Prevention of contrast-induced nephropathy with Na/K citrate

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Aims

Contrast-induced nephropathy (CIN) is a frequent complication of many radiological procedures involving the application of contrast media. It represents a significant health problem that causes the increase in mortality, morbidity, and medical costs. For the prevention of CIN, a number of methods have been proposed to be effective. Among them, alkalinization of urine takes an important place. Although the Na/K citrate is a well-known agent for urine alkalinization, it has not been studied in the prevention of CIN.

Methods and results

Two hundred and two patients who underwent coronary angiography were included in the study. They were randomized into groups receiving the drug Na/K citrate per os and to the control group. Serum creatinine and glomerular filtration rate were determined in all patients immediately before coronary angiography, and 48 h after the procedure. CIN criteria were a creatinine increase of >25%, reduction in the glomerular filtration rate by >25%, or an increase in serum creatinine of >44 μmol/L. The incidence of CIN in the group receiving Na/K citrate was significantly lower when compared with the control group (4% compared with 20%, P = 0.0001). Patients who had a urine pH <6 had a more than ten-fold higher incidence of contrast nephropathy compared with patients whose urine pH was >6.

Conclusion

Alkalinization of urine using the Na/K citrate may reduce the incidence of CIN.

Keywords

Contrast-induced nephropathy • Alkalinization • Urine • Citrate

Introduction

Contrast-induced nephropathy (CIN) is an iatrogenous kidney injury caused by i.v. or intra-arterial administration of a contrast medium. It represents one of the leading causes of acute renal insufficiency.1,2 In the USA and Europe, it causes 10% of acquired intra-hospital cases of acute renal insufficiency.3 Its frequency varies and depends on the type and amount of a contrast medium and the characteristics of the patients receiving contrast. The frequency of CIN ranges from 2% in the low-risk patients to 50% in the high-risk patients.4–6 The most important risk factors for CIN development are pre-existing renal insufficiency, diabetes, age, volume, and type of a contrast medium. Today contrast nephropathy represents a significant health issue. It causes longer hospital stays and increases healthcare expenses, mortality, and morbidity.7–12

Potential pathogenetic mechanisms are:

• a direct toxic action of a contrast medium on kidney tubule cells that causes a disruption of mitochondrial function, creation of free radicals, damage, and programmed cell death.13,14
• vasoconstriction as a response to radiocontrast reducing the blood flow through the renal medulla causing ischaemia and consequent cell damage.15,16

The treatment of CIN is exclusively supportive and the prevention of this complication is very important. Different approaches have been tested in the prevention of CIN with more or less success. Hyperhydration is widely accepted as the best method of preventing contrast nephropathy and today it is the only one generally accepted.17

The use of NAC (N-acetyl cysteine), recommended in the past, is not suggested by recent meta-analyses.18 Haemodialysis and...
Prevention of contrast-induced nephropathy

haemofiltration may be efficient, in the prevention of CIN, but are reserved for the high-risk patients. Attempts to prevent CIN with various substances, such as furosemide, vitamin C, statins, and numerous other strategies, have been largely unsuccessful. The result of studies on bicarbonate in the prevention of CIN have not been uniform and vary from very good results to inefficiency or even toxicity. The supposed mechanisms of action of NaHCO₃ in the prevention of CIN have been ascribed to:

1. Alkalinization of urine
   Free radicals are mainly created in acid medium and suppressed by alkaline pH. Therefore.

2. Neutralization of peroxynitrite
   Vasocostriction caused by the administration of contrast mediums causes ischaemia. Superoxide is created and reacts to NO in a kidney’s medulla, so-called peroxynitrite is formed and it is a very strong oxidant. NaHCO₃ neutralizes the action of peroxynitrite and this also represents one of possible mechanisms to prevent CIN by using bicarbonates.

