Prevention of contrast-induced nephropathy by use of bicarbonate solution - preliminary results and literature review

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Abstract

Introduction: The incidence of contrast-induced nephropathy has increased simultaneously with the increase in contrast medium use in diagnostic and interventional procedures. The incidence of contrast-induced nephropathy in the general population is low, but increases exponentially in patients with risk factors, such as diabetes and chronic kidney disease. Several strategies have been used in order to prevent contrast-induced nephropathy. The most efficient strategies are saline hydration (0.9% or 0.45%), use of low- or iso-osmolality contrast medium, and sodium bicarbonate infusion. **Objective:** The aim of this study was to review the pertinent literature and to assess the efficacy of hydration with 1.3% sodium bicarbonate compared with hydration with 0.9% saline solution in preventing contrast-induced nephropathy in high-risk patients. **Material and methods:** A systematic search of the literature was conducted in PubMed by using the following keywords: bicarbonate, nephropathy, contrast medium, and acute kidney failure. In addition, 27 patients with diabetes and/or chronic kidney disease, diagnosed with some kind of cancer were randomized for study. **Results:** None of the patients developed contrast-induced nephropathy characterized as a 0.5 mg/dL-increase and/or a relative 25%-increase in baseline creatinine. **Conclusions:** The literature review strongly suggested that sodium bicarbonate is effective in preventing contrast-induced nephropathy. Regarding the randomized study, saline solution and bicarbonate solution had similar efficacy in preventing contrast-induced nephropathy. However, the small number of patients does not allow definite conclusions.

Keywords: contrast media, sodium bicarbonate, acute kidney failure, sodium chloride.

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Introduction

Currently, iodinated contrast media are widely used in radiological procedures. Intervention radiology widens even more their application. In the United States, they are used in more than 10 million procedures annually, which obviously increase the likelihood of developing contrast-induced nephropathy (CN).[1-2] That entity is the third cause of acute kidney injury acquired at hospitals in the United States, with a prevalence of approximately 11%.[3] Rihal *et al.* have found a prevalence of acute kidney injury after coronary angiography of 3.3%, showing that patients with chronic kidney disease are at higher risk for developing that condition, and that contrast nephropathy increases the risk of in-hospital and late deaths in those patients.[4] Another study with 2,860 patients has reported a 3.7% prevalence, and has confirmed the fact that patients with previous alteration of renal function are at higher risk for developing contrast-induced acute kidney injury.[5] Diabetes mellitus has also been considered a risk factor for developing CN. A recent study with diabetic patients with previous creatinine equal to or lower than 1.3 mg/dL has found a CN prevalence of 12.3%.[6] Unfortunately, several physicians, when requiring a contrast-enhanced exam, are not acquainted with the risk of CN. A research with 203 Israeli physicians at university-affiliated hospitals has shown that more than half did not know about the potential risk for developing CN and less than half of them considered diabetes mellitus type 2 as a risk factor for complications.[7]

Material and Methods

An electronic search was conducted in PubMed for terms, such as nephropathy, contrast medium, bicarbonate, N-acetyl cysteine, acute kidney failure, and the most relevant articles in each subcategory were used for this literature review.

Definition of CN

Although the definition of CN has not yet reached a consensus, currently, CN is most frequently defined as the elevation of at least 0.5 mg/dL in baseline creatinine within the 48 hours following intravenous administration of iodinated contrast medium and/or a reduction of at least 25% in glomerular filtration in that same time interval. It is worth noting that the definition of CN comprises the exclusion of other concomitant causes of acute kidney injury.[8] The type of definition or criterion used influences the result obtained for CN prevalence. For example, in a Japanese retrospective study with 1,157 patients, the CN prevalence, defined as an increase equal to or greater than 0.5 mg/dL, was 4%. When using the criterion of relative increase, that is, an increase equal to or greater than 25% in the baseline value of creatinine, CN prevalence was 13.8%. When considering both criteria, CN prevalence was 13.9%.[9]

Physiopathology of CN

The physiopathology of CN is still controversial. Several mechanisms have been held responsible for kidney injury, but the generation of free radicals and renal vasoconstriction have been considered as the major factors involved in the genesis of the injury.[3]

