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Prevention of acute renal failure post-contrast imaging in cardiology: a randomized study

N. ALESSANDRI, L. LANZI, C.M. GARANTE, F. TERSIGNI, R. SERGIACOMI, M. PETRASSI, A. DI MATTEO, F. TUFANO

Department of Cardiology, "Sapienza" University, (polo pontino), Rome, Italy

Abstract. – BACKGROUND: The Contrast-Induced Nephropathy (CIN) is the third most common cause of Acute Renal Failure (ARF) and the worsening in a pre-existing Chronic Renal Failure (CRF), with a foreseeable increase of morbidity, mortality, length of the stay in hospital and, as a consequence, of the health costs. We studied the effectiveness of N-AcetylCysteine (NAC) associated with sodium bicarbonate (Na_2HCO_3) infusion in order to prevent CIN in patients undergoing coronary angiography with administration of contrast medium.

MATERIALS AND METHODS: 296 patients with indication to perform coronary angiography were included in a randomized, observational study. All patients were randomly assigned to receive pre- and post-contrast hydration with 1500 ml of 0.9% saline solution infusion (Group A) or NAC (1200 mg × 2 days) + Na_2HCO_3 (Group B). The primary end-point was to examine CIN appearance, defined as a raise in serum values of Cr (Creatinine) ≥ 0.5 mg/dl or ≥ 25% within 24-72 hours after the exposure to the contrast medium.

RESULTS: It has been observed a frequency of CIN of 9.4% in Gr. A compared to 7.2% in Gr. B. Nevertheless, when we put these results through a more accurate screening according to gender, degree of raise in creatinine levels and the extent of change in GFR (Glomerular Filtration Rate), we observed a very different behaviour. In patients with normal Cr and CrCl (Clearance of Creatinine) the frequency of CIN was similar in both group A and B (approximately 5%). In patients with normal Cr but reduced ClCr the use of NAC was more effective than hydration in preventing CIN (0% vs 18% in prevalence respectively in B and A group).

In patients with moderately reduced Cr and CrCl, hydration with saline solution was more effective than NAC + Na_2HCO_3 (8.6% vs 17.6%) while in patients with severe CRF the combined use of NAC + Na_2HCO_3 showed off to be very successful in preventing CIN compared to the merely hydration (0% vs 50%).

CONCLUSIONS: In patients affected by severe CRF who are undergoing investigations with contrast medium administration, such as coronary angiography, the combined use of NAC + Na_2HCO_3 infusion significantly reduces the risk of developing CIN.

In other circumstances the final result is related to the degree of previous GFR or creatinine values alteration or to gender. In such situations the combined use of both substances is more questionable and sometimes ineffective.

Key Words:
Prevention acute renal failure, Contrast-induced nephropathy (CIN), N-acetylcysteine, Bicarbonate.

Abbreviations

CIN = Contrast-Induced Nephropathy
PTCA = Percutaneous Coronary Angioplasty
ARF = Acute Renal Failure
CRF = Chronic Renal Failure;
GFR = Glomerular Filtration Rate
NAC = N-Acetyl-Cisteine
ASA = Acetyl-Salicylic Acid
NaCl = Sodium chloride
Na_2CO_3 = Sodium bicarbonate
♂ = Male gender
♀ = Female gender
Cr-Cl = Creatinine Clearance
Cr = Serum Creatinine
CKD = Chronic Kidney Disease

Introduction

The Contrast-Induced Nephropathy (CIN) is currently the third most common cause of acute renal failure (ARF) and worsening in a pre-existing renal function impairment in patients undergoing diagnostic imaging studies. It is associated with a significant increase in morbidity, mortality, prolonged stay in hospital and, as a consequence, with the increase in health costs[1,2].

