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Research Article

Vitamin C for the Prevention of Postoperative Atrial Fibrillation after Cardiac Surgery: A Meta-Analysis

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Abstract

Purpose: Several studies have investigated the administration of vitamin C (vitC) for the prevention of postoperative atrial fibrillation (AF) after cardiac surgery. However, their findings were inconsistent. The purpose of this meta-analysis was to evaluate the efficacy of vitC as prophylaxis for the prevention of postoperative AF in cardiac surgery.

Methods: A systematic search of PubMed, EMBASE, Google Scholar, the Cochrane Library, and clinical trial registries, was performed. 9 studies, published from August 2001 to May 2015, were included, with a total of 1,037 patients. Patients were randomized to receive vitC, or placebo.

Results: Cardiac surgery patients who received vitC as prophylaxis, had a significantly lower incidence of postoperative AF (random effects OR=0.478, 95% CI 0.340 – 0.673, $P < 10^{-4}$). No significant heterogeneity was detected across the analyzed studies (I^2=21.7%), and no publication bias or other small study-related bias was found.

Conclusion: Our findings suggest that VitC is effective as prophylaxis for the prevention of postoperative AF. The administration of vitC may be considered in all patients undergoing cardiac surgery.

Introduction

Atrial fibrillation (AF) is the most frequent postoperative complication after cardiac surgery.[1] The prevalence of postoperative AF ranges, roughly, from 25% in coronary artery bypass graft (CABG) procedures, to 65% in valve replacement procedures.[2]

Postoperative AF after cardiac surgery doubles the morbidity rate, and raises the mortality rate as well. Most common complications of postoperative AF are acute myocardial infarction, ischemic stroke and acute renal failure.[2,3] The economic burden of AF, from the increased morbidity and prolonged hospital stay, has been estimated in the US alone at $1 billion.[2]

A variety of therapeutic strategies have been proposed as prophylaxis for postoperative AF.[4] β-blocker administration is advised in all patients, as well as amiodarone in high risk patients.[5] Corticosteroids, biatrial pacing, and sotalol have been used with various success rates.[6-8] *A number of studies have* identified postoperative AF as an inflammatory condition.[9,10] The need for newer treatments, with fewer side-effects, that can be administered for longer periods of time, has led investigators to study drugs that target oxidative stress.[11]

Apart from corticosteroids, drugs that are known to target oxidative stress include N-acetylcysteine, polyunsaturated fatty acids, and vitamins C (vitC) and E.[12-15]

In the present meta-analysis, we sought to evaluate the strength of evidence for vitC supplementation in cardiac surgery as prophylaxis for postoperative AF.

Materials and Methods

Inclusion criteria

Eligible for inclusion in our study were cohort studies and randomized controlled trials (RCTs) that evaluated the efficacy of vitC in cardiac surgery as prophylaxis for postoperative AF.

Identification of studies & study selection

We searched in PubMed (1951 up to April 2015), Cochrane Library (1997 up to April 2015), Google Scholar (1951 up to April 2015), EMBASE (1985 up to April 2015), and clinical trial registries (1997 up to April 2015). Clinical trial registries queried in our study were: EU Clinical Trials Register, WHO international clinical

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trials registry platform, ClinicalTrials.gov, Iranian Registry of Clinical Trials, Australia and New Zealand's (ANZCTR), Pan African Clinical Trial Registry (PACTR), Clinical Trials Registry - India (CTRI), Cuban Public Registry of Clinical Trials (RPCEC), German Clinical Trials Register (DRKS), and Chinese Clinical Trial Registry (ChiCTR).

Predefined search terms were: 'vitamin C', 'ascorbic acid', 'ascorbate' and 'atrial fibrillation', 'arrhythmias' and 'cardiac surgery', 'cardiothoracic surgery', 'heart surgery', 'cardiopulmonary bypass', 'coronary artery bypass graft', 'CABG', 'valve surgery', 'valvular surgery'.

Titles, abstracts, and full text were screened for eligible studies by two reviewers. There were no language restrictions.

Data extraction & quality assessment

Standardized data extraction forms were used. Data included definition of postoperative AF, days of follow-up after surgery, baseline patient characteristics, number of treatment groups and intervention used, vitC regimen used, and primary and secondary outcomes of the study. Quality assessment of RCTs was performed with the Jadad score. The Jadad is a 5 point scale score that divides RCTs in 'high' quality: 5, 'good' quality: 3-4, and 'poor' quality: 0-2. Non-randomized studies were assessed with the Newcastle-Ottawa scale, a 9 point scale that attributes a maximum score of 9 points, 4 points for selection, 2 points for comparability, and 3 points for outcome.