The effect of the contrast medium on renal perfusion can be divided into two phases. The first lasts a few seconds and is characterized by renal vasodilatation with a consequent increase in renal blood flow. It is immediately followed by the second phase, which is characterized by vasoconstriction and a decrease in blood flow and glomerular filtration.[10,11]

The reduction in renal blood flow can result from the high osmolality of the contrast medium. That would increase intratubular hydrostatic pressure, reducing the glomerular filtration pressure, thus reducing glomerular filtration rate. That theory is supported by the reduction in those adverse effects with the use of a low-osmolality contrast medium.[2,12] Another possible mechanism could be the direct action of increased osmolality on blood vessel musculature, causing vasoconstriction, an apparently calcium-mediated phenomenon. That fact is supported by the decrease in vasoconstriction observed with the use of calcium channel blockers in patients receiving iodinated contrast medium.[10-12]

Adenosine is a vasodilator that acts in the peripheral circulation, but it is a vasoconstrictor for the renal cortex. Studies with dogs have shown that theophylline, an adenosine antagonist, and dipyridamole, its agonist, reduces and increases, respectively, the vasoconstricting effects of the contrast medium.[13,14]

Peptides, such as endothelin, angiotensin II, vasopressin, atrial natriuretic peptide, and bradykinin, play a role in controlling renal hemodynamics. Endothelin, a potent vasoconstrictor, reduces renal plasma flow and glomerular filtration rate. Endothelin, which is released by endothelial cells, has been described as an important substance in the hemodynamic changes observed in CN.[15]

Changes caused by the iodinated contrast medium on vasodilating substances can contribute to acute kidney injury. The contrast medium causes a reduction in the synthesis of nitric oxide (NO) in the renal cortex,[16] and pharmacological inhibition of the action of prostaglandin and NO.[17]

Endothelial dysfunctions caused by diabetes, hypertension, and atherosclerotic disease can explain the increased risk for acute kidney injury due to CN in those conditions.[3]

The vasoconstriction from CN is suggested to be caused by the tubulo-glomerular feedback mechanism, triggered by macula densa, when the latter is in contact with hypertonic solutions. Angiotensin II, adenosine, and calcium can participate as mediators causing vasoconstriction of the afferent arteriole, which results in a reduction in the glomerular filtration rate and increase in renal vascular resistance. There is solid evidence that adenosine is the major mediator of tubulo-glomerular feedback.[12]

Some studies have shown alterations of the proximal tubule produced by a contrast medium, suggestive of a direct cause of injury, based on the alteration in the energetic metabolism of tubules in the presence of the contrast medium.[18,19]

Tubular obstruction has been considered to be a cause of CN based on the observation that nephrograms are usually dense after contrast injection and the kidneys become enlarged, simulating a ureteral obstruction. When persistent, it can cause a reduction in renal plasma flow. However, there is no anatomo-pathological evidence confirming those findings.[11,12]

The increase in proteinuria concomitant with hypertonic contrast medium injection, suggests that an increase in permeability of the glomerular basal

membrane occurs in the presence of iodinated contrast media. The clinical value of that finding is yet to be elucidated, and, to date, its is of no value in monitoring CN.[20,21]

Currently, it is difficult to precisely determine which tubular alterations are directly caused by contrast media and which are associated with ischemia, with cell injury and an increase in the production and decrease in the removal of free radicals.[10,12]

Risk factors for CN

Patients with diabetes and/or previous chronic kidney disease are at the greatest risk for developing CN.[4-6] A reduction in the effective circulating volume and hypovolemia are also considered risk factors for CN. In fact, hydration protects against CN, while the use of diuretics increases the frequency of CN.[22-23] Alterations that cause a reduction in the effective circulating volume, such as cardiogenic shock, use of intra-aortic balloon, hypotension, congestive heart failure, and ejection fraction below 40%, have been listed as possible risk factors for CN.[24] Older studies also considered the female sex as a risk factor for CN. However, a study with 1,383 patients have attributed that to the older age of women undergoing contrast medium procedures, as well as to their poorer previous kidney function, as compared with men.[25]

