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Does ascorbic acid protect against contrast induced- acute kidney injury in patients undergoing coronary angiography – a systematic review with meta-analysis of randomized controlled trials

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Abstract:

Objectives: To perform a systematic review with meta-analysis of randomized controlled trials (RCTs) comparing the use of ascorbic acid with placebo or other treatment options against contrast induced-acute kidney injury (CI-AKI) in patients undergoing coronary angiography.

Background: CI-AKI remains the most widely discussed and debated topic in cardiovascular medicine with its incidence on a rise due to an increasing number of contrast media-enhanced radiological procedures being performed.

Methods: Medline, Embase and Cochrane central databases were searched from inception to May 2013, without language restrictions. For a study to be selected, it had to report the incidence of CI-AKI as an outcome measure. Studies were excluded if at least one study arm did not have ascorbic acid administered alone or with saline hydration. Data was extracted by 1 author and random checks were made by a co-author.

Results: Nine RCTs reported data on the incidence of CI-AKI in 1536 patients who had completed the trial and were included in the final analysis. Patients receiving ascorbic acid had 33% less risk of CI-AKI compared to patients receiving placebo or alternate pharmacological treatment [risk ratio (RR) by random effects model: 0.672 (95% CI: 0.466-0.969), $p=0.034$].

Conclusions: Ascorbic acid provides effective nephroprotection against CI-AKI and may form a part of effective prophylactic pharmacological regimens.

Keywords: ascorbic acid; contrast-induced nephropathy, acute kidney injury; angiography

Abbreviations:

CI: Confidence interval

CI-AKI: Contrast induced-acute kidney injury

CM: Contrast media

CrCl: Creatinine clearance

MeSH: Medical subject headings

RCTs: Randomized controlled trials

ROS: Reactive oxygen species

RR: Risk ratio

SCr: Serum creatinine

Introduction:

Rationale- Contrast induced-acute kidney injury (CI-AKI) is one of the most widely discussed and debated topic in cardiovascular medicine. The incidence of CI-AKI is on a rise. This is due to an increasing number of contrast media (CM)-enhanced radiological procedures being performed and a rise in the octogenarian population with co morbidities such as hypertension, diabetes mellitus, renovascular disease, all of which predispose to renal impairment. It is therefore imperative that more attention be given to develop a better understanding of the aetiology of CI-AKI, devise novel methods of its diagnosis at an earlier stage before renal failure has ensued and formulate effective prophylactic and therapeutic regimens to reduce its incidence.

Traditionally, ascorbic acid has been used as a dietary supplement. Today there is strong evidence that it acts as a potent antioxidant by scavenging physiologically relevant reactive oxygen species (ROS)(1,2). As oxidative stress has been implicated as a contributing factor in the aetiology of CI-AKI(3), use of ascorbic acid as a nephroprotective agent is therefore but logical.

Objective- To assess whether ascorbic acid reduces the incidence of CI-AKI, we reviewed randomized controlled trials (RCTs) that assess its nephroprotective role in reducing CI-AKI compared with placebo or other pharmacological agents in patients undergoing coronary angiography.

Methods:

1. **Protocol:** The research question, search strategy, inclusion criteria, and statistical analyses were prespecified.
2. **Eligibility criteria:**
 - a. Types of studies: RCTs assessing the use of ascorbic acid in reducing CI-AKI compared to placebo or other pharmacological treatments, in patients undergoing

