

# THE EFFECT OF ADMINISTRATION OF ASCORBIC ACID IN PREVENTION OF CONTRAST INDUCED NEPHROPATHY IN PATIENTS WITH RENAL IMPAIRMENT UNDERGOING CORONARY INTERVENTION

By

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## ABSTRACT

**Background:** Contrast-induced nephropathy is a potentially avoidable complication caused during procedures involving the use of radiographic contrast media. All subjects, especially the high-risk ones, should be subjected to available preventive protocols prior to and after such procedures.

**Objective:** To evaluate the role of a hydration protocol involving the use of ascorbic acid plus the conventional sodium chloride hydration protocol N acetyl cysteine.

**Patients and methods:** The current study was conducted on 86 patients presenting to the Cardiology Department at National Heart Institute to undergo elective percutaneous coronary intervention (PCI) during the period from April 2011 to November 2011. The study population was divided into two equal groups: Group 1 received ascorbic acid prior and after the procedure and group 2 received the conventional hydration measures without ascorbic acid. Both groups received normal saline and NAC (N Acetyl Cysteine).

**Results:** There were no significant group differences regarding sex, incidence of diabetes mellitus, pre-existing renal impairment, age, hypertension, dyslipidemia, and the type and amount of contrast. Addition of ascorbic acid by hydration with normal saline and N- acetylcysteine decreased significantly the rise in serum creatinine 48 hours ( $P=0.023$ ) and 7 days ( $P=0.001$ ) following coronary intervention. CIN occurred in one patient in ascorbic acid group versus 4 patients in the control group ( $P=0.36$ ). Ascorbic acid did not show a significant effect regarding the protection against the contrast induced nephropathy versus the conventional hydration therapy.

**Conclusion:** Ascorbic acid did not show a significant effect regarding the protection against the contrast induced nephropathy versus the conventional hydration therapy.

**Keywords:** Ascorbic Acid, Renal Impairment, Percutaneous coronary intervention, contrast-induced nephropathy.

## INTRODUCTION

Contrast-induced nephropathy is a leading cause of morbidity and mortality

in high-risk patients undergoing any procedure involving the use of radiographic contrast media. It is most commonly defined as rise in serum

creatinine level of at least 0.5 mg/dl within 48 hours of contrast medium administration (*Barrett and Parfrey, 2010*).

The incidence of CIN is variable and ranges from 5% to 50% in various series. The likelihood of developing CIN increases with worsening of the baseline renal function (*Waybill and Waybill, 2010*).

The occurrence of contrast-induced nephropathy is related to the number of the patients' co-existing clinical risk factors. Among the many risk factors, pre-existing renal impairment, advancing age, the presence of diabetes mellitus as well as the volume, and type of contrast agent administered are the most important. The precise pathophysiologic mechanisms responsible for the development of contrast-induced nephropathy are complex and incompletely understood. Reducing the risk of developing contrast-induced nephropathy is available by prevention. This can be achieved by means of adequate peri-procedural hydration, using N-acetylcysteine as well as the selection of low osmolar or iso-osmolar contrast agents in the least amount possible (*Cavusoglu et al., 2010*).

Management of contrast nephropathy is mainly by prevention. This can be achieved by assessment of the risk-benefit ratio prior to performing the procedure, as well as the patient's receiving adequate hydration and having normal electrolyte levels. Also use of the new low osmolar contrast agents should be undertaken in patients with higher serum creatinine levels (*Curhan, 2010*).

N-Acetylcysteine has been proven to be a very valuable tool in the prevention

of contrast-induced nephropathy. It acts as a scavenger of oxygen-free radicals, increases the expression of nitric oxide synthetase, which improves the blood supply and has an anti-apoptotic effect. All of these actions lead to amelioration of the renal effects of the dye (*Shyu et al., 2010*).

The action of other antioxidant agents has not been investigated. Ascorbic Acid is a sugar acid with antioxidant properties. The conventional hydration protocols involve the use of ascorbic acid as a peri-procedural hydration protocol (*Dvoršak et al., 2013*).

**The current study was done to** evaluate the role of a hydration protocol involving the use of ascorbic acid plus the conventional sodium chloride hydration protocol and N acetyl cysteine.