Even though there are pathophysiological foundations for positive effects of NaHCO₃, the studies have shown its variable efficiency in the prevention of CIN. Favourable results of the prevention protocols when using bicarbonates have been noted in the studies that have also noted significant alkalinization of urine, but a similar protocol was not efficient in the study when the dose of bicarbonate was insufficient to alkalinize the urine. It is supposed that NaHCO₃ is preventive only in patients in whom sufficient alkalinization has been reached; supposedly urine pH is one of the important factors in the prevention of CIN. New meta-analyses support the use of bicarbonates in the prevention of this complication.

K/Na citrate is well known as a urine alkalinization medium. It is mainly administered to patients with kidney stones (cystine, uric acid, and calcium stones) which require alkalinization.

So far, no studies have evaluated the efficacy of citrates for the prevention of CIN.

Taking into the account that alkalinization of urine may be a strategy to prevent CIN we decided to test the hypothesis that alkalinization of urine, using Na/K citrate, reduces the frequency of contrast nephropathy in patients after coronary angiography. We undertook a randomized trial administering Na/K citrate for the prevention of CIN in the population of patients undergoing coronary angiography.

Methods

The research was fully carried out in the Clinic of Internal Medicine of University Clinical Hospital Mostar, Department of Invasive Cardiology, with the support of the Laboratory of University Clinical Hospital Mostar.

We tried to calculate the appropriate sample size to achieve a significant reduction of the incidence of CIN from 20% in the control group to 5% in the Na/K citrate group. The analysis using the χ² test showed that the required sample size was 200 patients, comprising the two groups, to achieve a reduction of 20% with α = 0.05.

The protocol of this study was approved by the Ethics Committee of University Clinical Hospital Mostar, and written informed consent was obtained from all patients. The study complies with the Declaration of Helsinki.

All adult (>18 years) patients scheduled for coronary angiography were screened for inclusion and exclusion criteria.

Patients were excluded for any of the following reasons: end-stage renal insufficiency (eGFR <15 mL/min), acute renal insufficiency. A history of reaction to contrast media, use of potentially nephrotoxic medicines (48 h before and 24 h after the procedure), pulmonary oedema, multiple myeloma, factors predisposing to kidney injury (diarrhoea, vomiting, dehydration, bleeding, etc.), exposure to contrast media within 7 days before the procedure, pregnancy, non-compliance and use of NAC, teofiline, dopamine, fenoldopam, manitol, and NaHCO₃ within 48 h before coronary angiography. The patients were randomized into two groups:

- **Group 1:** group taking Na/K citrate
- **Group 2:** control group

**Study protocol**

After enrolment, patients were randomized either to the Na/K citrate group or to the control group. We used a blocked randomization, a block size of 4, and an allocation ratio of 1:1 (Urbaniai, G. C., & Plous, S. 2011). Research Randomizer (Version 3.0).

As for all the patients, we determined urine pH an hour before coronary angiography. Patients randomized to the citrate group received the Na/K citrate solution (Uralyt U, Madaus granulat, Germany) (hexakaliumpentacitrat), a dose of 5 g of granules diluted in 200 mL of water.

We again measured urine pH immediately before coronary angiography, i.e. 1 h after the administration of the medicine. Four hours after the administration of the first dose, the patients took another dose of the same medicine with standard hydration. Patients randomized to placebo received twice 200 mL of water instead of Na/K with standard hydration. Both patients and investigators were unaware of treatment assignment, but patients and examiners could have become aware of the difference between colour and taste of the hydration solution.

All patients with an eGFR <60 mL/min/1.73 m² were hydrated with i.v. normal saline at a rate of 1 mL/kg/h for 2 h before and 12 h after coronary angiography. Patients with an eGFR ≥60 mL/min/1.73 m² were hydrated with oral hydration, i.e. at least 2000 mL of water starting 2 h before coronary angiography. The rate of infusion was reduced in patients who developed signs of pulmonary congestion. All additional infusions were strongly discouraged and initiated only if indicated for other reasons. Additional oral fluid intake was encouraged in all groups.

