Razavi Int J Med. 2017 March; 5(1):e37341. doi: 10.5812/rijm.37341.

Published online 2016 November 19. **Review Article**

Efficacy of Ascorbic Acid on Reducing the Development of Contrast-Induced Nephropathy

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Received 2016 April 24; **Revised** 2016 October 03; **Accepted** 2016 October 03.

Abstract

Introduction: To assess the benefits of prophylactic ascorbic acid to reduce development of contrast-induced nephropathy (CIN) in patients undergoing percutaneous coronary interventions (PCIs).

Methods: PubMed was searched with the search strategy of (vitamin C OR ascorbic acid) AND (kidney OR renal) AND (PCI OR percutaneous coronary Intervention OR cardiac OR heart). There was no date and language restriction for the selection of the articles. All the randomized controlled trials (RCTs) which investigated the efficacy of AA on reducing the incidence of CIN were included. Totally 267 articles were found at the initial search; however, only 10 RCTs were eligible to be included. Odds ratio is presented for each of the articles as the effect size.

Conclusions: Controversial findings were reported on the efficacy of AA on reducing the CIN development; due to various limitations of these articles, there is still great debate among the cardiology and radiology communities, which increases the need for further researches.

Keywords: Contrast-Induced Nephropathy, Ascorbic Acid, Vitamin C

1. Introduction

Contrast- induced nephropathy (CIN) is known as one of the main causes of renal dysfunction and hospital-acquired acute renal failure (ARF) following surgery. Although it is often transient, CIN can be associated with long term morbidity, 1-year mortality, and medical cost rate in hospitalized patients. Although the prevalence of CIN has been reported to be low (< 2%) in general population, high risk patients (those with preexisting renal insufficiency and diabetes mellitus) have shown an incidence of 12% - 50% (1). Moderate to severe chronic kidney disease (CKD) defined as estimated glomerular filtrationrate (eGFR) less than 60 mL/min/1.73 m^2 is proposed as the principal risk factor for the development of CIN.

Congestive heart failure which needs cardiac operation with application of contrast media is also suggested as a risk factor of CIN. An increasing trend has been observed regarding the presence of cardiovascular diseases and the incidence of acute renal failure (ARF). Cardiovascular disease (CVD) related risk factors have shown positive association with chronic kidney disease (CKD) and ARF (2).

Radiographic contrast agents can increase post ischemic oxidative stress, free radicals production, and hypoxia of the medullary environment resulting in ARF (3). The exact underlying causes of CIN are not clear; however, disruption of the balance between the high metabolic needs of tubular segments and their hypoxic environment due to stimuli might be one of the reasons for the reperfusion injury and increased incidence of induced nephropathy.

Several methods have been investigated for preventing CIN in high risk cases by developing various types of prophylaxis. Receiving isotonic hydration and iso-osmolar contrast agents have been beneficial in preventing CIN in patients undergoing PCI; however, performing various strategies have revealed conflicting results (4, 5).

Ascorbic acid (vitamin C) is an antioxidant which has been able to ameliorate renal function and structure in animal models through reducing the release of phospholipid oxidation product following oxidative-inflammatory response (6-8). There are limited evidence regarding the beneficial property of Ascorbic Acid (AA) on reducing CIN in high risk patients; nevertheless, it seems that it might be beneficial in terms of its antioxidant and vasodilatory effects. The purpose of this review is investigation of the effects of preoperative administration of AA in reducing CIN in patients undergoing PCI.

2. Methods

PubMed was searched based on the following search strategy:(vitamin C OR ascorbic acid) AND (kidney OR renal) AND (PCI OR percutaneous coronary Intervention OR cardiac OR heart). The most relevant articles were extracted in the first place based on their title and abstract, and then according to their full text. Only the randomized controlled trials (RCTs) relevant to the purpose of this review, without any date and language restrictions, were extracted. The reference lists of the included articles were searched to reduce the possibility of missing any relevant articles. All the articles that had compared the efficacy of AA in combination with other placebo drugs were excluded (Figure 1). The odds ratio (OR) of the development of CIN was calculated for all the included studies as the effect size.

