

Evaluation of Curcumin (Turmeric Extract) Effect on Prevention of CIN in Patient Under Elective Coronary Angiography, a Randomized Double Blind Placebo-controlled Clinical Trial

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Introduction. Curcumin is turmeric extract that have anti-proliferative, anti-cancer, and anti-oxidant effects and has been shown that it may have reno-protective properties. This study conducted to evaluate the efficacy of curcumin in the prevention of CIN.

Methods. This randomized placebo-controlled clinical trial was carried out on 138 patients with chronic stable angina scheduled for elective coronary angiography that had renal insufficiency. Patients were randomized to receive curcumin or placebo in addition to standard hydration with saline 0.9% before nonionic iso-osmolar contrast agent administration for angiography. Serum creatinine was measured 12h before, 24h and 48h after contrast injection. CIN, mainly, defined as increase in creatinine of ≥ 0.5 mg/dL or $\geq 25\%$ from the baseline.

Results. Serum creatinine change was 0.19 ± 0.31 mg/dL which was 0.22 ± 0.33 and 0.16 ± 0.29 in placebo and curcumin group, respectively. In 'repeated measure analysis' no statistically difference was found in serum creatinine level between pre-intervention, and 24 hours and 48 hours after intervention. CIN was occurred less frequently, though statistically insignificant, in curcumin group (22.7%) compared with placebo group (32.3%).

Conclusion. It was found that although curcumin reduced the incidence of CIN, this difference was not statistically significant. It seems that, like other antioxidant substances studied in previous studies, although curcumin can reduce apoptosis and oxidative stress at cellular level, but in high risk patients for CIN, such as patients with renal insufficiency, it does not produce more protective effects than hydration with normal saline.

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INTRODUCTION

In recent years, the use of contrast agents (CA) has increased due to magnificent use of imaging techniques and interventions and despite the development in their molecular structure, these materials still have harmful effects that can occur from mild allergic to severe complications such as

contrast-induced nephropathy (CIN),¹ which is one of the most important side effects. CIN is the third cause of acute renal failure in hospitalized patients.² There is also no definitive treatment in order to reverse the side effects, and studies have shown that even mild renal failure can lead to permanent kidney damage.³

The exact pathogenesis of CIN is not fully understood.⁴ Current evidence suggests several measures for preventing CIN, such as pre-angiography hydration, minimizing contrast dose, and using non-ionic iso- or low- osmolality contrast.⁵ In addition, the clinical trials have shown the effectiveness of several drugs such as N-acetyl cysteine (NAC),⁶ theophylline,⁷ and statins⁸ in preventing CIN. Despite the use of various prophylactic measures and low-osmolality contrast with low side effects, isotonic fluid injection is the only effective method for preventing CIN,⁹ which indicates that the protective effects of the proposed drugs are not universally agreed.¹⁰⁻¹³ Therefore, finding an appropriate and effective CIN prevention method is still required.

There are also a number of herbal medicines that shown to have renal protective effects. These herbal medicines have been used in nephropathy due to various types of diabetes, drug and chemical toxicity, and generally in chronic renal failure.¹⁴⁻¹⁶ Curcumin (CC) is a substance that causes the yellow color of a turmeric plant and is responsible for its early phytochemical effects. In recent years, it has been shown that CC has antioxidant, anti-inflammatory, and anti-proliferative effects, which inhibits the free and active O₂ and OH-radicals.¹⁵ Therefore, its use in oxidative stress-induced nephropathy, such as diabetic nephropathy and CIN, has been considered. Previous studies have reported that CC can have protective effects against free radicals in patients with diabetic nephropathy¹⁷ and can be considered as a prevention and also a treatment for diabetic nephropathy.¹⁸ The inhibitory effects of CC on oxidative stress in diabetic nephropathy in rats were also shown.¹⁹ Its anti-proliferative effect, protecting the progression of renal fibrosis in animal models, has also been reported in a study.²⁰ Curcumin effects in protecting against contrast-induced nephropathy have been investigated in animal models and promising results have been reported. Meanwhile, human studies have not been conducted to evaluate the protective effects of this substance in contrast-induced nephropathy.

Therefore, this clinical trial was designed and carried out to investigate the protective effects of turmeric-derived curcumin on contrast-induced nephropathy in patients undergoing selective coronary angiography that referred to Taleghani Hospital, Tehran, in 2017 to 2018.

