEI			
Negative	19 (19.6%)	26 (25%)	> .05
Positive	78 (80.4%)	78 (75%)	
NYHA Functional Class III-IV			
Negative	61 (62.9%)	70 (67.3%)	> .05
Positive	36 (37.1%)	34 (32.7%)	
LV Ejection Fraction < 40%			
No	78 (80.4%)	94 (90.4%)	< .05
Yes	19 (19.6%)	10 (9.6%)	
Contrast Media Volume ≥ 140			
No	51 (52.6%)	56 (53.8%)	> .05
Yes	46 (47.4%)	48 (46.2%)	
Elective PCI			
No	22 (22.7%)	29 (27.9%)	> .05
Yes	75 (77.3%)	75 (72.1%)	
Mehran's Nephropathy Risk Score			
≤ 5	38 (39.2%)	43 (41.3%)	> .05
6-10	49 (50.5%)	53 (51%)	
11-16	9 (9.3%)	8 (7.7%)	
≥ 17	1 (1%)	0 (0%)	
Coronary Artery (s) Underwent PCI			
0	22 (22.7%)	29 (27.9%)	> .05
LADA	33 (34%)	38 (36.5%)	
LCX	13 (13.4%)	8 (7.7%)	
RCA	24 (24.7%)	18 (17.3%)	
LADA+LCX	2 (2.1%)	2 (1.9%)	
LADA+RCA	2 (2.1%)	7 (6.7%)	
LCX+RCA	1 (1%)	0 (0%)	
SVG	0 (0%)	2 (1.9%)	

Data are expressed as number (%) of patients. The values were compared using the
Chi-square or Fisher exact test. ACEI/ARB = angiotension-converting enzyme inhibitor/ angiotensin receptor blocker; NYHA = New York Heart Association; LV = left ventricular; PCI = percutaneous coronary intervention; LADA = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; SVG = saphenous vein graft.

Table 3. Biochemical Follow-up After Treatment

	Placebo	Treatment	Normal Distribution	*P*
Day 2 Serum Cr (mg/dL)	1.23 ± 0.35 (0.6-2.6)	1.15 ± 0.27 (0.5-2.11)	No	> .05**
Day 2 Serum Urea Nitrogen (mg/dL)	22.38 ± 12.07 (10-80)	20.86 ± 8.69 (5-60)	No	> .05**
Day 5 Serum Cr (mg/dL)	1.18 ± 0.28 (0.6-2)	1.15 ± 0.29 (0.64-21)	No	> .05**
Day 5 Serum Urea Nitrogen (mg/dL)	21.60 ± 10.28 (8-62)	20.84 ± 9.31 (5-62)	No	> .05**
Day 2 GFR (mL/min)	56.30 ± 15.30 (19-99)	59.36 ± 15.57 (23-116)	Yes	> .05*
Day 5 GFR (mL/min)	58.02 ± 14.87 (29-99)	60.24 ± 17.66 (26-118)	No	> .05**
Post-intervention Serum K (mEq/L)	4.16 ± 0.37 (3.20-5.20)	4.29 ± 0.47 (3-5.80)	No	> .05**
Post-intervention Serum Na (mEq/L)	138.78 ± 3.59 (128-148)	139.36 ± 3.05 (132-146)	No	> .05**
Post-intervention Urine pH	5.78 ± 0.72 (5-7)	6.90 ± 0.55 (6-8)	No	< .001**
Post-intervention Venous Blood pH	7.37 ± 0.059 (7.17-7.48)	7.40 ± 0.056 (7.23-7.53)	No	< .05**
Arterial pH During Angioplasty/graphy	7.43 ± 0.047 (7.29-7.53)	7.43 ± 0.07 (7.14-7.55)	No	> .05**
Delta Urine pH (pH2-pH1)	0.124 ± 0.462 (-1-2)	1.57 ± 0.57 (0-3)	No	< .001**
Delta Venous Blood pH (pH2-pH1)	-007 ± 0.056 (-0.21-0.10)	0.012 ± 0.049 (-0.15-0.09)	No	< .05**

Data are presented as mean value ± SD (min-max).
*The values were compared using the independent t test.
**The values were compared using the Mann-Whitney U test. GFR = glomerular filtration rate based on MDRD equation.

urine pH against CIN based on the previous study,[36] Fisher exact test failed to show any relationship between baseline or post-treatment urine ph and CIN development (Supplemental Table 2). Knowing the fact that there might be a variation in urine and blood alkalinization intensity in response to oral administration of an alkaline agent,[45] the urine and venous blood pH differences (ΔpH = post-treatment pH - baseline pH) were calculated for each patient and then the means were compared between CIN-positive and CIN-negative patients. CIN-negative patients in the treatment group showed a significantly higher increase in urine PH than their CIN-positive counterparts in the same group (1.64 ± 0.58 vs. 1.20 ± 0.42, $P < .05$) (Table 4).

Adverse Clinical Events

Two patients (2.27%) in the placebo vs. one (1.09%) in the treatment group ($P > .05$) were re-admitted due to CIN and none required dialysis. There was no other adverse event during and after the study period.