Over the past 10 years the use of iodinated radiocontrast agents in the field of diagnostic imaging has greatly increased particularly in

Corresponding Author: Alessandri Nicola, MD; e-mail: Alessandrinicola@libero.it

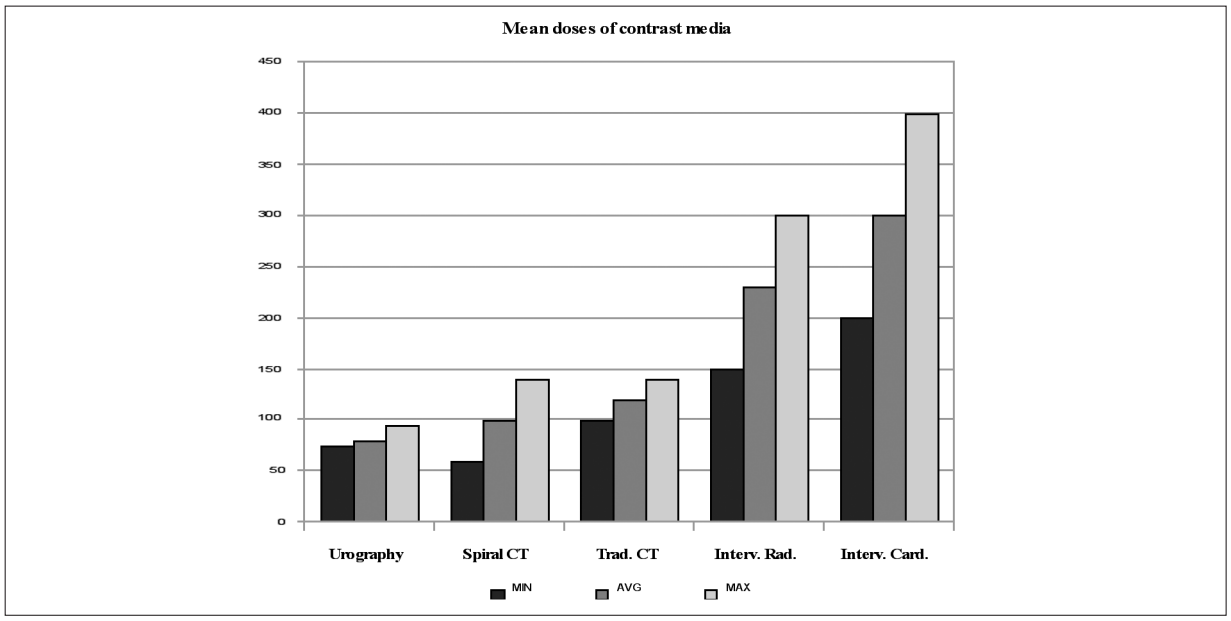

Figure 1. Mean doses of contrast media used in various types of diagnostic radiology and cardiology studies[5].

Cardiology. The contrast media used today are less harmful than in the past. Conversely, compared to other clinical areas, the use of contrast agents in cardiologic procedures such as ventriculography, Percutaneous Coronary Angioplasty (PTCA) or cardiac Computed Tomography is associated with a higher prevalence of CIN[3,4]. This is probably due to the large number of investigations in this area and the higher dosage used (Figure 1).

Adverse reactions to contrast agents are typically classified in: renal/non-renal and early or delayed reactions. The events may be: mild, moderate, serious or of I, II, III, IV grade (Table I). In particular we want to emphasize the renal adverse events of which contrast medium can be responsible, such us a type of usually reversible ARF.

Nephrotoxicity from contrast media is defined as a renal function drop, characterized by a proportional increase in serum creatinine value ≥25% or its absolute increase of 0.5 mg/dl (44 mol/L) compared to baseline which occurs within 24-72 hours after the administration of contrast agents in the absence of alternative causal factors[6].

Although ARF or exacerbation of a pre-existing chronic renal failure (CRF) are complications not so rarely observed after a diagnostic procedure with administration of contrast medium, such clinical picture is usually reversible if the creatinine serum level returned to baseline values within 2-3 weeks[6,7].

In other cases the nephrotoxicity of contrast media may show itself in the form of ARF with the onset of oliguria, increased serum creatinine > 1.5 mg/dl and by degrees the need for haemodialysis or the progressive development of a chronic renal function damage[7-10].