Statistical analysis

We compared the incidence of postoperative AF in patients receiving vitC, versus patients receiving placebo. Results of studies were reported as Odds Ratios (ORs) of postoperative AF given treatment with vitC, with a 95% confidence interval (CI). A standard meta-analysis with inverse variance weights was used to estimate the combined ORs along with their 95% CIs.[16] We used the standard non iterative method of moments proposed by DerSimonian and Laird.[17] The percentage of variability between studies due to heterogeneity was evaluated by the inconsistency index I^2 (ranging between 0–100%). We also performed a random-effects meta-regression in order to identify the effect of study-level covariates that potentially influence the outcome and explain the between-studies variability.[18,19] Publication bias was estimated using the rank correlation method,[20] and the regression method of Egger's.[21] The potential time trend of the combined estimate over the years was evaluated by applying the standard cumulative meta-analysis approach.[22,23] We also reiterated the analysis by removing each time a single study, in order to find influential studies. Data was analyzed using STATA 10. We used the PRISMA checklist (S1 PRISMA Checklist).

Results and Discussion

Using the predefined search terms, 4,798 potentially eligible studies were initially generated by the literature search. 4,785 records were excluded due to duplication, abstract unavailability, or inappropriate information, after titles, abstracts or full text were reviewed. 15 studies were reviewed as potentially appropriate. 3 studies were excluded, as they administered vitC combined with other treatments under evaluation.[24-26] 2 studies in clinical trial registries were excluded for not posting results, and authors were unavailable for comment.[27,28] 1 study in a Russian language journal was excluded, as the journal was unavailable in electronic or print form, and the journal did not make its articles available outside the Russian Federation.[29] Finally, 9 studies were included: 7 studies published in journals indexed in the United States National Library of Medicine, 1 study published in a non-indexed journal, and 1 study from the US National Library of Medicine clinical trial registry.[30-38] 2 studies were prospective cohort studies[31,33] (Figure 1). 7 studies were RCTS.[30,32,34-38]

Postoperative AF is essentially an in-hospital phenomenon. This is not surprising, since 70% of patients develop postoperative AF before the 4th postoperative day, and 94% of patients before the 6th postoperative day.[3] The studies included in the meta-analysis defined AF either as the occurrence of an electrocardiographically confirmed episode of AF during hospitalization, or as an episode that required intervention or cardioversion. Patients were included in the meta-analysis irrespective of surgery type. 3 of the studies enrolled only patients undergoing CABG.[31,33,34]

All studies included in the meta-analysis reported patients' baseline characteristics including, age, gender, type of surgery, ejection fraction, presence of diabetes mellitus, presence of hypertension, preoperative use of β-blockers. In all studies, baseline characteristics were evenly matched, without any outliers.

All included RCTs were of good methodological quality (the mean Jadad score was 3.1, with a range 1-5). Two studies were prospective cohort studies and were assessed with the Newcastle-Ottawa scale. They were of good methodological quality, with a Newcastle-Ottawa score of 9 and 7 respectively, out of a possible maximum score of 9.[31,33] No significant heterogeneity was observed among included studies (χ^2= 10.21 p=0.251, I^2=21.7%, τ^2=0.0560). Pooled treatment effect analysis showed that the administration of VitC as prophylaxis significantly lowered the incidence of postoperative AF (OR=0.478, 95% CI=0.340 - 0.673) (Figure 2). The heterogeneity was low, but nevertheless we applied the meta-regression approach to all reported baseline study-level characteristics (age, gender, type of surgery, ejection fraction, presence of diabetes mellitus, presence of hypertension, preoperative use of β-blockers). We used both the mean values for treated and not treated individuals as a covariate in a meta-regression model, and in all cases the results were not statistically significant (P>0.05). Begg's and Egger's tests showed no

apparent publication bias (Egger's test t=-1.10, p= 0.322, Begg's test p= 0.548; funnel plot, Figure 3). The cumulative random-effects meta-analysis, using the 'first vs. subsequent' method (p=0.600), provided evidence against time-trend bias (Figure 4). The influential analysis did not reveal any study that influenced the results, since in each case the overall estimate and the 95% CI had only minor fluctuations, and the overall conclusions were not altered.

