Prevention of contrast induced nephropathy with sodium bicarbonate (the PROMEC study)

Prevenção de nefropatia por contraste com bicarbonato de sódio (o estudo PROMEC)

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Data de submissão: 15/05/2014.
Data de aprovação: 07/07/2014.

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DOI: 10.5935/0101-2800.20140051

Abstract

Introduction: Contrast-induced nephropathy is a common complication of radiographic procedures. Different measures have been used to avoid this damage, but the evidence is controversial. New investigations are required to clarify it. We investigated the efficacy and safety of sodium bicarbonate solution compared with sodium chloride solution to prevent contrast induced nephropathy in patients with or at risk of renal dysfunction. **Methods:** A prospective, single-center, randomized clinical trial conducted from May 1, 2007 to February 8, 2008. Inpatients in a tertiary center, scheduled to undergo a procedure with the nonionic radiographic contrast agent iohexol. There were 220 patients with serum creatinine levels of at least 1.2 mg/dL (106.1 µmol/L) and/or type 2 diabetics, who were randomized to receive an infusion of sodium chloride (n = 113) or sodium bicarbonate (n = 107) before and after contrast dye administration. The intervention were "A" group received 1 ml/kg/hour of normal saline solution, starting 12 hours before and continuing 12 hours after iohexol contrast. "B" group received 3 ml/kg of sodium bicarbonate solution (150 mEq/L) one hour prior to procedure and then drip rate was decreased to 1 ml/kg/hour until 6 hours post procedure. Our main outcome measure was change in serum creatinine. **Results:** The mean creatinine value after the procedure was 1.26 mg/dL in the saline group and 1.22 mg/dL in the bicarbonate group (mean difference: 0.036; CI 95%: -0.16 to 0.23, p = 0.865). The diagnosis of contrast-induced nephropathy, defined by increase in serum creatinine on 25% or more within 2 days after administration of radiographic contrast, was done in twelve patients (12%) in the bicarbonate group and eighth patients (7.1%) in the saline group (RR: 1.68, CI 95%: 0.72 to 3.94). **Conclusion:** Our

Resumo

Introdução: A nefropatia induzida por contraste é uma complicação comum de procedimentos radiográficos. Medidas diferentes têm sido utilizadas para evitar estes problemas, mas a evidência é controversa. Novos estudos são necessários para esclarecer isso. Investigamos tanto a eficácia quanto a segurança de uma solução de bicarbonato de sódio em comparação com a solução de cloreto de sódio para evitar nefropatia por contraste em pacientes com ou em risco de desenvolver disfunção renal. **Métodos:** Estudo prospectivo, randomizado clínico, conduzido em um único centro, entre 01 de maio de 2007 e 8 de fevereiro de 2008. Os pacientes internados em um centro terciário, agendados para passar por um procedimento radiográfico com uso de contraste não iônico. Havia 220 pacientes com níveis de creatinina sérica de pelo menos 1,2 mg/dL (106,1 mmol/L) e/ou diabéticos do tipo 2, que foram escolhidos aleatoriamente para receber uma infusão de cloreto de sódio (n = 113) ou bicarbonato de sódio (n = 107) antes e após a administração do meio de contraste. A intervenção foi: grupo "A" recebeu 1 ml/kg/hora de solução salina normal, começando 12 horas antes e continuando por 12 horas após o uso do contraste iohexol. Os pacientes do grupo "B" receberam 3 ml/kg de uma solução de bicarbonato de sódio (150 mEq/L), 1 hora antes do procedimento e, em seguida, o gotejamento foi reduzido a 1 ml/kg/hora por até 6 horas após o procedimento. Nosso principal indicador de desfecho foi a alteração na creatinina sérica. **Resultados:** O valor médio da creatinina após o procedimento foi de 1,26 mg/dL no grupo que recebeu a solução salina e 1,22 mg/dL no grupo do bicarbonato (diferença média: 0,036, IC 95%: -0,16 a 0,23, p = 0,865). O diagnóstico da nefropatia induzida por contraste, definida pelo aumento de creatinina no soro em 25% ou mais dentro de 2 dias após a administração de contraste radiográfico, foi realizado em doze pacientes (12%) no grupo do bicarbonato e oitavo pacientes (7,1%) no grupo da solução salina (RR: 1,68, IC 95%: 0,72-3,94). **Conclusão:** Nossa investigação

investigation showed that there were no differences between normal saline solution (extended infusion) *vs.* bicarbonate solution for nephroprotection.

