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Sodium Bicarbonate Prevents Contrast-Induced Nephropathy in Addition to Theophylline

A Randomized Controlled Trial

Wolfgang Huber, MD, Toni Huber, MD, Stephan Baum, PharmD, Michael Franzen, MD, Christian Schmidt, MD, Thomas Stadlbauer, MD, Analena Beitz, MD, Roland M. Schmid, MD, and Sebastian Schmid, MD

Abstract: In this study, we investigated whether hydration with sodium bicarbonate is superior to hydration with saline in addition to theophylline (both groups) in the prophylaxis of contrast-induced nephropathy (CIN). It was a prospective, randomized, double-blinded study in a university hospital on 2 general intensive care units (63% of investigations) and normal wards.

After approval of the local ethics committee and informed consent 152 patients with screening serum creatinine ≥ 1.1 mg/dL and/or at least 1 additional risk factor for CIN undergoing intravascular contrast media (CM) exposure were randomized to receive a total of 9 mL/kg bicarbonate 154 mmol/L (group B; $n = 74$) or saline 0.9% (group S; $n = 78$) hydration within 7 h in addition to intravenous application of 200 mg theophylline. Serum creatinine was determined immediately before, 24 and 48 h after CM exposure. As primary endpoint we investigated the incidence of CIN (increase of serum creatinine ≥ 0.5 mg/dL and/or $\geq 25\%$ within 48 h of CM).

Both groups were comparable regarding baseline characteristics. Incidence of CIN was significantly less frequent with bicarbonate compared to sodium hydration (1/74 [1.4%] vs 7/78 [9.0%]; $P = 0.035$). Time course of serum creatinine was more favorable in group B with decreases in serum creatinine after 24 h (-0.084 mg/dL [95% confidence interval: -0.035 to -0.133 mg/dL]; $P = 0.008$) and 48 h (-0.093 mg/dL [-0.025 to -0.161 mg/dL]; $P = 0.007$) compared to baseline which were not observed in group S.

In patients at increased risk of CIN receiving prophylactic theophylline, hydration with sodium bicarbonate reduces contrast-induced renal impairment compared to hydration with saline.

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From the II. Medizinische Klinik und Poliklinik (WH, AB, RMS), Klinik für Anaesthesiologie (SS), Klinik und Poliklinik für Vaskuläre und Endovaskuläre Chirurgie (TS) and Krankenhausapotheke (SB), Klinikum rechts der Isar der Technischen Universität München; München; Caritas-Krankenhaus St. Josef, Klinik für Urologie, Regensburg (TH); Kliniken des Landkreises Neumarkt i.d.OPf., Medizinische Klinik I, Neumarkt in der Oberpfalz (CS), Germany; and Universitätsklinik für Innere Medizin I, Landeskrankenhaus, Salzburg (MF), Austria.

Correspondence: Sebastian Schmid, Klinik für Anaesthesiologie, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Straße 22, 81675 München, Germany (e-mail: seb.schmid@tum.de).

WH and TH have equally contributed to this work.

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Abbreviations: CIN = contrast-induced nephropathy, CM = contrast media, ICU = intensive care unit.

INTRODUCTION

Contrast-induced nephropathy (CIN) is the 3rd most frequent cause of hospital-acquired acute renal failure.^{1–9} The most recent studies define CIN as an increase of serum creatinine of at least 0.5 mg/dL and/or 25% within 48 h of contrast media (CM) application. CIN according to this definition is associated with prolonged hospitalization and increased mortality.^{7–15} The incidence of CIN is associated to a number of risk factors such as pre-existing renal impairment, old age, diabetes, nephrotoxic drugs, and high amount of contrast-medium. In high-risk groups, the incidence of CIN is up to 50%. A recent overview on prophylactic strategies reported a total of 1901 cases of CIN among 16,461 patients (11.5%).¹⁶