Prevention of CN

Osmolality

Osmolality of the contrast medium has been associated with the development of CN, high-osmolality contrast media being more nephrotoxic than iso-osmolality or low-osmolality contrast media.[26] On the other hand, the superiority of iso-osmolality contrast media over low-osmolality contrast media is still controversial.[27] McCullough *et al.* have assessed 16 randomized, double-blind studies, in a total of 2,727 patients, and concluded that the use of iso-osmolality contrast medium was better than that of low osmolality contrast medium for preventing CN, mainly in patients with chronic kidney disease and diabetes mellitus.[28] A more recent meta-analysis has compared the use of low-osmolality contrast media with the iso-osmolality contrast medium, iodixanol. It included 16 randomized studies, in a total of 2,763 patients. The use of iso-osmolality contrast medium did not associate with a lower incidence of CN, when the low-osmolality contrast media were assessed as a whole. However, when analyzing the different types of low-osmolality contrast media individually, iodixanol (iso-osmolality contrast medium) caused less CN compared with ioxaglate (RR: 0.58; p = 0.022) and iohexol (RR: 0.19; p = 0.002), but showed no difference when compared with iopamidol, iopromide, and ioversol. Thus, the superiority of the iso-osmolality contrast medium seems to be relative, being effective when compared with some, but not all low-osmolality contrast media. [29]

Volume of contrast medium used

The volume of the contrast medium also influences its nephrotoxicity, and a correlation exists between the use of a greater volume and the increase in the CN frequency.[30] However, a recent study with 5,256 patients undergoing coronary angiography, has found a paradoxical result: the increase in the contrast medium volume associated with the reduction in the incidence of CN. In patients receiving < 115 mL of contrast medium, the incidence of CN was 16%; in those receiving from 115 to 160 mL, it was 14%; in those receiving from 161 to 225 mL, it was 8%; and, finally, in patients receiving > 225 mL, it was 7%. Those differences were statistically significant, and were explained by the authors as a possible tendency in clinical practice. In reality, that study indicates that the volume of contrast medium may not interfere in the genesis of CN.[31]

Saline solution

At the beginning of the 1980s, the first studies were published showing the efficacy of the 0.9% saline solution-based hydration for preventing CN. It is worth emphasizing that, when saline solution-based hydration was simultaneously used with diuretics, the frequency of CN increased.[30,32]

Two small studies (n = 39 and 37 patients) have compared the infusion of a high volume of saline solution (250 to 300 mL/hour) for a shorter period of time (immediately before or during exposure to contrast medium) with the traditional protocols (1 mL/kg/h, initiating 12 hours before exposure). The results were similar for the modified and traditional protocols.[33-34]

The two following studies have compared oral hydration with prolonged intravenous hydration, and the results were contradictory. In the PREPARED study[35], no difference was observed in the development of CN in the group with oral hydration as compared with the group with intravenous hydration. On the other hand, in the study by Trivedi *et al.*[22], the group receiving intravenous hydration developed CN less frequently than the group receiving oral hydration.

In 2002, Mueller *et al.* published a study comparing hydrations based on 0.9% sodium chloride and 0.45% sodium chloride, and showed the superiority of the 0.9% sodium chloride hydration, a result confirmed in other studies.[23,32]

Other maneuvers

Studies on the use of calcium channel blockers are scarce and the results are not consistent.[36] The use of dopamine at the so-called "renal" dose has been studied, and its benefit in preventing CN has not been comfirmed.[37-38] Fenoldopam, an agonist for dopamine receptors has been assessed in three randomized studies. The comparison between fenoldopam and placebo regarding the relative risk for CN has favored fenoldopam, but with no statistical significance.[39-40] The lack of effect of the drug may be attributed to insufficient doses to cause renal vasodilation. The use of theophylline or aminophylline has been assessed in nine clinical trials, and the results were conflicting.[41-44] Other vasodilating drugs that showed no benefit as compared with placebo in preventing CN were the atrial natriuretic peptide,[45] endothelin antagonists,[46] prostaglandin E_1,[47] ACE inhibitors[2,48], and L-arginine.[49] In reality, endothelin antagonists not only did not benefit but also increased the risk of CN for users.[46] Prophylactic hemofiltration has been associated with a reduction in the adverse events related to CN in high risk patients.[50,51] On the other hand, early dialysis after contrast medium use showed no benefit regarding the development of CN.

