



# Could Vitamin E Prevent Contrast-Induced Acute Kidney Injury? A Systematic Review and Meta-Analysis

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Several clinical studies have proposed a protective role for vitamin E ( $\alpha$ -tocopherol) against contrast-induced acute kidney injury (CIAKI). The aim of study was to assess the effects of vitamin E for the prevention of CIAKI. A systematic review and meta-analysis was conducted using MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. Randomized controlled trials (RCTs) reporting the effects of vitamin E on CIAKI development and measurements of renal function were included. Four trials including 623 participants were analyzed in the meta-analysis. All participants received intravenous hydration in addition to vitamin E or placebo. The incidence of the vitamin E group (5.8%) was lower than that of the control group (15.4%). Compared with the control, vitamin E significantly reduced the risk ratio (RR) of CIAKI by 62% (0.38; 95% confidence interval [CI], 0.22, 0.63;  $P < 0.010$ ). In addition, vitamin E reduced serum creatinine (SCr) increase after contrast administration (standardized mean difference [SMD],  $-0.27$ ; 95% CI,  $-0.49, -0.06$ ;  $P = 0.010$ ). However, changes in glomerular filtration rate (GFR) after contrast administration were not significantly different between vitamin E and the control group (SMD, 0.21; 95% CI,  $-0.01, 0.43$ ;  $P = 0.060$ ). Heterogeneity within the available trials was not observed. Our meta-analysis provides evidence that vitamin E plus hydration significantly reduced the risk of CIAKI in patients with renal impairment compared with hydration alone.

**Keywords:** Acute Kidney Injury; Contrast Media; Meta-Analysis; Vitamin E

## INTRODUCTION

Contrast-induced acute kidney injury (CIAKI) is an acute deterioration of renal function after contrast media administration in the absence of other causes (1). CIAKI is one of the most common causes of hospital-acquired acute kidney injury, and incidence is increasing due to an increasing number of contrast media enhanced procedures for diagnosis and intervention (2). The risk increases in patients with certain factors such as preexisting renal impairment, diabetes, congestive heart failure, advanced age, and concurrent administration of nephrotoxic drugs (3). It ranges from 5% in those with mild renal impairment to 50% in those with diabetes and severe renal insufficiency (4,5). It has been associated with increased in-hospital stay, complications and long-term mortality (6,7). Levy et al. (8) reported a significantly increased risk of in-hospital mortality (34% vs. 7%) for those patients who developed CIAKI.

Development of CIAKI involves multiple complementary pathophysiological processes (9). Contrast agent induces renal vasoconstriction with resultant medulla ischemia (10), and hypoperfusion generates reactive oxygen species (ROS) that lead to additional renal injury (11). Moreover, contrast agent has di-

rect tubular toxicity (11).

Unfortunately, there is no effective therapy once CIAKI has been initiated (9). There have been many studies to prevent CIAKI through blocking its pathophysiological processes. Intravenous hydration is the key therapy to date, because it increases tubular urine flow and diminishes contrast concentration and the viscosity of tubular lumens. Vasodilators including fenoldopam and dopamine, have been utilized considering decreasing renal vascular resistance (12,13), and antioxidants including N-acetylcysteine, vitamin C were utilized to scavenge ROS (14,15). To date, only intravenous hydration and N-acetylcysteine are routinely used as acute kidney injury guidelines, as the Kidney Disease Improving Global Outcomes Group recommended (16).

Vitamin E ( $\alpha$ -tocopherol) has been used as a dietary supplement due to its potent antioxidant and anti-inflammatory properties (17). The protective effects of vitamin E against CIAKI were reported (18-20), however it remains unclear. To examine whether vitamin E reduces the development of CIAKI, we systematically reviewed the randomized controlled trials (RCTs) that assessed the effectiveness of vitamin E in the prevention of CIAKI compared with placebo in high-risk adults undergoing procedures using contrast.