## PATIENTS AND METHODS

This study was done at National Heart Institute from April 2011 to November 2011 on 86 patients underwent clinically driven non-emergent intervention, either diagnostic coronary angiography or coronary angioplasty + stenting, to examine the efficacy of ascorbic acid administration in decreasing the incidence of contrast induced nephropathy in patients with renal impairment (serum creatinine 1.5-3 mg/dl).

**Inclusion criteria:** Patients undergoing clinically driven, non-emergent coronary intervention at National Heart Institute were eligible for inclusion if their serum creatinine concentration was  $\geq 1.5$  mg/dL and  $\leq 3$  mg/dl on their most recent sample drawn within one week of the planned procedure.

**Exclusion criteria:** Known acute renal failure end stage renal disease requiring dialysis, intravascular administration of contrast medium within the previous 6 days, anticipated re-administration of contrast medium within the following 6 days, use of Vitamin C supplements on daily basis during the week before the procedure, inability to administer the study medication at least 2 hours before the procedure, serum creatinine  $\geq 3$  mg/dl, patients with hemodynamic instability, allergy to radiographic contrast, patients who received ionic type of contrast, and patients with manifested heart failure and  $EF \leq 40\%$ .

**Patients were divided in two equal groups:**

**Group 1:** Patients with renal impairment who were planned for coronary intervention with Co-administration of Ascorbic Acid, and **Group 2:** Patients with renal impairment who were planned for coronary intervention without co-administration of ascorbic acid. Both groups received good hydration with normal saline 50-100 ml/hour starting before the procedure and continued for 6 hours after plus N acetyl cysteine.

**Study Protocol:**

The patients were randomly assigned to receive either 3 g of ascorbic acid supplied in effervescent tablets given orally or placebo at least 2 hours before the start of the index procedure, followed by 2 g of ascorbic acid or placebo the night of the procedure, and the morning after the procedure. Randomization, preparation of the study drugs and random assignment of treatment were done.

An oral dose of 600 mg twice daily was given to all patients the day before and the day of procedure which was the most commonly used regimen, Hydration with 50 to 100 mL/h IV normal saline was started in all patients from randomization until at least 6 hours after the procedure. The variation of the hydration rate allowed for adjustments according to the volume status of the patients, and the presence of clinical heart failure was excluded from the start.

Accurate hourly recording of all in-hospital volume inputs was done in patients undergoing percutaneous coronary interventions. All patients were encouraged to drink if they were thirsty. The type of contrast agent was non-ionic low osmolar standard in all patients. Baseline serum creatinine concentration was measured from blood sample drawn at the time of the procedure after 48 hours and 7 days after the procedure during the follow up at the post cath outpatient clinic. All measurements were performed in a single hospital laboratory with consistent methodology which was the national heart institute.

**All patients were subjected to:**

1. Full history taking with special emphasis on the known pre-disposing factors of CIN.
2. Physical examination including vital signs.
3. Laboratory investigations with special care on serum creatinine which was measured at the time of admission, every day of the following two days in the post cath unit, and after one week of the time of procedure.

4. Echocardiography: A transthoracic echocardiographic evaluation was performed to all patients after hospital admission with special care on the left ventricular ejection fraction to exclude patient with low EF  $\leq$  40%.
5. Coronary intervention was done in the standard fashion. After local infiltration anesthesia by 2% lignocaine, the right common femoral artery was punctured using seldinger's technique in case of coronary angiography. 5000 IU heparin was given and 10,000 IU in case of Angioplasty +/- stenting. After angioplasty, all patients were admitted to the coronary care unit, where the conventional anti-ischaemic therapies were continued and follow up of their serum creatinine.

#### Statistical Analysis:

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for the Social Science

(SPSS 15.0.1 for windows; SPSS Inc, Chicago, 2001). Data was presented and suitable analysis was done according to the type of data obtained for each parameter. Descriptive statistics was mean, standard deviation ( $\pm$  SD), Minimum and maximum values (range) for numerical data. Frequency and percentage of non-numerical data. Analytical statistics: Student t-test was used to assess the statistical significance of the difference between two study group means. Chi-Square test was used to examine the relationship between two qualitative variables. Fisher's exact test was used to examine the relationship between two qualitative variables when the expected count was less than 5 in more than 20% of cells. Correlation analysis (using Pearson's method) was used to assess the strength of association between two quantitative variables. A significant p-value was considered when it was equal or less than 0.05.