N-acetyl cysteine

In a pioneering study published in 2000, Tepel *et al.* tested N-acetyl cysteine, an antioxidant, as a protective maneuver against CN. In that prospective, randomized, controlled study, 83 patients were divided into two groups. The N-acetyl cysteine group received hydration with 0.45% saline solution, at a rate of 1 mL/kg/h, initiated 12 hours before and continued for 12 hours after the exam, in addition to 600 mg of N-acetyl cysteine, orally, twice a day, on the day preceding the exam and on the day of the exam. The control group received hydration with 0.45% saline solution, at a rate of 1 mL/kg/h, initiated 12 hours before and continued for 12 hours after the exam, in addition to placebo for N-acetyl cysteine. The primary endpoint was an increase of at least 0.5 mg/dL in baseline creatinine. The prevalence of CN was 2% in the N-acetyl cysteine group (1/41) and 21% in the control group (9/42) ($p = 0.01$).[52] However, no patient in the two groups had clinically significant CN. Thus, that study suggested that N-acetyl cysteine was highly effective in preventing CN. The possible protective mechanisms of N-acetyl cysteine against CN have not yet been totally elucidated. N-acetyl cysteine is known to act as an eliminator of oxygen free radicals. In a study by Drager *et al.*, the levels of 15-isoprostane F2t, a specific marker of oxidative stress, significantly increased in patients receiving iodinated contrast medium but not N-acetyl cysteine, while those levels remained unaltered in patients receiving contrast medium and N-acetyl cysteine.[53]

Zagler *et al.* carried out a meta-analysis with randomized, placebo-controlled studies using N-acetyl cysteine in patients with baseline creatinine > 1.2 mg/dL undergoing coronary angiography, receiving concomitant intravenous hydration, and using low-osmolality contrast medium. The primary endpoint was defined as an increase of 0.5 mg/dL or of 25% in baseline creatinine within 48 hours after the exam. They identified 589 studies and selected 13, based on the above criteria. The total number of patients was 1,892, and the reduction in the relative risk for developing CN favored, in a borderline way, the N-acetyl cysteine group [OR 0.68 (95% CI: 0.46-1.01)]. The authors concluded that the efficacy of the use of N-acetyl cysteine for preventing CN in coronary angiography is unconclusive.[54] Other meta-analyses studying N-acetyl cysteine provided conflicting results, making the real efficacy of using that drug for preventing CN questionable.[54,55]

It is worth noting the existence of an ongoing Brazilian randomized, controlled, multicenter trial (2,300 patients) using either N-acetyl cysteine, 600 mg, orally, every 12 hours (two doses before and two doses after the contrast-enhanced procedure) or placebo, in patients undergoing angiography. The initial endpoint is the occurrence of CN, defined as a 25% increase in baseline creatinine, within 48 to 96 hours after the exam. From September 2008 to April 7th, 2009, in 35 centers, 810 patients were included (mean age, 69 years), 18% with baseline creatinine > 1.5 mg/dL, 57% diabetics, and 13% with a history of heart failure. To date, that is the largest multicenter trial attempting to determine the efficacy of N-acetyl cysteine in preventing CN in patients undergoing contrast-enhanced angiography.[56]

Sodium bicarbonate

The use of sodium bicarbonate in hydration for preventing CN is based on the assumption that the injury

caused by the contrast medium would be potentialized by the acid tubular medium. In 2004, Merten *et al.*[32] published a study comparing the incidence of CN in two groups, one receiving saline solution-based hydration and the other receiving sodium bicarbonate. The study showed a significant difference between the groups, favoring the use of bicarbonate. The positive results of that study encouraged other attempts of urine alkalinization for preventing CN, such as the use of acetazolamide.[57]