Because of the complex mechanisms underlying the onset of contrast nephropathy, until now there is no consensus in using a fixed prophylactic protocol in order to prevent CIN. Many strategies have been taken into account to prevent such complications. Among those the recent introduction in clinical practice of the use of N-acetylcysteine (NAC) seems to be able to reduce the appearance of CIN.

More conventional strategies, besides, entail the use of sodium bicarbonate in 5% glucose solution or intravenous saline (NaCl 0.9%) infusion before and after the use of contrast medium and are considered useful in reducing the development of CIN

Table I. Degree of anaphylactic and anaphylactoid reactions.

Grade I	Only marks on the skin: hives, rash
Grade II	As the I most nausea, cough dyspnea, tachycardia, hypotension
Grade III	As the II most vomiting (not just being sick), diarrhoea, bronchospasm, cyanosis, shock
Grade IV	Cardiac arrest

in patients at high risk for ARF[11]. As the volume depletion is a risk factor for the development of renal failure, the intravenous administration of a saline solutions is able to correct a possible subclinical volume reduction, a condition due to osmotic diuresis produced by contrast media.

In this randomized study was reported the results of 296 patients, undergoing coronary angiography, pre-treatment hydration protocol with sodium chloride or sodium bicarbonate plus orally administration of NAC. The main aim was to identify patients at major risk of developing CIN and to turn out a clear and unanimously accepted protocol to prevent CIN in patients undergoing imaging studies with contrast media.

Materials and Methods

In this retrospective investigation we analyzed a total of 296 patients who underwent an hemodynamic study and coronary angiography with or without percutaneous angioplasty in the Catheterization Laboratory of the Cardiology Department, "Sapienza" University (Pontine Branch), between February 2008 and June 2010, equal to 29 months of observation.

All patients with ischemic heart disease and indication for a coronary angiography were randomly included in this study. Exclusion criteria were the presence of acute renal failure, haemodialysis replacement, known allergies in general and in particular for the contrast medium or N-acetylcysteine. In each patients the presence of cardiovascular risk factors such as diabetes, hypertension, hyperlipidemia, age, sex, etc. was evaluated.

All patients were administered a dose of contrast agent between 1.5 mL and 3 mL/kg. The total dose changed depending on the number of projections or procedures performed. Moreover, it has never been performed a ventriculography control. In all cases we used a non-ionic contrast medium with low osmolality (Iomeron).

The whole group was treated with prophylactic antibiotic therapy (3rd generation cephalosporin 30 mg/kg per day in 2 doses), while anti-platelet therapy was discontinued 3 days before the procedure (ASA and/or ticlopidine) and replaced with low molecular weight heparin (1 IU/kg twice a day). Therapy with nitrates and calcium channel blockers was maintained.

Patients were randomly selected to receive a treatment with 0.9% sodium chloride (NaCl) solution infusion before and after the coronary angiography or N-acetylcysteine (NAC) administration plus hydration with sodium bicarbonate (Na_2HCO_3).

Group A patients (Gr. A) were assigned to receive treatment with saline solution of 0.9% NaCl twelve hours before the angiographic study and continued the infusion until the day after the procedure (500 mL of 0.9% NaCl three times a day).

For patients in Gr. B (Gr. B) N-acetylcysteine (NAC) was administered twice a day in two doses of 600 mg from the day before until the day after the procedure. These patients also received 160 mEq of Na_2HCO_3 in 350 mL of 5% glucose solution 2 mL/kg/h since two hours before the administration of contrast medium. The infusion was prolonged for the following six hours after the procedure with an infusion rate of 1 mL/kg/h.

