

“CONTRAST” STUDY: COMPARISON OF NEPHROPROTECTIVE THREE PROTOCOLS: ACETYLCYSTEINE-SODIUM BICARBONATE-THEOPHYLLINE, TO PREVENT CONTRAST-INDUCED NEPHROPATHY

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Aim. The purpose of this study was to compare three prophylactic regimens, sodium-bicarbonate based hydration, sodium-bicarbonate + N-acetylcysteine (NAC), and sodium-bicarbonate + NAC + theophylline, for the prevention of contrast induced nephropathy.

Material and methods. We prospectively randomized 151 patients with baseline eGFR values between 30–59 ml/min/1.73m² who were also undergoing coronary angiography with three prophylactic treatments: intravenous hydration with sodium-bicarbonate (3 ml/kg/h for 1 hours before and 1 ml/kg/h for 6 hours after contrast exposure, group 1; n=50), hydration + NAC (600 mg p.o. twice daily the preceding day and the day of angiography, group 2; n=50), and hydration + NAC + theophylline (600 mg p.o. NAC and 200 mg theophylline p.o. twice daily for the preceding day and the day of angiography, group 3; n=51). The incidence of contrast induced nephropathy (0,5 mg/dl increase in serum creatinine from the baseline value 48 hours after intravascular injection of contrast) from the three groups was compared.

Results. Of the 151 patients, 4 patients (7.8%) in group 3 experienced CIN (p=0.01). CIN did not develop in group 1 and 2.

Conclusion. Among patients with eGFR values between 30–59 ml/min/1.73m² undergoing coronary angiography, use of sodium-bicarbonate based hydration alone and sodium-bicarbonate with NAC was associated with a reduction in the rate of contrast induced nephropathy. Sodium-bicarbonate with theophylline therapy was found to have no effect for the prevention of contrast-induced nephropathy.

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Key words: contrast nephropathy, angiography.

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“КОНТРАСТ” ИССЛЕДОВАНИЕ: СРАВНЕНИЕ НЕФРОПРОТЕКТИВНОСТИ ТРЕХ ПРОТОКОЛОВ: АЦЕТИЛЦИСТЕИН — НАТРИЯ БИКАРБОНАТ — ТЕОФИЛЛИН, ДЛЯ ПРЕДОТВРАЩЕНИЯ КОНТРАСТ-ИНДУЦИРОВАННОЙ НЕФРОПАТИИ

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Цель. Целью данного исследования стало сравнение трех профилактических режимов терапии: гидратации на основе натрия бикарбоната, натрия бикарбоната + N-ацетилцистеин (NAC), натрия бикарбоната + NAC + теофиллин, для профилактики контраст-индуцированной нефропатии.

Материал и методы. Мы рандомизировали 151 больного с исходной скоростью клубочковой фильтрации (СКФ) со значениями между 30–59 мл/мин/1.73м², которые проходили коронарную ангиографию, с тремя профилактическими схемами лечения: внутривенная гидратация натрия бикарбонатом (3 мл/кг/час в течение 1 часа до и через 1 мл/кг/ч в течение 6 часов после контрастного воздействия, 1 группа; n=50), гидратация + NAC (600 мг перорально, два раза в день, предшествующий день и день ангиографии, 2 группа; n=50), и гидратация + NAC + теофиллин (600 мг перорально NAC и 200 мг теофиллина перорально дважды в день в течение предыдущего дня и в день ангиографии, 3-я группа; n=51). Появление контраст-индуцированной нефропатии (0,5 мг/дл увеличение сывороточного креатинина от базового уровня

через 48 часов после внутрисосудистого введения контраста) сравнивали в трех группах.

Результаты. Из 151 пациентов, у 4 больных (на 7,8%) в группе 3 была отмечена контраст-индуцированная нефропатия (p=0.01). Контраст-индуцированная нефропатия не развивалась в группах 1 и 2.