Besides extracorporeal CM elimination including dialysis and continuous venovenous hemofiltration, there are numerous pharmacological approaches including hydration with crystalloids or sodium bicarbonate, antioxidants such as N-acetylcysteine or ascorbic acid, statins, and vasodilators including endothelin antagonists and fenoldopam.^{17,18} Due to its antagonism of adenosine-mediated renal vasoconstriction also theophylline can be classified as a selective renal vasodilator. We analyzed published studies regarding the effectiveness of prophylactic strategies: theophylline had the lowest relative risk (RR 0.48, 95% confidence interval (CI): 0.26–0.89) compared with controls, N-acetylcysteine (RR 0.65, 95% CI: 0.48–0.88), statins (RR 0.51, 95% CI: 0.34–0.77), and sodium bicarbonate (RR 0.62, 95% CI: 0.45–0.86) while furosemide significantly increased the risk of CIN (RR 3.27, 95% CI: 1.48–7.26).

Because the above-mentioned prophylactic approaches have different modes of action, their combination might further reduce the risk of CIN. However, combined prophylactic strategies were rarely investigated due to the large number of patients required to compare 2 or 3 groups to placebo, or to detect small differences in effect sizes when comparing 2 prophylactic agents without a placebo group.

Furthermore, with increasing evidence for prophylactic effects of several agents comparisons to placebo can be questioned from an ethical viewpoint.

Therefore, there is no definite ranking of the preventive strategies. The strongest recommendation to date is to use any hydration regimen and to avoid nephrotoxic agents.

Regarding a strong pathophysiological rationale, its practicability and the strongest risk reduction reported in recent overviews and meta-analyses, theophylline might be a

reasonable choice for pharmacological prophylaxis. Of the different types of hydration especially bicarbonate infusion with its ability to reduce oxygen consumption and therefore interfering with a different aspect of pathophysiology seems the ideal combination for theophylline.

Therefore, it was the aim of our prospective randomized trial to investigate the effect of hydration with sodium bicarbonate compared with saline in addition to theophylline prophylaxis which all patients received.

METHODS

Study Design

This was a single-center, randomized, double-blinded trial. The study was approved by the local ethics committee (Ethikkommission der Fakultät für Medizin der Technischen Universität München, project-number 1446/05, approved on December 21, 2005) and was registered at the registration site of the US National Institute of Health (clinicaltrials.gov; Identifier: NCT02643602; principal investigator: Huber Wolfgang; date of registration: December 30, 2015).

Informed consent was obtained from the patients or their representatives. In case of an emergency examination concerning intensive care unit (ICU) patients without legal-representatives available, the inclusion was at the discretion of the treating physician.

Study Population

The study took place in 4 different departments at a university hospital between 2006 and 2012. We included 196 patients with an age of at least 18 years and with an increased risk for CIN undergoing administration of CM. High risk was defined by a serum creatinine level ≥ 1.1 or ≥ 0.8 mg/dL plus an additional risk factor like diabetes mellitus, renal failure in past medical history, or nephrotoxic medication (aminoglycoside, vancomycin, amphotericin B, and diuretic). Exclusion criteria were pre-existing renal replacement therapy, unstable serum creatinine levels (difference of more than ± 0.4 mg/dL within 3 days before contrast application), contraindications for theophylline or sodium bicarbonate (allergies, tachycardia, alkalosis, and hypokalemia) and additional interventions that might influence renal function. We included patients in the ICU and on normal ward in our study.

Randomization

The patients were randomized in 1 of 2 groups for prophylaxis of CIN: Group B received bicarbonate whereas the control group S received sodium chloride infusion. Both groups received 200 mg theophylline.

The setting of the study was double-blinded. An independent institution provided the computer-generated randomization list (block-randomization in blocks of 10 patients; Institut für Medizinische Statistik und Epidemiologie, Ismaninger Str. 22, 81675 Munich, Germany).