Keywords: acute kidney injury; contrast media; saline waters; sodium bicarbonate.

mostrou que não houve diferença entre soro fisiológico normal (infusão prolongada) contra uma solução de bicarbonato para nefroproteção.

Palavras-chave: bicarbonato de sódio; lesão renal aguda; meios de contraste; solução salina.

Introduction

The image studies that require radiographic contrast dye are integral part of the modern medical practice. The radio-contrast media is used in more than 10 million annual procedures in the USA.[1] A complication of the use of radio-contrast is the contrast-induced nephropathy (CIN),[2-4] with an incidence between 3 and 16%,[5,6] and contributing as a major cause of acute renal failure in hospitalized patients.[3,6,7] Several theories of the pathogenesis of CIN exist, one of them postulating the effect of oxygen free radicals and hyperosmolar stress on the renal medulla.[8,9] Some authors favor the use of bicarbonate for preventing of CIN, arguing that alkalinization with bicarbonate in the renal tubules diminishes renal damage.[10,11] The free radicals hypothesis was evaluated by Merten *et al.* and their results suggested that bicarbonate as the anion in the hydration fluids significantly reduces contrast-induced nephropathy.[11] However, it is not clear whether in the Merten's study normal saline solution was less effective than bicarbonate solution because of the shortest hydration time, as has been demonstrated in other trial.[12] Therefore, we aimed to determine whether bicarbonate solution is more effective in preventing the development of CIN than extended hydration with normal saline solution in patients undergoing elective procedures.

Methods

Study design and population

This single-center randomized clinical controlled trial compared 24 hours infusion of sodium chloride *vs.* 7 hours infusion of sodium bicarbonate as the hydration fluid to prevent CIN in patients with known risk factors. Eligible patients included individuals aged 18 years or older, inpatients at Hospital Universitario San Vicente de Paúl (Medellin, Colombia), who were scheduled to undergo tomography scan using contrast or angiography (included coronariography) with the nonionic radiographic contrast agent iohexol (640 mOsm/L, 647 mg of iohexol per milliliter), and either with serum creatinine ≥ 1.2 mg/dL (106.1 µmol/L) or type 2 *Diabetes Mellitus*.

Exclusion criteria included: current clinical diagnosis of exacerbated congestive heart failure, ejection fraction < 35% by previous echocardiography, signs of acute pulmonary edema within 48 hours before the procedure, systolic blood pressure < 90 mmHg or requirement of vasopressors support, patients with exposure to contrast 30 days prior to the study, known allergy to contrast dye, chronic renal disease with dialysis therapy, criteria for dialytic urgency, pregnancy, requirement of an emergency procedure (e.g., aortography for diagnosis of aortic aneurism), patients with serum potassium < 3 mEq/L (because of the risk of hypokalemia induced by bicarbonate), uncompensated *diabetes mellitus* (four different values > 200 mg/dL in the previous 24 hours) or patient or physician refusal to participate.

The study was reviewed and approved by the institutional ethical committees of the Universidad de Antioquia and the Hospital Universitario San Vicente de Paúl. All patients gave written informed consent in presence of two witnesses.

Protocol

Patients were identified as study candidates by a research assistant, based on daily review of records and information at the Hospital's radiology service and also based in laboratory test reports. Eligible patients were randomly assigned in a 1:1 ratio to either saline or bicarbonate using sealed, opaque envelopes. The sequence was based on a random number table and stratified by diagnosis of *diabetes mellitus* (yes or no) and type of procedure (coronariography *vs.* others). The sequence and the envelopes were locked in the data-coordinating center, and the investigator opened the envelope only in the moment of patient admission to the study.

Patients assigned to the "A" group received 1 ml/kg/hour of 0.9% saline infusion (154 mEq/L) starting 12 hours before and continuing 12 hours after iohexol contrast exposition. Patients assigned to the "B" group

received 3 ml/kg of sodium bicarbonate solution (150 mEq/L) during one hour prior to procedure followed for infusion at 1 ml/kg/hour until 6 hours post procedure. This solution was mixed in the hospital pharmacy by adding 75 ml of 1000 mEq/L sodium bicarbonate solution to 425 ml of 5% dextrose in H_2O, diluting the dextrose concentration to 4.25%.

