Vitamin C in the Prevention of contrast-Induced Nephropathy among high-risk patients undergoing coronary angiogram: A Meta-Analysis

**Abstract**

Background: Contrast-Induced nephropathy (CIN) is one of the leading causes of acute kidney injury. The most common procedures associated with CIN are coronary angiography and contrast enhanced computed tomography (CT) [1]. The most common definition in use is an increase in serum creatinine (SCr) of >25% of the baseline values occurring following the intravascular administration of contrast media without an alternative explanation [2]. Generation of reactive oxygen species is thought to play a role in the pathogenesis of CIN, hence researches have been conducted into the potential role of antioxidants in the prevention of contrast-induced nephropathy [13]. Vitamin C, a potent antioxidant in humans has the ability to oxidize free radicals, and has been studied in different trials to measure its ability to prevent CIN among patients undergoing coronary angiogram.

Objective: To determine if vitamin C prevents CIN among High-risk patients (Creatinine Clearance <60 ml/min/m2, Diabetics, and on administration of high-volume contrast media).

Methodology: All studies, limited to randomized clinical trials were sought for this analysis through PubMed, the Cochrane Library, ClinicalTrials.gov. Database was searched using the terms “vitamin C”, “Prevention”, “acute kidney injury” and “contrast-induced nephropathy”. Adult patients (40-90 years old) with Creatinine Clearance of <60 ml/min/m2 or baseline creatinine >1.2 mg/dl, Diabetes Mellitus Type II, and were administered with high-volume contrast media (>100ml) undergoing coronary angiogram were included in the study. Exclusion Criteria were patients with normal baseline renal function, without risk factors for CIN, with EGFR < 30 ml/min/m2, with regular intake of Vitamin C and were on dialysis. Statistical data were obtained using Review Manager (RevMan) Version 5.3 freeware program. P Value was obtained using the Cochran–Mantel–Haenszel test (CMH). Included patients were given Vitamin C at doses of 1 gram to 3 grams, taken orally or administered intravenously pre-and post coronary angiogram.

Results: Seven hundred and one (N=701) patients were included in this meta-analysis. CIN occurred in 3.5% of patients (N=25) in the ascorbic acid group and in 6% of patients (N= 42) in the placebo group (p value of 0.03).

Conclusion: Vitamin C given at doses 1 gram to 3 grams in combination with hydration prior to coronary angiogram may have a significant effect in the prevention of CIN in high-risk patients.

Keywords: Vitamin C prevention, contrast-induced nephropathy, and acute kidney injury

Introduction:

Cardiovascular disease, especially coronary artery disease, remains the most common cause of morbidity and mortality in a patient with renal insufficiency [15]. Factors that include accelerated atherosclerosis, endothelial dysfunction, coronary artery calcification, left ventricular structural and functional abnormalities, and diabetes predispose a patient with Renal Insufficiency to coronary artery disease warranting coronary angiogram, this warrants coronary angiogram which remains the gold standard in diagnosing coronary artery disease [14].

Two principal mechanisms conceivably participating in the pathogenesis of CIN are the induction of renal parenchymal hypoxic injury and a direct endothelial/vascular and tubular toxicity. Reactive oxygen species (ROS) are thought to take part in both injurious pathways and may serve as a link between these processes [16].

CIN is an acute decline in renal function that occurs 24 to 48 hours after intravascular injection of contrast medium (CM). The commonest definition is an increase in serum creatinine (SCr) of >25% of the baseline values occurring following the intravascular administration of CM without an alternative explanation [2]. The most common clinical course of CIN is characterized by a rise in SCr beginning 24–48 h following exposure, peaking within 3–5 days, and resolving within 1 week [3].

Risk of CIN is increased in patients with an estimated glomerular filtration rate (eGFR) <60 mL/min, or creatinine levels >106.1 mmol/L (>1.2 mg/dL), diabetes mellitus, and high volume of contrast media [11].

A risk score for the prediction of CIN after percutaneous coronary intervention (PCI) was reported by Mehran et al. in 2004 [4].

| Risk Factors | Integer Score | | Class of Risk | Risk Score |
|---|---|---|---|---|
| Hypotension | 5 | | Low | ≤5 |
| IABP | 5 | | | |
| CHF | 5 | | | |
| Age >75 y | 4 | | Medium | 6 to 10 |
| Anemia | 3 | SUM | | |
| Diabetes | 3 | → | | |
| Contrast media volume | 1 for each 100 $cc^3$ | | High | 11 to 16 |
| eGFR <20 mL/min/1.73 $m^2$ | 6 | | | |
| eGFR 20–40 mL/min/1.73 $m^2$ | 4 | | | |
| eGFR 40–60 mL/min/1.73 $m^2$ | 2 | | Very high | ≥16 |

IABP indicates intra-aortic balloon pump; CHF, congestive heart failure; and eGFR, estimated glomerular filtration rate (mL/min per 1.73 $m^2$).