In order to maintain blinding of the treating physician and the patient, 2 lots of infusion bottles were produced in the clinical pharmacy (1 with sodium chloride and 1 with bicarbonate) and labeled according to the legal regulations for clinical trials. Each bottle was printed with a consecutive number according to the randomization list. Both sodium bicarbonate and saline are clear and colorless fluids, thus indistinguishable for the attending staff and patient.

In group B, the study medication consisted of 0.154-M sodium bicarbonate, whereas in group S it contained sodium chloride 0.9%. Every patient received 3 mL/kg bodyweight (maximum 330 mL) of the study medication over 1 h before contrast exposure. Additionally, 200 mg theophylline were administered in both groups as a short infusion half an hour before the diagnostic procedure. After contrast application every patient was hydrated with another 1 mL/kg bodyweight per hour (maximum 110 mL/h) of the study medication for 6 h.

Primary Endpoint

As primary endpoint we determined the incidence of CIN as a raise in serum creatinine of $\geq 25\%$ or ≥ 0.5 mg/dL within 48 h after contrast application. Serum creatinine levels were determined before, 24 and 48 h after CM.

Secondary Endpoints

Secondary endpoints were serum creatinine levels over time and creatinine clearance. Furthermore, we investigated the change in pH, bicarbonate- and sodium-concentration in blood and urine. Urine was analyzed before, 6, 24, and 48 h after application of CM. We reviewed the patients' medical record for treatment with dialysis within 30 days after contrast application.

Statistical Analysis

Considering data of previous studies, we assumed an incidence of CIN of 10% in group S and 1.25% in group B. With a statistical power of 80% and an error probability of 5% we calculated a sample size of 108 patients per group (University of California; Department of Biostatistics) resulting in a total number of 13 patients with CIN. After 210 patients reported for eligibility and inclusion of 196 patients, a total number of 157 complete datasets comprising the total observation period of 48 h were available. Of the 39 cases excluded from the final analysis, 17 patients could not be included due to postponing of the diagnostic procedure or nonapplication of CM. Eleven patients died or were discharged before the end of the observation period. In total, we identified 13 cases with an increased serum creatinine of 0.5 mg/dL and or 25%.

Regarding a prolonged recruitment period, the number of patients reported for eligibility being in line with the total sample size and the overall cases of CIN being exactly the number predicted, the ethics committee approved our request to stop further recruitment and un-blind the group allocation.

Before de-blinding each of these 13 patients was analyzed using a checklist whether the criteria for CIN were fulfilled. Patients with other possible reasons for a raise in creatinine levels such as sepsis were excluded. Out of these 13 cases, 8 fulfilled the predefined criteria of CIN. This resulted in a final number of 152 un-blinded datasets including 8 cases with CIN (Figure 1). Our final analysis was restricted to patients with complete datasets. Therefore, we did not include 17 patients who did not receive CM, as these patients were not at risk for developing CIN. Five ICU patients underwent CM procedures in a critical state and died within 48 h after the CM procedure most probably due to the severe underlying disease. Therefore, these patients were not included in the final analysis. Furthermore, in 6 patients, the final determination of serum creatinine after 48 h was not available due to early discharge. Consequently, these patients were considered as dropouts for the primary endpoint analysis. To preclude a bias we performed a secondary analysis including 4 of these patients based on the available data which included at least the 24 h serum creatinine value.