Two other important studies involving the use of sodium bicarbonate for preventing CN have been published. The first, with 264 patients, was a prospective, randomized study published in 2007, and compared the incidence of CN in the following three groups: saline solution; bicarbonate; and N-acetyl cysteine + saline solution. Hydration with bicarbonate proved to be better regarding the incidence of CN.[58] The other study published was retrospective, and showed a deleterious effect of bicarbonate on CN. That study assessed 7,977 patients undergoing contrast-enhanced exams, ranging from tomographies to cardiac catheterizations. The incidences of CN were as follows: 11% in the non-treated group; 15% in the group treated with bicarbonate and N-acetyl cysteine; and 31% in the group treated with bicarbonate. However, the retrospective characteristic of the study did not allow adequate stratification of risk factors, and, thus, those results should be interpreted cautiously.[59]

Joannidis *et al.* have analyzed nine randomized clinical trials comparing the use of bicarbonate for preventing CN in 2,043 patients. The OR was 0.45 (95% CI: 0.26-0.79), indicating a beneficial effect of the treatment with bicarbonate as compared with the treatment with saline. However, a significant heterogeneity ($p = 0.016$) and evidence of bias ($p = 0.012$) were identified in the studies. After adjusting, OR was 0.65 (95% CI: 0.36-1.20). That meta-analysis suggests, but does not confirm, that bicarbonate is effective in preventing CN.[60]

Hogan *et al.*, analyzing seven controlled and randomized clinical trials comparing sodium bicarbonate-based hydration with saline-based hydration in 1,307 patients, have found a significant reduction in acute kidney injury associated with the use of contrast medium in patients receiving hydration with sodium bicarbonate [5.96% in the bicarbonate arm versus 17.23% in the saline arm; RR = 0.37 ($p = 0.005$)]. The authors have concluded that, sodium bicarbonate-based hydration proved to be superior to saline-based hydration for preventing CN.[61]

Ho *et al.* have assessed randomized, controlled clinical trials with sodium bicarbonate, and have shown a significant reduction in the risk for CN (defined as an increase > 25% in baseline creatinine) [RR = 0.22 ($p < 0.0001$)]. The prevalence of CN requiring dialysis was 1.4%, and no statistically significant difference was observed between the groups. Considering the limited data available, the study concluded that bicarbonate is superior to saline for preventing CN.[62]

Navaneethan *et al.* have assessed 12 studies comparing hydration with sodium bicarbonate with hydration with normal saline, both with and without N-acetyl cysteine in 1,854 patients. Hydration with sodium bicarbonate significantly decreased the risk of CN [RR = 0.46; (95% CI: 0.26 – 0.82)], with no significant difference in the following: need for dialysis (9 studies with 1,215 patients); in-hospital mortality (11 studies, 1,640 patients); and congestive heart failure. The authors have concluded that hydration with sodium bicarbonate reduced the incidence of CN in comparison with hydration with normal saline.[63]

Meier *et al.* have selected 17 randomized controlled studies comparing sodium bicarbonate-based hydration and normal saline-based hydration for preventing CN in 2,633 individuals. Hydration with bicarbonate associated with a significant reduction in the risk of CN [RR = 0.52 ($p = 0.003$)]. Neither dialysis need ($p = 0.20$) nor mortality ($p = 0.53$) differed. The authors have concluded that sodium bicarbonate-based hydration was superior to normal saline in preventing CN.[64]

Kanbay *et al.* have defined CN as an absolute (≥ 0.5 mg/dL) or relative (≥ 25%) increase in creatinine levels. Primary endpoint was defined as CN, and secondary endpoint as the change in creatinine in relation to baseline value, need for dialysis, and death. Seventeen controlled, randomized trials were pooled. The general prevalence of CN was 11.3%; RR was 0.54 (95% CI: 0.36-0.83) for the comparison between bicarbonate and saline, and 0.57 (95% CI: 0.35-0.95) for the comparison between bicarbonate and N-acetyl cysteine. Neither the need for dialysis nor death rate differed. The authors have concluded that hydration with sodium bicarbonate decreased the prevalence of CN as compared with other forms of prevention.[65]

Thus, several meta-analyses have suggested that sodium bicarbonate-based hydration is superior to saline solution in preventing CN, as shown in Table 1.[60-65]

A recent meta-analysis assessing ten studies has shown conflicting results with the use of N-acetyl cysteine and hydration with sodium bicarbonate

Table 1 Meta-analyses of contrast-induced nephropathy prevention comparing the use of bicarbonate and saline solution