Заключение. Среди пациентов со значениями СКФ между 30–59 мл/мин/1.73м² при прохождении коронарной ангиографии, использование гидратации только натрия бикарбонатом и натрия бикарбонатом с NAC было связано со снижением частоты контраст-индуцированной нефропатии. Терапия натрия бикарбонатом с теофиллином не оказалась действенной в профилактике контраст-индуцированной нефропатии.

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Ключевые слова: контраст нефропатия, ангиография.

Introduction

Cardiovascular diseases are increasingly becoming the major cause of morbidity and mortality worldwide [1, 2]. Coronary angiography (CAG) is the gold standard method for the diagnosis of coronary artery disease (CAD) [3–5]. CAG-related complications are rare (less than 1–2%) and contrast-induced nephropathy (CIN) is an important one that increases in-hospital and long-term morbidity and mortality as a result of acute and chronic renal failure [4].

CIN was first defined in 1960 and is the third leading cause of hospital-acquired acute renal failure [6–8]. While

the incidence of CIN is below 2% in patients with normal-functioning kidneys and 5% in mild renal failure, it can rise to up to 50% in patients with diabetes together with severe renal failure [6, 8, 9]. CIN is defined as at least 0.5mg/dl or 25% increase in serum creatinin (SCre) levels 48 hours after contrast media exposure [6, 8, 9]. In-hospital mortality is 35.7%, and 1-year mortality is 55% in patients requiring dialysis [6–9].

Although hydration with 0.9% NaCl came forward previously, recent studies revealed lower CIN incidence with hydration with sodium bicarbonate [6]. Since oxida-

tive stress plays an important role in CIN pathogenesis, free oxygen radical scavenger sodium bicarbonate seems more promising than saline in the prevention of CIN.

NAC is a potent antioxidant agent which has vasodilator effects on renal tissue. There are more than 70 clinical trials in literature about NAC's role in CIN prevention [10]. NAC was reported to reduce the relative risk of CIN by 32–56% in some meta-analysis [10–12].

Theophylline is a competitive adenosine antagonist [11,13]. Adenosine, caused by the destruction of ATP due to contrast agents, vasoconstrict afferent arteriole of the kidney, and the degradation of adenosine forms precursors of free oxygen radicals [14,15]. A meta-analysis of 7 randomized controlled studies showed significant results in favour of prophylactic theophylline administration against CIN [12].

Our aim in this study was to compare 3 previously unexplored approaches (hydration with sodium bicarbonate, hydration with sodium bicarbonate + oral NAC, and hydration with sodium bicarbonate + oral NAC + oral theophylline) for CIN prevention in patients with moderate degrees of chronic renal disease (estimated Glomerular Filtration Rate (eGFR) 30–60 mL/min/1.73m²).

Material and methods

Patients. We enrolled 151 consecutive patients with eGFR 30 to 60 ml/min/1.73m² who were referred to Istanbul University Cardiology Institute for elective CAG. Istanbul university Cerrahpaşa Medical Faculty ethical committee approved our study, and written informed consent was obtained from all patients.

The GFR was estimated using the formula of modification of diet in renal disease (MDRD) Formula:

MDRD formula (mL/dk/1.73m²): 186 x serum creatinine (µmol/L) x age (For women multiple by 0.742)

Calculations were made automatically from an on-line site, http://nkdep.nih.gov/professionals/gfr_calculators/orig_con.htm site.

Patients with acute coronary syndrome, contrast medium exposure within 10 days, eGFR <30 and >60 ml/min/1.73m², cardiogenic shock, New York Heart Association class 3–4, pregnancy, age <21 years, known allergy to NAC, theophylline or contrast agents, contraindications to theophylline, >4 Lown arrhythmia classification, hemodynamic instability or patients taking drugs that may interact with theophylline were excluded from the study.

All of the nephrotoxic drugs were discontinued at least 24 hours before contrast media exposure.

Study protocol. All patients were hydrated with an initial intravenous bolus of 3 ml/kg/h of alkaline saline solution with NaHCO₃ for 1 hour before the procedure, followed by infusion of 1 ml/kg/h of the same solution during and for 6 hours after the procedure. The NaHCO₃ solution was prepared by adding 154 mL of 1000mEq/L NaHCO₃ to 846 mL of 5% dextrose in water.