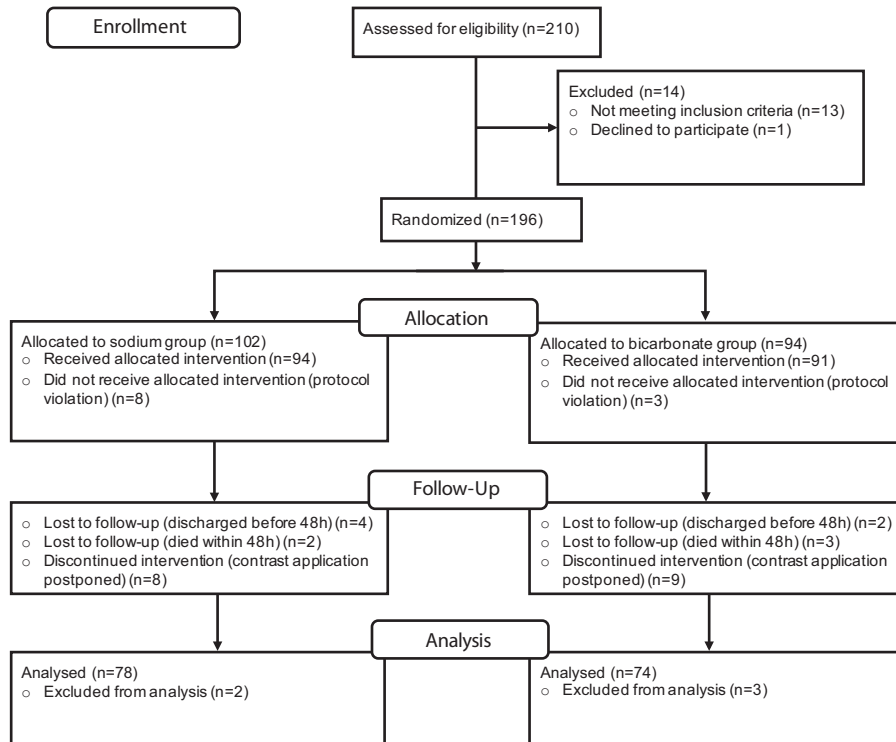


FIGURE 1. CONSORT flow diagram.

The statistical analysis was performed using IBM SPSS (Version 23.0; IBM, New York, NY). Dichotomous values were compared using chi-squared test. Difference in quantitative parameters was analyzed with Mann–Whitney *U* test for unpaired and Wilcoxon test for paired parameters. Results were considered as statistically significant with an error probability below 5%.

RESULTS

Patient Characteristics

Baseline characteristics showed no difference between the 2 groups regarding preinterventional serum creatinine or creatinine clearance, Mehran or Cigarroa risk score, or premedical condition. The amount of CM administered was comparable between the 2 groups (Table 1). The majority of patients (125/152, 82%) received a CT scan. Other procedures included coronary angiography (11/152; 7%), transjugular portosystemic shunts (9/152; 6%), and other angiographies (7/152; 5%). Patients received either Imeron 300, 350, or 400 (Bracco Imaging Deutschland GmbH, Konstanz, Germany) according to the radiologists' preference but the distribution between the 2 groups was comparable. Out of 152 patients, 96 (63%) underwent the contrast procedure during an ICU stay. The other patients were on normal ward.

Primary Endpoint

Incidence of CIN

Overall, the incidence of CIN was low with 8 out of 152 patients (5.3%). CIN was significantly less frequent in the bicarbonate group (1 out of 74 patients; 1.4%) compared with

the saline group (7 out of 78 patients; 9.0%; $P = 0.035$; Figure 2). This results in an absolute risk reduction of 7.6% and an RR reduction of 84% in group B. A secondary analysis confirms these findings, revealing an incidence of 1/75 (1.3%) in group B compared with 7/81 (8.6%; $P = 0.039$) in group S.

Secondary Endpoints

Time Course of Serum Creatinine

Furthermore, there was a significant decrease of serum creatinine in group B at 24 h (-0.084 mg/dL [95% CI: -0.035 to -0.133 mg/dL]; $P = 0.008$) and 48 h (-0.093 mg/dL [-0.025 to -0.161 mg/dL]; $P = 0.007$) after CM application (Figure 3). By contrast, serum creatinine levels did not change after 24 h (-0.021 mg/dL [0.026 to -0.068 mg/dL]; $P = 0.15$) and 48 h (-0.049 mg/dL [0.024 to -0.122 mg/dL]; $P = 0.082$) compared to baseline in group S.

