Electronic Physician (ISSN: 2008-5842) http://www.ephysician.ir
February 2016, Volume: 8, Issue: 2, Pages: 1973-1977, DOI: http://dx.doi.org/10.19082/1973

Evaluation of different sodium bicarbonate regimens for the prevention of contrast medium-induced nephropathy

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Type of article: Original

Abstract

Introduction: The rapid decline in renal function caused by radiographic contrast agents usually is transient, but it can result in chronic kidney disease. The pathophysiology of contrast-induced nephropathy (CIN) is poorly understood, but it may include acute hypoxia-induced oxidative stress and free radicals generated within the acid environment of the renal medulla. Thus, the alkalization of urine by sodium bicarbonate has been regarded as resulting in the reduction of CIN. The aim of this study was to determine whether a long-duration sodium bicarbonate regimen is more effective than a short-duration regimen in reducing CIN.

Methods: One hundred patients were assigned randomly to treatment with sodium bicarbonate solution using either the short regimen (intravenous bolus 3 mL/kg/h of 166 mEq/L sodium bicarbonate for 1 hour immediately before radiocontrast) or the long regimen (initial intravenous bolus of 3 mL/kg/h of 166 mEq/L sodium bicarbonate for 6 hr). Patients with renal dysfunction (estimated glomerular filtration rate [eGFR], 60 mL/min/1.73 m^2 or less) who underwent elective or emergent coronary angiography (CAG) with/without percutaneous coronary intervention (PCI) at Nephrology Department (Theodor Bilharz Research Institute) were enrolled in the study. Data were analyzed by SPSS version 12, using Kruskal Wallis, ANOVA, Chi square test and Spearman rank correlation coefficient.

Results: There was a significant increase in serum creatinine and a decrease in eGFR 48 hr post-intervention in group 1 (short regimen) with no statically difference regarding those parameters group 2 (long regimen). Serum potassium clearly was decreased significantly post procedure in both groups.

Conclusions: The results of our study indicated that the long regimen of bicarbonate supplementation was a more effective strategy to prevent CIN than the short regimen.

Keywords: CIN, NaHCO3, coronary angiography

1. Introduction

The rapid decline in renal function caused by radiographic contrast agents usually is transient, but it can result in chronic kidney disease (CKD) or even end-stage renal disease (ESRD). Contrast-induced nephropathy (CIN) is a leading cause of new-onset renal failure in hospitalized patients, with the highest risk observed in patients with CKD (1, 2). It is associated with significantly increased in-hospital and long-term morbidity and mortality and acceleration of chronic renal disease (3). Since there is no specific therapy for CIN and the disease is iatrogenic, prevention is of paramount importance. The pathophysiology of CIN is poorly understood, but it may include acute vasoconstriction resulting in renal hypoperfusion, hypoxia-induced oxidative stress, and free radicals generated within the acid environment of the renal medulla (4, 5). Thus, the alkalization of urine by sodium bicarbonate has been regarded as resulting in the reduction of CIN (6-11). Putting into consideration that the alkalization of urine can be used to prevent CIN, our aim was to evaluate whether a longer duration of sodium bicarbonate infusion is more beneficial than a shorter duration infusion in reducing the frequency of contrast nephropathy in patients after coronary angiography.

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Received: December 03, 2015, Accepted: February 02, 2016, Published: February 2016
iThenticate screening: February 02, 2016, English editing: February 05, 2016, Quality control: February 07, 2016