Patients were randomized by using a randomization method in a 1:1:1 ratio to receive one of the following regimens:

- Group 1: Intravenous hydration with sodium bicarbonate (n=50)
- Group 2: Intravenous hydration with sodium bicarbonate plus NAC (600 mg p.o. twice daily the day before and the day of CAG) (n=50)
- Group 3: Intravenous hydration with sodium bicarbonate bicarbonate plus NAC (600 mg p.o. twice daily the day before and the day of CAG) plus theophylline (200 mg p.o. twice daily the day before and the day of CAG) (n=51)

We used a computer-generated randomization scheme for group assignment.

CAG. CAG was performed using the femoral approach with Standard Judkins method. A nonionic, low-osmolar contrast agent, iopromid (Ultravist 300 mL iv flacon, Bayer®) was used in all patients. For all patients, the amount of contrast given during the procedure was recorded by nursing staff. Urine output was monitored for 12 hours after the procedure. The SCr and blood urea nitrogen (BUN) levels were measured 48 hours after contrast media exposure.

Follow-up and Endpoints. The primary endpoint of the study was the incidence of CIN, and the secondary endpoint was the need for dialysis. Follow-up data were obtained from the hospital's database. An absolute 0.5 mg/dL increase in SCr levels 48 hours after administration of radiocontrast medium was considered as CIN. Patients who developed CIN by 48 hours were closely followed, and BUN and SCr levels were repeated at the 5th and 10th day. If there was no evidence of significant decline in levels of BUN and SCr, a nephrology consultation was requested.

Statistical analysis. All of the statistical analysis was performed by Istanbul University Cerrahpaşa Medical Faculty Biostatistical department. Demographic features were analysed by arithmetic averages and standard deviations were measured (mean ±SD). Categorical variables were evaluated with the chi-square test. P-value lower than 0.05 was considered statistically significant. The association between two quantitative variables was assessed by correlation test and pearson-Brova's correlation coefficient (r value) was used. Negative "r" value referred inverse relation and positive "r" value referred relation in the same direction. While absolute "r" values less than 0.250 were considered an indicator of ignorable weak commitment, absolute "r" values ≥0.5 sought to mention casualty links. Oneway Anova test was used for analysis of more than two variables. Effects of related variables were evaluated by linear regression test. SPSS for Windows 15.0 statistical package program was used.

Results

151 patients participated in our study and were divided into 3 groups. Patients' demographic features are given in Table 1.

There were no differences among groups regarding age, sex, hypertension, diabetes, peripheral arterial dis-

Table 1

Demographic and clinical features of groups

Characteristic	Hydration group N:50	Hydration+NAC N:50	Hydration+NAC+theophylline N:51	p value
Age	68.3 (\pm 10.2)	67.2 (\pm 9.4)	65.3 (\pm 10.3)	NS
Chronic heart failure	12 (%24)	19 (%38)	9 (%7.6)	P<0.05
Diabetes mellitus	15 (%30)	17 (%34)	24 (%47.1)	NS
Hypertension	32 (%64)	30 (%60)	31 (%60.7)	NS
Peripheral arterial disease	2 (%4)	1 (%2)	2 (%4)	NS
History of MI	22 (%44)	27 (%54)	7 (%13.3)	P<0.05
Male gender	34 (%32)	36 (%72)	35 (%68.6)	NS
SAP	22 (%44)	15 (%30)	16 (%31.4)	NS
USAP	17 (%34)	23 (%46)	22 (%43.1)	NS
Heart failure	5 (%10)	8 (%16)	5 (%9.8)	NS
Initial eGFR (mL/dk/1.73m)	53.1 \pm 7.9	50.2 \pm 8.5	49.8 \pm 6.6	NS
Initial BUN level (mg/dL)	27.8 \pm 7.4	25 \pm 9.6	28.1 \pm 11.7	NS
Initial creatinine level (mg/dL)	1.33 \pm 0.1	1.36 \pm 0.2	1.39 \pm 0.2	NS

P<0.05: statistically significant, NS: statistically non-significant.