Maximum Changes in Serum Creatinine Within 48 h

The difference of the maximum serum creatinine value within 48 h and the baseline serum creatinine (Δ creatinine_{max} – creatinine_{baseline}) was significantly higher (0.036 ± 0.25 mg/dL) in group S compared with group B (-0.034 ± 0.27 mg/dL; $P = 0.035$) (Additional file 1 SDC Figure 1, <http://links.lww.com/MD/A986>).

Effects of Bicarbonate Hydration Therapy

Hydration with bicarbonate resulted in a significant increase of serum bicarbonate levels after 6 h (1.1 mmol/L [95% CI: -0.2 to 2.3 mmol/L], $P = 0.001$), 24 h (1.1 mmol/L [-0.2 to 2.3 mmol/L], $P < 0.001$), and 48 h (1.1 mmol/L [-0.3 to 2.4 mmol/L]; $P = 0.008$; Additional file 2 SDC Figure 2, <http://>

TABLE 1. Baseline Characteristics and Risk Factors for Contrast-Induced Nephropathy

	Sodium Group (n = 78)	Bicarbonate Group (n = 74)	P Value
Age	66.1 ± 13.3	64.4 ± 15.7	0.543
Male	52 (66.7%)	44 (59.5%)	0.357
Patients on intensive care unit	51 (65.4%)	45 (60.8%)	0.559
Mechanical ventilation	18/51 (36.0%)	21/45 (45.7%)	0.356
TISS-28 score	16.5 ± 5.9	16.8 ± 6.6	0.857
SAPS II score	34.0 ± 9.9	34.9 ± 14.2	0.944
Body weight, kg	79.8 ± 19.3	76.8 ± 15.8	0.334
Baseline creatinine, mg/dL	1.38 ± 0.65	1.25 ± 0.69	0.151
Screening creatinine, mg/dL	1.38 ± 0.72	1.28 ± 0.72	0.100
Creatinine clearance, mL/min per 1.73 m ²	63.2 ± 33.1	73.3 ± 44.2	0.273
Sodium, mmol/L	138.0 ± 7.9	139.0 ± 7.2	0.114
Potassium, mmol/L	3.90 ± 0.45	3.90 ± 0.49	0.534
BUN, mg/dL	37.01 ± 21.58	32.05 ± 19.66	0.103
Total amount of contrast media, mL	113 ± 70	102 ± 58	0.208
Intra-arterial amount of contrast, mL	17 ± 67	19 ± 65	0.719
Number of CT scans	62 (79.5%)	63 (85.1%)	0.362
Cigarroa score	2.1 ± 2.1	1.7 ± 1.4	0.145
Mehran score	8.8 ± 3.4	8.7 ± 3.8	0.477
Diabetes	21 (26.9%)	20 (27.0%)	0.988
Hypertension	47 (60.3%)	40 (54.1%)	0.440
History of renal disease	29 (37.2%)	26 (35.1%)	0.793
SIRS	22 (28.2%)	20 (27.0%)	0.871
Multiorgan failure	18 (23.1%)	14 (18.9%)	0.530
Catecholamines	23 (29.5%)	19 (25.7%)	0.599
Diuretics	44 (56.4%)	43 (58.1%)	0.833
Vancomycin	20 (25.6%)	10 (13.5%)	0.060
≥1 Nephrotoxic medication	61 (78.2%)	53 (71.6%)	0.349

Categorical variables are given as number and percentage, continuous variables as mean ± standard deviation.

BUN = blood urea nitrogen, CT = computed tomography, SAPS = Simplified Acute Physiology Score, SIRS = septic inflammatory response syndrome, TISS = Therapeutic Intervention Scoring System.

links.lww.com/MD/A986). By contrast, serum bicarbonate levels did not change in group S.