Demographic data, current medication, and medical history were recorded at baseline. Serum creatinine was measured before initiating the pre-procedural hydration. Urine samples were obtained to analyse the specific weight and pH of the urine. Two days after coronary angiography, serum creatinine was analysed again, using autoanalyzer Olympus AU640, Laboratory of University Clinical Hospital Mostar (average % bias 2.55 ± 2.1). We measured urine pH immediately after taking the samples, using the automatic pH indicator (SCHOTT instruments, Lab. 850). We calculated eGFR according to the MDRD formula: (186.3 × serum creatinine – 1.154) × (years – 0.203) × (0.742 for women), and the Cockroft–Gault formula: CCr (mL/min) = [(140 – age) × weight (kg)]/[(Serum Cr (mg/dL) × 72) × 0.85 if female.

In the study, we used iopamiro 370; Iopamidoil (P Bracco) contrast medium. The amount of the contrast medium administered during coronary angiography was precisely measured for each patient (mL).
The primary endpoint of the study was development of CIN, defined as a >25% increase in serum creatinine concentration, and/or a >25% decrease in eGFR and/or a >44 μmol/L absolute increase in serum creatinine from baseline within 48 h after contrast exposure. The secondary endpoint was the mean peak increase in serum creatinine concentration within 48 h after contrast exposure.

### Statistical analysis

During statistical processing we applied the normalization test to assess if the value of some variable was significantly different from the normal Gauss distribution. For the assessment as to the significance of the differences between the two groups, we used the t-test (for continuous variables) or Fisher’s exact test (for categorical variables). Data are expressed as mean (SD), and all tests are two-tailed, with differences reported as significant if $P < 0.05$. We used the correlation test for the association of the variables of urine pH and the creatinine increase after the administration of a contrast medium. For statistical data processing, we used standard statistical programme package Graphpad Prism 4.

### Results

We screened 278 consecutive patients scheduled to undergo coronary angiography. Out of the 278, a total of 232 patients were randomized to receive K/Na citrate + hydration or hydration alone. A total of 202 patients completed the study. Thirty patients were excluded from the study because of the incomplete data; urine pH not properly measured before the procedure ($n = 12$ patients); creatinine values 48 h after the procedure not available ($n = 18$ patients); volume of the contrast medium administered not documented ($n = 3$ patients).

Baseline clinical characteristics were similar between the two groups, except for the serum albumin values (Table 1).

The basal values of serum creatinine were somewhat higher in the test group compared with the control group, but the difference was not statistically significant ($P = 0.1275$). Two days after coronary angiography there was a significantly higher increase in serum creatinine in the control group compared with the test group ($P = 0.0004$), and a statistically significant decrease in the eGFR in the control group compared with the test group ($P = 0.0078$) (Table 2).

The incidence of CIN was significantly lower in the test group (K/Na citrate) compared with the control group of the patients ($P = 0.0001$) (Figure 1).

Twenty-one patients (out of 102) in the control group, and only four patients (out of 100) in the citrate group had CIN.

The average urine pH immediately before coronary angiography in the CIN patients was $5.54 \pm 0.47$ ($n = 25$). The average urine pH before coronary angiography in the non-CIN patients was $5.89 \pm 0.1$ ($n = 177$) ($P = 0.0009$).

Immediately before coronary angiography, urine pH values in the control group were $5.86 \pm 0.626$. Immediately before coronary angiography (an hour after the administration of the Na/K citrate), urine pH values in the test group were significantly higher $6.93 \pm 0.455; (P < 0.0001)$.