Abbreviations: BUN — blood urea nitrogen, eGFR — estimated glomerular filtration rate, calculated by MDRD formula, NAC — N-acetylcysteine, SAP — Stable angina pectoris, USAP — Unstable angina pectoris.

ease and history of myocardial infarction, however the incidence of patients with heart failure and history of myocardial infarction was significantly less in the third group than other groups ($p<0.05$). The reasons for hospital admission are shown in Table 1. There were no differences between groups according to CAG indications. Renal function tests (SCre and BUN levels) were performed before the procedure, and they were similar among groups (Table 1). Renal function tests after contrast exposure, contrast volumes and incidence of CIN are given in table 2. The mean contrast volume used and urine output measured for 12 hours after contrast exposure were not different between groups.

CIN only developed in the NAC + theophylline group ($p=0.01$) (Table 2). SCre levels returned to baseline levels in all of the patients who experienced CIN, and none of them required dialysis. 2-year follow-up of these patients by hospital data revealed no death, no major adverse cardiac events or need for dialysis.

The BUN levels measured at the 48th hour were not significantly different between the 3 groups. However, when were compared each treatment group, the SCre levels measured at the 48th hour were significantly higher in group 3 than group 1, and in group 3 than group 2 ($p=0.038$ and $p=0.006$, respectively) (Table 2).

No side effects due to sodium bicarbonate, NAC nor theophylline administration were detected during the study.

We also noted all of the medications that patients were chronically receiving. All medications, except clopidogrel, were similar between groups. Clopidogrel usage was significantly higher in the NAC + theophylline group ($p=0.013$). Other biochemical parameters (haemoglobin, haematocrit, sodium, potassium, uric acid, and proteinuria) measured before CAG were not different among groups.

Table 2

Renal functions after the procedure and incidence of contrast-induced nephropathy

	Group 1* (n=50)	Group 2** (n=50)	Group 3*** (n=51)	p value
Contrast volume (mL)	105.5 \pm 56.3	101.9 \pm 46.3	97.9 \pm 50.5	NS
Diuresis (12 hour)	1420 \pm 105	1390 \pm 120	1404 \pm 110	NS
48. hour BUN (mg/dL)	28.3 \pm 11.4	25 \pm 10.2	29.5 \pm 10	NS
48. hour creatinine (mg/dL)	1.32 \pm 0.2	1.31 \pm 0.2	1.43 \pm 0.3	P<0.05
Contrast-induced nephropathy	0 (%0)	0 (%0)	4 (%7.8)	P=0.01

*only hydration with NaHCO₃, ** hydration with NaHCO₃ + NAC therapy, *** hydration with NaHCO₃ + NAC + theophylline therapy.

P<0.05: statistically significant, NS: statistically non-significant.

Abbreviation: BUN — blood urea nitrogen.

Discussion

We compared 3 strategies for protection from CIN in patients with moderate degree renal failure (eGFR 30–60mL/min/1.73m²) undergoing elective CAG and found that CIN only occurred in hydration + NAC + theophylline group. CIN did not develop in the hydration group or in the NAC plus hydration group.

Currently, many strategies have been studied to prevent CIN development, but unfortunately no medication or strategy has been proven to totally prevent CIN development (6,9,10,16). Medications promising and displaying positive results are NAC, theophylline, statins, ascorbic acid and sodium bicarbonate [6, 9, 10,16].