Furthermore, hydration with sodium bicarbonate resulted in significant alkalinization of blood pH levels (30 min: 0.029 [95% CI 0.016–0.042]; $P = 0.002$; 6 h: 0.038 [0.059–0.017]; $P < 0.001$; 24 h: 0.038 [0.052–0.023]; $P < 0.001$), which was not observed in group S (Figure 4).

Mean serum potassium did not change significantly after administration of bicarbonate in group B. Since mean values within the normal range do not preclude single values markedly outside the range, we also investigated the incidence of serum potassium values below 3.0 mmol/L which was found in only 2 patients (2.6 and 2.8 mmol/L). Hypokalemia in these patients was not symptomatic and was reversible within 6 h by potassium substitution.

Furthermore, serum sodium in group S was significantly higher compared with baseline after 48 h (1.9 mmol/L [95% CI 0.9–2.9 mmol/L], $P = 0.003$), which was not observed in group B (0.05 mmol/L [–1.0 to 1.1 mmol/L], $P = 0.69$).

No severe side effects of theophylline were observed, in particular no tachycardia requiring pharmacological intervention was observed.

Need for Dialysis

The retrospective analysis of the patients' medical record revealed dialysis therapy in 17% of the patients in group S compared with 9% in group B within 30 days after contrast

application. Although not statistically significant ($P = 0.189$) there is an absolute risk reduction of 8% and an RR reduction of 47%.

DISCUSSION

CIN is associated with prolonged hospital stay and mortality. Data on prophylactic efficacy of different prophylactic strategies are conflicting and there is a lack of data investigating potential synergistic effects of prophylactic measures. Therefore, we investigated the effects of sodium bicarbonate prophylaxis in addition to theophylline prophylaxis in 152 patients.

In patients at increased risk of CIN receiving prophylactic theophylline, we found that additional hydration with sodium bicarbonate reduces contrast-induced renal impairment compared to hydration with saline.

Theophylline and sodium bicarbonate interact with different mechanisms in the pathophysiology of CIN. Theophylline inhibits renal vasoconstriction thus increasing renal oxygen supply. Buffering with bicarbonate lowers renal oxygen consumption and reduces the amount of free oxygen radicals. The administration of theophylline in combination with bicarbonate hydration reduces the risk of CIN.

Mismatch of oxygen demand and oxygen supply is responsible for organ failure in different pathophysiological conditions. Especially in the setting of sepsis it is the main reason for multiorgan failure and increased mortality.¹⁹ Besides

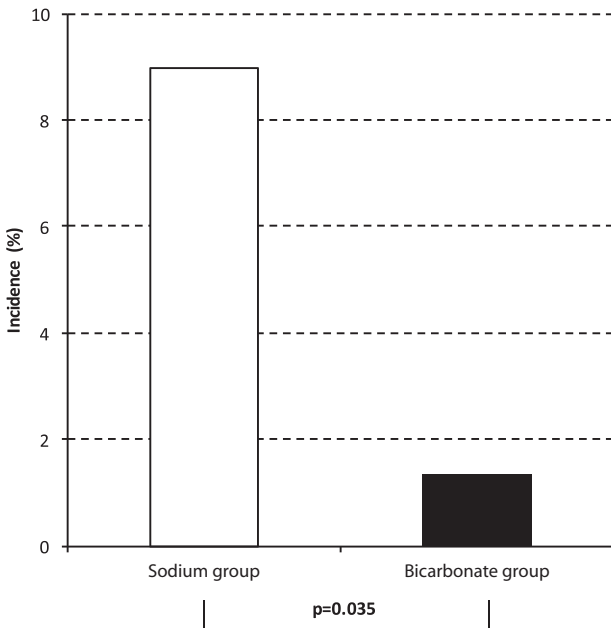


FIGURE 2. Incidence of contrast-induced nephropathy.

direct cytotoxic effects of CM and an imbalance of fluid state it is also the key factor in the development of CIN.^{20–22} Adenosine mediated vasoconstriction results in decreased renal plasma flow.²³