Reference	Definition of contrast-induced nephropathy (creatinine)	Number of studies	RR bicarbonate *versus* saline
Kanbay *et al*[65]	≥ 0.5 mg/dL ou ≥ 25%	17	0.54 (95% CI; 0.36-0.83)
Meier *et al* [64]	Several*	17	0.52 (95% CI; 0.34 - 0.80)
Joannidis *et al*[60]	Not defined	9	0.45 (95% CI; 0.26 - 0.79)
Navaneethan[63]	Not defined	12	0.46 (95% CI; 0.26 - 0.82)
Ho *et al*[62]	≥ 25%	8	0.22 (95% CI; 0.11 - 0.44)
Hogan *et al*[61]	≥ 25%**	7	0.37 (95% CI; 0.18 - 0.714)

* 7 studies ≥ 25%; 2 studies ≥ 0.5 mg/dL; 6 studies ≥ 25% and/or ≥ 0.5 mg/dL. ** most studies.

when compared with the use of N-acetyl cysteine and hydration with saline solution, depending on the definition of CN adopted. When defining CN as the 25% increase in baseline creatinine in 72 hours, the combination of N-acetyl cysteine and sodium bicarbonate showed no significant decrease in the incidence of CN, compared with the group receiving N-acetyl cysteine and saline solution. When adopting the CN definition of baseline creatinine levels ≥ 0.5 mg/dL, a significant protection was observed with the combination of N-acetyl cysteine and bicarbonate [RR: 0.31 (95% CI: 0.11 - 0.7)]. The need for dialysis did not differ.[66]

Table 2 shows the major strategies for CN prevention in patients at risk, the most used methods, and the evidence level for each one.

Preliminary results of our study comparing bicarbonate and 0.9% saline solution

The study comprised 27 patients of the Hospital do Câncer of the Fundação PIO XII of the city of Barretos, São Paulo state, over the age of 18 years, undergoing computed tomography with radiocontrast medium. The patients had their glomerular filtration rate (GFR) estimated by use of the "Modification of Diet in Renal Disease" (MDRD) formula, greater than 30 mL/min/1.73m^2 and equal to or lower than 60 mL/min/1.73m^2, and/or had diabetes mellitus type I or type II. The exclusion criteria were a GFR estimated by use of the MDRD formula out of the study range (unless the patient had diabetes), a change in creatinine level ≥ 0.5 mg/dL in 24 hours preceding the exam, occurrence of pulmonary edema on the day of the exam, non-controlled arterial hypertension, emergency computed tomography, exposure to contrast medium at an interval shorter than 48 hours, allergy to iodinated contrast medium, pregnancy, refusal to provide written informed consent, and administration of dopamine, mannitol, fenoldopam, or N-acetyl cysteine during the study period. Patients were randomized into two groups. Group 1 (bicarbonate) received

Table 2 Methods for preventing contrast-induced nephrotoxicity in patients at risk

Intervention	Most used method	Evidence level	Comments
Intravenous hydration with 0.9% SS)	0.9% SS 1 mL/kg/h, 12 hours before and 12 hours after the procedure	Several randomized studies and meta-analyses[30,32-34]	0.9% SS is superior to 0.45% SS [23,32]
Sodium bicarbonate (154 mEq/L)	NaHCO3 3 mL/kg/h, 1 hour before the procedure and 1 mL/kg/h, 6 hours after the procedure	Several randomized studies and meta-analyses [32,49-54]	Dilute 154 mL of 8.4% sodium bicarbonate in 846 mL of distilled water for obtaining the solution
Type of contrast medium	Low-osmolality or iso-osmolality contrast medium	Some randomized studies and a few meta-analyses [26-28]	The literature is still controversial whether iso-osmolality contrast medium is superior to low- osmolality contrast medium[29]
N-acetyl cysteine	600 mg, orally, 12/12 hours, 24 hours before and after the procedure	Still controversial[54,55]	Large ongoing multicenter study[56]

SS: saline solution.