According to gender (males ♂ and females ♀), creatinine clearance (CrCl) and serum creatinine (Cr) values we further subdivided the patients in:

Group A (Gr. A):

A1: Cr ♂ < 1.2 mg/dL, ♀ ≤ 1 mg/dL and Cl-Cr > 70 mL/min; 56 ♂ with mean age 60.43±7.09 years and 22 ♀ with mean age 63.18±8.46 years;

A2: Cr ♂ < 1.2 mg/dL, ♀ ≤ 1 mg/dL and Cl-Cr > 40 < 70 mL/min; 9 ♂ with mean age 79±3.61 years and 7 ♀ with mean age 77.21 ± 3.14 years;

A3: Cr ♂ < 1.2 mg /dL and ♀ ≤ 1 mg/dL and Cl-Cr < 40 mL/min; 0 ♂ and 0 ♀.

A4: Cr ♂ ≥ 1.2 mg/dL, ♀ > 1 mg/dL and Cl-Cr > 70 mL/min; 10 ♂ with mean age 57.4±7.27 years, 0 ♀.

A5: Cr ♂ ≥ 1.2 mg/dL, ♀ > 1 mg/dL and Cl-Cr > 40 < 70 ml/min; 32 ♂ with mean age 71±9.29 years and 14 ♀ with mean age 69.76±10.79 years;

A6: Cr ♂ ≥ 1.2 mg/dL ♀ > 1 mg/dL and Cl-Cr < 40 mL/min; 0 ♂ and 8 ♀ with mean age 76.75±8.88 years;

Group B (Gr. B):

B1: Cr ♂ <1.2 mg/dL and ♀ ≤ 1 mg/dL and Cl-Cr > 70 mL/min; 52 ♂ with mean age 60.69±8.56 years and 24 ♀ with mean age 61.33±6.8 years;

B2: Cr ♂ < 1.2 mg/dL and ♀ ≤ 1 mg/dL, and Cl-Cr > 40 < 70 mL/min; 6 ♂ with mean age 75.5±3.54 years and 8 ♀ with mean age 72±5 years;

B3: Cr ♂ < 1.2 mg/dL and ♀ ≤ 1 mg/dL and Cl-Cr < 40 mL/min; 0 ♂ M , 0 ♀.

B4: Cr ♂ ≥ 1.2 mg/dL and > ♀1 mg/dL and Cl-Cr > 70 mL/min; 0 ♂, 0 ♀.

B5: Cr ♂ ≥ 1.2 mg/dL and ♀ > 1 mg/dL and Cl-Cr > 40 < 70 mL/min, 26 ♂ with mean age 71.15±5.6 years and 8 ♀ with mean age 67.75±11.98 years;

B6: Cr ♂ ≥ 1.2 mg/dL and ♀ > 1 mg/dL and Cl-Cr < 40 mL/min; 8 ♂ with mean age 81.23 ± 3.18 years and 6 ♀ with mean age 57.75 ± 4.74 years.

According to our reference laboratory, the normal range for blood creatinine value ranged from 0.7 to 1.2 mg/dL for men and from 0.5-1 mg/dL for women while creatinine clearance, corrected for gender and age, was considered normal for the mean values between 70-130 mL/min.

The measurements were performed in our Laboratory 24 hours before the procedure as well as 24, 48 and 72 hours after the procedure. If values emerged to be high, creatinine monitoring was continued until them returned to normal levels.

The primary endpoint in our study was to observe the development of CIN, defined as a proportional increase in serum creatinine ≥ 25% or an absolute increase of 0.5 mg/dL (44 mol/L) compared to baseline within 24-72 hours after administration of contrast medium.

Statistical Analysis

Data were expressed as mean ± SD. The difference in serum creatinine before and 24, 48 and 72 hours after the procedures has been developed by statistical analysis with Student's t-test. *p* value < 0.05 was considered statistically significant.

Results

296 patients (Males = 199, Females = 97) with a mean age of 65.55 ± 9.95 years (M = 64.52 ± 9.58 F = 66.08 ± 9.64) were subjected to continuous observation of renal function and divided into: Gr. A composed of 158 patients (M = 107, F = 51) pre-treated with saline solution and Gr. B consisting of 138 patients (M = 92, F = 46) pre-treated with NAC and sodium bicarbonate.

On average it was observed the presence of 2±1 cardiovascular risk factors among the sample with an overall percentage of 34% of diabetics, 70% and 50% of hypertensive and dyslipidemic (cholesterol triglycerides) patients respectively.