- coronary angiography. No language, publication date, or publication status restrictions were imposed.
- b. Types of participants: Participants of any age with or without documented pre-existing renal impairment undergoing coronary angiography were considered.
 - c. Types of intervention: Ascorbic acid alone (or with saline hydration) in one treatment arm. The route of administration of ascorbic acid could be oral and/or intravenous. Patients in the comparison group may either receive: saline hydration and/or placebo/other nephroprotective agent.
 - d. Types of outcome measures: For a RCT to be included, it had to report incidence of CI-AKI as an outcome measure. CI-AKI was defined as an absolute increase in SCr of ≥ 0.5 mg/dl ($44 \mu\text{mol/L}$) or a relative increase of $\geq 25\%$ from the baseline value following administration of CM during the angiography.
3. **Information sources:** Electronic databases: Medline, Embase, and Cochrane Central databases from the date of inception until 15th May, 2013 were systematically searched. No limits were used for electronic literature search. Tangential electronic exploration of related articles (i.e. using links to related references to search for additional articles) was also done. The last search was run on 20th May 2013. Extensive hand searches of bibliographies of relevant reviews and related journals were also done.
 4. **Search:** Search terms included variants of vitamin C, ascorbic acid, nephropathy, contrast nephropathy, contrast induced nephropathy, contrast media, contrast agent, kidney, renal, angiography, arteriography using text words and *Medical Subject Headings* (MeSH) terms. Search strategy using Medline database is as follows:

Search history:

1. MEDLINE; "vitamin C".ti,ab; 14581 results
2. MEDLINE; "ascorbic acid".ti,ab; 22487 results
3. MEDLINE; exp ASCORBIC ACID/; 34524 results
4. MEDLINE; 1 OR 2 OR 3; 48039 results
5. MEDLINE; kidney*.ti,ab; 311331 results
6. MEDLINE; renal.ti,ab; 427591 results
7. MEDLINE; exp KIDNEY/; 289995 results
8. MEDLINE; "contrast induced nephropath*".ti,ab; 868 results
9. MEDLINE; "contrast nephropath*".ti,ab; 239 results
10. MEDLINE; nephropathy.ti,ab; 36572 results
11. MEDLINE; "contrast media".ti,ab; 9299 results
12. MEDLINE; "contrast agent*".ti,ab; 17645 results
13. MEDLINE; exp CONTRAST MEDIA/; 88039 results
14. MEDLINE; 11 OR 12 OR 13; 95541 results
15. MEDLINE; 5 OR 6 OR 7 OR 10; 722617 results
16. MEDLINE; 8 OR 9; 1064 results
17. MEDLINE; 14 AND 15; 10603 results
18. MEDLINE; 16 OR 17; 10786 results
19. MEDLINE; "angiograph*".ti,ab; 130279 results
20. MEDLINE; exp ANGIOGRAPHY/; 189985 results
21. MEDLINE; "arteriograph*".ti,ab; 17695 results

22. MEDLINE; 19 OR 20 OR 21; 253190 results

23. MEDLINE; 4 AND 18 AND 22; 10 results

5. **Study selection:** Eligibility assessment was performed by one author (US) in an unblinded standardized manner using study eligibility form based on 'Cochrane consumers and communication review group's data extraction template'. Random checks were made by co-author (AU). The title and abstract of the retrieved records were screened. Conference abstracts and letters retrieved from electronic databases were also included in screening process.
6. **Data collection process:** Data extraction was performed using 'Cochrane consumers and communication review group's data extraction template'. Author (US) extracted the relevant data from included studies which was checked by the second author (AU). There were no disagreements between the two review authors. Corresponding author of one study included for final analysis was contacted via email, for clarification of information but there was no response(4).
7. **Data items:** Information was extracted from each included trial on the variables mentioned in the data eligibility section.
8. **Study quality and risk of bias in individual studies:** To assess the quality of the study, guidelines in 'Cochrane Handbook for Systematic Reviews of Interventions' were followed(5). A scoring system to grade the study quality was not used as strongly discouraged by 'Cochrane Collaboration'(5). To explore variability in study results (heterogeneity), we specified the following hypothesis before conducting the analysis. We hypothesized that effect size may differ according to the methodological quality of the studies; hence random effects model was to be primarily used.

9. Statistical analysis: Statistical analysis was performed by author (US), using

‘Comprehensive Meta Analysis’ statistical software (Version 2.2.064), Biostat Inc. NJ, USA.

Summary measures: The primary outcome measure was reduction in risk of CI-AKI with ascorbic acid quantified by computing pooled risk ratio (RR) with 95% confidence interval (CI) using random-effects model.