## MATERIALS AND METHODS

### Search strategy

Electronic searches were performed using MEDLINE (1944 to May 2016), the EMBASE database (1947 to May 2016), and the Cochrane Central Register of Controlled Trials (1997 to May 2016). To achieve the maximum sensitivity of the search strategy and identify all studies, we combined the terms: “contrast,” “vitamin E,” “tocopherol,” “kidney,” or “nephropathy” as either keywords or MeSH terms. No restrictions were made regarding the language, population, or publication type.

### Study selection

We included RCTs providing information on the effects of vitamin E ( $\alpha$ -tocopherol) on CIAKI.  $\alpha$ -tocopherol treatment was considered regardless of dosage, route, duration of administration, or combined usual care. There were no restrictions made in terms of sample size, participant characteristics, or study duration. The primary outcome was the development of CIAKI. The secondary outcomes were changes in serum creatinine (SCr) levels, and glomerular filtration rate (GFR) between before and after contrast exposures and adverse effects. Eligibility assessment was performed independently by 2 reviewers (MHC and HWP). Disagreements between reviews were resolved by discussion with the third reviewer (KSK).

### Data extraction

Two authors (MHC and SC) independently extracted data using a standardized extraction sheet. Differences in data interpretation were resolved by consensus. The following were collected by: first author, publication year, study design, study location, period of study, sample size, inclusion criteria, demographic data, details of study protocol, outcomes including incidence of CIAKI, changes in SCr levels and GFR, and adverse reactions. We also extracted information for key indicators of assessment of risk of bias.

### Assessment of risk of bias

Risk of bias for each study was assessed by 2 authors (MHC and HWP) independently, using the Jadad scale for RCTs (21). Differences were resolved by discussion with the third author (KSK). Jadad scale assesses the quality of a randomization, double blinding, withdrawals and dropouts. A Jadad score of 4 or more corresponds to good trials, whereas a total score of 3 or less corresponds to poor trials.

### Data analysis

For categorical outcomes, estimates for the risk ratio (RR) and 95% confidence intervals (CIs) were analyzed. Continuous outcomes were analyzed using the standardized mean difference (SMD) and 95% CIs. We tested the heterogeneity between trials

using  $I^2$  statistics (22). Heterogeneity was considered to be statistically insignificant if the  $I^2$  value was less than 50%. If heterogeneity was found to be insignificant, the fixed-effects model was used. Sensitivity analysis was performed by removing each study sequentially and examining its contribution to the results. Publication bias was evaluated by inspection of the funnel plot and the Begg’s test. All statistical analyses were conducted using Review Manager version 5.3.5 (Cochrane Collaboration, Oxford, UK) and Comprehensive Meta-Analysis software version 3.0 (Biostat Inc., Englewood, NJ, USA).

## RESULTS

### Study selection

The search of MEDLINE, EMBASE database, and the Cochrane Central Register of Controlled Trials provided a total of 306 citations. After adjusting for duplicates 218 citations remained. Of these, 212 studies were excluded because after reviewing the title and abstracts it appeared that they clearly did not meet the eligibility criteria. In all, 2 articles were excluded after reading their full texts. Finally, we included 4 eligible articles in the quantitative analysis (18-20, 23). No relevant trials were identified from the hand search of relevant articles. The flowchart of study selection is presented in Fig. 1.

### Study characteristics

A summary of included studies characteristics is presented in Table 1. The included studies involved 623 participants. The mean age of all participants in all studies was greater than 60 years. All of them had baseline renal impairment. The proportion of participants with diabetes mellitus ranged from 36% to 64%, and was a total of 46% (286/623). One trial evaluated par-

