Prospective Randomized Trial of Na/K Citrate for the Prevention of Contrast-Induced Nephropathy in High-risk Patients

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Abstract

**Background:** Contrast-induced nephropathy (CIN) or contrast-induced acute kidney injury (CI-AKI) refers to an acute kidney injury (AKI) occurring after exposure to contrast media, commonly used in diagnostic procedures or therapeutic angiographic interventions. Recently, Na/K citrate, used for urine alkalinization, has been assessed for preventing CIN. This experiment evaluated Na/K citrate’s efficacy in preventing CIN in high-risk patients undergoing cardiac catheterization.

**Methods:** A prospective randomized clinical trial involved 400 patients with moderate- to high-risk factors for CIN undergoing elective percutaneous coronary intervention (PCI). They were randomly assigned to either the control or Na/K citrate groups. The Na/K citrate group (n = 200) received a 5 g Na/K citrate solution diluted in 200 mL water 2 hours before and 4 hours after the first administration, along with intravenous hydration for 2 hours before and 6 hours after the procedure. In contrast, the control group (n = 200) received only intravenous hydration. Serum creatinine (SCr) levels were measured before contrast exposure and 48 hours afterward. CIN was defined as a 25% increase in serum creatinine (SCr) or > 0.5 mg/dL 48 hours after contrast administration. The significance level was set at *P* < 0.05.

**Results:** CIN was observed in 33 patients (16.5%) in the control group and 6 patients (3%) in the Na/K citrate group. The incidence of CIN was found to have a significant difference between the 2 groups 48 hours after receiving the radiocontrast agent (P < 0.001).

**Conclusion:** Our results show that Na/K citrate is helpful and substantially reduces the incidence of CIN.

**Keywords:** Contrast media, Citrate, Percutaneous Coronary Intervention

**Introduction**

Contrast-induced acute kidney injury (CI-AKI) or contrast-induced nephropathy (CIN) is a recognized and severe complication associated with the administration of iodine contrast medium after radiological interventions or cardiac catheterization. In clinical studies, CIN is defined as a rise in serum creatinine concentration 44.2 µmol/L (0.5 mg/dL) or 25% more than the baseline 48 hours after contrast exposure in the absence of any other causative factor (1-3). The specific pathophysiological mechanisms of CIN are complicated and unknown. The CIN incidence has been reported as 2% in the general population without risk factors and 50% in patients with high risk, such as preexisting certain risk factors or chronic renal disorder (4, 5). The main risk factors for the development of CIN include diabetes mellitus, advanced age, urgent versus planned PCI, decreased renal perfusion, hypertension, contrast volume, hypotension, female sex, congestive heart failure, high-osmolar contrast, and chronic kidney...
disease (CKD) (5, 6). CIN is the third inducing reason for hospital-acquired AKI, responsible for >10% of total cases and associated with an increase in the risk of CKD development and dialysis, an increase in the cost of healthcare, and also elevated morbidity and mortality (7, 8). Thus, CIN remained a significant complication in the procedures and a challenge among cardiologists and radiologists.

Recently, studies have evaluated that the alkalinization of urine by bicarbonate could prevent CIN (9-11). Na/K citrate is a urine alkalinization medium that is assessed for effectiveness and CIN reduction (12).

We planned a second study to assess Na/K citrate’s effectiveness in preventing CIN in high-risk patients undergoing elective PCI based on the hypothesis that alkalinizing renal tubular fluid can be used to prevent CIN and the fact that, to date, few studies have examined its efficacy.

Methods

Study Protocol and Population

Ethics Committee of Qom University of Medical Sciences validated the study protocol (IRCT2015011618389N3). Written informed consent was collected from all participants before enrollment. The study was performed in line with the principles of the Declaration of Helsinki.