Chart 1: Mehran Risk score

Vitamin C, a potent antioxidant in humans, has the ability to oxidize free radicals. It has been studied in different trials to measure its ability to prevent CIN among patients undergoing coronary angiogram.

In the meta-analysis of Sadat Et.al. entitled: Does Ascorbic Acid Protect Against Contrast-Induced Acute Kidney Injury in Undergoing Coronary Angiography, they concluded that Ascorbic acid provides effective nephroprotection against CI-AKI and may form a part of effective prophylactic pharmacological regimens [5]. However, the meta-analysis including studies on patient's without renal insufficiency or renal insufficiency threshold was not mentioned. This meta-analysis will focus only on studies on patients with baseline renal function of less than 60 ml/min./1.73 m2 and or EGFR <60ml/min/m2 and in patients at high risk for developing contrast-induced nephropathy. The Primary Objective of this study is to determine if vitamin C prevents CIN among patients with Creatinine Clearance of <60 ml/min/m2, Diabetics, and to those given with high-volume contrast media (>100ml).

## Methodology

### Data Sources and Searches

All randomized controlled trials (RCTs) assessing the effect of Vitamin C in the prevention of CIN among patients with creatinine clearance of 30-60 ml/min./m2, Diabetes Melliitus Type II and those administered with >100ml of contrast media were included in this study.

PubMed, the Cochrane Library and ClinicalTrials.gov databases were searched using the terms “vitamin c/ascorbic acid," “prevention", and “contrast induced nephropathy. Results were restricted to the English language articles.

Study Selection

There were 17 studies searched at the Cochrane Library and Pubmed. 6 studies were retrieved for evaluation and 5 studies were used in this meta-analysis. (See figure 1). Included studies were from 2004 to 2016. 351 subjects were given 1 gram to 3 grams Vit C 2 hours prior up to 2 days post coronary angiogram and 350 subjects were in the placebo group. Inclusion criteria were 1. Adult (40-90 years old) participants undergoing coronary angiogram 2. Assignment of participants to administration of Vitamin C at doses of 1 to 3 grams, taken orally or intravenously plus hydration 24 hours prior and post coronary angiogram 3. Patients with Preexisting Renal impairment (serum creatinine >1.2 mg/dl or EGFR <60 ml/min/1.73 m2. 4. Patients with risk factors identified in the Mehran CIN risk score.

Exclusion Criteria were 1. Patients with normal baseline renal function. 2. Patients with EGFR < 30 ml/min/m2. 3. Patients with regular intake of Vitamin C. 4. Patients on Hemodialysis. Baseline study characteristics are shown in Table 1. Due to incomplete data from 2 studies, baseline characteristics of patients was not obtained.

Data Extraction and Validity Assessment

Five (5) trials eligible for inclusion in this study were extracted and the following information were collected: (see Table I) primary author, year of publication, language, country of origin, study design, allocation sequence generation, number of participants, dosage and duration of treatment. There were Three independent investigators (Rainnier Ong, MD and Lou Andrew Palanca, MD, Leanna Agustin MD) extracted relevant data and any disagreements on its merits were resolved by consensus discussion. Assessment of validity of the included studies was performed using the quality scale for metaanalytic reviews provided by our recent training at St. Luke’s Medical Center – Quezon City, Philippines.

The risk of bias tool encompasses 8 domains which included allocation concealment, physician caring for the patient blinded regarding the treatment, intention to treat analysis conducted and person making an outcome assessment blinded regarding treatment, groups being compared balanced in terms of known determinants outcome, groups treated equally in terms of other medication received, frequency of follow up and general quality of care, dropout rates between the groups comparable and outcome detection methods used in similar in both groups. A checklist was generated (shown in Table II) and studies were given an assessment of "yes", "no", or "No information (NI)."