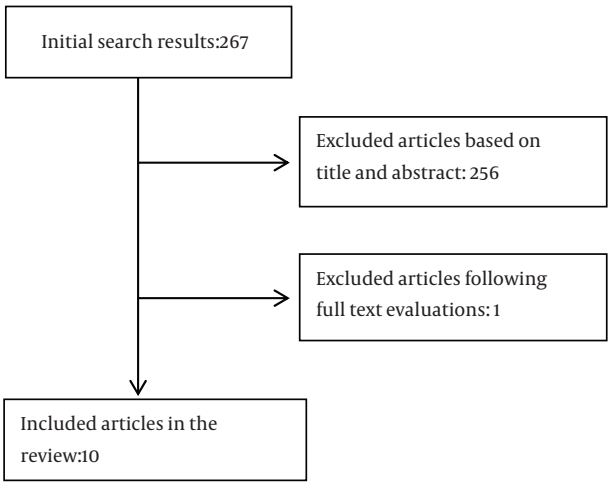

Figure 1. Flowchart of the Included Articles

Data regarding the author/year/patients grouping/interventions/effect size were extracted from each article and summarized in Table 1.

The quality of the extracted RCTs was assessed and summarized in Table 2 based on the centre for evidence-based medicine/critical appraisal worksheets.

3. Results

Based on our final search results, the efficacy of AA was investigated in 10 articles, in total. Comparisons were made between the combination of AA and NAC with NAC alone in one article (12), AA with NAC in 2 articles (13, 18), and AA with NS (placebo) in 6 articles by presenting the effect size of OR (10, 11, 14-17).

One article compared the preventing efficacy of randomly applying AA or placebo with using contrast agents at different osmolarity (iso-osmolar or low-osmolar) (14). In this study, randomization was only regarding the administration of AA or placebo, not about the applied contrast agent.

The study of Khaledifar et al compared the efficacy of AA with NAC; however, they did not reveal any results regarding the incidence of CIN in estimated patients. Therefore, the OR effect size could not be calculated for their results, and their results were only about the change of the serum Cr and changes of the GFR (9). The obtained outcome in all the included studies was the incidence of CIN; however, the absolute increase in serum creatinine and relative decrease in serum creatinine clearance were also estimated in all the included articles.

In all the included articles in this study, CIN was identified by an absolute increase of $\geq$ 0.5 mg/dl in serum Cr or a relative increase of Cr, $\geq$ 25% measured 2 to 5 days after the procedure or decrease $\geq$ 25% of GFR after 72 hours. ARF was also identified as a decrease in renal function necessitating acute hemodialysis, ultrafiltration, or peritoneal dialysis within the first 5 days after intervention.

Exclusion criteria in all the included articles were the patients with chronic kidney disease who underwent coronary and/or peripheral angiography and/or angioplasty, with known acute renal failure, end-stage renal disease requiring dialysis, intravascular administration of contrast medium within the previous 6 days, anticipated readministration of contrast medium within the following 6 days, use of vitamin C supplements on a daily basis during the week before the procedure, or inability to administer the study medication at least 2 hours before the procedure.

5. Discussion

It seems that almost 10% of the causes of hospital ARF are related to the administration of contrast agents which are essential for most of the cardiovascular radiographic procedures. The responsible mechanism related to the occurrence of contrast-induced acute kidney injury (CI-AKI) might be the production of reactive oxygen species and medullary hypoxia. Precautions should be regarded to evaluate the risk of CIN in patients undergoing PCI. In high risk patients, additional provisions and strategies are under investigation, such as applying antioxidants with the purpose of reducing the incidence rate of CIN through scavenging reactive oxygen species that facilitate cell necrosis following myocardial infarction and after angioplasty. AA as a powerful, water-soluble antioxidant is able to inhibit cell death and reactive oxygen species ef-

Table 1. Effectiveness of the Ascorbic Acid in Reducing CIN, Extracted From the Articles