A nonblinded, prospective, randomized controlled study was performed at Shahid Beheshti Hospital, a referral center in Qom, Iran, between October 2016 and April 2021. All adult patients (>18 years) considered for PCI were examined for exclusion and inclusion criteria. Patients with at least 2 of the CIN risk factors and with at least moderate risk for CIN as described by the risk score of Mehran (13) (diabetes mellitus and hypertension recorded in their history), age >75 years, systolic heart failure (with ejection fraction <40%), renal impairment (glomerular filtration rate (eGFR) <60 mL/min/1.73m²; baseline serum creatinine >1.5 mg/dL) were included in the study. Patients having acute renal insufficiency, pulmonary edema, end-stage renal insufficiency (eGFR <15 mL/min), lactation and pregnancy, multiple myeloma, allergic reaction to contrast media or Na/K citrate, cardiogenic shock, exposure to contrast media 7 days before the experiment, renal impairment leading to dialysis, uremia, and receiving NAC, sodium bicarbonate, mannitol, dopamine, metformin, diuretics, theophylline, fenoldopam, and nephrotoxic medicines 48 hours before the experiment were excluded from the study.

We screened 456 consecutive patients scheduled for PCI (Figure 1). A total of 56 patients were excluded from the study—38 did not meet the inclusion criteria (determined by the cardiologist), and 18 declined to participate. At total of 400 patient candidates were randomly selected for either the control group (n = 200) or the Na/K citrate group (n = 200) using blocked randomization, with a block size of 4 and an allocation ratio of 1 to 1. An online computer-generated random numbers list was prepared based on the different combinations of blocks. Therefore, 6 different combinations, including AABB, ABAB, BBAA, BABA, ABBA, and BAAB, were used for the patient’s assignment. The combination sequence and the number of applications from each combination were determined based on throwing a dice. Patients in the Na/K citrate group (n = 200) had 5 g Na/K citrate solution diluted in 200 mL of water 2 hours before and 4 hours after the procedure and intravenous hydration (1 mL/kg/h) through normal saline, maximum 100 mL/h for 2 hours before and 6 hours after the procedure; however, the control group (n = 200) had twice 200 mL of water and intravenous hydra-

![Figure 1. Study design](http://mjiri.iums.ac.ir)
tion via the same method. We measured urine PH 1 hour before the first dose and 1 hour after the second dose of receiving Na/K citrate. Serum creatinine (SCr) was estimated before contrast exposure and after 48 hours.

In the overall population, various parameters were examined. The glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault formula for men, adjusting for women by multiplying the result by 0.85: (140 – age) × weight (kg) / (SCr × 72). Kidney performance was categorized based on eGFR values according to the phases outlined by the United States National Kidney Foundation: normal kidney function (GFR ≥90 mL/min without proteinuria), mild kidney injury (GFR 60–89 mL/min with evidence of kidney injury), moderate injury (GFR 30–59 mL/min), intense injury (GFR 15–29 mL/min), and kidney impairment (diabetes, GFR <15 mL/min/1.73m²). All tests were conducted using the same method in the same laboratory. PCIs were administered through the femoral artery, utilizing the low-osmolar nonionic contrast agent iohexol (Omnipaque; GE Healthcare), with a dose of approximately 205 mL in each group. Echocardiographic assessments were conducted using the same method in the same laboratory. Of all patients were performed before exposure.

**Study Endpoints**

The primary endpoint of the experiment was CIN progression, characterized by an elevation in SCr by either 44.2 µmol/L (0.5 mg/dL) or 25% above the baseline 48 hours after contrast agent application, without any other identifiable cause. The secondary outcomes included changes in eGFR and SCr 48 hours after exposure to the contrast agent.

**Statistical Analysis**

A minimum acceptable difference mean of 6.5, 80% power, a confidence interval of 95%, and standard deviations (SD) of 22.93 and 23.05 were used to calculate the sample sizes for the 2 groups. Each group’s minimum required sample size was estimated to be 196, and a total of 400 people were considered (12).

The categorical data were presented as percentages and numbers, while the continuous data were displayed as means ± SD. Comparing constant parameters were analyzed using the student’s t test and paired t test for values distributed normally or the Wilcoxon rank sum test and the Mann-Whitney U test for values distributed non-normally. The chi-square or Fisher’s exact test was used to compute the categorical parameters if the frequency expected was <5. Treatment effects between the 2 groups were compared using the 1-way Analysis of Covariance (ANCOVA), adjusting for baseline values and confounding factors. The significance level was determined by 2-tailed P < 0.05.

**Results**

The baseline characteristics of the patients are provided in Table 1. No meaningful difference was observed between the experimental groups in age, sex, body mass index, hemoglobin, hematocrit, diabetes mellitus, hyperlipidemia, smoking, LVEF, eGFR, and dose of contrast agent.