Improvement of oxygen supply is one of the key concepts in reducing mortality and the rate of complications in septic patients.²⁴ Therefore, there is a rationale to prevent adenosine-induced vasoconstriction in patients at risk for developing CIN. In total, at least 15 clinical trials and the most recent meta-analyses demonstrated a reduction of contrast-induced renal impairment by prophylactic administration of theophylline, an adenosine antagonist.^{7,16,25,26}

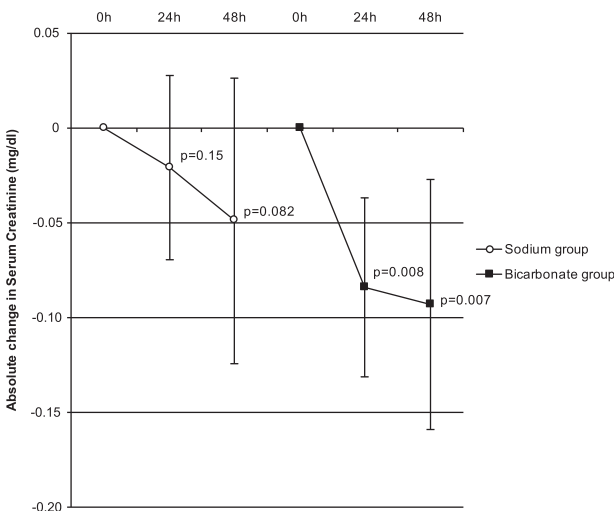


FIGURE 3. Time course of serum creatinine presented as absolute change and 95% confidence intervals. P values indicate difference to 0h value.

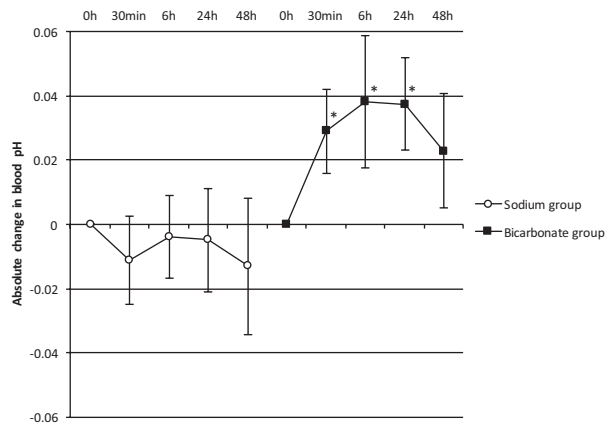


FIGURE 4. Time course of blood pH presented as absolute change and 95% confidence intervals. *Significant ($P < 0.013$) difference to 0h value.

For ethical reasons, we did not include a control group without the administration of theophylline. The incidence of CIN in group S (9.0%) is in line with the incidence of CIN in patients who received theophylline in the recent meta-analysis of Dai et al⁷ (7.9%). Therefore, the prophylactic effect of adenosine antagonism in our study seems similar to the effect published in literature. As we did not see any side effects, the administration of theophylline is safe even in critical ill patients.

With only 1 of 74 patients (1.4%) developing CIN the incidence in group B is even lower. The combination of the two prophylactic regimes is superior to prophylaxis with theophylline only. Hydration with bicarbonate for prophylaxis of CIN has been investigated in more than 20 clinical trials with heterogeneous but mostly positive effects.^{16,27} A recent meta-analysis focusing on patients with renal impairment was able to show a benefit for bicarbonate.¹⁵ The positive effects of bicarbonate hydration have also been reported in the prevention of postoperative renal failure in major vascular and cardiothoracic surgery.^{28,29}

Prophylaxis with bicarbonate is based on two major principles. First, buffering with bicarbonate helps maintain a neutral pH and therefore reduces oxygen consumption of the kidneys.³⁰ Second, increasing tubular pH decreases the generation of free radicals that are responsible for CIN.^{30,31} The positive effect on blood pH and serum bicarbonate levels is evident in our study. Administration of bicarbonate is safe as we did not see severe hypokalemia or hypernatremia in our patients.