MATERIALS AND METHODS

Trial Design

This study was a randomized double-blind, placebo-controlled clinical trial conducted in two parallel groups, which included the group receiving the extract of turmeric and the placebo group, called group A and B; respectively.

Participants

This study was carried out on CKD patients with chronic stable angina who were candidate for elective coronary angiography referred to Taleghani Hospital.

Inclusion Criteria. 1) Candidate for elective coronary artery catheterization (equal to or above 18 years of age), 2) Basic serum creatinine level > 1.2 mg/dL; or clearance Cr < 60 mL/ min (stage 3 or 4 CKD).

Exclusion Criteria. Unstable angina or recent myocardial infarction; need for urgent angiography; cardiac arrhythmias; acute or uncorrected heart failure; intravenous contrast infusion in the past ten days; malignancy; pregnancy; acute renal failure, or recent creatinine changes greater than 0.3 mg/dL; use of nephrotoxic agents in the last week, including aminoglycosides, vancomycin; patients in chronic dialysis; patients with a history of allergy to contrast agents and turmeric; calculated Mehran score less than 5; use of statin with antioxidant effect, as well as patients who are not satisfied with entering a research project.

Settings

This study was set by Cardiac Catheterization Department, Taleghani Hospital, Tehran, Iran.

Intervention

Before the intervention, the goals and method of implementing the plan for patients were explained and written consent was obtained. Then, according to ethics codes, demographic data of patients including age, gender, and their past medical history including heart disease, kidney disease, diabetes mellitus, dyslipidemia, hypertension, congestive heart failure, hospitalization, cancer and liver cirrhosis, hypotension during the intervention and use of the intra-aortic pump were recorded. Mehran score were calculated for all patients, and risk of CIN were also calculated based on Figure 1. Calculated Mehran score less than 5 excluded from

research.^{21,22} Medication history including Statins, angiotensin-antagonists and angiotensin receptor blockers, Allopurinol, and other drugs were also recorded. Fasting blood glucose was measured and patients with undiagnosed diabetes were identified (Fasting blood glucose greater than 126 mg/dL). Serum creatinine was measured 12 hours before, and 24 and 48 hours after intervention in Taleghani Hospital’s lab. The estimated glomerular filtration rate (eGFR) was calculated by the Cockcroft-cault²³ formula and recorded. Contrast type and volume implemented for each patient were also recorded.

Drug and placebo were prepared and packed by a fellow of the Faculty of herbal medicine in the form of similar capsules and encoded by the presenter for intervention.

All patients were hydrated with normal saline 0.9% (1 cc/kg body weight /hour in EF equal to 40%; and 0.5 cc/kg body weight /hour in EF less than 40%); for 24 hours which began 12 hours before the angiography intervention and continued until 12 hours later.

Patients in the case group received turmeric extract in the form of 500 mg capsules prepared by the Faculty of Herbal Medicine of Shahid Beheshti University in the form of a single dose every 12 hours from 24 hours before the intervention to 48 hours later. The amount of turmeric extract in each capsule was analyzed and all of them were filled

with 500 mg of turmeric extract. Patients in the control group received placebo, in the same form and size as the original drug, as a single dose every 12 hours from 24 hours before the intervention to 48 hours later.

Angiography was done according to the standard method by femoral or radial catheterization. In all patients, visipaque contrast agent was used as a non-ionizing iso-osmolar contrast with dose of 30 mL.

Outcomes

Primary Outcomes. 1) Change in serum creatinine level after 48 hours of contrast administration, 2) CIN (increased creatinine serum equal to or greater than 0.5 mg/dL or more than 25% relative to baseline creatinine, 48 hours after contrast administration).

Secondary Outcomes. eGFR changes 48 hours after contrast injection was considered as secondary outcome.