2. Material and Methods

The protocol of this study was approved by the Ethics Committee of Theodor Bilharz Research Institute, and written informed consent was obtained from all patients. The study complies with the Declaration of Helsinki. All adult patients, i.e., those over the age of 18 who were scheduled for coronary angiography, were screened for inclusion and exclusion criteria. Between November 2013 and November 2014, 200 patients were considered eligible for the trial. After 100 exclusions, 100 patients were assigned randomly to either the short-duration or the long duration treatment with sodium bicarbonate solution. The short-duration treatment consisted of intravenous bolus 3 mL/kg/h of 166 mEq/L sodium bicarbonate for 1 hour immediately before the injection of the radiocontrast, with subsequent treatment with the same fluid at a rate of 1 mL/kg/h during the contrast exposure and for 6 h after the procedure. The long-duration treatment consisted of initial intravenous bolus of 3 mL/kg/h of 166 mEq/L sodium bicarbonate for 6 hr before the injection of the radiocontrast, after which the patients received the same fluid at a rate of 1 mL/kg/h during the contrast exposure and for 6 h after the procedure. Demographic data, current medication, and medical history were recorded at baseline. Serum creatinine (S. Cr), eGFR, and serum potassium were measured before initiating the pre-procedural hydration. Urine samples were obtained to analyze the pH of the urine one hour prior to the procedure. Two days after coronary angiography, serum creatinine, eGFR, and serum potassium were analyzed again. We calculated eGFR according to the MDRD formula (20). Change in creatinine, percent change in creatinine, percent change in eGFR, change in serum potassium, and urine pH were compared between the two groups. The side effects of the high-dose of sodium bicarbonate, such as congestive heart failure, respiratory disorder, and low potassium, were carefully evaluated during the study. CIN was defined as an increase of more than absolute 0.5 mg/dL and/or relative 25% in serum creatinine after 48 hr. Consecutive patients with renal dysfunction (estimated glomerular filtration rate [eGFR], 60 mL/min/1.73 m^2 or less) who underwent elective or emergency coronary angiography (CAG) with/without percutaneous coronary intervention (PCI) at our institution were enrolled. The eGFR was calculated using the MDRD formula. 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, the use of potentially nephrotoxic medicines (48 h before and 24 h after the procedure), pulmonary edema, multiple myeloma, exposure to contrast media within 7 days before the procedure, pregnancy, patient non-compliance, and the use of either N-acetylcystein, dopamine, fenoldopam, or mannitol before coronary angiography. Patients were randomized to one of the two regimens of volume supplementation described below. Randomization with stratification for intra-arterial and intravenous radiographic contrast procedures were performed by using sealed envelopes, 1:1 to each group (12). The analysis was performed according to the intent-to-treat principle. All patients were hydrated with intravenous normal saline at 1 mL/kg/h for 12 hr before exposure to the contrast and 12 h after coronary angiography. The rate of infusion was reduced in patients who developed signs of pulmonary congestion. Data were analyzed by SPSS version 12, using Kruskal Wallis, ANOVA, Chi square test and Spearman rank correlation coefficient.

3. Results and Discussion

Between November 2013 and November 2014, 200 patients were screened, and, after 100 exclusions, 100 patients were randomly assigned to treatment either with short regimen (60 minutes) bicarbonate solution prior to contrast administration (50 patients) or with long regimen (6 hr prior to the intervention) (50 patients). Thus, the final study population was 100 patients. No side effects of sodium bicarbonate infusion were observed, and discontinuation of protocol dose of infusion was not necessary in any of the patients. Our findings showed that there were no significant differences between the two groups in age, gender, smoking, body mass index, diabetes mellitus, hypertension, percutaneous coronary intervention, and volume of contrast administered (Table 1). There were no statistical differences in baseline urine pH, baseline S. Cr., baseline eGFR by MDRD, or baseline serum potassium (S. K.) between the two groups (Table 2). There was a significant increase in S. Cr., and a significant decrease in eGFR by MDRD 48 hr post-intervention in group 1 (short regimen) with no statically difference regarding those parameters in group 2 (long regimen). S. K clearly was decreased significantly post-procedure in both groups (short and long regimens). There was no correlation between S. K. and S. Cr. and eGFR by MDRD 48 hr post intervention in both groups. Also, a highly-significant negative correlation between s. Cr and eGFR by MDRD was reported in both groups (Table 3). Note that acute deterioration in renal function can be caused by radiographic contrast agents, but, generally, it is mild and transient. However, acute deterioration can result in lasting renal dysfunction and the need for renal replacement therapy (1). Contrast-induced nephropathy (CIN) is a leading cause of new onset renal failure in hospitalized patients, with the highest risk observed in patients with pre-existing impaired renal function (2). It is associated with significantly increased long-term morbidity and mortality, acceleration of chronic renal disease, and increased costs of medical care (13). The pathophysiology of CIN is poorly understood, but it may