By analysing both groups of the patients, we noticed a significant correlation between urine pH immediately before coronary angiography and the increase (change) of creatinine 48 h after the

<table>
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<tr>
<th>Table 1</th>
<th>Baseline characteristics</th>
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<tbody>
<tr>
<td>Variable</td>
<td>Control group, $n = 102$</td>
</tr>
<tr>
<td>Age (years ± SD)</td>
<td>62.13 ± 10.1</td>
</tr>
<tr>
<td>Sex (male/female, %)</td>
<td>63/37</td>
</tr>
<tr>
<td>Body mass index (kg/m² ± SD)</td>
<td>27.32 ± 2.48</td>
</tr>
<tr>
<td>Smoking (yes, %)</td>
<td>54</td>
</tr>
<tr>
<td>SBP (mmHg ± SD)</td>
<td>141.1 ± 21.49</td>
</tr>
<tr>
<td>DBP (mmHg ± SD)</td>
<td>84.78 ± 11.63</td>
</tr>
<tr>
<td>Haemoglobin (g/L ± SD)</td>
<td>138.2 ± 12.10</td>
</tr>
<tr>
<td>Serum albumin (g/L ± SD)</td>
<td>40.57 ± 2.35</td>
</tr>
<tr>
<td>Baseline SCr (μmol/L ± SD)</td>
<td>89.35 ± 23.97</td>
</tr>
<tr>
<td>eGFR (MDRD) (mL/min ± SD)</td>
<td>75.7 ± 18.3</td>
</tr>
<tr>
<td>eGFR &lt; 60 mL/min (%)</td>
<td>22.5</td>
</tr>
<tr>
<td>eGFR (Cockroft–Gault)</td>
<td>88.74 ± 22.93</td>
</tr>
<tr>
<td>Diabetes mellitus (yes, %)</td>
<td>45/55</td>
</tr>
<tr>
<td>CM volume (mL ± SD)</td>
<td>231.2 ± 95.85</td>
</tr>
<tr>
<td>Diuresis first day (mL ± SD)</td>
<td>1887 ± 671</td>
</tr>
<tr>
<td>Diuresis second day (mL ± SD)</td>
<td>1768 ± 634</td>
</tr>
<tr>
<td>Cardiac catheterizations (%)</td>
<td>33</td>
</tr>
<tr>
<td>PCI (%)</td>
<td>40</td>
</tr>
<tr>
<td>PCI in STEMI (%)</td>
<td>27</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; SCr, serum creatinine; CM, contrast media; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; SD, standard deviation.

### Table 2 | The increase in creatinine and the decrease in glomerular filtration 2 days after coronary angiography are significantly higher in the control group compared with the citrate group |

<table>
<thead>
<tr>
<th>Variable</th>
<th>Citrate group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine baseline (μmol/L)</td>
<td>93.96 ± 18.39</td>
<td>89.35 ± 23.97</td>
</tr>
<tr>
<td>Serum creatinine after 48 h (μmol/L)</td>
<td>95.23 ± 21.55</td>
<td>98.63 ± 27.88</td>
</tr>
<tr>
<td>Absolute change (μmol/L)</td>
<td>1.470 ± 13.55</td>
<td>9.451 ± 17.43*</td>
</tr>
<tr>
<td>Relative change (%)</td>
<td>2.07%</td>
<td>10.7%*</td>
</tr>
<tr>
<td>eGFR—baseline (mL/min/1.73 m²)</td>
<td>71.1 ± 16.2</td>
<td>75.7 ± 18.3</td>
</tr>
<tr>
<td>eGFR—after 48 h (mL/min/1.73 m²)</td>
<td>70.79 ± 17.28</td>
<td>68.62 ± 19.09</td>
</tr>
<tr>
<td>Absolute change (mL/min/1.73 m²)</td>
<td>−0.055 ± 14.34</td>
<td>−8.828 ± 15.2*</td>
</tr>
<tr>
<td>Relative change (%)</td>
<td>&lt;1%</td>
<td>11%*</td>
</tr>
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* $t$-test; $P < 0.05$.
Discussion

