

Hydration with Sodium Bicarbonate Does Not Prevent Contrast Nephropathy: A Multicenter Clinical Trial

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Abstract

Background: Radiographic contrast media exposition can cause acute renal function impairment. There is limited and conflicting evidence that hydration with sodium bicarbonate prevents contrast-induced nephropathy (CIN) in patients undergoing cardiac catheterization.

Objective: The present study was aimed at determining whether sodium bicarbonate is superior to hydration with saline to prevent nephropathy in patients at risk undergoing cardiac catheterization.

Methods: Three hundred and one patients undergoing coronary angiography or percutaneous coronary intervention with serum creatinine ≥ 1.2 mg/dL or glomerular filtration rate (GFR) < 50 ml/min were randomized to receive hydration with sodium bicarbonate starting 1 hour before the procedure and 6 hours after the procedure, or hydration with 0.9% saline. CIN was defined as an increase of 0.5mg/dL in creatinine in 48h

Results: Eighteen patients (5.9%) developed contrast induced nephropathy: 9 patients in the bicarbonate group (6.1%) and 9 patients in the saline group (6.0%), $p = 0.97$. The change in serum creatinine was similar in both groups, 0.01 ± 0.26 mg/dL in the bicarbonate group and 0.01 ± 0.35 mg/dL in the saline group, $p = 0.9$. No statistical difference was observed between the change in glomerular filtration rate (0.89 ± 9 ml/min vs. 2.29 ± 10 ml/min, $p = 0.2$ bicarbonate group and saline group, respectively).

Conclusion: Hydration with sodium bicarbonate was not superior to saline to prevent contrast media induced nephropathy in patients at risk undergoing cardiac catheterization. (Arq Bras Cardiol 2012;99(6):1129-1134)

Keywords: Kidney diseases; fluid therapy; sodium bicarbonate; coronary angiography; clinical trial.

Introduction

Contrast induced nephropathy (CIN) is a potential and important complication of the use of iodized radiological contrast agents. The development of CIN is associated with higher morbidity and mortality rates¹⁻⁴ and increased length of hospitalization⁴ in patients undergoing cardiac catheterization.

One of the most used definition of CIN is an increase in serum creatinine greater than 0.5 mg/dL, occurring 48 hours after exposure to contrast media^{1,5}. In patients undergoing contrast-enhanced radiographic procedures, the incidence of CIN is approximately 3.5%¹, ranging from 1% in previously healthy patients to more than

50% in high-risk groups⁶⁻⁸. The main risk factors for CIN are previously impaired renal function^{1,9-11} and diabetes mellitus¹. Moreover, other important risk factors are age¹ and the volume of contrast media administered during the procedure^{1,10}.

Although effective preventive measures have been exhaustively sought¹², only a few, such as hydration¹³ and the use of low-osmolality¹⁴ or isosmolar¹⁵ contrast agents, have proved useful.

In an initial study, hydration with sodium bicarbonate demonstrated to be superior to hydration with saline infusion for the prevention of CIN¹⁶. However, there is limited and controversial data regarding assessing the efficacy of sodium bicarbonate in patients undergoing cardiac catheterization¹⁷⁻²³.

This is a multicenter, randomized clinical trial, which was carried out to evaluate the effect of hydration with sodium bicarbonate for prevention of CIN in patients at mild to moderate risk for developing CIN undergoing coronary angiography or percutaneous coronary interventions (PCI).

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Methods

Patients

The study randomized 301 patients at moderate to high risk for developing CIN who were referred for elective coronary angiography or PCI at 6 centers.

Patients were eligible for the study if they had one of the following criteria: serum creatinine ≥ 1.2 mg/dL or glomerular filtration rate (GFR) < 50 mL/min. The GFR was calculated using the Modification of Diet in Renal Disease group equation (MDRD)²⁴. The exclusion criteria were as follows: age < 18 years, use of radiographic contrast media during the last 21 days, history of dialysis, cardiac insufficiency class III-IV NYHA, and emergency procedures. The ethics committees of the 9 hospitals approved the study protocol. Written informed consent was obtained from all patients included in the study.

Protocol of the Study

The patients were randomized to receive hydration with sodium bicarbonate, or 0.9% saline by randomly drawing sealed envelopes. Randomization was stratified manner by the type of the procedure to be performed (coronary angiography or PCI). The patients randomized for the sodium bicarbonate group received 154 mEq/l of sodium bicarbonate in 5% dextrose and H₂O, and patients randomized for saline solution received hydration with 0.9% saline infusion, according to the protocol reported by Merten et al¹⁶. The initial intravenous bolus was 3 mL/kg/h for 1 hour immediately before contrast injection. After that, patients received the same fluid at a rate of 1 mL/kg/h during contrast exposure and for 6 hours after the procedure. The 2 fluids were administered in an open-label basis.