Before contrast exposure and 48 hours after that, the variations in eGFR and SCr were compared between the groups (Tables 2 and 3). The median concentration of SCr significantly rose from 1.11 mg/dL to 1.13 mg/dL 48 hours after postradiocontrast exposure in the Na/K citrate group (P = 0.006). The median concentration of SCr in the control participants rose meaningfully from 1.08 mg/dL to 1.20 mg/dL 48 hours after the application of radioccontrast (P < 0.001).

In the Na/K citrate group, the median eGFR declined, not significantly—from 72.68 mL/min/1.73 m² to 70.84 mL/min/1.73 m² 48 hours after radioccontrast screening (P = 0.010). The median eGFR declined significantly from 80.32 mL/min/1.73m² to 73.1 mL/min/1.73m² 48 hours after administration of radioccontrast in the control group (P < 0.001).

CIN was observed in 33 (16.5%) patients in the control group and 6 (3%) in the Na/K citrate group. A significant variation was observed regarding CIN between the groups 48 hours after administration of radioccontrast (P < 0.001) (Figure 2).

![Table 1. Baseline clinical and procedural characteristics of the patients](http://mjiri.iums.ac.ir)
Na/K Citrate for the Prevention of CIN

Table 2. Biochemical and renal function changes before and 48 hours after contrast medium exposure

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline</th>
<th>48 h After Exposure</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>Na/K citrate Group</td>
<td>1.11 ± 0.20</td>
<td>1.13 ± 0.18</td>
</tr>
<tr>
<td></td>
<td>Control Group</td>
<td>1.08 ± 0.21</td>
<td>1.20 ± 0.23</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m2)</td>
<td>Na/K citrate Group</td>
<td>72.68 ± 21.44</td>
<td>70.84 ± 19.82</td>
</tr>
<tr>
<td></td>
<td>Control Group</td>
<td>80.32 ± 23.93</td>
<td>73.10 ± 21.5</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD; *Within-group comparisons were assessed using Paired t-test for normally distributed values and the Wilcoxon rank sum test for non-normally distributed values; eGFR = estimated glomerular filtration rate

Table 3. Results of ANCOVA adjusting for Baseline values of dependent variable

<table>
<thead>
<tr>
<th>Group</th>
<th>MD</th>
<th>SE</th>
<th>CI 95% for MD</th>
<th>Effect size</th>
<th>Power</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (Na/K citrate Vs. control)</td>
<td>-0.057</td>
<td>0.043</td>
<td>-0.055 - 0.101</td>
<td>0.254</td>
<td>0.694</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>eGFR (Na/K citrate Vs. control)</td>
<td>2.254</td>
<td>1.682</td>
<td>0.782 - 0.860</td>
<td>0.206</td>
<td>0.813</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

MD: mean differences after intervention between two groups; SE: Standard error of mean
P-value*: Obtained from ANCOVA after adjusting for baseline values of dependent variables

Figure 2. Incidence of contrast-induced nephropathy is significantly lower in the Na/K citrate group (n=200) compared to the control group (n=200)

Discussion

The efficiency of Na/K citrate in preventing CIN was examined. To our knowledge, our prospective trial showed for the second time that Na/K citrate prophylactic administration significantly reduced the incidence of CIN in individuals with a higher risk of developing CIN. Several investigations have studied the inhibitory influences of urine alkalinization on CIN (6, 9-12, 14). Our findings are in agreement and corroborate the recent meta-analysis by Zhang B et al who concluded that alkalinization of urine is beneficial for preventing CIN in those with preexisting renal failure (10). In a similar study by Markota D et al, 100 patients who underwent coronary angiography received Na/K citrate solution, 5 g granules diluted in 200 mL water, before coronary angiography. The CIN incidence 48 hours after contrast exposure was meaningfully lower in the citrate group compared with the controls (12). This was in line with our study that urine alkalinization by Na/K citrate may decrease the incidence of CIN in those undergoing cardiac catheterization. In a prospective, randomized trial by Klima T et al, 169 patients with renal dysfunction (eGFR <60 mL/min) who underwent intravascular contrast exposure received sodium bicarbonate intravenously orally before and after the procedure. Our findings contradicted this study, suggesting that alkalinizing renal tubular fluid did not reduce the CIN incidence in patients with renal impairment treated with intravascular radiographic contrast procedures (14). Different pharmacologic and therapeutic interventions are used to reduce the CIN incidence involving diuretics, calcium antagonists, statins, N-acetyl cysteine (NAC), nicorandil, fenoldopam, ascorbic acid, adenosine antagonists, thophylline, pentoxifylline, atrial natriuretic peptide, allopurinol, and other alternative substances (7, 8, 15-18). NAC has garnered significant scholarly attention, leading to numerous trials and meta-analyses to assess its effectiveness in preventing CIN. However, the findings regarding NAC have been contradictory, and the optimal therapeutic approaches remain uncertain (7, 19, 20). Procedures approved to counteract CIN include periprocedural intravenous hydration, using low-osmolar and/or iso-osmolar contrast agents instead of high-osmolar agents, and restricting the contrast media dose (21, 22). Iohexol—a nonionic low-osmolar contrast agent—was employed to decrease adverse effects and occurrence of CIN.