Randomization

Randomization software were used in order to allocate patients in two groups. A randomized code was generated for each patient and was enveloped by a nurse who was blinded to the intervention and outcomes. The envelope was opened 12 hours before intervention by an Internist to determine whether CC or placebo each patient have to be

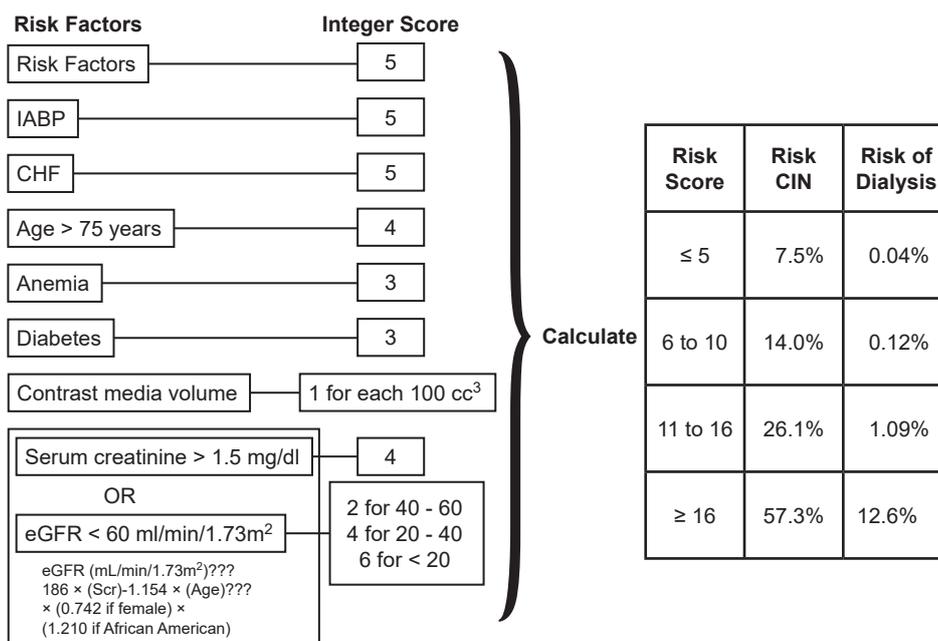


Figure 1. It shows Mehran score criteria.

given. Randomization was done by a statistician who was blinded to the whole process of intervention. Placebo or CC was administered by an internist who was blinded to the results of intervention. Catheterization was done a cardiologist who was unaware of whether patients had received placebo or CC. Lab staff were also blinded. Results were recorded by a senior internal disease resident who was unaware of whether patients had received placebo or CC.

Statistical Methods

Parametric and nonparametric tests were used to check the consistency of the groups. Due to normal distribution of data, chi square analysis was used to determine difference in contrast induced nephropathy incidence in two groups. Repeated measure analysis were also used to examine the CC serum level as well as eGFR changes in the two groups. *P* value < .05 was considered as a significant statistical level. SPSS version 22 was used as statistical software.

RESULTS

In this study, 132 patients with chronic renal failure assigned to cardiac catheterization were selected to participate in the study. 4 patients who were not consent with research terms were excluded. 8 patients were also excluded due to use of nephrotoxic drugs in the last week (2 patients), contrast allergic (2 patients), cardiac arrhythmia (1 patient), uncorrected heart failure (1 patient), Contrast infusion in the last 10 days (1 patient) and possible allergy to turmeric (1 patient). 132 patients were randomly assigned into two groups. Four patients in the placebo group were excluded from the final analysis due to lack of intervention and/or laboratory data.

Patients were enrolled in the study from august 2017 to September 2018. Reaching to estimated sample size was considered as the endpoint for patients' recruitment.

Normal Distribution

Data on serum creatinine level and estimated glomerular filtration (eGFR) before and after intervention for normal distribution were investigated by Skewness and Kurtosis indices, indicating the normal distribution of data; baseline Cr: 1.14 ± 0.22 , 24h Cr: 1.43 ± 0.22 , 48h Cr: 1.55 ± 0.22 , baseline eGFR: 0.81 ± 0.22 , 24h eGFR: 0.36 ± 0.22 , and 48h eGFR: 0.52 ± 0.22 .

Baseline Data

Demographic and base line laboratory data, summarized in Table 1, were not significantly different between two groups.

Primary Outcomes

Creatinine level was significantly increase in both curcumin and placebo group; however, creatinine level changes were not significantly different in two groups. In 'repeated measure analysis' no statistically difference was found in creatinine serum level changes from pre-intervention to 24 hours and 48 hours after intervention (Table 2, Figure 2)

Contrast induced nephropathy occurred in 35 patients (27.1%), which the incidence rate in placebo and curcumin groups were 32.3% and 22.7%, respectively. There was no significant difference regarding CIN in two groups (Table 2).