A general clinical evaluation was made by a physician investigator, and pre-contrast fluid was administrated. Nurses in charge of patient's care followed the infusions and any potential adverse reactions, and they informed to the investigators in required cases. A new medical evaluation was made by a physician investigator at 24 and 48 hours after the end of infusion. Serum creatinine, serum potassium and venous blood gases were obtained 48 hours after the procedure. Patients who developed CIN were followed until the end of hospitalization to evaluate dialysis requirements or death. The following comorbidities were extracted from the clinical records: *diabetes mellitus* (medical diagnosis or pharmacological treatment), hypertension (medical diagnosis or at least one antihypertensive medication continuously during the last month), coronary artery disease (previous history of myocardial infarction, instable o stable angina or cardiologist´s diagnosis), chronic kidney disease (previous clinical diagnosis by internist or nephrologist) and heart failure confirmed by previous echocardiography.

Study end Points

The primary outcome measure was the change in serum creatinine. Secondary outcomes were development of contrast-induced nephropathy, defined by an increase in serum creatinine of 25% or more within 2 days after administration of the radiographic contrast, and development of complications as I) superficial phlebitis: presence of inflammatory signs on the route of the vein where the infusion was administrated; II) hypokalemia: serum potassium < 3 mEq/L; III) metabolic alkalosis: arterial pH > 7.45 with serum bicarbonate > 24 mEq/L; and IV) decompensated heart failure: signs of volume overload requiring a therapeutic intervention to resolve them. Primary and secondary outcomes were evaluated and determined within 48 hours after administration of radiographic contrast. Primary and secondary outcomes were determined at the hospital's laboratory and by study personnel blinded to the treatment status of the patient.

Statistical Analysis

We calculated 106 patients per group in order to detect a 20% difference in the change of levels of creatinine, assuming a mean value of 1.5 mg/dL after the procedure with an alpha error of 0.05 and a beta error of 0.2. An independent data and safety monitoring board conducted two pre-planned interim analyses, after 70 patients and 140 patients had been enrolled. Guidelines for stopping the study by efficacy were in accordance with the modified O' Brien - Fleming procedure.[13,14]

The analysis of efficacy was performed based on the intention to treat principle. A model of covariance analysis (ANCOVA), considering the initial value of creatinine as co-variable, was developed to test, the effect of the intervention. For binary variables a Fisher's exact test was used to test the null hypothesis of no differences between groups. For all the analyses a p value less than 0.05 was considered statistically significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed the manuscript.

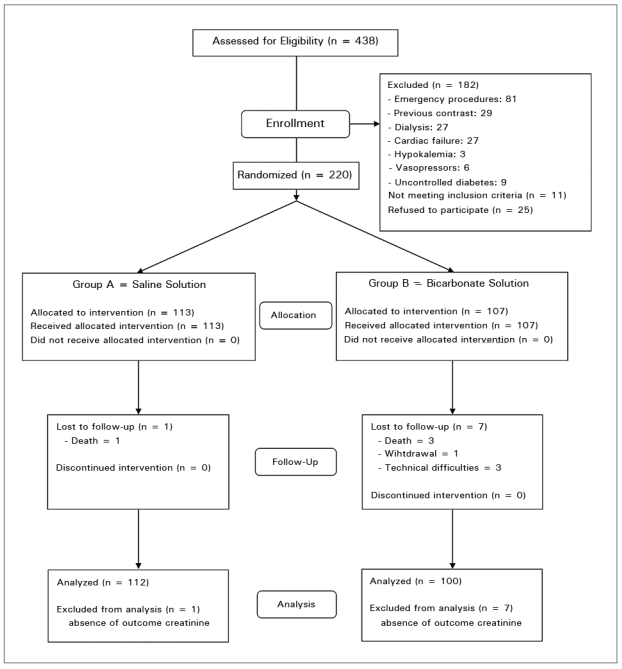
Results

Between May 1, 2007 and February 7, 2008; 1180 patients were screened and 438 were considered eligible for the trial. After 207 exclusions, 231 patients were randomly assigned to treatment either with bicarbonate solution (111 patients) or with normal saline solution (120 patients). Among those randomized, 11 patients were never exposed to contrast dye (4 in the bicarbonate solution group and 7 in the saline solution group). Thus, 220 patients were the final study population (Figure 1). There were not creatinine values after the procedure in 8 patients, seven in the bicarbonate group and one in the saline group. The reasons were death in four patients (three in bicarbonate group and one in the saline group), withdrawal of the study in one patient and technical difficulties in three patients.