Planned method of analysis: In addition, influence of using a fixed effect model on RR was also assessed. The effect of removal of one study each time on RR was also assessed to identify the impact of individual studies on pooled effect size. Cumulative analysis was performed by organizing the studies in chronological order to observe the trend in pooled RR over time. Heterogeneity was quantified using I^2 statistic (with 95% CI), which represents the percentage of the total variation in estimated effects across studies that is due to heterogeneity rather than to chance. Heterogeneity was graded after Higgs et al: I^2 values of the order of 25%, 50% and 75% may be considered as low, moderate and high heterogeneity respectively(6).

Risk of bias: The possibility of publication bias was assessed by subjectively evaluating a funnel plot of standard error of logarithm of RR for asymmetry. Because graphical representation is subjective, we also conducted Egger’s regression asymmetry test as formal statistical test for publication bias(7). To assess if the entire effect was an artefact of bias, Orwin’s *Fail-safe N* was used(7). To assess how much of an impact bias might have on effect size (RR), Duval and Tweedie’s *Trim and Fill* method was used. We acknowledge that other factors such as differences in trial quality or true study heterogeneity, could produce asymmetry in funnel plots.

Results:

Study selection: The search of Medline, Embase and Cochrane central database provided a total of 63 citations. After adjusting for duplicates, 56 remained. Of these, 47 were discarded because after reviewing the abstracts it appeared that these papers clearly did not meet the eligibility criteria. One of these 47 articles was an RCT reported as a conference abstract which although used ascorbic acid in one treatment arm, but did not report the incidence of CI-AKI (% or number of cases)(8). The authors were not contactable hence the study was excluded.

A total of 9 RCTs were identified for inclusion in the review and meta-analysis(4,9-16). Seven of these had full text which was examined in more detail. Two were conference abstracts which met the eligibility criteria, hence were included in the analysis(13,16). No relevant RCTs were identified from the hand search of relevant articles that could be included. Similarly no unpublished studies were identified. There was no disagreement among the authors regarding study selection. A flow diagram of study selection is presented in Figure 1.

Study characteristics:

These are tabulated in Table 1.

Methods

All nine studies finally selected for the review and meta-analysis were RCTs, all published in English language. All included studies had reported incidence of CI-AKI and had SCr levels checked between 24 hrs up to 5 days.

Participants

All studies reported adult population undergoing coronary angiography. All studies had patients with baseline renal impairment.

Intervention and Outcomes

The interventions and outcomes are tabulated in Table 1.

Risks of bias within studies: All included trials were randomized, hence minimizing the chance of bias within studies compared to observational studies. The quality of studies may be assessed from Table 2, which tabulates the relevant study characteristics according to ‘Cochrane handbook for systematic reviews of interventions’.

Results of individual studies

All studies reported incidence of CI-AKI as number of cases except one study Hamdi et al(16), for which event rate was imputed. The event rate of the included studies is presented in Figure 2.

Synthesis of results:

Nine RCTs reported data on the incidence of CI-AKI in 1536 patients who had completed the trial and were included in the final analysis. Ascorbic acid was given to 740 patients while 796 patients were in control group receiving alternate treatment. Overall incidence of CI-AKI in patients receiving ascorbic acid was 9.59% compared to 16.83% in control arm. In the pooled analysis using random effects model, patients receiving ascorbic acid had 33% less risk of CI-AKI compared to control group [RR: 0.672 (95% CI: 0.466-0.969), $p=0.034$] (Figure 2).

Evaluation of the 95% CI shows that range of risk lowering varied from 54% to 4% with ascorbic acid. Low degree of non significant heterogeneity was present ($I^2=27.49\%$, $\chi^2=11.03$, degree of freedom (df): 8, $p=0.200$).