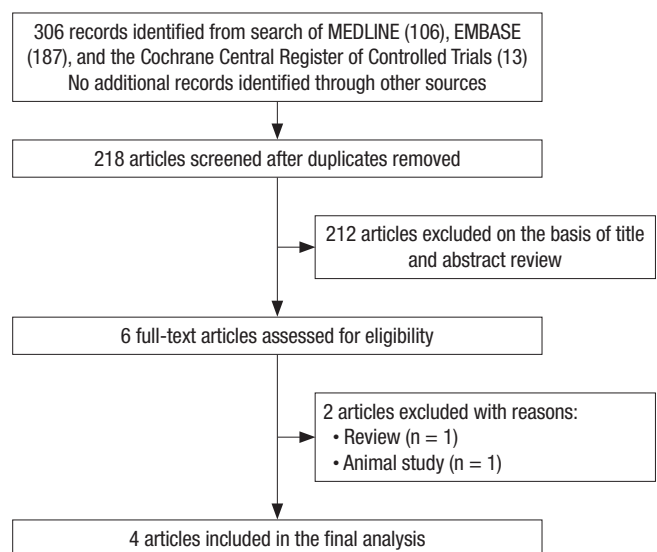
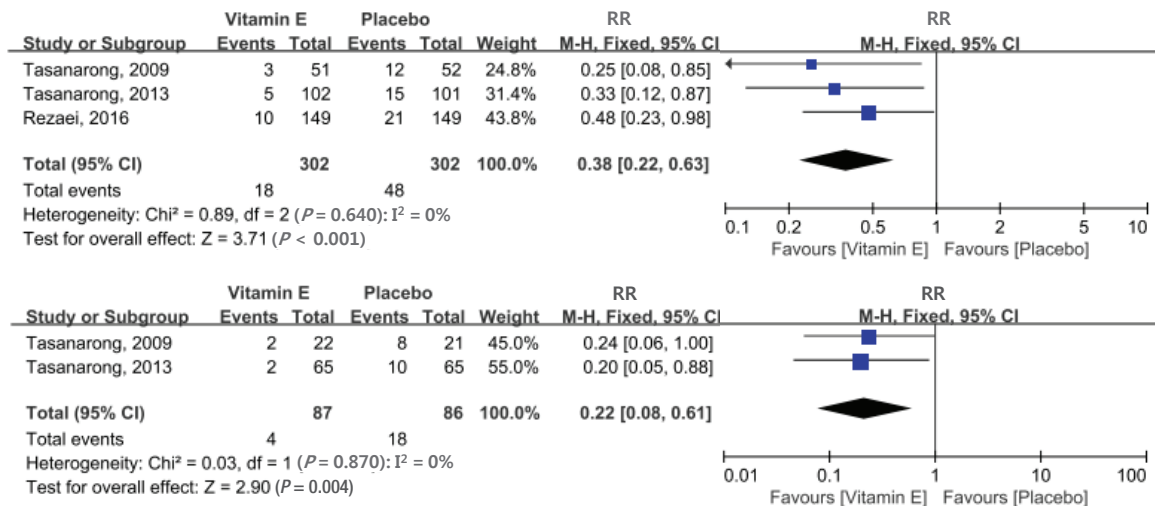


Fig. 1. Flowchart of study selection.

**Table 1.** Description of the included studies

Descriptions	Tasanarong et al. (19)	Kitzler et al. (23)	Tasanarong et al. (20)	Rezaei et al. (18)
Study design	RCT	RCT	RCT	RCT
Location	Thailand	Austria	Thailand	Iran
Period of study	2006.1–2007.6	2002.8–2003.7	2008.1–2010.12	2014.2–2015.6
Total number	103	19	203	298
Inclusion criteria	Patients undergoing CA with SCr $\geq$ 1.2 mg/dL and CrCl $\leq$ 60 mL/min	Patients undergoing CT with SCr $>$ 1.25 mg/dL for males, and 1.09 mg/dL for females	Patients undergoing CA with eGFR $\leq$ 60 mL/min/1.73 m <sup>2</sup>	Patients undergoing CA with eGFR $<$ 60 mL/min/1.73 m <sup>2</sup>
GFR measure	Creatinine clearance using CG formula	eGFR using MDRD formula	eGFR using MDRD formula	eGFR using MDRD formula
Mean age, yr	66	74	67	67
Baseline SCr, mg/dL	1.64	1.35	1.60	1.3
Contrast media	Iopromide	Iopromide	Iopromide	Iodixanol
Vitamin E route	Oral	Intravenous	Oral	Oral
Vitamin E dose, duration (total dose)	472.5 mg at 48, 24 hours and in the morning before exposure (1,417.5 mg)	540 mg at 12, 6 hours before and 6, 12 hours after exposure (2,160 mg)	350 mg starting 5 days before and ending 2 days after exposure (2,800 mg)	600 mg at 12 hours before and 400 mg at 2 hours before exposure (1,000 mg)
Definition of CIAKI	$\geq$ 0.5 mg/dL or $\geq$ 25% increase in baseline SCr at 48 hours after exposure	$>$ 25% increase in baseline SCr at 48 hours after exposure	$\geq$ 0.5 mg/dL or $\geq$ 25% increase in baseline SCr at 48 hours after exposure	$\geq$ 0.5 mg/dL or $\geq$ 25% increase in baseline SCr within 72 hours after exposure
Jadad score (21)	4	5	5	5