DISCUSSION

The results of this trial showed that, in patients with moderate-to-severe renal dysfunction who undergo planed coronary angiographic procedures, the CIN occurrence is not significantly different in those receiving isotonic saline compared with those receiving isotonic saline plus Oral Na/K citrate solution. Moreover, there was no CIN-preventive effect even in the high-risk patients (Table 4). However, there was a probable preventive effect in a subgroup of patients with at least 1.6 unit increase in urine pH after intervention (Table 4). The overall incidence of CIN in our study was 12.29%. The

Table 4. Relationship Between Contrast-induced Nephropathy Development and Urine or Venous Blood pH Changes Following Administration of Na/K Citrate

pH Changes Based on Intervention Type	Primary Endpoint	N	Mean ± SD	*P*
Placebo				
Delta urine pH	No	76	0.092 ± 0.467	> .05**
	Yes	12	0.25 ± 0.453	
Delta blood pH	No	47	-0.005 ± 0.040	> .05*
	Yes	10	0.012 ± 0.082	
Treatment				
Delta urine pH	No	81	1.642 ± 0.577	< .05**
	Yes	10	1.20 ± 0.422	
Delta blood pH	No	49	0.013 ± 0.051	> .05*
	Yes	7	0.016 ± 0.029	

*The values were compared using the independent t test.
**The values were compared using the Mann-Whitney U test.
Delta pH = pH2-pH1; N = Number of patients; SD = Standard deviation.

CIN risk score of 91% of the participants belong to Mehran's class I-II (44) so the expected CIN incidence rate should be somewhat between 7.5% -14% which is in accordance with our observation. The most frequent Mehran's class in Maioli et al. study was I-II and the reported CIN incidence rate was 10.8%.[8] The present study showed that different definitions of CIN would lead to different incidence rates (Supplemental Table1). In the REMEDIAL (Renal Insufficiency Following Contrast Media Administration Trial) trial the reported CIN incidence rate within 48 hours was 7.36%.[31] The Mehran's class II was the mode in their study and the unexpectedly low CIN incidence rate could be explained by knowing the fact that creatinine usually peaks 4 to 5 days after contrast exposure,[8,19,22,46] so assessing the CIN occurrence at 48 hours could account for the observed underestimation . If the assessment had been limited to the first 48 hours in our study, the CIN incidence rate would have decreased to 7.26%. The same pattern was reported by Maioli et al.[8] So, it's obvious that, studies limiting the CIN assessment to the first 48 hours have dramatically underestimated the CIN incidence rates.

There is no specific treatment for CIN, so prevention is the best strategy. Adequate hydration is the cornerstone of all preventive approaches.[13,14,27] Hydration with sodium bicarbonate has long been considered in the prevention of CIN. The rationale behind this intervention, is the fact that the ROS production is significantly less in an alkaline medium created by bicarbonate.[8,28,31,34-37,39,47,48] The results of previous trials assessing the CIN-preventive effect of sodium bicarbonate are heterogeneous. Some studies reported the efficacy[28-31] although some well-designed studies failed to show a significant preventive effect.[8,32] A recent meta-analysis showed that Sodium bicarbonate has CIN-preventing effect among CKD patients.[39] A possible explanation for this discrepancy was hypothesized by Meier that urine alkalinization was not achieved in all trials and no efficacy was observed in studies with inadequate alkalinization.[37] Hence, it might be the achieved alkaline urine pH and not the administration of bicarbonates per se, that determine the incidence rate of CIN. Our findings support this hypothesis because we observed that patients' urine pH unevenly increased in response to administration of an equal dose of Na/K citrate. This defines a heterogeneous response to a constant dose of Na/K citrate, ranging from the highest urine pH increase (2.21) to the least (0.78). Surprisingly, CIN-preventive effect was only seen in patients with at least 1.6 unit increase in post-treatment urine pH (Table 4). In Cohen et al. study, which evaluated the efficacy of oral sodium bicarbonate for urine alkalinization, only 75% of participants reached the urine pH target ($\geq$ 7.0) within 6 hours.[45] This study excellently demonstrated that mean urine pH is a function of time following multi-dose administration of an alkaline agent . If alkaline agents are used to prevent CIN, it is crucial to monitor urine pH to check whether enough urine alkalinization achieved or not. Unfortunately only few trials monitored urine pH following bicarbonate administration in order to prevent CIN.[29,31,49] In the present study, the urine pH of patients in the treatment group was significantly lower than the placebo group at baseline but this pattern changed significantly following the treatment. We did not find any CIN-preventive effect for blood pH in spite of a significant transient alkalemia in the treatment group (Table 4). To our best knowledge, no study has assessed the possible preventive effect of blood pH on CIN up to now.[29,31,47,49] Markota et al. reported a possible CIN-preventive effect for Na/K citrate in patients who undergo coronary intervention.[36] There are some reasons for the discrepancy between their results and ours: firstly; They didn't assessed CIN within 5 days, secondly; they didn't calculate nephropathy risk score, and finally; they did not report the patients' baseline urine pH status. They reported that the pre-procedure urine pH value of > 6 has a significant CIN-preventive effect. However, our results failed to show such a CIN-preventive effect (Supplemental Table 2). Markota et al. measured the urine pH 1 hour after treatment which is prone to substantial underestimating of the real urine pH response.[45] The present study was a randomized prospective double blind trial, performed under usual clinical practice conditions. The study groups were well balanced in terms of CIN risk factors and other baseline characteristics except for the hemoglobin, the procedure duration time, the baseline urine pH values, DM and low EF%. Therefore these confounders were adjusted by the multivariate logistic regression model. However, some limitations should be noted. First, the single-center design represents a limitation, and like any other single-center study, reproducibility

and generalizability of this report will require further validation by a double-blind, placebo-controlled, adequately powered, multicenter trial. Second, the primary endpoint was assessed by measuring eGFR; So, the use of more accurate methods for determination of the GFR would be crucial. Finally, most of the participants in the present study were Caucasian thus, our results might not be extrapolated to other ethnic groups. In conclusion, hydration with isotonic saline plus oral Na/K citrate solution before and after contrast medium exposure is not more effective than hydration with isotonic saline alone for prevention of CIN in patients with CKD. However, a probable preventive effect might exist in a subgroup of patients with at least 1.6 unit increase in urine pH following oral Na/K citrate administration.

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CONFLICT OF INTEREST

None to declare.

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