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Study of combination of ascorbic acid and N-acetylcysteine in prevention of contrast induced nephropathy in patients with moderate renal insufficiency

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ABSTRACT

Introduction and aims: Despite fluid administration is the most effective strategy in contrast induced nephropathy (CIN) prevention, still the estimated prevalence of CIN up to 50% in high-risk patients. There is still a great debate as regarding the administration of antioxidants in reduction of CIN incidence. This study aims to determine whether addition of ascorbic acid to IV acetylcysteine could reduce CIN prevalence in patients with moderate chronic kidney disease.

Methods: We conducted prospective, randomized, double blind, placebo-controlled trial on 106 patients scheduled for elective coronary or aorto-iliac angiography. The patients were divided in two groups: Group 1 (n = 53) receive hydration and placebo while Group 2 (n = 53), received IV 1200mg acetylcysteine , 2g ascorbic acid and hydration before and after the procedure. Occurrence of more than a 25% increase in serum creatinine level within 5 days after contrast administration considered as CIN.

Results: The incidence of CIN was significantly lower in Group 2 (3.7%) compared with Group 1 (12%) p=0.02. A lower average serum creatinine (P= 0.01) and a higher average creatinine clearance was found in Group 2 after 5 days of contrast administration (P= 0.01). Patients receiving placebo had a longer hospital stay than patients receiving a combination of NAC and ascorbic acid (p<0.02).

Conclusion: In our study, prophylactic oral administration of the antioxidant ascorbic acid in addition to high dose IV N-acetylcysteine diminish the incidence of CIN in patients with moderate CKD with minimal adverse effects and at a low cost.

Key words: Ascorbic acid; N-Acetylcysteine; Contrast Nephropathy; Moderate CKD.

INTRODUCTION

Contrast induced nephropathy (CIN) defined as an elevation of serum creatinine of more than 25% or ≥0.5 mg/dl from baseline within 48 h after excluding other factors that may cause nephropathy, with serum creatinine levels peaking in 3-5 days and gradually returning to baseline levels within 7-10 days [1]. CIN was first described by Bartels et al in 1954 when he reported a case of acute renal failure following intravenous pyelography in a patient with myelomatosis [2].

The estimated prevalence among patients who have no risk factors is negligible ≤ 3% but it can be as high as 50%, depending on the presence of risk factors [3,4].

Due to the high prevalence of coronary artery disease , peripheral artery disease and atherosclerosis in chronic kidney disease (CKD) patients [5] and with the fact that, the angiography is currently replacing other procedures and remains the gold standard for diagnosis [6]; the preexisting renal dysfunction seems to be an important risk factor for CIN and this was proved in several researches [3,4].

Multiple mechanisms have been proposed for the pathogenesis of CIN including :reactive oxygen species (ROS) and endothelial dysfunction due to oxygen free-radical generation during post-ischemic reperfusion and based on this mechanism, the effect of the antioxidant as acetylcysteine and ascorbic acid in preventing CIN have been investigated with a conflicting results.

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N -Acetylcysteine became a popular, inexpensive agent for CIN prevention [7-9] and other agents as ascorbic acid still had unclear role but with encouraging results [10].

Aim of the Study:

Consequently, the proposed study is to determine whether addition of ascorbic acid to high dose IV acetylcysteine can prevent acute deterioration in renal function in patients with moderate renal insufficiency who undergo elective aorto-iliac or coronary angioplasty.

PATIENTS AND METHODS

Prospective, randomized, double-blind, placebo-controlled three years trial conducted on 106 patients scheduled for elective coronary or aorto-iliac angiography with or without intervention at Cairo University Hospitals from January 2014 to December 2016. All participants had agreed to take part in the study and had signed a declaration of informed consent.

All the patients had stable moderate renal insufficiency (creatinine clearance <60 mL/min). The Modification of Diet in Renal Disease (MDRD) equation was used to estimate the GFR of the study subjects.

Cardiac catheterization with coronary angiography and/or percutaneous coronary intervention was performed according to local standards using the femoral approach.

Participants were randomly assigned to receive either IV 1200mg acetylcysteine and 2g ascorbic acid or placebo at least 2 hours before the start of the index procedure, followed by 1200mg acetylcysteine and 2g ascorbic acid or placebo the night and the morning after the examination.

All the patients independently from the randomization will receive hydration with at least 100ml/h IV 0.9% or 0.45% sodium chloride in water, from randomization until at least 6 hours after the examination. All patients received low-osmolality contrast agent (ultravist iopromide).