First Author/Year/Reference Number	Patients Groups	Interventions	Result	Odds Ratios (OR) of the CIN Incidence
Khaledifar et al. 2015 (9)	N: 120; Each group:40; GrA: 26; GrB: 27; GrC: 26	All: NS: 100 mL/h; 12 hr before to 12 h after OP, IV.	Serum Cr Change: GrA:0.06 ± 0.12; GrB:0.08 ± 0.14; GrC:0.09 ± 0.13	No results regarding the incidence of CIN
		GrA: NAC, oral (600 mg) bid (from 24 h before to 24 h after OP.	GFR change: GrA: -1.22 ± 2.42; GrB: -2.75 ± 2.83; GrC -2.45 ± 2.83	
		GrB: AA; oral: 500 mg (250 mg, 12 h before and 12 h after OP. GrC: NS		
Spargias et al. 2004 (10)	N: 231; Gr1:118; Gr2:113	All: NS, 50 to125 mL/h 2 h before and 6 h after the OP.	Incidence of CIN: GR1:11/121 (9%); Gr2:24/117(21%), Mean serum Cr increase baseline to 2-5 days after the OP.	0.39; 95% CI, 0.18 to 0.83
		Gr1: AA, oral: 3 g, 2 h before and 2 g in the night and the morning after the OP; Gr2: Placebo	Gr1:1.46 ± 0.52 to1.52 ± 0.64; Gr2:1.36 ± 0.50 to 1.50 ± 0.54	
Boscheri et al. 2007 (11)	N:143; Gr1:74; Gr2:69	All: NS, Hydration, Gr1:AA, oral:1 g before OP. Gr2: Placebo	Gr1:5/74(6.8%); Gr2:3/69(4.3%)	1.59; 95%CI, 0.3663 to 6.9379
Briguori et al. 2007 (12)	N: 326, Gr1:111, Gr2:108, Gr3:107	All: NS, 1 ml/kg body weight per h, IV, Gr1: NAC, oral: 1200 mg twice daily before and on the day of administration of the contrast agent (total of 2 days). Gr2:(bicarbonate plus NAC gr); Gr3: AA+ NAC, IV: 3 g AA, 2 h before followed by 2 g the night and the morning after the OP.	CIN: Gr1:26 (24%), Gr3: 27 (26%); ARF: Gr1:1 (0.9%), Gr3:4(3.8%), Serum Cr increase by ≥ 25%: Gr1: 11 (9.9), Gr3: 10 (10.3); Serum CR increase by ≥ 0.5 mg/dL; Gr1: 12 (10.8); Gr3: 12 (11.2); eGFR decrease by ≥ 25%; Gr1: 10 (9.2); Gr3: 10 (10.3)	1.10; 95%CI, 0.5941 to 2.0492
Jo et al. 2009 (13)	N:212, Gr1:83, Gr2:91	Gr1: NAC, oral; 1,200 mg twice a day before and on the day of OP. Gr2: AA, oral; (3 g and 2 g before, and 2 g twice after the OP.	CIN, Gr1:1 (1.2%), Gr2: 4 (4.4%), increase of serum Cr, Gr1: -0.03 ± 0.18 , Gr2: 0.04 ± 0.20	3.78; 95%CI, 0.4128 to 34.4366
Alexopoulos et al. 2010 (14)	N:231; Gr1:144; Gr1AA:69; Gr1 Placebo: 75	Gr1: non-ionic IOCM iodixanol	CIN; Gr1AA: 5/69 (7.2%); Gr1 Placebo: 16/75 (21.3%)	Gr1: 0.29; 95%CI, 0.0993 to 0.8354
	Gr2: 87, Gr2AA: 44, Gr2 Placebo: 34	Gr2: LOCM	Gr2AA: 4/44 (9.1%); Gr2 Placebo: 7/34 (20.6)	Gr2: 0.38 95%CI, 0.1028 to 1.4467
Zhou and Chen 2012 (15)	Gr1: 74, Gr2: 82	All: NS, 1 mg/kg/h for 4 h before and at least 12 h after OP. Gr1: AA, IV and oral; 3 g IV Pre OP, 0.5 g every 12 h for 2 days post OP. Gr2: NS	CIN, Gr1: (6/82, 6.3%), Gr2: (4/74, 5.4%), increase in SCr, Gr1: 0.012 ± 0.146, Gr2: 0.022 ± 0.212	1.38; 95%CI, 0.3742 to 5.1008
Dvorsak et al. 2013 (16)	N:81, Gr1:40, Gr2:41	NS 50 - 100 mL/h for 2 hrpre- OP and 6 hr after OP, IV. Gr1:AA, oral; 5 gr (3gr before and 2 gr after the OP); Gr2:placebo	CIN, Gr1: 2/40 (3%); Gr2: 3/41 (7.3%); Cr serum increase; Gr1:10/40 (12.3%); Gr2:19/41 (23.4%)	0.67; 95% CI, 0.1054 to 4.2182
Albabtain et al. 2013 (17)	N:243; Gr1:62; Gr2:57; Gr3:58; Gr4:66	All: NS, 50 to 125 mL/h before and 6 h after the OP, IV. Gr1: NAC; oral, 600 mg twice daily for 2 days; Gr2:AA, oral; 3 g 2 h before OP, 2 g after OP, and 2 g 24 h after the OP. Gr3:NAc + AA; Gr4:NS	Relative decrease of Cr clearance: Gr1: 3.4%, Gr2:3.6%, Gr3: 5.5%	ORs of CIN of Grs (1, 2, 3)/4; (95% CI); Gr2: 0.45 (0.08 - 2.43) Gr3: 1.20 (0.33 - 4.38);
			Absolute increase of serum Cr; Gr1: 6.8%; Gr2:3.6%; Gr3: 5.5%;CIN: Gr1: 8.5%; Gr2: 3.6%; Gr3: 9.1%	There are not adequate data to for OR of the Gr2/Gr1
Brueck et al. 2013 (18)	N: 520; Gr1: 199; Gr2: 198; Gr3: 102	All: NS. 1.0 ml/kg/h; 12 h pre- to 12 h post OP.	CIN: Gr1: 53/192(27.6%); Gr2:62/193 (32.1%); Gr3:24/98(24.5%)	Gr3/Gr2, 0.6853; 95%CI, 0.3951 to 1.1886
		Gr1:NAC: 600 mg; Gr2:placebo: NS; Gr3:AA: 500 mg	absolute increase of serum Cr: Gr1: 0.15 ± 0.31/0.10; Gr2: 0.20 ± 0.35/0.20; Gr3: 0.17 ± 0.37/0.20	Gr3/Gr1, 0.8506; 95%CI, 0.4865 to 1.4871