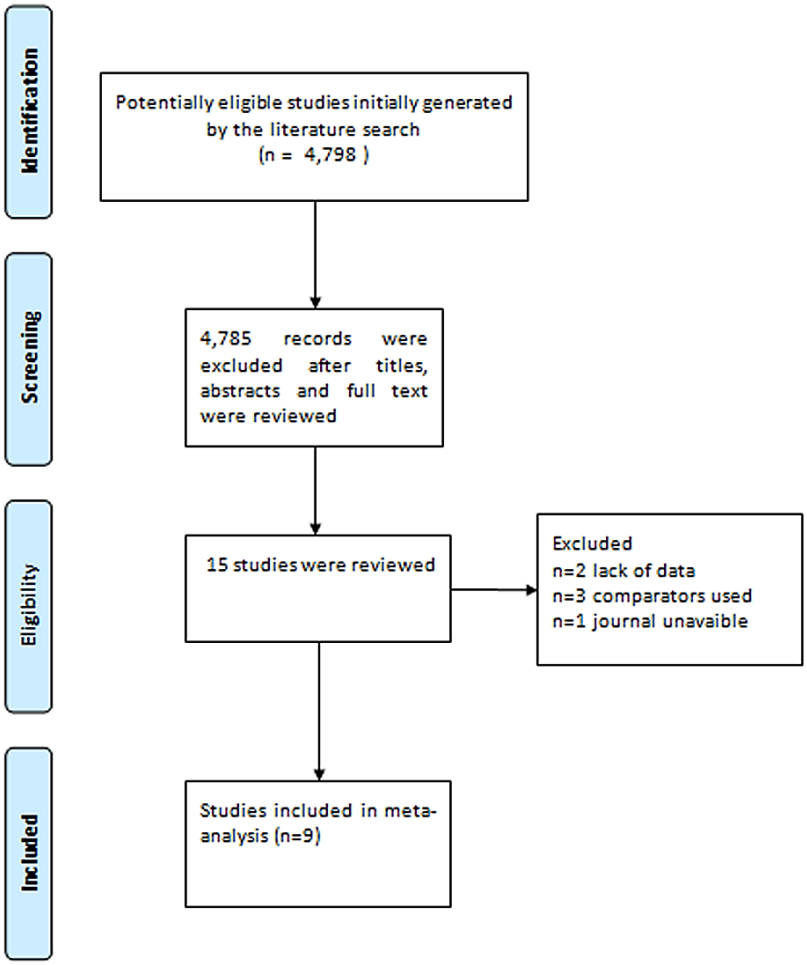

Figure 1. Flow chart for determining study inclusion. The process for screening, study selection for review, and exclusion criteria, is detailed in the chart.

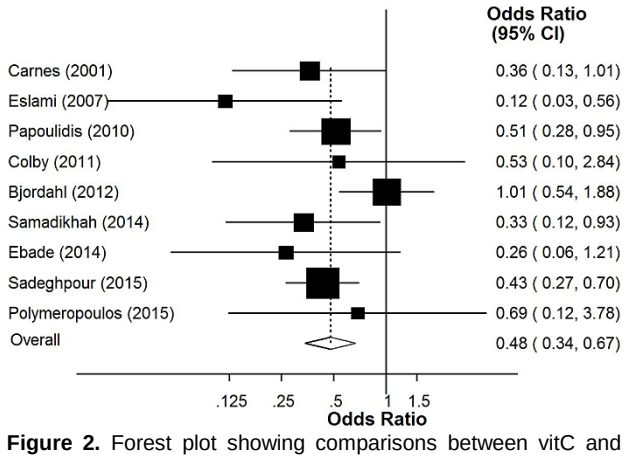

Figure 2. Forest plot showing comparisons between vitC and placebo. Square size indicates study size. Favorable outcomes for vitC are to the left of the vertical axis. On the right, odds ratios with 95% CIs for studies included in the meta-analysis are provided.

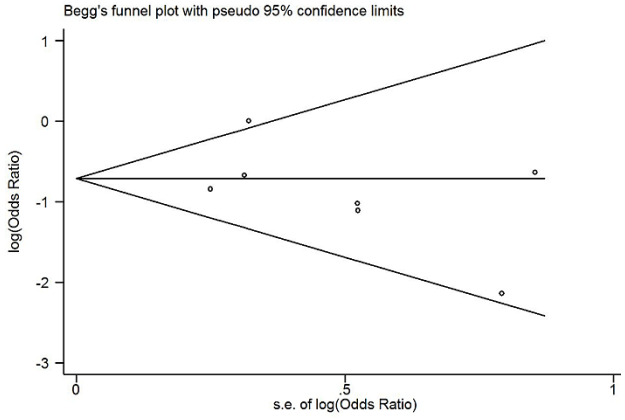

Figure 3. Funnel plot for evaluating publication bias. Standard error is plotted in the horizontal axis, against effect estimate in the vertical axis, with 95% confidence intervals outlining the cone. A visual inspection shows no asymmetry, indicating that there is no publication bias.