Careful history and examination were done to assess comorbid conditions such as diabetes mellitus and hypertension, previous exposure to contrast media, hydration status and the amount of the contrast medium were recorded for every patient.

Occurrence of more than a 25% increase in serum creatinine level within 5 days after contrast administration was considered as CIN**;** change in creatinine clearance and serum creatinine level were examined.

The main exclusion criteria were a glomerular filtration rate (GFR) <30 ml/min, regular dialysis before angiography, acute renal failure secondary to other pathologies, recent exposure to radiographic contrast media (within 2 days of the study) and inability to provide informed consent was were also considered as exclusion criteria.

Selected patients continued ACEIs or ARBs use due to a clinical indication and after the recommendations by their cardiologist.

Authorization had been given from the Scientific Council and the Ethical Committee of our hospital.

Statistical analysis

Data statistically described in items of mean and mode ± SD. Comparison of numerical variables between the study groups was done using Student t test for independent samples when comparing two groups and one-way analysis of variance (ANOVA) test when comparing more than 2 groups. Within group, comparison of numerical variables was done using paired t test. Correlation between various variables was done using Pearson moment correlation equation for linear relation. P values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

RESULTS

As demonstrated from table-1; 106 patients with stable moderate renal insufficiency who underwent elective coronary and aorto-iliac angiography with or without intervention between January 2014 to December 2016 at Cairo University Hospitals were included in the study, and they divided into two groups.

Group 1 (control group) included 53 receiving placebo and hydration both before and after the examination. Group 2 included 53 patients who receive IV 1200 mg acetylcysteine, 2g oral ascorbic acid and hydration both before and after the procedure.

As shown in table-1 : Baseline characteristics were generally comparable between the groups studied as regarding age, sex, as most of the study populations were males and BMI. In addition, they are similar as regarding the presence and the grade of hypertension.

Diabetic and hypertensive nephropathy were the most common causes of renal impairment of our patients followed by glomerulonephritis, obstructive uropathy and polycystic kidneys in both groups.

Both groups had comparable kidney function tests. Average baseline serum creatinine level was (1.39 Vs 1.52) mg/dl in Group 1 and 2 respectively and average the plasma urea level was (29.8, and 27.5) mg/dl in Group 1 and 2 respectively but these results are statistically insignificant.

As regarding, the angiographic procedure, 68% versus 71.7% undergoes coronary angiography in Group 1 and 2 respectively while aorto-iliac angiography were done in 32% and 28.3% respectively in Group 1 and 2. The volume of the contrast agent administered during angiography was comparable in both groups as shown in table 1.

Table-1: Basic characteristics of both groups

Characteristic	Control group (N=53)	Treatment group (N= 53)	P value
Age, year	57 (48-79)	57 (49-80)	0.7
Sex, male N (%)	38 (71.7 %)	39 (73.5%)	0.6
Body mass index, mean (± SD)	22.9 ±3.3	22.8 ±3.1	0.79
Hypertension, mmHg, mean (± SD) *Systolic* *Diastolic*	 137 ±11 79 ±7	 139 ±12 80 ±7	 0.44 0.35
Causes of renal impairment, N (%) Hypertensive nephropathy Diabetic nephropathy Glomerulonephritis Obstructive Polycystic kidneys Unknown	 18 (34) 18 (34) 4 (7.5) 8 (15) 2 (4) 3 (5.5)	 17 (32) 19 (36) 7 (13) 4 (7.5) 2 (4) 4 (7.5)	 NS NS NS NS NS NS
Angiographic procedure, N (%) Coronary Aorto-iliac	 36 (68) 17 (32)	 38 (71.7) 15 (28.3)	 0.63 0.55
Hypertension, N (%)	36 (68)	38 (71.7)	0.62
Diabetes mellitus, N (%)	34 (64)	36 (68)	0.64
Previous MI, N (%)	17 (32)	16 (30)	0.9
Previous CABG surgery, N (%)	5 (0.1)	2 (0.04)	0.17
Previous PCI, N (%)	11 (20.1)	9 (17)	0.88
Medications, N (%) *ACE inhibitors* *Angiotensin receptors blockers* *Diuretics*	 17 (32) 12 (22.6) 26 (49)	 15 (28.3) 14 (26.4) 28 (52.8)	 0.64 0.72 0.81
Blood urea, mg/dl	29.8 (18-58)	27.5 (20-61)	0.50
Serum creatinine, mg/dl	1.39 (1.2-3.1)	1.52 (1.2-2.9)	0.64
LVEF 35-50%, N (%)	14 (26.4)	13 (24.5)	0.74
Volume of contrast agent, mL, median (range)	130 (70-300)	140 (75-320)	0.70

PCI=Percutaneous coronary intervention, CABG= coronary artery bypass graft, MI= myocardial infarction, ACE, Angiotensin converting enzyme, LVEF= left ventricular ejection fraction, N= number, SD= slandered deviation, NS= non-significant.