RCT = randomized controlled trial, CA = coronary angiography, SCr = serum creatinine, CrCl = creatinine clearance, CT = computed tomography, eGFR = estimated glomerular filtration rate, GFR = glomerular filtration rate, CG = Cockcroft-Gault, MDRD = modification of diet in renal disease, CIAKI = contrast-induced acute kidney injury.



**Fig. 2.** The effect of vitamin E on the development of CIAKI. (A) Forest plot of risk ratios in all participants. (B) Forest plot of risk ratios in diabetic participants. CIAKI = contrast-induced acute kidney injury, RR = risk ratio, M-H = Mantel-Haenszel, CI = confidence interval.

participants who had participated in computed tomography (23), and the remaining trials evaluated participants having cardiac catheterization (18-20). Iopromide, which is a nonionic and low osmolar agent was used in 3 studies (19,20,23), and Iodixanol, which is a nonionic and iso-osmolar agent was carried out in 1 particular study (18). There were variations in vitamin E regimens (oral or intravenous, and starting 5 days before contrast administration or 12 hours before, and total dose of  $\alpha$ -tocopherol of 1,000 mg or 2,800 mg). All participants received intravenous hydration at a rate of 1 mL/kg/hr for 12 hours before and after procedures in addition to vitamin E or placebo. All studies evaluated the development of CIAKI, and there were no differences

in the definition of CIAKI as a rise in SCr of  $\geq$  0.5 mg/dL or a 25% increase from the baseline value within 48–72 hours after contrast media administration.

#### Assessment of risk of bias

All selected studies were RCTs. All of their Jadad scores were 4 or more, and they were evaluated as good trials in the assessment of risk of bias (Table 1).

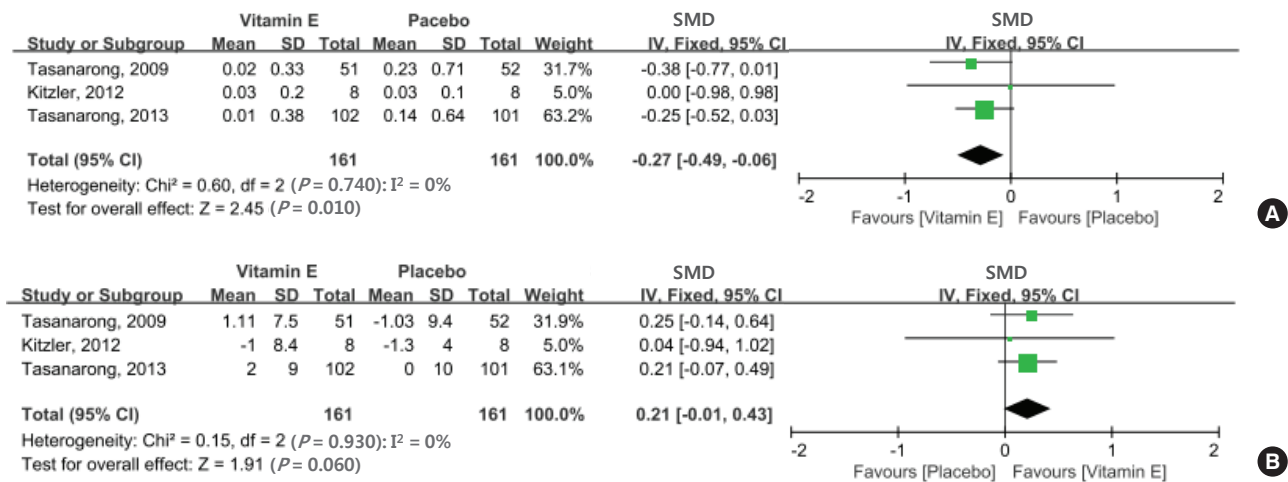
#### Effect of vitamin E on CIAKI

Incidence data was available for all 4 trials. CIAKI was developed in 66 of a total of 623 participants (10.6%), including 18 of 312