include acute vasoconstriction, resulting in renal hypoperfusion, hypoxia induced oxidative stress, and free radicals generated within the acid environment of the renal medulla (4). Thus, studies have begun to evaluate the effect of volume supplementation with sodium bicarbonate in prevention of CIN based on the hypothesis that alkalinizing renal tubular fluid with bicarbonate may reduce renal injury and increase medullary pH with subsequent slowing of the production of free radicals (14). Similarly, it was stated in (4) that the role of bicarbonate in protecting against CIN is attributed to buffering of subclinical acidosis-induced vasoconstriction, which is typical of acute settings and may amplify the vasoconstriction induced by the contrast itself. On the contrary, some studies have indicated that the effectiveness of sodium bicarbonate treatment to prevent CIN in high risk patients remains uncertain and that the magnitude of any benefit probably had ben overestimated (15, 16). However Klima et al. (16) explained these discrepant findings by the early termination of these studies, publication bias, small differences in the concentration, the overall amount of sodium bicarbonate applied, the type of the contrast procedure, and the patient selection. In our study we compared two procedures of CIN prevention in patients with renal dysfunction: group 1 (short regimen) in which the patients received sodium bicarbonate 20 minutes prior to the contrast administration and group 2 (long regimen) in which the patients received the same amount and concentration sodium bicarbonate but 7 hr prior to the intervention, taken into consideration that all patients in our study received non-ionic low osmolar contrast agents.

Table 1. Baseline clinical characteristics for the two groups that were studied

Variables	Group 1 (Short regimen group)	Group 2 (Long regimen group)	p-value
Age (yr)	58.06 ± 7.33	59.64 ± 6.39	0.254
Gender (F/M)	16:34 (32%:68%)	15:35 (30%:70%)	0.829
Smoking (yes)	41 (82%)	35 (70%)	0.160
BMI (kg/m^2)	27.34 ± 2.82	28.34 ± 2.83	0.080
DM	33 (66%)	30 (60%)	0.534
SBP (mmHg)	131.00 ± 12.82	129.60 ± 13.01	0.589
DBP (mmHg)	81.10 ± 10.70	80.20 ± 15.08	0.732
Catheter/ PCI	19 (38.0%)/31 (62.0%)	28 (56.0%)/22 (44.0%)	
Contrast Vol.	114.60 + 46.41	97.30 + 43.44	0.057

Data are expressed as mean ± standard deviation or number (%); SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 2. Pre-procedural and renal outcome values

Variables	Group 1 (Short regimen group)	Group 2 (Long regimen group)	p-value
Urine pH	5.95 ± 0.26	5.97 ± 0.24	0.662
Baseline S. Cr.	2.32 ± 0.41	2.26 ± 0.47	0.513
Baseline S. K.	4.21 ± 0.43	4.16 ± 0.42	0.606
Baseline MDRD	30.22 ± 6.07	30.97 ± 7.13	0.574
S. Cr. 48 hrs. post	2.42 ± 0.48	2.26 ± 0.49	0.093
S. K. 48 hrs. post	3.88 ± 0.33	3.92 ± 0.34	0.594
MDRD post	28.97 ± 6.57	31.06 ± 7.41	0.139

Data are expressed as mean ± standard deviation.