Group A

Consists of 158 patients with an average age of 65.06±10.04 years (M= 64.46±9.81, F = 68.18±10.2). Of this group 25% of patients were diabetic, 59% hypertensive, 39% dyslipidemic.

Group B

Consists of 138 patients with an average age of 64.25±9.01 years (M = 64.6±9.38, F = 63.53±8.38). Of this group 42% of patients were diabetic, 78% hypertensive, 59% dyslipidemic.

Patients belonging to Gr. A were treated before and after the use of contrast medium with NaCl 0.9% infusion and were examined for the appearance of CIN by monitoring their pre- and post-contrast blood values. The development of post-contrast nephropathy was, thus, verified in the various subgroups (Tables II-III):

Gr. A1: 4 out of 78 patients or a percentage of 5.1% (of which Gr. A1 M = 4; Gr. A1 F = 0) showed an average increase of Cr values of 50% equivalent to a mean fluctuation from a basal creatinine value of 1mg/dL to 1.5 mg/dL after 48-72 hours;

Gr. A2: 3 out of 16 patients or a percentage of 18% (of which Gr. A2 M = 3; Gr. A2 F = 0) showed an average increase of Cr values of 35% corresponding to a fluctuation from a basal creatinine value of 1 mg/dL to 1.4 mg/dL after 48-72 hours;

Table II. Frequency of contrast-medium-induced nephropathy in Gr. A.

Prevalence of contrast-medium-induced nephropathy in Gr. A			
Group	**Male**	**Female**	**Total**
A1	4/56 (7.1%)	0/22	4/78 (5.1%)
A2	3/9 (33%)	0/7	3/16 (18%)
A3	0	0	0
A4	0/10	0	0/10
A5	0/32	4/14 (17%)	4/46 (8.6%)
A6	0	0/8 (50%)	0/8 (50%)
Total	**7/107 (6.5%)**	**4/46**	**15/158 (9.4%)**

Table III. Frequency of contrast-medium-induced nephropathy in Gr. B.

Prevalence of contrast-medium-induced nephropathy in Gr. B			
Group	**Male**	**Female**	**Total**
B1	2/52 (3.8%)	2/24 (8.3%)	4/76 (5.2%)
B2	0/6	0/8	0/14
B3	0	0	0
B4	0	0	0
B5	4/26 (15%)	2/8 (25%)	6/34 (17.6%)
B6	0/8	0/6	0/14
Total	**6/92**	**4/46**	**10/138 (7.2%)**

Gr. A4: anybody in Gr. A4 showed a statistically significant increase of creatinine values before and after contrast medium administration;

Gr. A5: 4 out of 46 patients or 8.6% (Gr. A5 M = 0 Gr. A5 F = 4) showed an average increase of Cr of 40% corresponding to a fluctuation from a mean creatinine value of 1.35 mg/dL to 1.9 mg/dL in the next 48-72 hours;

Gr. A6: 4 out of 8 patients that is a percentage of 50% (Gr.A6 M = 0, Gr. A6 F = 4) showed an average increase of Cr values of 30% corresponding to a fluctuation from a mean basal creatinine value of a 1.7 mg/dL to 2 mg/dL in the subsequent 48-72 hours.

Group B patients were pre-treated with orally NAC plus Na_2HCO_3 infusion and afterwards the development of contrast medium-induced nephropathy was observed in various subgroups (Table VII):

Gr. B1: 4 of 76 patients or a percentage of 5.2% (Gr. B1 M= 2, Gr. B1 F= 2) showed an average increase of Cr values of 40% corresponding to a mean creatinine swinging from a baseline value of 0.8 mg/dL to 1.2 mg/dL after 48-72 hours;

Gr. B2: anybody in Gr. B2 showed a statistically significant increase of creatinine values before and after contrast medium administration;

Gr. B5: 6 of 34 patients or a percentage of 17.6% (Gr. B5 M = 4, Gr. B5 F = 2) showed an average increase of Cr values of 40% corresponding to a mean creatinine fluctuation from a baseline value of 1.43 mg/dL to 1.77 mg/dL past 48-72 hours;

Gr. B6: anybody in Gr. B6 showed a statistically significant increase of creatinine values before and after contrast medium administration;

Discussion

Classification of Contrast Media

Contrast agents are classified according to their osmolality, structure (monomeric or dimeric) and hydrophily (Tables III and IV).