**Table 2.** SCr levels and GFR measured at baseline and 48 hours after contrast administration in included trials

Outcomes	Studies	Vitamin E group		Control group	
		Baseline	48 hr after procedure	Baseline	48 hr after procedure
SCr, mg/dL	Tasanarong et al. (19)	1.62 ± 0.44	1.64 ± 0.59	1.67 ± 0.53	1.90 ± 0.87
	Kitzler et al. (23)	1.37 ± 0.2	1.36 ± 0.22	1.33 ± 0.12	1.36 ± 0.11
	Tasanarong et al. (20)	1.58 ± 0.48	1.59 ± 0.61	1.63 ± 0.53	1.77 ± 0.85
GFR, mL/min/1.73 m <sup>2</sup>	Tasanarong et al. (19)	42 ± 14	43 ± 16	41 ± 21	40 ± 24
	Kitzler et al. (23)	49.6 ± 11.4	50.9 ± 11.3	48.2 ± 7.4	45.6 ± 5.8
	Tasanarong et al. (20)	45 ± 13	47 ± 16	43 ± 13	43 ± 17

Values are means ± standard deviation.  
SCr = serum creatinine, GFR = glomerular filtration rate.



**Fig. 3.** The effects of vitamin E on measurements of renal function. (A) Forest plot of differences in SCr changes 48 hours after contrast administration between vitamin E and placebo groups. (B) Forest plot of differences in GFR changes 48 hours after contrast administration between vitamin E and placebo groups. SCr = serum creatinine, SD = standard deviation, SMD = standardized mean difference, IV = inverse variance, CI = confidence interval.

participants with vitamin E (5.8%), and 48 of 311 participants with placebo (15.4%). A total of 3 trials showed a reduction in the RR for the development of CIAKI in participants given vitamin E (18-20), and in a single small trial there was no development of CIAKI in either group (23). Overall, the pooled RR of CIAKI using a fixed-effects model was 0.38 (95% CI, 0.22, 0.63;  $P < 0.010$ , Fig. 2A). The statistical heterogeneity between trials was not observed with  $I^2 = 0\%$ . A sensitivity analysis showed that no study had a significant effect on the pooled data (data not shown). The funnel plot was slightly asymmetric (data not shown), however, the Begg's test showed no evidence of publication bias ( $P = 0.300$ ).

Incidence data in diabetic participants was available for 3 trials (19,20,23), and 1 (23) of 3 had no CIAKI developments. Within the diabetic subgroup, CIAKI was developed in 22 of 180 participants (12.2%), including 4 of 90 participants with vitamin E (4.4%), and 18 of 90 participants with placebo (20.0%). The pooled RR of CIAKI in diabetic participants was 0.22 (95% CI, 0.08, 0.61;  $P = 0.004$ ;  $I^2 = 0\%$ ; Fig. 2B).

A total of 3 trials included data of changes in SCr level and GFR between baseline and 48 hours after contrast administra-

tion across 322 participants (19,20,23). Table 2 displays a summary of SCr levels and GFR measured at baseline and 48 hours after contrast administration. The increase in SCr levels was significantly less in the vitamin E group than in the control group (SMD, -0.27; 95% CI, -0.49, -0.06;  $P = 0.010$ ; Fig. 3A). There was no statistically significant difference in changes of GFR (SMD, 0.21; 95% CI, -0.01, 0.43;  $P = 0.060$ ; Fig. 3B) between vitamin E and the control group. In both analyses, there were no evidences of statistical heterogeneity ( $I^2 = 0\%$ ) nor publication bias by Begg's test ( $P = 1.000$ ).