Table 3. Correlation between S. Cr., S. K., and eGFR by MDRD in the two groups

Variables	Short regimen				Long regimen			
	Creatinine		Potassium		Creatinine		Potassium	
	r	p-value	r	p-value	r	p-value	r	p-value
Potassium	-0.184	0.200	---	---	-0.235	0.101	---	---
MDRD	-0.856	0.001	0.157	0.276	-0.908	0.001	0.122	0.397

We observed a significant increase in S. Cr. and significant decrease in eGFR calculated by MDRD formula in (group 1) when we compare their levels prior to contrast administration with their levels 48 hr after the intervention (S. Cr: 2.32 ± 0.41 vs. 2.42 ± 0.48) and (eGFR by MDRD: 30.22 ± 6.07 vs, 28.97 ± 6.57). Regarding group 2, the results of our study showed no statistical difference in S. Cr. and eGFR calculated by MDRD 48 hr post-procedure (S. Cr: 2.26 ± 0.47 vs. 2.26 ± 0.49) and (eGFR by MDRD: 30.97 ± 7.13 vs. 31.06 ± 7.41). Also, we demonstrated a

significant inverse correlation between S. Cr. and eGFR calculated by MDRD for both group 1 and group 2 (group 1: $r = -0.856$, $p < 0.001$) and (group 2: $r = -0.908$, $p < 0.001$). In agreement with our study, Briguori et al. (17) found that the long-term regimen of sodium bicarbonate was superior to the short regimen. This was in agreement with with Recio-Mayoral et al. (18). On the contrary, Klima et al. (16) and Mueller (4) stated that both regimens (the long and the short regimens) have the same effectiveness with very high safety, even in patients with NYHA class I or II heart failure, and, thus, the short-term regimen may be the regimen of choice because it is very easy to apply, even to outpatient procedures (15-17).

Our research also showed that S. K. has significantly decreased post procedure in both group 1 and group 2 (group1: 4.21 ± 0.43 vs. 3.88 ± 0.33) and (group 2: 4.16 ± 0.42 vs. 3.92 ± 0.34). Also, we demonstrated a non-significant negative correlation between S. Cr. and S. K. in both groups (group 1: $r = -0.184$) and (group 2: $r = -0.235$). This was in agreement with Walter et al. (19) who reported that the infusion of sodium bicarbonate can shift potassium from the extracellular to the intracellular space by increasing blood pH. However, this should be reserved for situations with severe educational environments (19). In contrast, Kim (20) stated that sodium bicarbonate is no longer recommended to lower potassium, although it may be appropriate in patients with severe metabolic acidosis (20). Regarding the pH of urine, we found that it was (5.95 ± 0.26) in group 1 and (5.97 ± 0.24) in group 2, showing no statistical difference and highlighting the fact that both regimen had almost the same alkalinizing efficacy with no proven extra benefit for patients with pH values greater than 6.

4. Conclusions

We should stress the importance of sodium bicarbonate infusion prior to the administration of the contrast medium to guard against CIN, especially in renally-impaired patients who could easily be susceptible to CIN. In addition, the results of our study indicated that the long regimen of bicarbonate supplementation was a better and more efficient strategy to prevent CIN than the short regimen.

Acknowledgments:

The authors thank the Nephrology Department (Theodor Bilharz Research Institute) for helping us in this research.

Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

Both authors contributed to this project and article equally. Both authors read and approved the final manuscript.