All of them hold as iodine carrier a benzoic tri-iodide ring in positions 1-3-5. The contrast agents that enclose a single ring are defined benzoic acid monomers; those containing two linked rings (and six atoms of iodine) are dimers. In addition to the number of benzoic rings, the contrast media are categorized by the nature of the ligands in 2-4-6 position: if them are carboxyl radicals (which in aqueous solutions are dissociated into hydrogen and carboxylic ions) the medium is defined ionic. In presence of nitrogen residues, there is no need for salification with ions of opposite charge and the contrast medium is definite as non-ionic[12].

Iodinated contrast agents, classically divided into ionic or non-ionic, differ from each other according to their osmolality (Table V):

- First-generation contrast agents are high-osmolar ionic monomers (about 1500 to 1800 mOsm/kg H_2O);
- Second-generation contrast media also termed low-osmolar, are non-ionic monomers with lower osmolality (about 600 to 850 mOsm/kg) compared to the first-generation contrast agents;

Table IV. Classification of contrast media.

Agent	Structure	Osmolality (mOsm/kg H_2O)
I generation	Ionic monomers	1500-1800
II generation	Non-ionic monomers	600-850
III generation	Non-ionic dimers	290

- New contrast media are non-ionic dimer molecules with an osmolality lower than the previous ones and iso-osmolar with normal plasma.

In addiction, contrast media are divided into hepatotropic and those with more accentuated renal tropism. The last one are used in hemodynamic procedures and between them do not show significantly dissimilar pharmacokinetic profiles. All are water soluble, have low plasma protein binding and are filtered by the glomerulus in renal excretion within maximum 20-30 minutes after administration. The half-life of this type of contrast medium is about 1-3 hours. 24 hours after it is deleted from 70 to 85% of the injected dose. Only 15-30% of it is removed by the extra-renal route[12]. Although in patients with chronic renal failure and reduced filtration fraction its elimination is slow and can last for weeks.

Hypotesis on the Contrast Induced Nephropathy Pathogenesis

The pathways by which contrast media can induce ARF are still obscure. Kidney damage can be induced by an alteration in glomerular's hemodynamic and/or by direct toxicity on renal tubules with concomitant tubular obstruction. These mechanisms may act individually or combined in various ways.

It's rare to observe CIN in well working kidneys, so it is hypothesized that some renal function impairment would be necessary to display the clinical picture. In dogs, the pathological picture is characterized by vacuolation of the proximal tubule cells and initially by medullary vasodilatation followed by sub-cortical vasoconstriction. The vasoconstriction is mediated in part by endothelin and adenosine, but also by high osmolarity contrast medium[13,14], responsible for vessels compression induced by the raised hydrostatic pressure of the tubulo-interstitium. Despite of increasing blood flow in renal medulla, it occurs a medullary hypoxia that may lead to ischemic damage due to the imbalance between the O_2 supply and the augmented demand lead by the contrast medium induced osmotic diuresis[(15)]. These events might explain the lower frequency of renal failure induced by iso-osmolar or low-osmolality contrast agents[16]. Finally, even though it is suggested a role of Tamm-Horsfall protein in inducing tubular obstruction, there are no considerable evidences in this regard[17].

The direct toxicity of contrast agents was well detected by studies *in vitro*[18,19] and it's resultant to the cellular integrity destruction, free radicals generation and apoptosis.

In light of the items listed so far we can say that the processes implicated in the pathogenesis of contrast nephropathy are various and include: renal ischemic injury, toxic damage against tubular epithelial cells, intra-tubular obstruction, shift of the haemoglobin oxygen saturation curve, immunological reactions.