Imbalance between increased vasoconstriction associated with adenosine, endothelin and free oxygen radicals and decreased vasodilatation associated with nitric oxide and prostaglandins and direct toxic effect of contrast media on renal tubular cells are the most common mechanisms of CIN [6, 7, 9]. SCre begins to rise 24 hours after

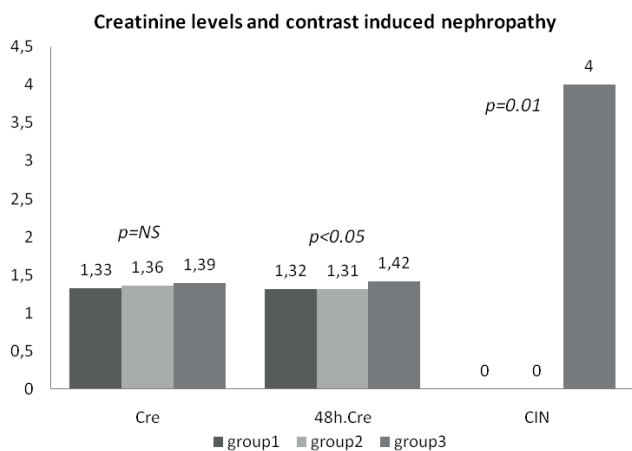


Figure 1. Creatinine levels and contrast induced nephropathy

contrast media administration, peaks on the 5th day, and most of the time returns back to normal levels within 10 days [6, 8, 9]. Incidence of patients requiring dialysis after contrast medium exposure is rare (1–4%) (2).

Our findings reveal absolute benefit of hydration with sodium bicarbonate and positive contribution with NAC for CIN protection. The importance of hydration in preventing CIN is accepted by physicians today, but which hydration protocol is better still remains unclear. Hydration with sodium bicarbonate has some advantages over hydration with 0.9% NaCl. First of all, sodium bicarbonate is a reactive free radical scavenger with antioxidant properties. It reduces free radical formation by alkalinizing renal medulla and urine and protects kidney from oxidant injury. Another advantage of sodium bicarbonate over saline is that sodium bicarbonate might be used in urgent situations because it is effective when given only 1 hour before contrast exposure [17–20].

We observed no increase, in fact a slight decrease, in SCre levels at the 48th hour in NAC + hydration group (initial cre=1.36 48th hour cre=1.31, $p>0.05$). This finding may indicate additional benefit of NAC compared to hydration alone (Fig. 1).

Recently published studies demonstrate that NAC might be more effective in patients who receive smaller amounts of contrast media (75–117 mL), high-osmolar contrast media, NAC therapy the day before the procedure, over 12 hours of hydration, and also in patients who are over 65 years, have diabetes and in whom SCre levels are not very high [10–12]. Some of these factors overlap with our study design so that we may have achieved positive results with NAC.

On the other hand, other published studies have shown that NAC therapy reduces SCre levels independent from eGFR values, even in patients with initial normal SCre levels by increasing renal tubular creatinine excretion. Therefore, some researchers state that creatinine levels are already reduced in patients on NAC therapy and NAC has no effect on CIN prevention [12, 21].

The prophylactic administration of theophylline does not appear to prevent CIN according to our findings. The renoprotective effect of theophylline is more obvious in patients with severe renal failure, however we excluded these patients [12,13]. Another probable explanation may be the decreased level of adenosine-related vasoconstriction due to adequate renoprotective effect obtained from sodium bicarbonate and NAC may be another explanation why we could not observe the benefits of theophylline. In fact, there are contradictory findings about theophylline in the literature. In an animal model, theophylline has not been employed to improve microcirculatory blood flow, intra-renal hypoxia nor contrast-associated free radical formation after 30 minutes of iv contrast infusion [22]. Also most of the favourable results with theophylline in the literature are obtained from placebo-controlled studies and focused on to investigate the efficacy of saline in the hydration arm [12, 13, 23, 24]. Demir et al study which was designed in patients without renal failure nor diabetes; theophylline was not only found to have adverse effect on CIN but was also associated with side-effects. The investigators showed increases in serum creatinin levels by adding theophylline 200 mg/day to saline hydration and concluded that the adenosine receptor gene polymorphism or the different distribution of adenosine receptors in normal kidneys compared to injured ones may be the reason of this phenomenon [23]. Abizaid et al reported that aminophylline plus saline hydration does not reduce the incidence of CIN when compared with saline hydration alone [25]. Malhis et al searched for the theophylline’s ability to reduce the incidence of CIN and stated that iv administration of theophylline in addition to sodium bicarbonate hydration prevents CIN in moderate and high risk patients. However the volume of contrast used in the procedures was higher in the group of patients who developed CIN than who did not developed CIN (196.4 ± 116.8 ml vs 138.2 ± 74.3 ml $p=0.006$) [26].