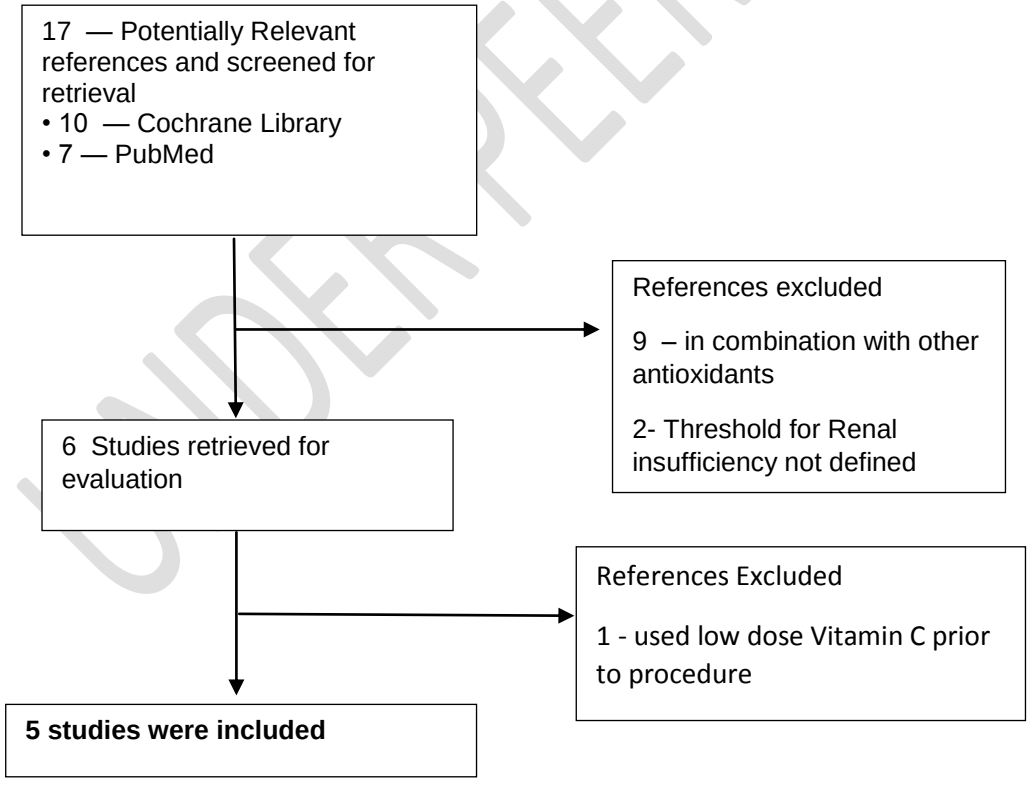


Figure 1: flow chart for identification of selected trials

| Study | Design | Patients enrolled (N) | experiment group (n) | control group (n) | Dose | Route | Control |
|---|---|---|---|---|---|---|---|
| Hosseign et al. | Randomized Double Blind Control Trial | 90 | 45 | 45 | 2 g of oral vitamin C before the procedure | Oral | Placebo |
| Dvorsak et al. | Randomized Double Blind Control Trial | 83 | 40 | 41 | 3 g orally before the procedure and 2 g after the procedure in the evening and the next | Oral | Placebo |
| Boscheri et al. | Randomized Double Blind Control Trial | 143 | 74 | 69 | 1 g ascorbic acid or prior to and after angiography. | Oral | Placebo |
| Zhou et al. | Randomized Double Blind Control Trial | 156 | 74 | 82 | Vitamin C 3 Grams intravenous injection before the procedure and oral 1 g per day for 2 days after the procedure | Oral And IV | Placebo |
| Spargias et al. | Randomized Double Blind Control Trial | 238 | 118 | 113 | Ascorbic acid, 3 g at least 2 hours before the procedure and 2 g in the night and the morning after the procedure, | Oral | Placebo |

Table I. Baseline Study characteristics

| RISK OF BIAS | Boscheri (2008) | Dvorsak (2013) | Hosseign (2016) | Spargias (2004) | Zhou (2012) |
|---|---|---|---|---|---|
| Subtle Bias | | | | | |
| Were there attempts of allocation concealment? | YES | YES | YES | YES | YES |
| Was the physician caring for the patient blinded regarding the treatment? | YES | YES | YES | YES | YES |
| Was an intention to treat analysis conducted? | YES | YES | YES | YES | YES |
| Was the person making an outcome assessment blinded regarding the treatment? | YES | YES | YES | YES | YES |
| Frank Bias | | | | | |
| Were the groups being compared balanced in terms of known determinants outcome? | YES | YES | YES | YES | YES |
| Were the 2 groups equally in terms of other medications received, frequency of follow up and general quality of care? | YES | YES | YES | YES | YES |
| Are there dropout rates between the groups comparable? | YES | YES | NI | YES | YES |
| Are the outcome detection methods used similar in both groups? | YES | YES | YES | YES | YES |

Table II. Risk of bias summary used

Statistical Analysis

Statistical analysis was performed using Review Manager (RevMan) Version 5.3 freeware program developed by the Cochrane Collaboration. For this meta-analysis, the homogeneity among studies were examined using the chi-square test and I2 test. The effect measure used was odds ratio (OR) for dichotomous data reported with 95% confidence intervals (CIs). A Forest plot was generated by combining the OR of the included studies using random effects model.