## RESULTS

Of the 86 patients randomized and completed the study. None developed acute renal failure requiring dialysis.

Patients in group two include 32 males 74.4 % and 11 females 25.6% with a mean age 60.19 %  $\pm$  7.22. There was no statistically significant difference between both groups regarding the sex and the age distribution of the patients ( $p > 0.05$ ). There were no statistically significant differences between both groups regarding the presence of diabetes mellitus, dyslipidemia, family history, hypertension and smoker ( $p > 0.05$ ).

Pre-existing renal impairment: Defined as a baseline serum creatinine level more than 1.5 mg/dl) this study include patients with already have Pre-existing renal impairment so the comparison here regarding the base line serum creatinine .the mean basal creatinine was 1.64 $\pm$ .15 in group one (Ascorbic Acid group) and 1.66 $\pm$ .21 in group two (Traditional group) There was no statistically significant difference between both groups regarding mean basal serum creatinine ( $p > 0.05$ ) (**Table 1**).

**Table (1): Comparison between two study groups as regard personal data, regard risk factors and Baseline serum creatinine levels among the study population regarding mean value and standard deviation**

Parameters		Types	Ascorbic group (group 1) N=43		Traditional group (group 2) N=43		P
			Mean	±SD	Mean	±SD	
Age			57.58	6.81	60.19	7.22	0.089
Gender	Male		28	65.1%	32	74.4%	.0.348
	Female		15	34.9%	11	25.6%	
DM	Yes		30	69.8%	26	60.5%	0.365
	No		13	30.2%	17	39.5%	
Dyslipidemia	Yes		5	11.6%	7	16.3%	0.534
	No		38	88.4%	36	83.7%	
Family History	Yes		1	2.3%	3	7.0%	0.616
	No		42	97.7%	40	93.0%	
HTN	Yes		26	60.5%	31	72.1%	0.254
	No		17	39.5%	12	27.9%	
Smoker	Yes		16	37.2%	19	44.2%	0.510
	No		27	62.8%	24	55.8%	
Baseline serum creatinine			1.64	0.15	1.66	0.21	0.516

Regarding the age, it was found that the old age patients were associated with more decrease in renal function and increased incidence of contrast induced nephropathy with highly significant correlations and this was shown in the two

groups. Multivariate linear regression revealed that the old age group has a highly significant impact on the deterioration of serum creatinine during the 48 hours and 7 days follow up (Table 2).

**Table (2): Correlations between age and each of baseline, 48 hours and 7 days creatinine level among study group 1 (Ascorbic acid group) and group 2 (Traditional group) patients**

Creatinine level		Baseline Cr. (mg/dl)	48hr Cr. (mg/dl)	7days Cr. (mg/dl)
Groups				
Age (Group 1)	r	0.425	0.623	0.614
	P	0.005	0.0001	0.0001
Age (Group 2)	r	0.402	0.469	0.472
	P	0.008	0.001	0.001

Dye type and amount, in the two groups Non-ionic dye was used in all patients 100 % the mean volume of dye in group one was  $183.72 \pm 60.48$  milli-liters and  $60.48 \pm 7.22$  milli-liters in group two There was no statistically significant difference between both groups regarding the amount of dye ( $p > 0.05$ ).

There was no statistically significant difference between the two groups regarding the type of procedure. There

was no statistically significant difference between both groups regarding mean basal serum creatinine. There were statistically significant difference between both groups regarding mean 48hr Cr. (mg/dl) and 7days Cr. (mg/dl).

As a primary end point the comparison between the two groups was found that no statistical significance regarding the development of contrast induced nephropathy (Table 3).

**Table (3): Comparison between two study groups as regard amount of contrast, regard procedures details and basal, 48 hours and 7 days creatinine level and contrast induced nephropathy**

Parameters		Types	Ascorbic group (group one)		Traditional group (group two)		
			Mean	±SD	Mean	±SD	
Amount of contrast (ml)			183.72	60.48	195.35	72.22	0.421
Procedure	Diagnostic		19	44.2%	16	37.2%	0.510
	PCI		24	55.8%	27	62.8%	
Baseline Cr. (mg/dl)			1.64	0.15	1.66	0.21	0.516
48hr Cr.(mg/dl)			1.76	0.21	1.89	0.30	0.023
7days Cr.(mg/dl)			1.70	0.18	1.88	0.30	0.001
CIN 0.5	Yes		0	.0%	3	7.0%	0.241
	No		43	100.0%	40	93.0%	
CIN 25%	Yes		1	2.3%	3	7.0%	0.616
	No		42	97.7%	40	93.0%	
CIN	Yes		1	2.3%	4	9.3%	0.360
	No		42	97.7%	39	90.7%	

## DISCUSSION

In the current study, there were no significant group differences regarding sex, incidence of diabetes mellitus, pre-existing renal impairment, age, hypertension, dyslipidemia, the type and amount of contrast.