In all trials, none of patients who developed CIAKI required renal replacement therapy. Few participants in the vitamin E group experienced minor adverse effects, including nausea, vomiting, and abdominal discomfort (19,20), however no serious adverse effects of vitamin E were reported.

**DISCUSSION**

We identified 4 RCTs involving 623 participants. The meta-analysis showed that vitamin E plus hydration reduced the risk of CIAKI by 62% and SCr increase after contrast administration

compared with hydration alone. However, changes in GFR after contrast administration were not significantly different between the vitamin E plus hydration and hydration alone. Our findings indicate that the use of vitamin E is reasonable in patients with pre-existing renal impairment.

CIAKI is generally described as an acute deterioration of renal function within a narrow time interval, following contrast media administration. It is commonly defined as a rise in SCr of  $\geq 0.5$  mg/dL or a 25% increase from the baseline value within 48–72 hours after contrast media administration (24). Although it follows a benign course in most cases, it carries a risk of increased in-hospital stay, permanent renal insufficiency, dialysis, and death (6,7). To prevent it, many studies have been performed to investigate possible solutions.

Vitamin E refers to a group of fat soluble compounds, including 4 tocopherols and 4 tocotrienols, of which  $\alpha$ -tocopherol has the highest biological activity (25). Due to its potent antioxidant anti-inflammatory properties, vitamin E has been studied for the prevention of chronic diseases to be associated with oxidative stress and inflammation (17,25). Vitamin E has the ability to bind to ROS, which are known to play a key role in CIAKI causing extensive damage to DNA, proteins, and carbohydrates, as well as to defend against damage caused by ROS (26). Furthermore, vitamin E is inexpensive and generally considered safe (27). These facts provided the rationale to investigate vitamin E treatment for the prevention of CIAKI.

Up to date, 4 RCTs (18-20,23) have been carried out to evaluate the effectiveness of vitamin E in protecting against CIAKI. As all individual trials (18-20), the meta-analysis showed that vitamin E plus hydration significantly reduced the risk of CIAKI by 62% compared with standard method, hydration alone. All trials (19,20,23) reported that vitamin E plus hydration could not alter the change of SCr levels and GFR after contrast administration. However, combining all individual results, vitamin E plus hydration significantly reduced the increase in SCr levels after contrast administration. Our analysis showed that vitamin E provided effective nephroprotection against CIAKI.

We identified 4 trials, which were all RCTs, with similar inclusion criteria, and clinical characteristics of participants, and were evaluated as good trials in the assessment of risk of bias. Therefore clinical heterogeneity between studies was insignificant.

Our meta-analysis has some points of limitation. Firstly, trials and enrolled participants included in the review were small in number. This led to a wide CI, which might be the cause of the negative result from secondary outcome. It also led to low statistical power to evaluate publication bias and statistical heterogeneity. Secondly, there were variations in the type of contrast agent, site of contrast administration, and vitamin E regimen. A meta-analysis found that there was a similar incidence of CIAKI between iopromide and iodixanol (28). Whether intraarterial contrast administration is more risky than intrave-

nous administration is still up for debate (29). The need for a high dose is recognized because vitamin E is tightly regulated at the tissue level (30). Vitamin E is believed to be inherently of low toxicity and rarely shows adverse effects; however, this does not negate any unknown potential harmful effects associated with high dose (27). Finally, we could not investigate the beneficial effects of vitamin E on the serious outcomes of CIAKI such as in-hospital morbidity, mortality, or dialysis dependency.

In conclusion the meta-analysis showed that vitamin E had the potential to protect against CIAKI in high-risk patients. However, we must interpret the results cautiously since this meta-analysis was performed including only a small number of trials. Large trials to examine the risk of CIAKI and serious renal outcomes, and change in SCr and GFR with various vitamin E regimens are warranted. However, we believe that low cost and lack of serious adverse effects justify the use of vitamin E at this stage in the research.

## DISCLOSURE

The authors have no potential conflicts of interest to disclose.

## AUTHOR CONTRIBUTION

Conceptualization: Cho MH, Kim KS. Data curation: Cho MH, Park HW, Chung S, Kim KS. Investigation: Kim SN. Writing - original draft: Cho MH. Writing - review & editing: Kim KS.

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