CIN is one of the leading causes of acute kidney injury, and accounts for 10% of acquired intra-hospital cases of acute kidney injury. The frequency of CIN ranges from 2% in the low-risk patients to 50% in the high-risk patients. There is no specific treatment for established CIN and prevention is the best strategy. Adequate hydration is the basis of all preventive strategies. Attempts of preventing acute kidney injury with various substances such as NAC, vitamin C, statins, furosemide and numerous other strategies have shown controversial results. The use of bicarbonates has long been considered in the prevention of CIN. The pathophysiological rationale for the use of bicarbonates is that alkalinization of urine reduces the frequency of CIN. It is of interest that in one recent study of chronic renal disease as well as progression of chronic kidney disease, alkalinization by oral administration of bicarbonates slowed down progression of chronic kidney disease.

Urine alkalinization can also be achieved using citrates, but they have not been studied in the prevention of CIN so far. K/Na citrate is safe and well-tolerated medium used for alkalinization of urine. It is mainly administered to patients with kidney stones who require alkalinization to achieve urine pH above which no contrast nephropathy occurred was a pH of 7. In contrast, our data show that the limit is even somewhat

Table 3 Incidence of contrast-induced nephropathy depending on urine pH immediately before coronary angiography

<table>
<thead>
<tr>
<th>Urine pH</th>
<th>CIN (yes/total)</th>
<th>P-value</th>
</tr>
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<tr>
<td>&lt; 6.0</td>
<td>22/67 (32.8%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>&gt; 6.0</td>
<td>3/135 (2.2%)</td>
<td></td>
</tr>
</tbody>
</table>

CIN, contrast-induced nephropathy.

or no monitoring of urine pH. The aforementioned data suggest that it is the achieved urine pH and not the use of bicarbonates itself that determine the occurrence or its absence of CIN.

The study by Assadi showed that the use of acetazolamide which alkalinizes the urine reduces the frequency of CIN. It is of interest that in one recent study of chronic renal disease as well as progression of chronic kidney disease, alkalinization by oral administration of bicarbonates slowed down progression of chronic kidney disease.

As expected in our study the K/Na citrate increased urine pH by 1 unit on average compared with the basal values.

The results of the present studies documented a clear correlation between contrast nephropathy and the urine pH measured before coronary angiography. In patients with a lower urine pH, a greater increase in creatinine was noticed 48 h after coronary angiography compared with the patients with higher urine pH. The study by Assadi et al. showed that the critical urine pH value above which no contrast nephropathy occurred was a pH of 7. In contrast, our data show that the limit is even somewhat

Figure 1 Incidence of contrast-induced nephropathy is significantly lower in the Na/K citrate group (n = 100) compared with the control group (n = 102) (Fisher’s exact test, P = 0.0004). Values are expressed as a percentage of CIN (CIN – developed/total number of the patients in the group).

Figure 2 Serum creatinine change 2 days after coronary angiography significantly correlates with pre-procedural urine pH (Pearson test r = −0.3482, Cl: −0.4640 to −0.2207, P < 0.0001, r² = 0.1212). SCr, serum creatinine (µmol/L) (urine pH < 6.0, n = 67; urine pH > 6.0, n = 135).
lower, i.e., a urine pH of 6. It is also possible that such different results were influenced by the fact that Assadi investigated children and that we measured urine pH only 1 h after citrate administration. In our study, when urine pH was > 6 before coronary angiography, the frequency of CIN was 10 times lower compared with the patients with a baseline urine pH < 6. Such correlation supports the hypothesis that a low urine pH is a risk factor predisposing to the development of contrast nephropathy.

The patients in the control group had a significant increase in serum creatinine and decrease in the eGFR after administration of the contrast medium compared with the group of patients administered citrate. In addition, CIN occurred significantly less frequently after the administration of citrate (4%) compared with the control group (20%).

Undoubtedly, adequate hydration, accurate indication of contrast medium, and volume of administered contrast medium remain the basis of CIN prevention. In addition, however, the results of our study document that oral administration of citrates is an efficient, simple, and economical strategy to prevent CIN.

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Conflict of interest: none declared.

References