The prevalence of contrast nephropathy is highly variable according to data reported in literature: it ranges from 2% in low risk population up to 50% in high-risk population. This vast variability comes from: the presence or absence of risk factors for renal failure, the lack of an unambiguous definition of post-contrast nephropathy, the volume and the type of contrast medium used, the retrospective or prospective prevalence evaluation method, the characteristics of radiological procedure in use and from the significantly increased frequency of cardiological contrast medium-using procedures in emergency settlements on patients burdened with risk factors for ARF development[20,21] (Tables VI and VII). The estimated mortality for patients who develop this complication has been reported to be higher than 34%[22].

According to the most established hypothesis on the pathogenesis of post-contrast damage, it appears to be due to renal vasoconstriction or oxygen free radicals generation associated with dehydration and/or volume depletion induced by contrast medium hyperosmolality. These factors promote the onset of a renal function impairment.

Nevertheless, the mechanisms underlying CIN appear to be numerous and only partially known.

Table V. Type of contrast media.

Ionic monomers	Ionic dimers	Non-ionic dimers	Non-ionic monomers
Diatrizoate (Gastrografin) Iothalamate (Conray)	Ioxaglate (Hexabrix)	Iodixanol (Visipaque)	Iopamidol (Iopamire) Iomeprol (Iomeron) Iohexol (Omnipaque) Iopromide (Ultravist) Iobitrilol (Xenetix)

Among them we would like to remember the direct toxic effect of contrast media on tubular cells, free radicals induced damage and the vasoconstriction that results in medullary ischemia.

Many strategies have been tested in animal models and in humans to prevent the development of CIN. Among these, a large interest has been facing two substances such as N-acetylcysteine and Na_2HCO_3 responsible for a high protective role, in opposition to contrast media harm, in reducing the chemical action of free radicals and modulating osmolality in the renal tubules, which results in a defensive function against the development of CIN[23-25]. N-acetylcysteine (NAC) a non-toxic derivative of L-cysteine, known as a mucolytic agent, is actually the precursor of a potent antioxidant agent such GSH and exerts vasodilator effect and cell's detoxifying properties. It is inexpensive, easy to use and above all characterized by the absence of significant side effects.

Several literature's reported data comparing the merely hydration to pre-treatment with Na_2HCO_3 infusion or NAC administration showed a nephropathy relative risk reduction of 56%. Despite this preliminary remarks somebody disagrees in defining NAC and/or Na_2HCO_3 protective for renal function than hydration alone. These works, whose interpretations often oppose each other, gave an unclear model: the heterogeneity of the groups examined and compared with each other. In these type of works, patients with normal Cr value and normal or pathological Cl-Cr value are compared to those with altered Cr value and not divided according to the severity of this alteration.

It is known that the behaviour of a normal kidney in response to a detrimental factor, such as contrast media, is sufficient to face the injury compared to a kidney with a 80% of pathologic or lacking gromeruli and a markedly reduced glomerular filtration rate.

Looking at the overall results of the two groups analyzed (Gr. A vs. Gr. B) we can argue that them do not diverge from those showed in literature on behalf of NAC or Na_2HCO_3 clinical use. In our records, in fact, Gr. B is more protected from renal impairment than Gr. A (7.2% vs 9.4%).

Table VI. Risk factors for CIN.

Risk factors for contrast-induced nephropathy
1. Renal failure (Cr > 1.5 mg/dL or Cl- Cr < 60 mL/min)
2. Heart failure or other causes of renal hypoperfusion
3. Diabetic nephropathy (DN)
4. High dose of contrast material
5. Multiple myeloma

Table VII. Impact of CIN in regard of risk factors and degree of renal impairment.

Impact of cin in regard of main risk factors and degree of renal impairment
Negligible if normal renal function, even in presence of DM
4-11% if Cr 1.4-4 mg/Dl
9-38% with Cr 1.5-4 mg/dL and DM
> 50% with Cr > 4.5 mg/dL, especially those with DM

In patients with normal Cr and Cl-Cr values, CIN development revealed to be essentially comparable in both groups B1 and A1 (5.2% vs 5.1%). These results emphasize that, in the absence of a kidney damage, the risk of developing contrast- induced nephropathy is very low and that the treatments were equally effective, even if were observed small variations between genders.