Only 4 patients of the 151 patients (2.6%) experienced CIN in our study. We should note in this report that 2.6% is an acceptable CIN incidence for the patients in moderate-risk group for CIN at the present time. In a similarly-designed study by Baskurt et al; the investigators studied the role of theophylline, NAC and saline hydration that was given before CAG for the prevention of CIN in patients with moderate degree renal failure. While a total of 12 patients of the 217 patients (5.5%) experienced CIN in saline hydration only and NAC + saline hydration group, none of the patients in theophylline + NAC + hydration group experienced CIN ($p=0.033$) [12]. We observed less CIN due to the development of CAG techniques and the use of less contrast media (119.9 ml vs 101.7 ml). Another possible explanation of this result may be the decreased level of adenosine-related vasoconstriction due to effective renoprotection obtained from sodium bicarbonate and NAC, so the benefit of theophylline could not be shown.

The number of patients on clopidogrel therapy was statistically higher in the NAC + theophylline group. Clopidogrel interacts with many drugs. A possible interaction between clopidogrel and theophylline may be the reason of CIN development in this group. However, we couldn't find any reported interaction between clopidogrel and theophylline in literature [27].

Conclusion

Hydration with sodium bicarbonate is an absolutely effective and safe approach for CIN prevention after elective CAG in patients with moderate degree of renal failure. NAC plus sodium bicarbonate combination therapy may provide further benefits. Theophylline therapy doesn't seem to provide additional benefit in preventing CIN in this group of patients. These findings should be confirmed in larger randomized trials.