Results

There were 701 subjects included in this meta-analysis, 25/351 (3.5%) in the experimental group and 42/350 (6%) in the placebo group developed CIN. Study characteristics and baseline data are shown in Table I. Forest plot analysis (see figure II) showed that Vitamin C prevents CIN among patients with serum creatinine >1.2 mg/dl or ECC of <60 ml/min/m2, diabetics and those given with high volume of contrast media (>100ml) vs the placebo group (p= 0.03, CI 0.33, 0.93). Homogenous data were

likewise obtained (Cochran's Q test for heterogeneity, p=0.54, and Higgins' I2=0%).

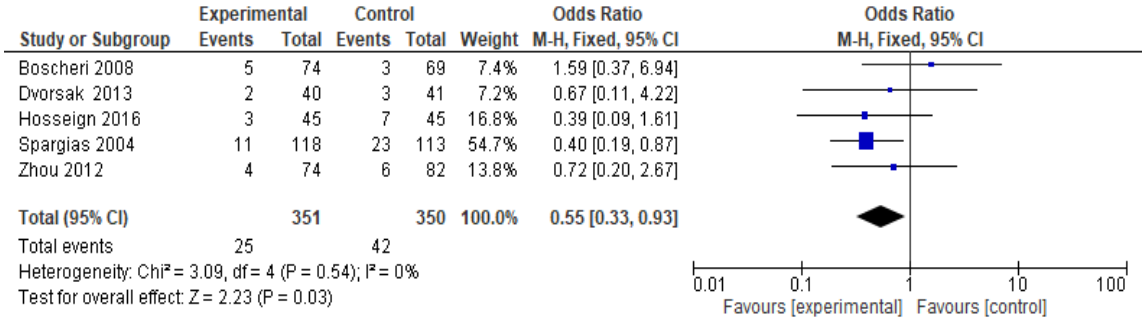


Figure II: Forest Plot Analysis showing the occurrence of CIN between the Experimental Drug vs. Placebo

Discussion

Clinical Study suggested that Reactive oxygen species play a critical role in the pathogenesis of CIN in patients with renal insufficiency. Hence, recent studies have focused on the potential role of antioxidants to prevent this side effect. Recent studies have concluded that Vitamin C has the potential to prevent contrast induced nephropathy by its oxidative mechanism. Antioxidants can decrease oxidative damage directly *by* reacting with free radicals, indirectly by inhibiting the activity, expression of free radical generating enzymes and enhancing the activity or expression of intracellular antioxidant enzymes [12]. When viewed in the forest plot, 4 out of the 5 studies included in this meta-analysis favor the experimental drug vitamin C compared with placebo.

Limitation

One of the main limitations of the study is that the combination of data from 2 studies may not be appropriate because the baseline patient's characteristics were incomplete in those studies. Even though that baseline study characteristics of each study showed no significant difference for the two groups in question, and the parameters are consistent across studies, it is still possible that the presence of differentiation of the patient's characteristics like age, gender, and volume of contrast administered can be a potential limitation. Another limitation of this study is that it does not include patients with eGFR <30 ml/min/1.73 m2, as of this writing no study has yet to be published targeting this population due to ethical consideration. Lastly, due to the presence of incomplete studies and still ongoing clinical trials, it is possible that the inclusion of these studies into the meta-analysis could change the outcome of the results.

## Conclusion

Vitamin C given at doses 1 gram to 3 grams in combination with hydration prior to coronary angiogram could have significant effect in the prevention of CIN among high-risk patients.

## Recommendation

Vitamin C in combination with adequate hydration can be recommended as a preventive measure in developing CIN patients with renal insufficiency. It is safe, cost effective, and readily available.