When Cr value was normal but Cl-Cr was reduced we detected a significant difference between Gr. B2 and Gr. A2. In such circumstances the combined use of both substances (NAC + Na_2HCO_3) shows to have a high protective effect against CIN (0% vs 18% respectively).

In patients with baseline medium-to-moderate renal insufficiency (Gr. A5 and Gr. B5) the simply hydration with saline solution has been shown to significantly reduce the occurrence of contrast induced nephropathy, whereas in the group treated with NAC this complication was more frequent (8.6% vs 17.6% respectively). Yet in these subgroups can be observed a slight difference between males and females.

The maximum protecting effectiveness of the two combined substances (N-acetylcysteine and Na_2HCO_3) was observed in the groups of patients with more impaired renal function (Gr. B6 and Gr. A6). In fact, the estimated prevalence of CIN in patients with severe renal insufficiency (Cr > 1.5 mg/dL and Cl-Cr < 40 mL/min) was 0% for Gr. B6 while for Gr. A6 patients, treated with simply hydration, it was about 50%.

Table VIII shows how the only hydration compared with the combined use of NAC + Na_2HCO_3 or placebo in several studies has had, in different groups of patients, a variety of protective behaviours that can be adequately explained by recent knowledge on renal protection mechanisms against the contrast media and on the physiopathology of renal impairment.

Table VIII. Randomized trials evaluating NAC for the prevention of Radio-CIN.

Lead Author	N° of patient	Placebo/group RCIN %	Renal entry criteria (Cr/Cl-Cr)	Oral NAC	Dose contrast
Positive studies					
Baker et al[26]	80	21%		IV dose	Coronary cath./PCI
Diaz-Sandoval et al[27]	54	45%	< 1.4/< 50	TP	Coronary cath./PCI
Kay et al[28]	200	12.2%	< 1.2/60	TP	Coronary cath./PCI
Shyu et al[29]	121	24.6%	< 2/< 40	400 mg × 2	Coronary cath /PCI
Tepel et al[30]	83	21.4%	< 1.2/50	TP	Coronary cath./PCI
Negative studies					
Allaqaband et al[31]	123	15%	< 1.6/60	TP	Coronary cath./PCI
Boccalandro et al[32]	179	12.3%	< 1.2/50	TP	Coronary cath./PCI
Briguori et al[33]	183	11%	< 1.2/70	TP	Coronary cath./PCI
Durham et al[34]	79	22%	> 1.7	1200 mg × 1	Coronary cath./PCI
Goldenberg et al[35]	80	7.7%	> 1.5	600 mg × 2	Coronary cath./PCI
Loutrianakis et al[36]	47	13%	> 1.5	TP	Coronary cath./PCI

TP = Tepel Protocol, 600 mg orally twice daily on the day before and the day of procedure; IV = Intravenous; NAC = N-acetylcysteine; RCIN = Radio contrast – induced nephropathy; Coronary cath. = Coronary catheterization; PCI = Percutaneous Coronary Intervention.

Conclusions

Nowadays there isn't still a well acknowledged therapy for the whole prevention of contrast-induced nephropathy. The common agreement is that general preventive measures should always be used, such as: opting for alternative examinations when possible, the use of low doses contrast medium, the avoidance of repeated surveys and of nephrotoxic substances or volume depletion during the employ of contrast agents.

Regarding to our results, besides it seems appropriate to classify the degree of renal insufficiency in order to expect the risk of CIN and better prevent it. In fact, the protective function of hydration or NAC + Na_2HCO_3 varies according to the degree of CKD (Chronic Kidney Disease).

The results from that randomized study demonstrate that the association of N-acetylcysteine with Sodium Bicarbonate is responsible for great benefit in patients with severe renal impairment and high risk of CIN.

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