Around one third of the patients in both groups experienced previous MI while 20.1% and 17% had previous PCI in Group 1 and 2 respectively. CABG was done in five and two patients respectively in Group 1 and 2. Thus, selected patients in both groups received ACEI (28%-32%) or ARBs (22%-26%) and diuretics (49%-52%).

Table-2 shows, six patients (12%) in Group 1 and two patients (3.7%) in Group 2 developed CIN as defined earlier. The difference between Groups 1 and 2 was highly statistically significant, P-value < 0.02.

Table-2: The clinical outcome in both groups

Outcome	Control group N= 53	Treatment group N= 53	RR (95% CI)	P value
Serum creatinine after first 5 days after angiography	2.28 mg/dl	1.72 mg/dl	-	**< 0.01**
Creatinine clearance after contrast administration (mL/min) Baseline After 5 days	 42.1 45.1	 43.5 59.6	 - -	 <0.53 **<0.01**
Acute contrast reduction in renal function, No (%) *	6 (12%)	2 (3.7%)	0.32	**< 0.02**
Length of hospitalization from admission to discharge (days), mean (SD)	4.5 (2.1)	3.3 (1.2)	0.56	**< 0.02**

CI, confidence interval, RR, relative risk, SD= slandered deviation
* Acute contrast decrease of renal function is defined as > 25% in serum creatinine within 5 days after exposed to contrast dye

Higher average serum creatinine were found in Group 1 (P= 0.01) and a lower creatinine clearance were found in Group 1 within 5 days of contrast administration in comparison to group 2 (P= 0.01).

None of the patients required transient hemodialysis or developed persistent renal failure. Patients received placebo had a longer hospital stay than patients received a combination of NAC and ascorbic acid and this result was statistically significant p<0.02.

DISCUSSION

We aim in this study is to determine whether addition of ascorbic acid to high dose N-acetylcysteine can prevent acute deterioration in renal function in patients with moderate renal insufficiency. Because CIN of new onset or an exacerbation of pre-existing renal dysfunction is common and prognostically important in those patients [11].

Despite adequate hydration (recommended by numerous guidelines as KIDIGO 2012, European Society of Cardiology CIN prevention guidelines, 2014 and European Society of Urogenital Radiology 2011 guidelines) is the most powerful preventive strategy for CIN [12,13], the estimated prevalence of CIN reach up to 50% in high-risk patients. In addition, patients with an increased risk for volume overload as CKD and left ventricular dysfunction, volume expansion cannot be used appropriately.

In this line of concept, number of prophylactic pharmacological agents have been investigated in a trial to reach the appropriate management and to bypass this obstacle for a common disease representing a significant clinical and economic problem [14].

Some agents show to reduce the incidence of CIN and became a popular tool for CIN prevention like NAC [7-9]. However, meta-analyses have failed to reach consensus as some guidelines recommend that, N - Acetylcysteine is not to be used alone also the Food and Drug Administration (FDA) do not approve it for the prevention of CIN [15,16] and in the most up-to-date comprehensive meta-analysis published in 2016 by Renfan Xu et al to analyse effectiveness of NAC for the prevention of CIN on 11 480 participants , found that, the incidence of CIN still high as 12.8% in patients using NAC .

They also demonstrated that, N- Acetylcysteine intake was not associated with reduction CIN risk in patients with diabetes or who undergoing peripheral angiography, or reduction of mortality and nephropathy requiring dialysis [17]. Therefore, the need for searching for other agents that may offer additional protection when combined with each other become necessary.

Ascorbic acid had a considerable attention because of its antioxidant and to lesser extent its vasodilatory effect. Ascorbic acid first investigated by Spargias K et al at 2004 on 231 patients with a serum creatinine concentration > or =1.2 mg/dl undergoing coronary angiography and the study shows an encouraging results as CIN occurred in 9% Vs 20% in CIN and placebo group respectively [10].

In the last few years, many researches on Ascorbic acid were done in trial to reach a consensus or a recommendation but AA still had unclear role and until now, current recommendation does not support its use in the prevention of CIN. These contradictory results explained by; heterogeneity of the patients, base line serum creatinine and usage of different dosage and rout of ascorbic acid, which definitely affects its bioavailability.

At the end, all of these studies concluded that, further investigations are needed regarding its optimal dose,

route of administration and suitable combination with other agents [18,19].