Risk of bias across studies:

Due to evidence of low heterogeneity, a funnel plot was drawn to explore it and assess any bias (Figure 3). The funnel plot showed evidence of minimal asymmetry which was quantified to be statistically non-significant by Egger’s regression intercept [Intercept 0.552 (95% CI: -1.428 – 2.533), df: 7.000, $p=0.530$]. Orwin’s *Fail-safe N* is 170, suggesting that there would need to be

over 150 studies with a mean RR of 1.0 added to the analysis before the cumulative effect would become trivial (defined as a RR of 0.98). Given that we were able to identify only 9 studies for the final analysis, it is quite unlikely that over 150 studies were missed. While there is a possibility that reduction in risk of CI-AKI with ascorbic acid is overstated, it is unlikely that the actual risk is zero. Using random effects model, *Trim and Fill* method suggested no asymmetry on the right of the mean and 1 study on the left of the mean, which if trimmed, the imputed RR would be 35% (instead of 33%). The above analyses reveal that the impact of bias was most likely trivial.

Additional analyses:

1. Use of fixed effect model showed 33% (95% CI: 13-49%) lower risk with ascorbic acid [RR: 0.670 (95% CI): 0.511-0.878, $p=0.004$] (Figure 2). Although degree of significance was higher compared to random effects model, the pooled effect size was similar with minor variation in the 95% CI.
2. Effect of removal of individual studies on pooled RR using random effects model was assessed using forest plot, showing that it favoured ascorbic acid use against CI-AKI at each step (Figure 4).
3. To assess how the trend in RR had changed from the earliest to latest studies, a cumulative analysis was performed with studies arranged in chronological order (Figure 5). The second row represents a summary analysis comprising of the first two studies, the third row represents a summary analysis comprising the first three studies and so on. There was a small but consistent cumulative trend towards a benefit with ascorbic acid. As none of the studies had excessively large sample size, we did not perform cumulative analysis trying to assess its impact on effect size.

4. Three studies had a sizable proportion of patients lost to follow up after randomization(12,14,17). After excluding these 3 studies from the analysis, it was observed that the benefit of ascorbic acid in offering nephroprotection increases, with further reduction in non-significant minimal heterogeneity and no evidence of publication bias [RR: 0.530(95% CI: 0.349-0.860), $p=0.003$; $I^2=9.120$, $\chi^2=5.502$, $df=5$, $p=0.358$; Egger's regression intercept= 1.086 (-2.570-4.743), $df=4$, $p=0.455$).

Discussion:

This pooled statistical analysis of systematically selected RCTs provides robust evidence that ascorbic acid reduces the risk of CI-AKI, albeit by somewhat small magnitude, in patients undergoing coronary angiography compared to alternate treatment strategies. As participants of these studies had documented pre-existing renal insufficiency, this indicates that ascorbic acid is effective in offering nephroprotection in this patient group. 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) system for grading evidence can be used to assess various factors which may decrease the quality of this evidence(18):

Study limitations- The trials included for meta-analysis although did not consistently report optimal randomization concealment (Table 2), and had variable lack of blinding, the outcome measures were not subjective; hence these may not be considered serious limitations. None of the trials was stopped prematurely and there was no evidence of selective reporting.

Inconsistent results- Heterogeneity among the trials was minimal. This may be due to true heterogeneity of the study populations. Also important to note is that there was variability among studies about the route ascorbic acid was used. As the bioavailability of oral and intravenous administration of ascorbic acid is different(19), this can affect the drug efficacy and hence variation of effect sizes between studies.

Indirectness of evidence- All included trials reported head to head comparison of ascorbic acid versus alternate treatment, hence there was no evidence of indirectness.

Imprecision- None of the trials had very small sample size compared to others and event rate was not negligible in studies.

Publication bias- Publication bias was non-significant and was found not to affect the pooled effect size of our meta-analysis.

Thus, it can be cautiously said that results of this systematic review with meta-analysis are reliable. Would it be possible to overturn the results of this meta-analysis by conducting another clinical trial? It is difficult to answer the question of what would the sample size be for the future trial because there are so many unknowns e.g. sample size, effect size, risk in each group etc. But assuming that the true effect size (odds ratio) in the population is 1 indicating no difference between groups, and assuming a risk of 15% in each group (based on the available study data), then a total sample size of 250 (125 patients in each group) will change the conclusions of the meta-analysis provided that the observed effect size is at least as large as the true effect size of 1.