References:


1. DAWSON P. Patient dose in multislice CT: why is it increasing and does it matter? Br J Radiol 2004;77, Spec No 1:S10-3.
2. MORCOS SK, THOMSEN HS, WEBB JA. Contrast-media-induced nephrotoxicity: a consensus report. Contrast Media Safety Committee, European Society of Uro genital Radiology (ESUR). Eur Radiol 1999;9:1602-13.
3. Jameson, J. L., Kasper, D. L., Fauci, A. S., Hauser, S. L., Longo, D. L., Loscalzo, J., & Harrison, T. R. (2018). *Harrisons principles of internal medicine* (20th ed.). New York: McGraw-Hill Education.
4. Mehran R,Aymong ED, Nikolsky E, LasicZ,IakovouI, FahyM,MintzGS, LanskyAJ, Moses JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol 2004;44:1393–9
5. Sadat, U., Usman, A., Gillard, J. H., & Boyle, J. R. (2013). Does Ascorbic Acid Protect Against Contrast-Induced Acute Kidney Injury in Patients Undergoing Coronary Angiography. *Journal of the American College of Cardiology*, *62*(23), 2167–2175. doi: 10.1016/j.jacc.2013.07.065
6. Dvoršak, B., Kanič, V., Ekart, R., Bevc, S., & Hojs, R. (2013). Ascorbic Acid for the Prevention of Contrast-Induced Nephropathy After Coronary Angiography in Patients With Chronic Renal Impairment: A Randomized Controlled Trial. *Therapeutic Apheresis and Dialysis*, *17*(4), 384–390. doi: 10.1111/1744-9987.12083
7. Boscheri, A., Weinbrenner, C., Botzek, B., Reynen, K., Kuhlisch, E., & Strasser, R. (2007). Failure of ascorbic acid to prevent contrast media induced nephropathy in patients with renal dysfunction. *Clinical Nephrology*, *68*(11), 279–286. doi: 10.5414/cnp68279
8. Spargias, K., Alexopoulos, E., Kyrzopoulos, S., Iacovis, P., Greenwood, D. C., Manginas, A., …

Cokkinos, D. V. (2004). Ascorbic Acid Prevents Contrast-Mediated Nephropathy in Patients With Renal Dysfunction Undergoing Coronary Angiography or Intervention. *Circulation*, *110*(18), 2837–2842. doi:10.1161/01.cir.0000146396.19081.73

9. Hadiani, L., Nough, H., Daryachahei, R., Najarzadegan, M., Mirzaee, M., Hemayati, R., … Namayandeh, S. (2016). Ascorbic acid effect on CIN incidence in diabetic patients after coronary angiography. Advanced Biomedical Research, 5(1), 69. doi: 10.4103/2277-9175.18063
10. Zhou, L., & Chen, H. (2012). Prevention of Contrast-Induced Nephropathy with Ascorbic Acid. *Internal Medicine*, *51*(6), 531–535. doi:10.2169/internalmedicine.51.6260
11. Evola, Salvatore, et al. "Risk Factors for Contrast Induced Nephropathy: A Study among Italian Patients." Indian Heart Journal, vol. 64, no. 5, 2012, pp. 484–491., doi:10.1016/j.ihj.2012.07.007.
12. Lü, Jian-Ming, et al. "Chemical and Molecular Mechanisms of Antioxidants: Experimental Approaches and Model Systems." Journal of Cellular and Molecular Medicine, vol. 14, no. 4, 2009, pp. 840–860., doi:10.1111/j.1582-4934.2009.00897.x.
13. Wang J, Zhang C, Liu Z, Bai Y. Risk factors of contrast-induced nephropathy after percutaneous coronary intervention: a retrospective analysis. *J Int Med Res*. 2021;49(4):3000605211005972. doi:10.1177/03000605211005972
14. Ramjattan NA, Lala V, Kousa O, Makaryus AN. Coronary CT Angiography. 2020 Aug 22. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 29262000.
15. Wang J, Zhang C, Liu Z, Bai Y. Risk factors of contrast-induced nephropathy after percutaneous coronary intervention: a retrospective analysis. *J Int Med Res*. 2021;49(4):3000605211005972. doi:10.1177/03000605211005972
16. Heyman S.N., Rosen S., Khamaisi M., Odee JM., Rosenberger C. (2011) Hypoxia, Oxidative Stress, and the Pathophysiology of Contrast-Media-Induced Nephropathy. In: Miyata T.,

Eckardt KU., Nangaku M. (eds) Studies on Renal Disorders. Oxidative Stress in Applied Basic Research and Clinical Practice. Humana Press. https://doi.org/10.1007/978-1-60761-857-7_12