In our study and other different studies on CIN, CKD had received a considerable attention and this cohort of patients represent the majority of patients' samples in most of these studies for several reasons. First, the CKD considered as a high risk, which is associated with a high prevalence of CIN [3,4].

The second point is, the presence of CKD also could affect the decision to proceed in these procedures [11].

All patients in our study received hydration and a low-osmolar contrast agent as recommended by nephrology and cardiology guidelines [12,13] due to the fact that patients with CKD are at an additional risk of renal ischaemia due to the increased metabolic demands [20].

In this study, the baseline characteristics were generally comparable between the groups studied as regarding age, sex and the cause of renal impairment. The volume of the contrast agent administered during angiography were also comparable in both groups studied. In addition, they had comparable kidney function tests as regards the serum creatinine level, plasma urea level.

Most of our patients had coronary artery disease. Based on their clinical situations, cardiologist consultation, on the (class I, level A) recommendation of the European Society of Cardiology guidelines on myocardial revascularisation and on some studies; ACEIs/ARBs were used in selected patients with adequate hydration because of their cardiac and their known mortality benefits [21].

Contrary to expectations, some studies showed that, ACEIs/ARBs use might be beneficial by inhibiting afferent vasoconstriction caused by contrast itself and by prevention of generation of reactive oxygen species (main mechanisms of CIN) [22,23].

Some studies, which focus on ACEIs/ARBs effect after contrast administration in CKD patients demonstrate that, taking an ACE-I was associated with a lower risk of CIN in patients with underlying CKD and no need to hold these medications prior to contrast exposure [24-26].

Meta-analysis of seven randomized controlled trials concluded that, patients treated with ACEIs had a trend toward a reduction in CIN compared with control patients [27].

Finally, the most recent study by Xiao-sheng Guo et al published in 2017 recommend that, patients with CKD to be prescribed ACEIs/ARBs when administrated moderate hydration in order to prevent CIN [28].

In our study and in most of studies conducted on ascorbic acid in the issue of CIN, we used oral ascorbic acid at the dose of 2 gm because large doses >6 gm/day may cause acidification of urine and promote free-radical production and additional kidney injury. In addition, the orally administered ascorbic acid doses of 2 to 3 g is have been shown to reverse endothelial vasomotor dysfunction [29,30].

The key finding of this study is that prophylactic oral administration of the antioxidant ascorbic acid in addition to high dose N-acetylcysteine diminish the incidence of CIN in patients with moderate CKD undergoing percutaneous coronary or elective aorto-iliac procedures. Only (3.7%) of the patients in Group 2 using hydration , combination of N-acetylcysteine and Ascorbic acid developed CIN as defined earlier versus 12% in group 1 who receive hydration and placebo and this was highly statistically significant result.

In addition, comparison between both groups studied show lower average serum creatinine and a higher average creatinine clearance after 5 days of contrast administration in Group using Ascorbic acid plus N-acetylcysteine. None of our patients required transient haemodialysis or developed persistent renal failure.

Patients receiving placebo had a longer hospital stay than patients receiving a combination of N-acetylcysteine and ascorbic acid and these result were statistically significant.

Our results also comes to agreement with a meta-analysis by Umar Sadat et al, which published in in 2013.They analyse nine randomized, controlled trials reported data on the incidence of CI-AKI in 1,536 patients. Ascorbic acid is always on of the study arms administered alone or with saline solution hydration. Ascorbic acid was given to 740 patients. Oral rout is represent the majority and IV rout was used only in two studies. Patients receiving ascorbic acid had a 33% less risk of CIN compared with patients receiving placebo or an alternate pharmacological treatment [18].

By literature review, there is three other recent researchers in English language were published. These researchers studied the effect of combination of N-acetylcysteine and Ascorbic acid in prevention of CIN. Analysis of these studies are summarized in table (3) [4,31-32,33,34].

Our study is different in many aspects as our study is double blind, no heterogeneity as we focus on CKD patients and we extend the period for CIN detection to 5 days after contrast administration.

However, as any research, we have some limitations as the small sample size and we need more sub classification of CKD grades, the presence or absence of other risk factors.

CONCLUSION

Our study is the second study after the research by Spargias K et al that show, prophylactic oral administration of the antioxidant ascorbic acid in addition to high dose N-acetylcysteine diminish the incidence of CIN in patients with moderate CKD undergoing percutaneous coronary or elective aorto-iliac procedures at a low cost.

Conflicts of Interest

Authors declare that there is no conflict of interests regarding the publication of this paper.

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