All the procedures were performed with low-osmolality ionic contrast medium (Hexabrix®, Ioxaglate; Guerbet Ltda, Rio de Janeiro, Brazil).

Outcomes

Serum creatinine was measured 24 hours before (baseline creatinine) and 48 hours after the procedure (post-procedure creatinine).

The primary outcomes were predefined as follow: 1) the occurrence of CIN, defined as an increase in serum creatinine ≥ 0.5 mg/dL 48 hours after exposure to contrast medium; 2) the variation in serum creatinine (post-procedure Cr – baseline Cr); and 3) the variation in GFR (post-procedure GFR – baseline GFR).

Secondary outcomes were need for dialysis during hospitalization, length of hospitalization, and in-hospital mortality.

The effect of sodium bicarbonate was also assessed in the following predefined subgroups: baseline GFR ≤ 40 ml/min, diabetes mellitus, age > 70 years, and patients receiving a contrast media volume ≥ 1.5 ml/Kg.

Analysis Statistics

Analysis was conducted on an intention to treat basis. The categorical variables were analyzed with the chi-square test or Fisher exact test as appropriate, and the continuous variables were analyzed with the Student *t* test for independent

samples. Data were expressed as mean \pm SD. For variables with nonparametric distribution, the Mann-Whitney test was used, data being expressed as median (25 percentile – 75 percentile). Sample size was calculated as 298 individuals, to detect a 50% change in the relative risk for CIN associated with the hydration with sodium bicarbonate^{16,18}, assuming a 10% incidence of CIN in the group randomized to saline, with a power of 80% and α error of 0.05.

Odds ratio and 95% confidence intervals were calculated for the primary end-point outcomes for prespecified subgroups. Statistical analysis was carried out with the SPSS software, version 11.0 (SPSS Inc. Chicago, Illinois, USA).

Results

A total of 301 patients were randomized, 151 to receive saline infusion and 150 to sodium bicarbonate. The mean baseline serum creatinine and GFR of the study population were 1.50 ± 0.49 mg/dL and 51.2 ± 13 mL/min respectively.

The baseline clinical characteristics and procedure related variables are shown in table 1. The mean age was 65.2 years. The groups were well balanced with respect to age, gender, blood pressure, diabetes mellitus, and drug therapy.

The volume of contrast medium used during the procedures and the distribution of diagnostic angiography and PCI were similar in both groups. All patients completed the study protocol. No adverse reaction to hydration was reported.

Primary Outcomes

Hydration with sodium bicarbonate was not superior to saline for prevention of CIN. The incidence of CIN was similar in the 2 groups, occurring in 9 patients (6.1%) in the sodium bicarbonate group and in 9 patients (6.0%) in the saline group ($p = 1.0$) (table 2).

The changes in serum creatinine from baseline to 48h after contrast exposition in the sodium bicarbonate and saline groups were also similar (0.01 ± 0.26 mg/dL vs. 0.01 ± 0.35 mg/dL, $p = 0.9$ respectively) (Table 2).

No significant difference was found when the changes in GFR were compared between the groups (0.9 ± 8.0 ml/min in the sodium bicarbonate group and 2.3 ± 10 ml/min in the saline group, $p = 0.2$) (Table 2).

Secondary Outcomes

No difference in secondary outcomes was observed between the groups (Table 2). The length of hospitalization, need for hemodialysis, and in-hospital death were similar in both groups. A total of 13 (4.3%) patients died in hospital, six in the sodium bicarbonate group and seven in the saline group. In the sodium bicarbonate group, 2 patients died following PCI complications, 2 patients died by postoperative complications of coronary artery bypass graft (CABG) surgery and 2 patients died of no cardiac causes. Only 1 of these deaths occurred in patients who developed CIN.