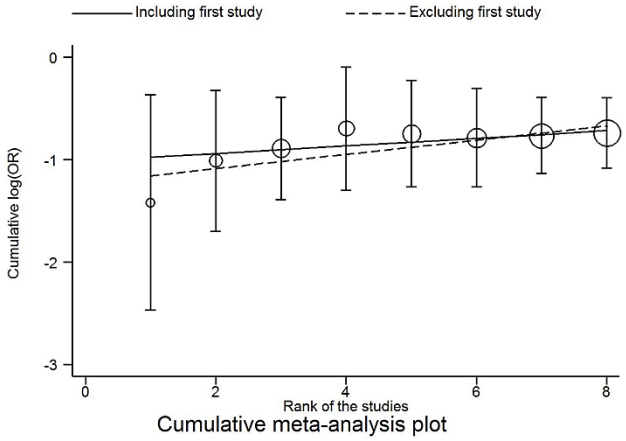

Figure 4. Cumulative meta-analysis using the first vs. subsequent method. There was a consistency in the results of consecutive studies, indicating that there was no time-trend bias.

Although postoperative AF is an old problem, its complete eradication has proven to be elusive. The reported incidence of postoperative AF varies widely between studies, due to differences in patient populations, type of surgery, and definition of AF used. None the less, it seems that the prevalence of postoperative AF has remained fairly stable the last decades, since older studies show similar prevalences of AF to these in studies conducted in the modern era.[39,40]

As the patient population is ageing, the incidence of AF is expected to rise, since age is a major predictor of postoperative AF.[41] Clinical practice guidelines recommend the use of amiodarone as a prophylactic agent for patients at high risk for postoperative AF.[42] There are, though, two caveats concerning the routine prophylactic use of amiodarone: there are no consistent clinical factors, apart from age and type of surgery, that can reliably predict new-onset AF, and amiodarone has side-effects, such as hypotension, and bradycardia, that its use requires monitoring.[41,43] Thus, the ideal prophylactic agent should have few or no side-effects, it should not require monitoring or long preoperative periods of time for administration, and finally, if possible, it should be relatively inexpensive. VitC is such a potential agent.

The prevailing theories for the pathogenesis of AF, recognize changes in the electrophysiological substrate as the possible culprit for arrhythmogenesis.[44-47] Pro-inflammatory changes and the peri-procedural oxidative stress, are thought to induce a series of changes in the conductance system of the heart through structural changes in the atrial myocardial tissue.[9,48] Differential expression of mitochondrial DNA, induction of enzymes such as NADPH oxidase and/or xanthine oxidase, the activation of the renin-angiotensin system, and the differential expression of gap junctions, are some of the changes that have been observed.[44-47] VitC is a lactone, comprising of 6 carbon molecules. VitC is an electron donor for a number of enzymatic systems, reducing potentially harmful free radicals by forming the more stable semidehydro-ascorbic acid, which does not regenerate enzymatically, but it is rather metabolised and discharged.[49] VitC may also have other beneficial pleiotropic actions, such as improvements in coronary microcirculation and endothelial function.[50,51]

Animal studies and the use of drugs with anti-inflammatory and antioxidant properties for the prophylaxis of postoperative AF, indicate an inflammation mediated mechanism for postoperative AF.[8,10,52] Drugs with anti-inflammatory and antioxidant properties include nonsteroidal anti-inflammatory drugs, vitC, vitamin E, corticosteroids, and colchicine.[53,54] Supporting the inflammation hypothesis is the correlation between the levels of markers of inflammation, including fibrinogen, white blood cell count, hsCRP, and IL-6, and the development of postoperative AF.[55] Postoperative inflammation markers peak around the 3rd postoperative day, which coincides with the bulk of postoperative AF: 2/3 of the cases of AF occur before the 4th postoperative day.[32] An increased white blood cell count correlates with postoperative AF, although the association is less straightforward in the case of other inflammatory biomarkers.[55] Peroxidase levels seem to be the most reliable prognostic marker, among serum biomarkers for oxidative stress, for new onset AF.[56] In postoperative AF, there is an increased peroxynitrite concentration, a free radical formed from hydrogen peroxide and nitrite, which is a target for vitC.[57,58]

The first studies conducted with VitC showed promising results. In 2012, Bjordahl et al.[30] in a carefully conducted, triple-blind study did not find any difference in the efficiency of vitC compared to placebo.[30] A meta-analysis, which included 5 studies conducted up to 2013, found that vitC might be useful, but that meta-analysis was hampered by the significant heterogeneity between studies.[12] The authors of the meta-analysis attributed the heterogeneity of the data to age as a possible confounder. Nonetheless, the heterogeneity of the included studies, did not allow for a definite conclusion. Newer studies with vitC, included in our meta-analysis, lowered the overall heterogeneity, and allowed for a methodologically sound pooling of the data. All included studies were adequately randomized, or, in the case of cohort studies, evenly matched for potential confounding factors, further strengthening our results.