*Merten et al. (2011)* randomized trial; patients with serum creatinine levels of at least 1.2 mg/dL were randomized to receive 3g ascorbic acid at least 2 hours before the procedure and 2g in the night and the morning after the procedure. Serum creatinine levels were measured at

baseline and two days after contrast administration (*Merten et al., 2011*).

In the current study, the number of patients having diabetes mellitus was 30 patients in group one (Ascorbic Acid group), 69.8 % 26 patients in group two (controlled group) 60.5%, whereas in the study of *Konstantinos et al. (2014)*, the number was 27% in the ascorbic acid group and 23% in the control group .

In the current study, the baseline serum creatinine level was slightly higher but not statistically different in patients receiving ascorbic acid treatment was applied by

*Konstantinos et al. (2014)*, the baseline serum creatinine level in general was higher in our study.

The higher baseline creatinine value, the greater is the risk of CIN. As shown in one of studies, if baseline plasma creatinine level is 1.2 mg/dL, the risk of CIN is 2%. In patients with values of creatinine in the range of 1.4 -1.9 mg/dL the risk of CIN compared with that in the previous group increases fivefold (10.4%). As for patients with baseline creatinine level >2.0 mg/dL, more than half of them (62%) subsequently develop CIN. However, baseline creatinine is not reliable enough for identification of patients at risk for CIN. This is because serum creatinine value varies with age, muscle mass, and gender. Since creatinine production decreases with age, a normal serum creatinine in an elderly patient generally correlates with at least moderate decrease in renal function (*Mehran and Nikolsky, 2012*).

In the current study, the mean serum creatinine concentration increased was during the 48 hours follow up, and the difference was statistically significant between the two groups. Regarding the 7 days follow up, it was found that serum creatinine concentration increased which was significant.

The mean level of serum creatinine at follow up was significantly higher compared to its baseline value in both groups but it was significantly lower in ascorbic acid group.

*Konstantinos et al. (2014)* stated that the mean serum creatinine concentration increased.

In the current study, the incidence of contrast-induced nephropathy occurred in one patient in ascorbic acid group (2.3%) and 9.3% in control group, while in the study of *Konstantinos et al. (2014)*, 5.9% in ascorbic acid group developed contrast-induced nephropathy and 8% of the control group developed contrast-induced nephropathy.

The higher number of patients who developed contrast-induced nephropathy by *Konstantinos et al. (2014)* compared to the current study could be explained that we have excluded patients with baseline serum creatinine greater than 3 mg%. In addition, the later in their study had higher incidence of diabetic patients and they used a variety of contrast agents not only the non-ionic dye that was used in the current study.

Several studies provided evidence that older age is an independent predictor of CIN. The reason for higher risk to develop CIN in elderly were not studied specifically and probably are multifactorial, including age-related changes in renal function (diminished GFR, tubular secretion, and concentrating ability). The presence of multi-vessel coronary artery disease, necessitating complex PCI, coupled with more difficult vascular access resulting from tortuosity and calcification of the vessels frequently requires greater amount of CM, and therefore represent additional factors of increased CIN in elderly (*Droppa et al., 2011*).

This agreed with the current study, as there was a positive correlation between the age of the patients and the serum creatinine level at both baseline and at

follow-up that reached statistical significance ( $p < 0.001$ ).

Most of the studies indicated that the higher volume of contrast is deleterious in the presence of other risk factors. Even relative low doses of contrast (less than 100 ml) can induce permanent renal failure and increase need for dialysis in patients with chronic kidney disease. As contrast volume increase, the risk for developing CIN sharply increases. As a general rule for patients with chronic kidney disease, a diagnostic catheterization should plan to use  $< 30$  ml of contrast agent and  $< 100$  ml if percutaneous coronary intervention is planned, this should be a reasonable goal (*Yang et al., 2015*).