Of the 7 deaths that had occurred in the saline infusion patients, four were related to postoperative complications in patients who underwent CABG, two died of cardiac causes

Table 1 - Baseline clinical characteristics and procedure related variables

	Saline n =151	Bicarbonate n = 150	p
Age, years (SD)	64,5 (± 12)	64,1 (± 12)	0,74
Male gender (%)	74,8	69,3	0,28
Black race (%)	16,0	14,9	0,78
Creatinine, mg/dL (SD)	1,49 (± 0,5)	1,50 (± 0,4)	0,85
Creatinine ≥ 2.5 mg/dL, n (%)	4 (2,6%)	7 (4,7%)	0,35
† GFR, mL/min (SD)	51,9 (± 13)	50,5 (± 13)	0,36
Blood Pressure (mm/Hg)			
Systolic	129,3 (± 21)	130,0 (± 20)	0,73
Diastolic	75,9 (± 12)	78,1 (± 12)	0,10
History of hypertension (%)	74,2	77,3	0,52
Diabetes mellitus (%)	29,8	28,7	0,83
Insulin (%)	11,3	12,0	0,84
Medical therapy			
Diuretics (%)	29,1	34,0	0,36
Ca++ channel blocker (%)	12,6	13,3	0,84
*ACE Inhibitor (%)	63,6	64,0	0,94
Angiographic findings (%)			0,81
Non-obstructive disease	26,5	25,0	
1 vessel disease	29,1	30,4	
2 vessel disease	19,2	18,2	
3 vessel disease	25,2	26,4	
‡ LV ejection fraction, % (SD)	56 ± 21	52 ± 17	0,35
Procedure type			0,44
Coronary angiography (%)	84,8		
§ PCI (%)	15,2	18,7	
Contrast Volume (mL)	125 (± 87)	124 (± 65)	0,86

*ACE: angiotensin-converting enzyme; †GFR: Glomerular filtration rate; *ACE: angiotensin-converting enzyme; §PCI: Percutaneous coronary intervention; ‡LV: left ventricular.

Table 2 - Primary and secondary outcomes in the saline and sodium bicarbonate group

	Saline (n =151)	Bicarbonate (n = 150)	p
Primary Outcomes			
Incidence of CIN* (%)	6.0	6.1	0.97
Change in Cr†, mg/dl	0.01 ± 0.3	0.01± 0.2	0.92
Change in GFR‡, ml/min	2.29 ± 10	0.89 ± 9	0.20
Secondary Outcomes			
Length of hospitalization, days	8.6 ± 9.7	7.5 ± 10	0.35
Dialysis (%)	0	0	1.00
Death (%)	3.4	4.7	0.81

*CIN: Contrast induced nephropathy; †Cr: serum creatinine; ‡GFR: glomerular filtration rate.

and 1 patient died due to no cardiac cause. None of the patients of this group who died developed CIN.

Sub-Groups Analysis

The lack of efficacy of sodium bicarbonate compared to normal saline was consistent among the prespecified subgroups including both low and high-risk patients (Table 3).

Discussion

The main finding of this multicenter clinical trial is that, in patients with mild renal dysfunction, hydration with sodium bicarbonate is not superior to saline infusion to reduce the incidence of CIN after cardiac catheterization. Moreover, hydration with sodium bicarbonate demonstrated no benefit in any of the predefined subgroups.

The pathophysiology of CIN is poorly understood. It certainly involves the interplay of multiples factors; however, little is known about the underlying cellular mechanisms²⁵. Evidence suggests that free radicals have important role in the development of CIN associated with direct injury to the tubular epithelium²⁶⁻²⁸. Once the acidic environment typical of renal tubules propitiates the formation of free radicals is possible that alkalinization of urine may reduce the incidence of CIN. In animal models of ischemic acute renal insufficiency, sodium bicarbonate is more protective than saline solution²⁹.

Merten and cols¹⁶ were the first to report an important reduction in the risk of CIN in patients hydrated with sodium bicarbonate (1.7% versus 13.6% $p=0.02$, sodium bicarbonate and saline solution, respectively). However, that was a single-center study that involved only 119 patients who underwent many types of procedures with radiological contrast and not only cardiac catheterization. Moreover, they used more than one type of contrast and the administration route of the contrast agent was not only intra-arterial.

Posterior studies evaluated sodium bicarbonate in the prevention of CIN in patients submitted to the angiography and/or PCI produced conflicting results¹⁷⁻²³. Some of these studies evaluated the use of sodium bicarbonate plus N-acetylcysteine^{17,19,21,23} and, therefore, do not allow for a

definitive conclusion regarding the benefit of isolated sodium bicarbonate in CIN prophylaxis, once the evaluation of two drugs simultaneously is an important confusion bias. Among studies that compared only sodium bicarbonate and saline solution, the results are also inconsistent^{18,20,22}. The present study is the only multicenter and has the largest sample size among the studies that evaluated hydration with bicarbonate as a single approach for CIN prophylaxis.