It is to be noted that no trial can be conducted that is guaranteed to change the conclusions of the meta-analysis. Also, it is easier to conclude a significant difference rather than a non-significant difference. If the meta-analysis result is changed to non-significant, then the best that we can say is that there is insufficient evidence of a beneficial effect of ascorbic acid. The additional analyses performed in this meta-analysis such as effect of removal of one study at a time (Figure 4) and cumulative analysis (Figure 5) also show a persistent benefit with ascorbic acid against CI-AKI. Due to above reasons, it would therefore not be advisable to conduct such a trial.

How ascorbic acid may offer nephroprotection-

The exact mechanism by which ascorbic acid may offer nephroprotection is unclear, but it has been widely used due to its antioxidant property. ROS-induced oxidative stress and renal vasoconstriction have been implicated in the etiology of CI-AKI. Hydroxyl radical ($\text{OH}\cdot$) is one of many free radicals which can cause oxidative stress. Haber Weiss/Fenton reaction cycle governs the generation of $\text{OH}\cdot$ from hydrogen peroxide (H_2O_2) and superoxide radical ($\text{O}_2^{\cdot-}$); with reduction of ferric to ferrous by $\text{O}_2^{\cdot-}$, ferrous acting as a catalyst for this cycle. Ascorbate being an efficient scavenger of ROS such as $\text{O}_2^{\cdot-}$, H_2O_2 and $\text{OH}\cdot$ can therefore reduce the oxidative stress(1). Being a reducing agent, ascorbic acid has the ability to reduce ferric to ferrous, thus potentially promoting the generation of ROS and acting as a pro-oxidant. But this pro-oxidant effect has been demonstrated mainly *in vitro*, corresponding *in vivo* data has been inconsistent (2,20,21). Redox-active free iron is required for the Haber-Weiss reaction but physiologically this labile iron pool is kept at the lowest sufficient level by keeping iron in bound form, exception being patients with iron overload conditions such as haemochromatosis (22). Under physiological conditions *in vivo*, ascorbate seems to predominantly maintain its antioxidant effect (2,20,21,23). Ascorbic acid acts as an antioxidant by donating an electron to potentially damaging oxidizing radicals; this one-electron oxidation of AH^- (reduced circulating form of ascorbic acid) results in the production of the ascorbyl radical ($\text{A}^{\cdot-}$) also called semidehydroascorbic acid. As a result, the reactive free radical is reduced(24). Further donation of an electron (double oxidation) results in generation of stable dehydroascorbic acid (DHA). Among the trials included in this systematic review, the antioxidant effect of ascorbic acid was demonstrated by Spargias et al (9). Ascorbic acid has also been reported to cause vasodilatation (25,26). This effect may be independent of its effect to ameliorate ROS-induced endothelial dysfunction (27). These findings are however not consistent (28).

In contrast to one's expectation that ascorbic acid can cause acidification of urine, there is consistent evidence that ascorbic acid in daily dosage range of 2-6gm/day in divided doses (29-31) (which is equivalent to the maximum daily dose used in RCTs included in the meta-analysis) does not acidify the urine. Surprisingly, it can increase the urine pH (30). Since, acidic environment which is typical of tubular urine promotes free-radical production (32) and high pH of normal extracellular fluid inhibits it (33,34), alkalinizing renal tubular fluid with pharmacological agents is a logical strategy to reduce renal injury.