Characteristics of the 220 patients completing the study are shown in Table 1. There were not important differences between the groups in baseline characteristics except in chronic renal disease, which was more frequent in the saline group.

The mean creatinine value after the procedure was 1.26 mg/dL in the saline group and 1.22 mg/dL in the bicarbonate group (mean difference: 0.036;

Figure 1. Study Flow.



CI 95%: -0.16 to 0.23, $p = 0.865$). The diagnosis of contrast-induced nephropathy, defined by increase in serum creatinine on 25% or more within 2 days after administration of radiographic contrast, was done in twelve patients (12%) in the bicarbonate group and eighth patients (7.1%) in the saline group (RR: 1.68, CI 95%: 0.72 to 3.94). There were no differences in the frequency of adverse events (Table 2).

Discussion

In the present study, the most important finding was the absence of a significant difference for the prevention of CIN when comparing the normal saline solution with bicarbonate solution in adult patients exposed to elective procedures with radiographic contrast dye.

Previous studies have compared bicarbonate solution with normal saline solution as a prophylactic intervention for renal protection.[11,15-17] These studies have tested several infusion protocols in different clinical scenarios with hospitalized patients. Using an infusion initiated one hour before and up to six hours after the procedure, Merten *et al.*[11] found that in 119 patients undergoing elective procedures hydration with sodium bicarbonate was superior to the normal saline solution for the prevention of CIN. However, the study was stopped prematurely because of an apparently not planned interim analysis, which raises some concerns about its interpretation. Using an infusion protocol similar to the Merten's one but in patients with emergency coronariography (n = 59), Masuda *et al.*[15] reported a significant difference in favor of the bicarbonate solution for the prevention of CIN. However, this study also was stopped prematurely based on ethical concerns regarding the risk of CIN in the sodium chloride group. Again, there was not clear specification about stopping guidelines for efficacy or safety monitoring. Ozcan *et al.*[16] compared three strategies of nephroprotection in patients undergoing elective coronariography (n = 264): infusion of sodium bicarbonate, sodium chloride, and sodium chloride plus oral N-acetylcysteine. Solutions were administered six hours before and six hours after the procedure, and they found that bicarbonate was superior to both saline solutions (i.e., alone and combined with N-acetyl-cysteine).

The studies published by Brar *et al.*[17] and Gomez *et al.*[18] in accordance with our findings, did not find differences in the prevention of NIC between the two nephroprotection strategies evaluated, sodium chloride *versus* sodium bicarbonate, in patients undergoing coronariography procedures. In the first study near half of the patients had co-intervention with N-acetyl-cysteine, and the hydration protocol (3 ml/Kg/h before coronary angiographic, decreased to 1.5 ml/Kg/h during the procedure and for 4 hour after the completion of the procedure) was different to the protocol used in our trial.[17] In the last study the hydration protocol was according to the protocol reported by Merten *et al.*[18]

A possible explanation for our results is the use of more volume of saline solution opposition to the studies of Merten, Ozcan and Masuda, in average, the patients assigned to the saline group in our study received 794 ml during 12 hours before the exposition to contrast dye, *versus* 198 ml 1 hour before contrast in the bicarbonate group. Also, the hydration in our study after the procedure was greater in the saline group with 794 ml in 12 hours *versus* 395 ml in 6 hours for the bicarbonate group.

Some studies have evaluated the effect of a co-intervention (N-acetyl-cysteine) plus bicarbonate;[19-21] therefore they are not directly comparable with our study. However, in both clinical trials the bicarbonate plus N-acetyl-cysteine groups presented less incidence of CIN.