References

1) Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. A cohort analysis. J Am Med Assoc. 1996; 275: 1489-94. doi: 10.1001/jama.1996.03530430033035, PMID: 8622223.
2) Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. Am J Med. 1983; 74: 243-8. doi: 10.1016/0002-9343(83)90618-6, PMID: 6824004.
3) Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation. 2002; 105: 2259-64. doi: 10.1161/01.CIR.0000016043.87291.33, PMID: 12010907.
4) Mueller C. Prevention of contrast-induced nephropathy with volume supplementation. Kidney Int Suppl. 2006; 69: S16-19. PMID: 16612395.
5) Bakris GL, Lass N, Gaber AO, Jones JD, Burnett JC Jr. Radiocontrast medium-induced declines in renal function: a role for oxygen free radicals. Am J Physiol. 1990; 258: F115-20. PMID: 2301588.
6) Marenzi G, Marana I, Lauri G, Assanelli E, Grazi M, Campodonico J, et al. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. N Engl J Med. 2003; 349: 1333-40. doi: 10.1056/NEJMoa023204, PMID: 14523141.
7) Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med. 1994; 331: 1416-20. doi: 10.1056/NEJM199411243312104, PMID: 7969280.
8) Stone GW, McCullough PA, Tumlin JA, Lepor NE, Madyoon H, Murray P, et al. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. J Am Med Assoc. 2003; 290: 2284-91. doi: 10.1001/jama.290.17.2284, PMID: 14600187.

9) Birck R, Krzossok S, Markowetz F, Schnulle P, van der Woude FJ, Braun C. Acetylcysteine for prevention of contrast nephropathy: meta-analysis. Lancet. 2003; 362: 598-603. doi: 10.1016/S0140-6736(03)14189-X, PMID: 12944058.
10) Hoffmann U, Fischereder M, Kruger B, Drobnik W, Kramer BK. The value of N-acetylcysteine in the prevention of radiocontrast agent-induced nephropathy seems questionable. J Am Soc Nephrol. 2004; 15: 407-10. doi: 10.1097/01.ASN.0000106780.14856.55, PMID: 14747387.
11) Merten GJ, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. JAMA. 2004; 291(19): 2328–34. doi: 10.1001/jama.291.19.2328, PMID: 15150204.
12) Recio-Mayoral A, Chaparro M, Prado B, Cózar R, Méndez I, Banerjee D, 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 Cardiol. 2007; 49(12): 1283–8. doi: 10.1016/j.jacc.2006.11.034, PMID: 17394959.
13) Rihal C, Textor S, Grill D, Berger P, Ting H, Best PJ, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation. 2002; 105: 2259–64. doi: 10.1161/01.CIR.0000016043.87291.33, PMID: 12010907.
14) Merten G, Burgess W, Gray L, Holleman J, Roush T, Kowalchuk G, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. J Am Med Assoc. 2004; 291: 2328–34 doi: 10.1001/jama.291.19.2328, PMID: 15150204.
15) Zoungas S, Ninomiya T, Huxley R, Cass A, Jardine M, Gallagher M, et al. Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. Ann Intern Med. 2009; 151: 631–8. doi: 10.7326/0003-4819-151-9-200911030-00008, PMID: 19884624.
16) Klima T, Christ A, Marana I, Kalbermatter S, Uthoff H, Burri E, et al. Sodium chloride vs. Sodium bicarbonate for the prevention of contrast medium-induced nephropathy: a randomized controlled trial. Eur Heart J. doi: 10.1093/eurheartj/ehr501, PMID: 22267245.
17) Briguori C, Airoldi F, D'Andrea D, Bonizzoni E, Morici N, Focaccio A, et al. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. Circulation. 2007; 115: 1211–7. PMID: 17309916.
18) Recio-Mayoral A, Chaparro M, Prado B, Cozar R, Mendez I, Banerjee D, 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 Cardiol. 2007; 49: 1283–8. doi: 10.1016/j.jacc.2006.11.034.
19) Walter A, Ali A, Kurt M, Carey S. Hyperkalemia Revisite. Tex Heart Inst J. 2006; 33(1): 40–7. PMCID: PMC1413606.
20) Kim H. Combined effect of bicarbonate and insulin with glucose in acute therapy of hyperkalemia in end-stage renal disease patients. Nephron. 1996; 72: 476–82. doi: 10.1159/000188917, PMID: 8852501.