While the exact pathophysiology of CIN remains unknown, previous studies have suggested the potential involvement of direct nephrotoxic effects of contrast agents, oxidative stress, hemodynamic changes, immune / inflammatory responses, and apoptosis in its pathogenesis. McCullough et al demonstrated that high osmolality from contrast agents plays a significant role in cell apoptosis (23). Moreover, the duration of contrast agents’ impact on kidney cells is crucial in CIN development. Romano et al found that the dose and duration of contrast agents increased renal cell apoptosis through stress kinase activation (24). After intravascular injection of contrast media, renal cells undergo various changes, including rapid and transient vasodilatation followed by vasoconstriction, resulting in increased renal vascular resistance and decreased renal blood flow (24-27). These hemodynamic changes induced by contrast agents may be attributed to the synthesis and release of renal vasoactive substances. Simultaneously, contrast agents’ toxicity in vascular endothelial cells leads to an increase in endothelin and adenosine and a decrease in NO and prostaglandins (27, 28).

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When the balance between these opposing forces shifts towards vasoconstriction, medullary ischemia and a reduction in GFR occur in the kidney (25, 26). Moreover, increasing the viscosity of tubular and vascular cells plays a role in CIN pathogenesis. Intravenous administration of contrast agents may raise blood viscosity and osmolality, decreasing renal blood flow and increasing the risk of AKI-associated microembolism (25, 29, 30). Contrast agents also contribute to acute kidney injury, partly through inflammation. A recent study by Kwasa et al investigated a cohort of 423 patients undergoing contrast-enhanced computed tomography scans without identified CIN risk factors. Comparing 215 patients with high CRP and 208 with normal CRP, the study revealed that previous inflammation elevated the risk of developing CIN (25, 31). Oxidative stress is a pivotal factor in all these mechanisms. Hypoxia, induced by reduced oxidative phosphorylation, enhances free radical production in mitochondria (32). Reactive oxygen species can trigger renal cell apoptosis through stress kinase activation and intrinsic pathways involving c-Jun N-terminal kinases, p38 MAPK, and caspases (33, 34). The potential bicarbonate mechanism for preventing CIN consists in inhibiting the generation of free oxygen radicals in an acidic medium induced by contrast media, preventing renal injury. Bicarbonates also neutralize the action of peroxynitrite, a potent oxidant produced in the kidney's medulla due to nitric oxide reaction, thus protecting the kidney from injury (12, 14).

Limitations
The present study had several limitations. The creatinine clearance was calculated using the Cockcroft–Gault formula, rather than a direct calculation. However, a greater double-masked, multicenter, and randomized experiment involving other clinical situations is needed to approve the valuable impacts of Na/K citrate on hindering CIN.

Conclusion
This study suggests that the use of Na/K citrate significantly reduced CIN in comparison to the protocol of hydration in patients with a high risk for CIN progression of. Thus, utilizing Na/K citrate may prevent CIN; nevertheless, more controlled clinical experiments are required to eliminate doubts concerning the proportional efficiency of Na/K citrate in preventing CIN.

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Ethical Approval
IRCT2015011618389N3.

Conflict of Interests
The authors declare that they have no competing interests.

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