Abbreviations: AA, ascorbic acid; CIN, contrast induced nephropathy; Cr, creatnine; Gr, group; N, number; NAC, N-acetylcysteine; NS, normal saline; OP, operation; OR, odds ratio.

fects in kidney that can impair macromolecules such as lipids, DNA, and proteins.

There is low numbers of evidence regarding the benefits of AA on preventing CIN in high risk patients and further studies are needed to accurately reveal the AA efficacy. The beneficial effects of AA have been studied in experimental models and in some clinical studies.

The study of Spargias et al. was the first clinical study which evaluated the beneficial effect of prophylactic oral application of vitamin C (ascorbic acid) on reducing the possibility of CIN in patients with weakened renal function undergoing an invasive cardiac surgery (10). Preoperative application of AA had statistically significant advantages in preventing increase in serum creatinine concentration and the incidence of CIN compared to placebo (10); these results were confirmed in other studies that showed lower rate of CIN incidence and serum creatinine increase in patients receiving AA compared to placebo (10, 14). A few studies have shown the decreased incidence of CIN following prophylactic administration of AA compared to placebo; however, their results were not statistically significant (16-18). Despite the beneficial effects of AA shown in some studies, there are some studies that did not support the prophylactic administration of AA in patients with renal impairment exposed to contrast media in comparison with placebo. Boscheri A et al. and Zhou et al. did not obtain advantages of AA prophylaxis (short-term application at high-dose AA) in reducing the incidence of CIN compared to NS(as a traditional or standard strategy); however, their patients received adequate hydration for 4 hours before and at least 12 hours after coronary catheterization as the most important preventive measure (11, 15).

Four of the included RCTs compared the efficacy of AA prophylaxis with another antioxidant, NAC, for preventing