Table 1 Baseline characteristics of the study population according to the assigned intervention

Characteristics	Saline Group n = 113	Bicarbonate Group n = 107
Inclusion criteria		
Diabetes Mellitus (%)	22 (19.5)	24 (22.4)
Creatinine ≥ 1,2 mg/dL (%) or	74 (65.5)	64 (59.8)
Both (%)	17 (15)	19 (17.8)
Age, mean (SD) [range]	59.8 (17.2) [18-88]	60.7 (17.1) [20-92]
Men (%)	66 (58.4)	61 (57)
Comorbilities		
Diabetes Mellitus (%)	39 (34.5)	43 (40.2)
Hypertension (%)	67 (59.3)	55 (51.4)
Coronary artery disease (%)	17 (15)	16 (15)
Chronic renal disease (%)	22 (19.4)	11 (10.2)
Heart failure (%)	11 (9.7)	10 (9.3)
Type of procedure		
Angiography	9 (8%)	7 (7%)
Contrast medium volumen, mean (SD) [range], ml	100.6 (38.2) [50-300]	99.3 (43.9) [40-320]
Weight, mean (SD) [range], Kg	66.2 (14.8) [36-110]	65.9 (13.4) [35-110]
Baseline serum creatinine, mean (SD) [range], mg/dL	1.32 (0.32) [0.7-2.7]	1.3 (0.4) [0.4-2.5]
Serum bicarbonate, mean (SD), mEq/L	21.4 (5.13) [7.1-32.2]	21.78 (4.59) [10.7-32.1]
Serum potassium, mean (SD), mEq/L	4.17 (0.63) [3.0-6.5]	4.18 (0.62) [3.0-6.1]

SI conversion factor: to convert serum creatinine values µmol/L, multiply by 88.4.

Table 2 Frequency of adverse events

Adverse Events	Normal Saline Group n = 113	Bicarbonate Group n = 103	*p* value (Fisher's exact test)
Phlebitis	1 (0.9%)	0	1
Hypokalemia	11 (10%)	14 (14%)	0.399
Metabolic Alkalosis	3 (2.7%)	8 (7.7%)	0.118
Decompensated Heart Failure	7 (6%)	3 (3%)	0.338

Many meta-analysis have been published in the last years, in which sodium bicarbonate is compared with normal saline solution.[22-31] Of these, the most favor the use of bicarbonate over normal saline solution. However most of them conclude that there is great heterogeneity and clinical trials with larger number of patients are needed, because studies with less than 200 patients have very low power and drag the results to the benefit.

Several strategies have shown usefulness for the prevention of CIN in diverse clinical circumstances. Hydration with normal saline solution has been considered the standard of care, since it demonstrated a diminution of the incidence of CIN from 14% to 0.7%.[12] Results with bicarbonate solution suggested greater effectiveness of this intervention, theoretically supported in its actions on the oxygen free radicals and consequently in the oxidative phenomena that affect the function of the kidney exposed to contrast dye. Nevertheless, the recent findings in studies with suitable times of hydration with saline solution have shown equivalence in the prevention of the CIN. Moreover, in a recent retrospective cohort study in the Mayo Clinic with 7977 patients, the authors found an increase of the risk of CIN with the use of bicarbonate.[32] The physiopathology or the potential explanations of these findings still are not clear.

Currently, as the understanding of the pathogenesis of the CIN is insufficient, the proposed prophylactics measures are not necessarily excluding. Indeed, they seem to agree in at least one circumstance: the suitable hydration of the patient, in which anyone of the evaluated solutions could be useful to prevent the CIN.

Therefore, the clinical context dictated by the urgency of the procedure, the availability of time, cost of interventions and specific contraindications of

patients, should determine the utilization of any of them. Finally, new trials are required to evaluate in a larger population the utility and safety of combined therapies to prevent CIN.

Limitations

Our study has some limitations. First, the study was performed at a single center, which may limit the generalizability of the results. Second, although the definition of CIN has been established between 48 and 72 hours after exposure to contrast medium, we do not know if the evaluation of renal function later is a better time to establish the real renal damage and the prognosis. Third, our patients were monitored only during hospitalization and we were not able to determine the presence of further complications. Finally, although the saline group showed a trend toward better outcomes this difference did not reach statistical significance. For this reason, despite we did a formal sample size calculation based on realistic assumptions, we cannot discard lack of power as a potential explanation for our results.

Conclusions

Our study demonstrates that the incidence of CIN in patients with elective procedures is similar when using nephroprotection with normal saline solution or bicarbonate solution without differences in the frequency of important adverse events. These results, added to those reported in previous studies, would allow to suggest that hydration with either solution would be appropriate to diminish the incidence of CIN in patients at risk.

Conflict of interest statement

The authors declare that there is not conflict of interest in this study. The results of this study have not been published previously.

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