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

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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 filtration rate (eGFR) less than 60 mL/min/1.73 m² 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.

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 ≥ 0.5 mg/dl in serum Cr or a relative increase of Cr, ≥ 25% measured 2 to 5 days after the procedure or decrease ≥ 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-
effects 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 Spargas 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 the beneficial effects in kidney that can impair macromolecules as the traditional or standard strategy; however, their results were not statistically significant (16-18).

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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 results were not statistically significant (16-18).
CIN in patients undergoing coronary angiography (9, 12, 13, 17, 18). They could not reveal any superiority between administering 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 ioxatral as an iso-osmolar agent and iophenidol, iomeprol, iobitridol, or iopental 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-osmolar 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 IOMC 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.

References

1. Bagshaw SM, Culleton BF. Contrast-induced nephropathy: epidemiology and prevention. Minerva Cardioangiologica. 2006;54(1):109-29. [PubMed: 16467746].
2. Mittalhenkle A, Stehman-Breen CO, Shlipak MG, Fried LF, Katz R, Young BA, et al. Cardiovascular risk factors and incident acute renal failure in older adults: the cardiovascular health study. Clin J Am Soc Nephrol. 2008;3(2):450-6. doi: 10.2215/CJN.02600607. [PubMed: 18256180].
3. Brezis M, Rosen S. Hypoxia of the renal medulla–its implications for disease. N Engl J Med. 1995;332(10):647-55. doi: 10.1056/NEJM199503093321006. [PubMed: 7845430].
4. Mueller C, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, et al. Prevention of contrast media–associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med. 2002;162(3):329-36. [PubMed: 11829290].
5. Tepel M, van der Giet M, Schwarzfeld C, Laufer M, Liermann D, Zidek W. Prevention of radiographic-contrast-agent–induced reductions in renal function by acetylcysteine. N Engl J Med. 2000;343(3):180-4. doi: 10.1056/NEJM200007203430304. [PubMed: 10906277].
6. Lloberas N, Torras J, Herrero-Fresneda I, Cruzado JM, Riera M, Hurtado I, et al. Postischemic renal oxidative stress induces inflammatory response through PAF and oxidized phospholipids. Prevention by antioxidant treatment. FASEB J. 2002;16(8):908-10. doi: 10.1096/fj.01-0880fje. [PubMed: 12039876].
7. Durak I, Ozbek H, Karaayvaz M, Ozturk HS. Cisplatin induces acute renal failure by impairing antioxidant system in guinea pigs: effects of antioxidant supplementation on the cisplatin nephrotoxicity. Drug Chem Toxicol. 2002;25(1):1-8. doi: 10.1080/DCT-10008468. [PubMed: 11850966].
8. Sai K, Umemura T, Takagi A, Hasegawa R, Kurokawa Y. The protective role of glutathione, cysteine and vitamin C against oxidative DNA damage induced in rat kidney by potassium bromate. Jpn J Cancer Res. 1992;83(1):45-51. [PubMed: 1544873].
9. Khaledifar A, Momeni A, Ibrahimian A, Kheiri S, Mohktari A. Comparison of N-acetylcysteine, ascorbic acid, and normal saline effect in prevention of contrast-Induced nephropathy. ARA/Atheroscler. 2015;8(4):228-32. doi: 10.2647730. [PubMed: 26478730].
10. Spargias K, Alexopoulos E, Kyrozopoulos S, Iokovis P, Greenwood DC, Manginas A, et al. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. Circulation. 2004;110(18):2837-42. doi: 10.1016/j.circres.2004.07.041. [PubMed: 15492300].
11. Boscheri A, Weinbrenner C, Botzek B, Reynen K, Kuhlisch E, Strasser RH. Failure of ascorbic acid to prevent contrast-media–induced nephropathy in patients with renal dysfunction. Clin Nephrol. 2007;68(5):279-86. [PubMed: 18044259].
12. Brigugori C, Airolli F, D’Andrea D, Bonizzi E, Morici N, Focaccio A, et al. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. Circulation. 2007;115(11):128-7. doi: 10.1161/CIRCULATIONAHA.106.687752. [PubMed: 17309106].
13. Jo SH, Koo BK, Park JS, Kang HJ, Kim YJ, Kim HL, et al. N-acetylcysteine versus Ascorbic acid for preventing contrast-Induced nephropathy in patients with renal insufficiency undergoing coronary angiography. NASPI study–A prospective randomized controlled trial. Am Heart J. 2009;157(3):576-83. doi: 10.1016/j.ahj.2008.10.010. [PubMed: 19249442].
14. Alexopoulos E, Spargias K, Kyrozopoulos S, Manginas A, Pavlides G, Voudris V, et al. Contrast-induced acute kidney injury in patients with renal dysfunction undergoing a coronary procedure and receiving non-ionic low-osmolar versus iso-osmolar contrast media. Am J Med Sci. 2010;339(1):25-30. doi: 10.1097/MJA.0b013e3181e6670. [PubMed: 19996728].
15. Zhou L, Chen H. Prevention of contrast-induced nephropathy with ascorbic acid. Intern Med. 2012;51(6):531-5. [PubMed: 22449658].
16. Dvorak B, Katic V, Eckart R, Bevc S, Hojs R. Ascorbic Acid for the prevention of contrast-induced nephropathy after coronary angiography in patients with chronic renal impairment: a randomized controlled trial. Thor Apher Dial. 2013;37(4):264-90. doi: 10.1111/j.1747-8020.2013.02387.x. [PubMed: 23918756].
17. Allabtain MA, Almasood A, Alshuraifah H, Alami H, Tamim H. Efficacy of ascorbic acid, N-acetylcysteine, or combination of both on top of saline hydration versus saline hydration alone on prevention of contrast-Induced nephropathy: a prospective randomized study. J Interv Cardiol. 2013;26(1):90-6. doi: 10.1111/j.1540-8181.2012.00767.x. [PubMed: 22994682].
18. Brueck M, Cengiz H, Hoeltgen R, Wieczorek M, Boedeker RH, Scheibelt C, et al. Usefulness of N-acetylcysteine or ascorbic acid versus placebo to prevent contrast-induced acute kidney injury in patients undergoing elective cardiac catheterization: a single-center, prospective, randomized, double-blind, placebo-controlled trial. J Invasive Cardiol. 2013;25(6):276-83. [PubMed: 23735352].