In the current study, by using the multivariate linear regression analysis, there was a significant correlation between the amount of contrast and the deterioration of serum creatinine.

All patients of both groups received a nonionic contrast agent (Iopromide), and all patients of both groups received N-acetyl cysteine.

The current study found no statistically significant differences between hydration using sodium chloride plus N-Acetyl cysteine and the administration of oral Ascorbic acid +Hydration with sodium chloride +N-Acetyl cysteine for the prevention of contrast-induced nephropathy. *Konstantinos et al. (2014)* concluded that hydration with ascorbic acid before contrast medium exposure is more effective than hydration with sodium chloride alone for prophylaxis against the development of contrast-induced renal failure (*Merten et al., 2011*). This difference in the data could be explained

by co-administration of N-Acetyl cysteine in the two groups and the smaller sample size in our current study compared to the later which could be the reason for failure to show the actual benefit of ascorbic acid for the prevention of CIN.

## CONCLUSION

Ascorbic acid may have an additive role with good hydration to decrease the rise in serum creatinine at 48 hours and 7 days but no significant effect on decreasing the incidence of contrast induced nephropathy may be due to the small sample of the study.

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## إستخدام حامض الأسكوربيك للوقاية من حدوث اعتلال الكلية المستحث باستخدام وسط التبييان فى معمل قسرة القلب فى مرضى يعانون من إضطراب فى وظائف الكلى

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**خلفية البحث:** إعتلال الكلية المستحث بإستخدام وسط التبييان هو ثالث مسبب رئيسي لحدوث الفشل الكلوي الحاد في المرضى الموجودين بالمستشفيات، ويقع معدل حدوثه العام بين 1% و6%، و يصل إلى بين 40% و50% في المرضى الذين يعانون من عوامل الخطورة المؤدية لأمراض الكلى مثل مرض البول السكري.

**الهدف من البحث:** تقييم دور بروتوكول الماء الذي يتضمن إستخدام حمض الأسكوربيك بالإضافة إلى بروتوكول ترطيب كلوريد الصوديوم التقليدي علاوة على ن أسيتيل سيستين.

**المرضى وطرق البحث:** أجريت الدراسة الحالية على 86 مريضاً قدموا إلى قسم أمراض القلب في معهد القلب الوطني للخضوع للتدخل التاجي الاختياري عن طريق الجلد في الفترة من أبريل 2011 إلى نوفمبر 2011. وقد تم تقسيم مجتمع الدراسة إلى مجموعتين متساويتين: المجموعة الأولى تلقت حمض الأسكوربيك قبل الإجراء وبعده، والمجموعة الثانية تلقت تدابير الترطيب التقليدية بدون حمض الأسكوربيك، كل المرضى وقد تم إعطاء محلول كلوريد الصوديوم بمعدل 1 مل لتر لكل كيلوجرام على مدى ست ساعات قبل القسرة، ثم اثنتا عشر ساعة بعد القسرة وعقار الن استيل سيستين.

**نتائج البحث:** لا توجد فروق ذات دلالة إحصائية بين المجموعتين فيما يتعلق بالجنس، والإصابة بمرض السكري، والقصور الكلوي الموجود مسبقاً، والعمر،

وارتفاع ضغط الدم، وخلل شحيمات الدم، ونوع ومقدار التباين. وقد وجدت الدراسة الحالية أن حمض الأسكوربيك يظهر حماية ضد ارتفاع الكرياتينين في المصل في المرضى المعرضين لخطر كبير مثل مرضى السكر والمجموعة العمرية، ولكن لم يظهر تأثيرًا كبيرًا فيما يتعلق بالحماية من التباين الناجم عن اعتلال الكلية مقابل العلاج المائي التقليدي.

**الإستنتاج:** إنخفض حدوث إعتلال الكلية الناجم عن التباين في المرضى الذين يعانون من إختلال كلوي طالما كان المرضى قد رطبوا جيدًا قبل الإجراء وباستخدام الصبغة غير الأيونية.

**الكلمات الدالة:** حمض الأسكوربيك، القصور الكلوي، التدخل التاجي عن طريق الجلد، إعتلال الكلية الناجم عن التباين.