Affect of route of administration on efficacy of ascorbic acid-

Following oral intake, ascorbic acid is absorbed by active transport in the intestine (35). Most of it (80-90%) is absorbed when the intake is up to 100 mg/day. With an increase in ascorbic acid intake, the corresponding plasma concentration increases reaching a plateau at a dose of 90-150mg/day (36). It is freely transported into cells, including leucocytes and red blood cells, becoming saturated with ascorbic acid at doses between 100 and 200 mg daily (19). In contrast to this, intravenous route tends to achieve higher peak plasma concentration e.g. 3gm intravenous ascorbic acid produces a peak plasma concentration of 1760 $\mu\text{mol/L}$ versus 206 $\mu\text{mol/L}$ for oral route at same dose (19). Following intravenous administration, predicted peak urine concentrations of ascorbic acid can be as much as 140-fold higher compared to oral administration (19). Similar to high requirement of ascorbic acid in individuals with higher oxidative stress such as in smokers (37), it is possible that higher plasma concentration of ascorbic acid which is achievable with higher intravenous doses may be more beneficial in individuals with pre-existing renal insufficiency. This meta-analysis did not compare the pooled treatment effect of RCTs using exclusive per oral and intravenous ascorbic acid administration

because only 2 RCTs used intravenous route exclusively and their pooled analysis would not have been meaningful.

Conclusions:

Ascorbic acid has the potential of protecting against CI-AKI in patients with pre-existing renal impairment and can form a part of effective prophylactic pharmacological regimens. The precise mechanism by which it may do so is as unclear as the aetiology of CI-AKI. To assess its full potential as a nephroprotective agent, further investigation is warranted regarding its optimal dosage and route of administration which affects its bioavailability.

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Figure Legend

Figure 1: Flow diagram of study selection: Flow of information through the different phases of systematic review from literature search to final analysis. [CI-AKI: contrast induced acute kidney injury, RCT: randomized controlled trials]

Figure 2: Forest plot of included studies- The event rate within different study arms is presented alongside the computed risk ratio (95% CI (lower and upper limit) with p-value. Forest plot shows effect size (black filled square) with 95% CI (black line through the filled square), in terms of risk ratio for individual studies and pooled risk ratio (unfilled diamond) for fixed and random effects model at the bottom. Studies favouring reduction on risk with ascorbic acid are on the left of the centre line and studies favouring other treatment options are on right of the centre line.

Figure 3: Funnel plot for subjective assessment of bias among the included studies. Studies with larger sample size tend to accumulate at the top of the funnel and close to the centre line, with small studies towards the base. Funnel plot appears to have minimal asymmetry.

Figure 4: Forest plot using random effects model demonstrating the effect of removal of individual studies on pooled effect size. A consistent trend in favor of ascorbic acid as nephroprotective agent was observed at each step.

Figure 5: Cumulative analysis of included studies in chronological order. The second row indicates cumulative analysis of first 2 studies and so on. A somewhat consistent trend towards benefit with ascorbic acid is evident.

Table 1: Baseline study characteristics. Total number of recruited patients in each trial, definition of CI-AKI as used by included trial, dose of ascorbic acid used and the treatment given to patients in control arm

Study	Patients recruited (n)	Baseline renal function	Definition of CI-AKI	Dose of ascorbic acid	Route ascorbic acid administered	Control arm
Spargias ⁹	238	SCr \geq 1.2mg/dl	\geq 0.5mg/dl absolute or 25% relative SCr increase 2-5 days after procedure	3gm at least 2hr before procedure , 2gm night and morning after procedure. Hydration with normal saline (NS) 50-125ml/hr intravenous from time of randomization to at least 6hrs after procedure.	Oral	Placebo with intravenous hydration as in ascorbic acid arm.
Boscheri ¹⁰	143	SCr $>$ 120 μ mol/l (1.4mg/dl)	25% rise in SCr from baseline at 48 hrs	1gm ascorbic acid 20 min before exposure to contrast medium . 500 ml NS 2hrs before and 500ml during angiography and subsequent 6 hrs.	Oral	Placebo with intravenous hydration as in ascorbic acid arm.
Jo ¹¹	212	SCr \geq 1.1mg/dl and /or Cr Clearance (CrCl) \leq 60ml/min	\geq 0.5mg/dl absolute or 25%	3gm (night before) and 2gm morning of procedure. 2 gm night and morning	Oral	1200mg N-acetylcysteine orally BD day