In contrast to the positive effect of bicarbonate on blood pH, hydration with sodium chloride has been associated with impaired renal function caused by hyperchloremic metabolic acidosis.^{32,33} Although we did not observe decreased blood pH levels in group S, this could be another reason for the increased incidence of CIN in the patients hydrated with sodium chloride.

Besides hydration with bicarbonate and application of theophylline, a number of different prophylactic regimes have been investigated in the context of CIN. N-acetylcysteine has been evaluated in different meta-analyses that lead to incongruent results. To date, there is no recommendation for its use in the prophylaxis of CIN.³⁴ In most studies, N-acetylcysteine was administered orally at least 24 h before CM. Its use seemed not sensible in our patients as we intended to cover emergency procedures as well as critically ill patients on the ICU.

Statins in the prophylaxis of CIN are highly recommended by several large meta-analysis that have been published within the last years.³⁵ Dosage and time of administration vary, but especially in older studies, the statin was administered between 6 and 12 h before CM. Again this is not suitable for patients undergoing an emergency procedure. However, some newer trials facilitate the administration of high-dose statin directly before the examination with positive results.³⁶ This regime in combination with bicarbonate and theophylline could be a promising way to further reduce the incidence of CIN and should be investigated in randomized trials.

A possible bias is the lack of a control group without any hydration or theophylline therapy. When planning the study, we considered it as problematic from an ethical viewpoint to withhold these potent prophylactic regimes from the study participants at increased risk of CIN. Therefore compared with other studies investigating CIN in ICU patients, our overall incidence is low.³⁷ Furthermore the difference between the 2 groups regarding stronger endpoints like need for dialysis was not statistically significant but showed only a trend favoring hydration with bicarbonate. We determined the incidence of CIN using a common definition (raise in serum creatinine of $\geq 25\%$ and/or ≥ 0.5 mg/dL), that has been validated in many studies. Among a plethora of CIN definitions—also including general definitions of acute renal impairment such as RIFLE, AKIN, and KDIGO—this definition was chosen for several reasons.

First, patients fulfilling these criteria have a higher incidence of major adverse cardiovascular events and increased mortality.^{12,14} Second, to make the data of this study comparable to previous and future trials on prevention of CIN, we chose the most frequently used definition of CIN. For example, among the 20 studies on bicarbonate prophylaxis meta-analyzed by Zhang et al, 13 used an increase in serum creatinine of 0.5 mg/dL or 25% as CIN definition. Another 6 trials used definitions included in the combined definition used in this trial.¹⁵

Another limitation of our study is the absence of biomarkers other than serum creatinine in order to detect CIN. Cystatin C, neutrophil gelatinase-associated lipocalin, or those combined in the NephroCheck[®] could have been used to detect renal failure at an earlier stage and/or with a higher sensitivity.^{38–40} Early detection carries the potential for intensified monitoring and earlier treatment aimed at limitation of the renal damage. However, analyzing serum creatinine is cheap and readily available even in smaller hospitals. It is still the cornerstone in the most recent definitions of acute kidney impairment such as AKIN and KDIGO.^{41,42}

As our study was designed as an exploratory single-center trial, the number of patients is limited, and the initially calculated sample size was not reached in the final analysis. This is predominantly related to a higher dropout rate than expected (see Figure 1). Therefore, the data need validation in a larger multicenter confirmatory trial.

It might be considered as strength of our study that 63% of the patients were critically ill and treated in the ICU, since ICU patients are generally underrepresented in the investigation of CIN.

In conclusion, patients at increased risk of CIN receiving prophylactic theophylline, hydration with sodium bicarbonate reduces contrast-induced renal impairment compared to hydration with saline.

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