a solution containing 154 mEq/L of sodium bicarbonate in water, at continuous infusion of 3 mL/kg/h, initiating one hour prior to the procedure, and at 1 mL/kg/h during the procedure and for six hours after the procedure. Group 2 (saline solution) received a solution containing 154 mEq/L of sodium chloride in water, at continuous infusion of 3 mL/kg/h, initiating one hour prior to the procedure, and at 1 mL/kg/h during the procedure and for six hours after the procedure. Primary endpoint was CN, characterized as a 0.5 mg/dL increase in baseline creatinine or 25% decrease in GFR or need for dialysis within 48 hours after contrast medium administration. All patients received 100 mL of an iodinated, non-ionic, low-osmolality contrast medium (Iodexol – 300 mg I/mL – Omnipaque™), and only one patient of the bicarbonate group received 150 mL of contrast medium for the exam. No statistically significant difference was observed between the groups regarding gender, race, body weight, age, and presence of diabetes mellitus or chronic kidney disease. Primary endpoint was not achieved by any patient in the groups studied. Table 3 shows the comparison of the parameters studied in each group prior to the exam and 48 hours after the administration of the iodinated contrast medium.

Conclusion

The use of iodinated contrast media is an important cause of nephrotoxicity in patients considered to be at high risk, particularly those with previous kidney disease (defined as baseline creatinine above the normality range) or with diabetes mellitus.[4-6,53] In that population, the prevalence of contrast-induced nephropathy can reach up to 50%,[50] which was observed in initial, older studies. In more recent studies, using preventive maneuvers, the incidence of CN is around 3%.[4,5] The development of CN increases costs and length of hospitalization, causes residual kidney injury in up to 30% of the times, causes chronic kidney disease stage 5, and is an independent risk factor for greater mortality, specially in the group of high-risk patients.[67]

The use of hydration with sodium bicarbonate is based on the hypothesis that alkalinization of the tubular fluid would reduce the generation of toxic free radicals. Almost all studies using bicarbonate resulted in urine alkalinization.[32,67] It is worth noting that in one of the few studies in which that did not occur, no protective effect was observed with the use of bicarbonate.[68]

Most randomized, controlled studies with an adequate number of patients have evidenced a benefit regarding CN prevention in patients receiving sodium bicarbonate. Likewise, the meta-analyses strongly suggest that the use of sodium bicarbonate be beneficial.[60-65] The most frequently used controls were infusion of saline solution isolated or in association with N-acetyl cysteine.[60-65] It is worth noting that the use of sodium bicarbonate showed no efficacy in decreasing mortality or need for dialysis.[63-65] The use of sodium bicarbonate may have selected the most severely ill patients, by preventing nephrotoxicity in those less severely ill.

The study by From *et al* is the current argument against the use of sodium bicarbonate for preventing CN.[59] In that study, patients receiving sodium bicarbonate had a greater prevalence of nephrotoxicity in comparison with those receiving no treatment and those treated with bicarbonate associated with N-acetyl cysteine. Despite the large number of patients studied (almost 8,000), the study is retrospective, and there was obviously no previous criterion of inclusion or randomization for the groups. A bias of most severely ill or "complicated" patients being assigned to the group receiving bicarbonate may have occurred. It is worth noting that the prevalence of CN was lower in the group with no treatment than in the group receiving bicarbonate.

Table 3 Medians of the laboratory parameters of patients in the bicarbonate (BIC) and saline solution (SS) groups

	BIC			SS		
	Pré	Post	p	Pré	Post	p
Creatinine (mg/dL)	1.0	1.0	0.206	0.95	0.95	0.634
Potassium (mEq/L	4.1	4.2	0.622	4.1	4.4	0.008
Plasma pH	7.38	7.39	0.082	7.39	7.39	0.394
Plasma bicarbonate (mEq/L)	25.5	27.8	0.029	25.9	26.7	0.689
urine pH	6	6	0.068	6	6	1
GFR (mL/min/1.73m^2)	58.3	66.2	0.398	88.9	78.5	0.109

Data are medians; Wilcoxon test.

In conclusion, literature review strongly suggests that the use of sodium bicarbonate in preventing CN is at least as efficient as the use of saline solution isolated or associated with N-acetyl cysteine. That form of prevention can be particularly useful in patients with limitation of infusion of greater saline solution volumes or in patients who cannot receive saline solution 12 hours before contrast medium use.

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