There were principally two limitations in our meta-analysis. Studies included in our analysis spanned the Middle East. Europe and North America. There were no studies included from the Indian Subcontinent, China, South America, or Subsaharan Africa. The second limitation of our study was due to inherent design differences concerning the administration of vitC (Table 1). Clearly, vitC is effective as prophylaxis, but which regimen, by which route, and for how long? High intravenous doses of viC may probably be the most effective administration route, but data on the effectiveness of each regimen are not readily comparable, and most studies in our meta-analysis used the oral route.

Table 1. Characteristics of Studies Included in the Meta-Analysis

Study	Country	Study Regimen	Participants (N)	Incidence of AF
Carnes, 2001	USA	2 g vitC p.o. the night before, 500 mg x2 p.o. for 5 days after surgery	VitC 43 Control 43 Total 86	VitC 7/43 - 16.3% Control 15/43 - 34.9%
Eslami, 2007	Iran	2 g vitC p.o. the night before, 500 mg x2 p.o. for 5 days after surgery	VitC 50 Control 50 Total 100	VitC 2/50 - 4% Control 13/50 - 26%
Papoulidis, 2010	Greece	2 g vitC i.v. 3 h before, 500 mg x2 for 5 days after surgery	VitC 85 Control 85 Total 170	VitC 38/85 - 44.7% Control 52/85 - 61.1%
Colby, 2011	USA	2 g vitC p.o. the night before, 500 mg x2 p.o. for 5 days after surgery	VitC 13 Control 11 Total 24	VitC 4/13 - 30.7% Control 5/11 - 45.4%
Bjordahl, 2012	USA	1 g vitC p.o. the evening before, 500 mg x2 p.o. for 5 days after surgery	VitC 89 Control 96 Total 185	VitC 27/89 - 30.3% Control 29/96 - 30.2%
Ebade, 2014	Egypt	2 g vitC i.v. after induction of anesthesia, 1 g 12 h after surgery, 1 g x3 for 6 days after surgery	VitC 20 Control 20 Total 40	VitC 3/20 - 15% Control 8/20 - 40%
Samadikhah, 2014	Iran	2 g vitC on operating day, 1 g for 5 days after surgery. Route n/a	VitC 60 Control 60 Total 120	VitC 6/60 - 10% Control 15/60 - 25%
Sadeghpour, 2015	Iran	2 g vitC on operating day, 1 g p.o. for 5 days after surgery	VitC 113 Control 177 Total 290	VitC 40/113 - 35.3% Control 99/177 - 55.9%
Polymeropoulos, 2015	Greece	500 mg x4 vitC i.v. 2 days before surgery, 500 mg x4 for 4 days following surgery	VitC 11 Control 11 Total 22	VitC 4/11 - 36.3% Control 5/11 - 45.4%

Ultimately, all prophylaxis agents for postoperative AF should lower mordibity, both in the short term, and in the medium term, and not just AF rates. 7 out of 9 studies included in our meta-analysis reported days of hospitalization, and although in some of these studies hospital length of stay was shorter, most studies were underpowered to address this question.[12,30,32-38] Sadeghpour et al.[37] specifically set to investigate whether vitC has an impact on hospital length of stay and ICU stay, and reported favorable outcomes. More studies may be needed in order to investigate the impact of vitC on morbidity in cardiac surgery patients.

Conclusion

In conclusion, vitC as prophylaxis for postoperative AF after cardiac surgery is effective. Due to the safe, and relatively inexpensive nature of vitC, supplementation with vitC may be considered in all patients undergoing cardiac surgery. None the less, it is not sufficiently documented if the clinical benefit seen by cutting postoperative AF rates translates also into fewer hospitalization days, or less overall morbidity.

Ethical Issues

The present study is a meta-analysis of published studies. No patients were enrolled in our study, thus no ethical considerations arose over the treatment allocation of individual patients. All the studies included in our meta-analysis reported that they had obtained informed patient consent, and ethics board approval, prior to study inception. 6 of the studies included in our meta-analysis reported additionally the absence of conflict of interest and/or grants the authors received.[30-34,38] We followed the ICMJE "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals". Meta-analysis in medical research prevents redundant research, and consequently contributes in a positive manner to improvement in clinical practice.

Conflict of Interest

The authors report no conflicts of interest.

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