Table 2. Quality Assessment of the Included RCTs

	Randomization Method/Blinding	Groups Similarity at the Beginning of the Study	Aside From the Allocated Treatment, were Groups Treated Equally?	Intention to Treat?-Lost to Follow Up?	Follow-up Period After the Operation
Khaledifar et al. (9)	NA/NA	Yes	Yes	NA-NA	2 to 5 d
Spargias et al. (10)	Locally in blocks of 10 by means of sealed boxes/double-blind	mean baseline serum Cr concentration and age was higher and the baseline CR clearance lower in the Gr1	Yes	Yes-7/238	2 to 5 d
Boscheri et al. (11)	-/Double blind	-	-	-	-
Briguori et al. (12)	Randomizarion block/Double blind	Yes	Yes	NA-25/351	48 h
Jo et al. (13)	Computer-generated permuted block of 6 patients/patients and investigators	Yes	Yes	Yes/38/212	1 m
Alexopoulos et al. 2010 (14)	Only for use of AA or placebo in each group, by blocks of 10 by means of sealed boxes/NO	Yes	yes	NA/NA	2 - 5 d
Zhou and Chen, 2012 (15)	NA/NO	Yes	Yes	Yes/18/174	2 d
Dvorsak, 2013 (16)	NA/double-blind	Gr1 had higher preprocedural Cr level	Yes	-2/83	3 to 4 d
Albabtain et al. (17)	Concealment of allocation to 1 of the 4 arms/NO	Yes	Yes	NA-	4 5 d
Brueck et al. (18)	Block randomization/ double blinded	Yes	Yes	Yes- 21/520	3 d

Abbreviations: AA, ascorbic acid; Cr, creatinine; Gr, group; NA, not available.

CIN in patients undergoing coronary angiography (9, 12, 13, 17, 18). They could not reveal any superiority between administrating AA instead of NAC or in combination with NAC, for preventing the incidence of CIN or reducing the increase of serum Cr.

NAC and AA are two antioxidants which are possibly effective in reducing the risk of CIN. The potential effect of AA in regenerating other antioxidants, acting as a co-antioxidant, has been investigated. Based on the calculated ORs, administration of the combination of AA with NAC will not lead to superior effects in reducing the possibility of CIN incidence compared to applying NAC alone; however, this result is not statistically significant (12). Although there is no statistically significant data, applying AA in combination with NAC, will not reduce the risk of CIN, or control the changes of serum Cr and eGFR compared with administrating NAC alone (12). This might be due to the effect of both of these antioxidants through a similar molecular pathway for reducing the reactive oxygen species generated after contrast exposure and also not revealing any additional effect when 2 agents are applied in combination. There are two other studies that have proposed no advantages of AA prophylaxis over NAC based on the ORs, as the effect size of their study; nevertheless, their results were not statistically significant (13, 18). Similar finding was proposed by Khaledifar et al. who showed no advantages of AA over applying NAC or NS for avoiding CIN; however, they did not present the data regarding the incidence of CIN and only they estimated the increase of the serum Cr and the changes of the GFR. Oral administration and lower dose of AA might be the reasons for its inappropriate preventive effects (9).

It has been proposed that the properties of the applied contrast agent can affect its nephrotoxicity; in this regard, high-osmolar, low-osmolar, and iso-osmolar contrast agents might lead to different levels of nephrotoxicity. The preventive efficacy of AA on patients received different types of contrast media during cardiac procedures was studied in one article in 2010 (14). The investigators used iodixanol as an iso-osmolar agent andiomeprol, iobitridol, or iopentol as non-ionic low-osmolar agents. They showed that the relative decrease in the incidence of CIN in AA group was similar in patients receiving iso-osmlar agents with those given low-osmolar agents. They showed that AA reduces the incidence of CIN compared with placebo in both groups; however, its benefits on patients given non-ionic IOCM iodixanol were statistically significant compared to the group with LOCM. So, it might be suggested that osmolarity of the contrast agents is not the main factor that affects the development of CIN.

Various factors such as patient selection, protocol of prophylaxis including dose of drugs and its administration form affect the selection of the best strategy for preventing CIN and AFR in patients undergoing heart procedures. According to the results, AA has some prophylactic effects which might be more prominent in high risk patients with renal insufficiency compared to those with normal renal function. Performing more accurate laboratory strategies including neutrophil gelatinase-associated lipocalin or cystatin C are proposed as better biomarkers

than measuring serum Cr for evaluating the preventive effects of pre-procedural administration of antioxidants on CIN (9).

Although prophylactic administration effect of AA in increasing renal perfusion seems not to be sufficient to reverse renal tubular injury, some protective effects have been proposed for AA in preventing renal dysfunction in patients with CIN after cardiac procedures.

In conclusion, due to several limitations of the presented studies, there is still a great debate among the cardiology and radiology communities regarding the efficacy of AA in reducing the incidence of CIN; therefore, further researches are needed in this regard. The major limitation is the small sample size of most of the articles; furthermore, the patients' renal impairment at the beginning of the study is another factor which was lower in AA group investigated in some articles.

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