References

- Charles H, Hennekens C. Increasing burden of cardiovascular disease. Current knowledge and future directions for research on risk factors. *Circulation*. 1998;97:1095–102.
- Murray CJ, Lopez AD. Global mortality, disability and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997;349:1436–42.
- Laskey W, Boyle J, Johnson LW. Multivariate model for prediction of risk of significant complication during diagnostic cardiac catheterization. *Cathet Cardiovasc Diagn* 1993;30:185–90.
- Donald SB, Daniel IS. Complications and the optimal use of adjunctive pharmacology. In: Donald SB, eds. *Grossman's cardiac catheterization, angiography, and intervention*. 7th ed. Philadelphia: Lippincott Williams and Williams; 2007; 36–75.
- Kern MJ, Roth R. Introduction to the catheterization laboratory. In: Kern MJ, ed. *The cardiac catheterization handbook*. 4th ed. Philadelphia: Mosby; 2003; 1–51.
- McCullough PA, Soman SS. Contrast-induced nephropathy. *Crit Care Clin*. 2005;21:261–80.
- Tumlin J, Stacul F, Adam A, et al. CIN Consensus Working Panel. Pathophysiology of contrast-induced nephropathy. *Am J Cardiol*. 2006;98: 14K-20K.
- McCullough PA, Adam A, Becker CR, et al. CIN Consensus Working Panel. Epidemiology and Prognostic Implications of Contrast-Induced Nephropathy. *Am J Cardiol*. 2006;98: 5K-13K.
- Meschi M, Detrenis S, Musini S, Strada E, Savazzi G. Facts and fallacies concerning the prevention of contrast medium-induced nephropathy. *Crit Care Med*. 2006;34: 2060–8.
- Diaz-Sandoval LJ, Kosowsky BD, Losordo DW. Acetylcysteine to prevent angiography-related renal tissue injury (the APART trial). *Am J Cardiol*. 2002;89: 356–8.
- Scholze A, Rinder C, Beige J, et al. Acetylcysteine reduces plasma homocysteine concentration and improves pulse pressure and endothelial function in patients with end-stage renal failure. *Circulation*. 2004 Jan 27;109: 369–74.
- McCulloch CE, Chertow GM. Theophylline for the prevention of radiocontrast nephropathy: a meta-analysis. *Nephrol Dial Transplant*. 2004;19: 2747–53.
- Huber W, Schipek C, Ilgmann K, et al. Effectiveness of theophylline prophylaxis of renal impairment after coronary angiography in patients with chronic renal insufficiency. *Am J Cardiol*. 2003;9: 1157–62.
- Stacul F, Adam A, Becker CR, et al. CIN Consensus Working Panel. Strategies to reduce the risk of contrast-induced nephropathy. *Am J Cardiol*. 2006;9;18: 59–77.
- Venkataraman R. Prevention of acute renal failure. *Crit Care Clin*. 2005;21:281–9.
- Baskurt M, Okcun B, Abaci O, et al. N-acetylcysteine versus N-acetylcysteine+theophylline for the prevention of contrast nephropathy. *Eur J Clin Invest*. 2009;39 (9): 793–9.
- Ozcan E, Guneri S, Akdeniz B, et al. Sodium bicarbonate, N-acetylcysteine, and saline for prevention of radiocontrast-induced nephropathy. A comparison of 3 regimens for protecting contrast-induced nephropathy in patients undergoing coronary procedures. A single-center prospective controlled trial. *Am Heart J*. 2007 September; 539–44.
- Hogan S, L'Allier P, Chetcuti S, et al. Current role of sodium bicarbonate-based preprocedural hydration for the prevention of contrast-induced acute kidney injury: A meta-analysis. *Am Heart J*. 2008; vol156;3: 414–21.
- Maioli M, Toso A, Leoncini M, et al. Sodium Bicarbonate Versus Saline for the Prevention of Contrast-Induced Nephropathy in patients With Renal Dysfunction Undergoing Coronary Angiography or Intervention. *J Am Coll Car*. 2008; vol152;8:599–604.
- Mayoral A, Chaparro M, Prado B, et al. The Reno-Protective Effect of Hydration With Sodium Bicarbonate Plus N-Acetylcysteine in Patients Undergoing Emergency Percutaneous Coronary Intervention (The RENO Study). *J Am Coll Car*. 2007; vol 49;12:1283–88.
- Lameire N, Adam A, Becker CR, et al. CIN Consensus Working Panel. Baseline renal function screening. *Am J Cardiol*. 2006;98: 21K-26K.
- Ix JH, McCulloch CE, Chertow GM. Theophylline for the prevention of radiocontrast nephropathy: a meta-analysis. *Nephrol Dial Transplant*. 2004;19: 2747–53.
- Demir M, Kutlucan A, Akin H, et al. Comparison of different agents on radiographic contrast agent induced nephropathy. *Eur J Gen Med* 2008;5 (4):222–7.
- Bagshaw SM, Ghali WA. Theophylline for Prevention of Contrast-Induced Nephropathy: A Systematic Review and Meta-analysis. *Arch Intern Med*. 2005;165:1087–93.
- Abizaid AS, Clark CE, Mintz GS, et al. Effects of dopamine and aminophylline on contrast induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency. *Am J Cardiol* 1999;83:260–3.
- Malhis M, Al-Bitar S, Al-Deen K. The role of theophylline in prevention of radiocontrast media-induced nephropathy. *Saudi J Kidney Dis Transpl* 2010;21 (2):276–83.
- <http://www.drugs.com/drug-interactions/theophylline.html>

Study limitations

The main limitations of our study were its single-centred basis and relatively small patient population size. Another issue is that it was not blinded. Furthermore, we did not include patients with mild or severe chronic renal failure, and our findings need to be clarified in these populations. We measured SCr levels only at the 48th hour, therefore we may have missed later increases in SCr levels and underestimated CIN incidence. We also did not study the effects of sodium bicarbonate on the urine or arterial pH, but these are influenced by other factors as well. It is also conceivable that we could have measured Cystatin-C levels as well. Cystatin-C is a sensitive marker of GFR, not affected by tubular transport, indicating renal functions better than creatinine.