			relative SCr increase within 48 hrs of contrast media exposure	after procedure (all doses 12 hrs apart).		before and on day of procedure
Zhou ¹²	174	SCr \geq 1.1mg/dl and /or eGFR < 60ml/min/1.73m ²	\geq 0.5mg/dl absolute or \geq 25% relative SCr increase within 48 hrs of contrast media exposure	Intravenous 3gm morning of procedure, oral 0.5gm on the night of procedure and next day morning (all doses 12 hrs apart). Intravenous NS hydration 1mg/kg/hr for 4 hrs before and at least 12 hrs after angiography.	Intravenous and Oral	Intravenous NS hydration 1mg/kg/hr for 4 hrs before and at least 12 hrs after angiography.
Komiyama ¹³	70	Baseline renal insufficiency (threshold not mentioned)	\geq 0.5mg/dl absolute or \geq 25% relative SCr	3gm before procedure, 2gm night and morning after procedure (12 hrs apart). NS hydration 1.5-2.5L.	Intravenous	Intravenous NS hydration 1.5-2.5L.
Brueck ¹⁴	520	Cr Clearance \leq 60ml/min	SCr >0.5mg/dl (44 μ mol/l)	500mg in 250ml NS infusion (over 30min) at 24hrs and 1 hr before	Intravenous	Placebo (as per ascorbic acid dose) and

			within 72 hrs of contrast media exposure	exposure to CM. NS (1mg/kg/hr) for 12 hrs before to 12 hrs after CM exposure.		intravenous NS (1mg/kg/hr) for 12 hrs before to 12 hrs after CM exposure.
Li ¹⁵	149	Baseline renal insufficiency (threshold not mentioned)	$\geq 0.5\text{mg/dl}$ absolute or $\geq 25\%$ relative SCr	Intravenous 3gm 2-4 hrs before procedure and oral 1.0gm on day 1 and 2 after procedure . Intravenous NS hydration	Intravenous and oral	Intravenous NS hydration
Albaptain ⁴	243	SCr $\geq 1.3\text{mg/dl}$	0.5mg/dl absolute increase in SCr and/or 25% relative decrease of Cr Cl, 4-5 days after procedure	3gm 2 hrs before procedure , 2 gm after angiogram and 2gm 24 hrs after angiogram . Intravenous NS 50-125ml/hr from randomization until at least 6 hrs after the procedure.	Oral	Intravenous NS hydration.
Hamdi ¹⁶	202	Not declared, baseline SCr=98.6 \pm 29 $\mu\text{mol/l}$)	25% increase in SCr 48-72hrs after	3gm 2hr before procedure, 2gm day after and next day.	Not reported	Intravenous saline hydration.

			angiogram			
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SCr: serum creatinine, Cr Clearance: Creatinine clearance, NS: normal saline

Table 2: Study characteristics to assess the risk of bias within studies. Relevant study characteristics according to 'Cochrane handbook for systematic reviews of interventions' for assessing risk of bias within included trials

Studies	Power calculation	RCT stopped early	Randomization	Concealment of randomization	Blinding	Investigator blinded	Patients blinded	Data assessment blinded	Patients lost to follow up N (%)
Spargias ⁹	Yes	No	Yes	Yes	Yes	Yes	Yes	No	7 (2.94)
Boscheri ¹⁰	Not mentioned	No	Yes	Yes	Yes	Yes	Yes	No	0
Jo ¹¹	Yes	No	Yes	Yes	Yes	Yes	Yes	No	38 (17.92)
Zhou ¹²	Not mentioned	No	Yes	Not declared	No	Not applicable	Not applicable	Not applicable	18 (10.34)

Komiyama ¹³	Not mentioned	No	Yes	Not declared	No	Not applicable	Not applicable	Not applicable	0
Brueck ¹⁴	Yes	No	Yes	Not declared	Yes	Yes	Yes	Not declared	37 (7.11)
Li ¹⁵	Not mentioned	No	Yes	Not declared	No	Not applicable	Not applicable	Not applicable	0
Albertain ⁴	Yes	No	Yes	Yes	No	Not applicable	Not applicable	Not applicable	0
Hamdi ¹⁶	Not mentioned	No	Yes	Not declared	Yes	Not declared	Not declared	Not declared	0