There are important differences among studies assessing sodium bicarbonate for CIN prophylaxis. First, different definitions of CIN have been used. Previous studies define CIN either as an absolute rise in serum creatinine of 0,5 mg/dl, or an increase of 25% in relation to baseline. In this study, we elect to use an absolute increase in serum creatinine of 0.5mg/dl as primary end point because we consider this definition has superior clinical relevance. This definition determines that the diagnosis of CIN is restricted to a smaller number of patients. It is conceivable that diverse results were obtained if a different CIN definition was used^{30,31}.

Variation in hydration protocols may account for different results. We use the same hydration protocol and bicarbonate administration carried out by the initial study of Merten and cols¹⁶. Only one additional study evaluated the same bicarbonate protocol and showed superiority of bicarbonate. However, that was a single-center study and that included only 59 patients²⁰.

Another potential source of variability is the type of contrast used by studies evaluating CIN prophylaxis. In our study, all patients received ionic low osmolality contrast media. Previous studies had tested sodium bicarbonate in patients that received ionic and nonionic contrast agents with different osmolality. This may also contribute to the inconsistent results seen in literature, as different contrast agents have different risk of CIN³².

Two meta-analyses recently published indicate superiority of the hydration with sodium bicarbonate in the prevention of the CIN. In both of them, the authors demonstrated significant heterogeneity between studies and evidence of publication bias favoring sodium bicarbonate therapy^{33,34}. Moreover, the findings were importantly influenced by the dramatic effect of the treatment demonstrated in small studies. Therefore,

Table 3 - Incidence of CIN and risk ratios in sub-group analysis

	n	SF 0.9%	Bicarbonate	OR	IC	p
DM	87	8.9	9.8	1.08	0.25 – 4.62	0.97
Non DM	214	4.7	4.7	1.00	0.28 – 3.56	1.00
GFR ≤ 40 ml/min	60	22.2	18.2	0.7	0.21 – 2.76	0.75
GFR > 40 ml/min	241	2.4	2.6	1.08	0.21 – 5.46	1.00
Age > 70	98	5.5	11.6	2.28	0.51 – 10.1	0.30
Age ≤ 70	203	6.3	3.8	0.6	0.16 – 2.17	0.42
Contrast Vol ≥ 1.5 ml/Kg	132	10.7	4.4	0.38	0.09 – 1.52	0.24
Contrast Vol < 1.5 ml/Kg	169	2.7	7.6	3.00	0.56 – 15.9	0.25

DM: Diabetes mellitus; GFR: Glomerular filtration rate

the results of these meta-analyses must be interpreted with caution because of those limitations.

Our study found no benefit of hydration with sodium bicarbonate in patients with mild to moderate renal dysfunction. However, this does not allow us to draw definite conclusion about the effect of sodium bicarbonate on very high-risk patients, once only 3.6% of the patients had serum creatinine ≥ 2.5 mg/dl. Nevertheless, considering that only 4% of the population who undergo cardiac catheterization present serum creatinine $> 2,0$ mg/dl¹, the present findings can be applied to the majority of the patients at risk for developing CIN.

The incidence of CIN observed in our study was lower in both groups compared to that of previous studies with a similar patient population^{23,35}. There are a number of possible explanations for this difference. Our study was specifically designed to compare two hydration protocols that were rigorously executed in the control and bicarbonate groups. It is conceivable to assume that adequate hydration determined the low incidence of NIC regardless of sodium bicarbonate use.

Once the rise of creatinine is a surrogate end-point, we also evaluate the effect of hydration with sodium bicarbonate in hard outcomes (in-hospital mortality, necessity of dialysis and length of hospitalization). Our study did not show any advantage of sodium bicarbonate over saline infusion. Higher than expected in-hospital mortality observed in this study can be explained by the high cardiovascular risk of patients, since that most deaths were due to complications of CABG.

Limitations of the Study

This study has some potential limitations. Serum creatinine was measured 48h after the procedure; although most clinical trials on preventive measures for CIN have

assessed creatinine during that period, it is possible that a later increase in serum creatinine may have passed unnoticed in some patients. Urinary pH was not measured after the procedure to determine the effectiveness of sodium bicarbonate. Only ionic low osmolality contrast media was used; therefore, the findings of this study may not be applied to patients who receive another type of contrast. Finally, sample size was calculated aiming at reaching statistical difference in primary outcomes. Therefore, although no trends were observed in subgroups, our study has limited statistical power for that analysis.

Conclusion

The results of this multicenter study indicated that hydration with sodium bicarbonate is not superior to hydration with saline infusion in patients with mild to moderate renal dysfunction who were undergoing coronary angiography.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

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