Secondary Outcomes

eGFR was calculated for patients based on baseline, 24h and 48h after contrast administration,

Table 1. Demographic data and base line characteristics

Variables	Total	Placebo (n = 62)	Curcumin (n = 66)	P
Sex				
Male	78 (69.9%)	36 (58.1%)	42 (63.3%)	> .05**
Female	50 (39.1%)	26 (41.9%)	24 (36.4%)	
Diabetic	57 (44.5%)	30 (48.4%)	27 (51.6%)	> .05**
Age	71.56 ± 9.43	72.37 ± 8.67	70.83 ± 10.11	> .05*
Baseline Cr, mg/dL	1.64 ± 0.30	1.64 ± 0.36	1.64 ± 0.23	> .05*
Baseline eGFR, mL/min	41.76 ± 12.12	41.81 ± 14.38	41.73 ± 9.85	> .05*

Data are presented as mean ± SD or n (%).

*Independent sample t-test, **Chi-square test

Cr, creatinine; eGFR, estimated glomerular filtration rate; SD, standard deviation.

Table 2. Change of Serum Cr Level Among the Study Groups

Variables	Total	Placebo (n = 62)	Curcumin (n = 66)	P
Baseline Cr, mg/dL	1.64 ± 0.30	1.64 ± 0.36	1.64 ± 0.23	> .05*
24h Cr, mg/dL	1.67 ± 0.34	1.69 ± 0.40	1.64 ± 0.27	> .05*
48 h Cr, mg/dL	1.83 ± 0.52	1.86 ± 0.61	1.80 ± 0.42	> .05*
48h Cr Change, mg/dL	0.19 ± 0.31	0.22 ± 0.33	0.16 ± 0.29	> .05*
Cr Change, %	0.11 ± 0.18	0.12 ± 0.18	0.09 ± 0.17	> .05*
Baseline eGFR, mL/min	41.76 ± 12.12	41.81 ± 14.38	41.73 ± 9.85	> .05*
24h eGFR, mL/min	41.16 ± 12.09	40.19 ± 13.70	42.00 ± 10.53	> .05*
48h eGFR, mL/min	38.76 ± 12.56	38.22 ± 15.05	39.24 ± 10.00	> .05*
Occurrence of CIN	35 (27.3%)	20 (32.3%)	15 (22.7%)	> .05**

Data are presented as mean ± SD or n (%).

*Independent sample t-test, **Fisher exact test

Cr, creatinine; eGFR, estimated glomerular filtration rate; SD, standard deviation

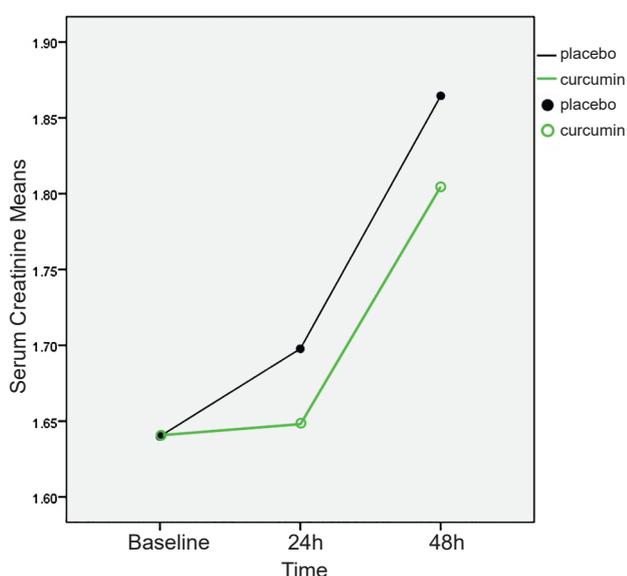


Figure 2. It demonstrates serum creatinine changes in two groups.

which showed a significant decreased in both groups. There was no significant difference regarding amount of eGFR changes among two groups (Table 2).

Considering the possible baseline data difference in two groups, the logistic regression test was also conducted to find possible predictors of CIN. It showed that age can have a role in occurrence of CIN (OR = 0.95, 95% CI: 0.95 to 0.99; $P < .05$) (Table 3).

Diabetic Patients' Subgroup

CIN occurrence was calculated separately in diabetic patients which was 21.1%, compared with 31.9% in none-diabetic patients (OR = 0.57, 95% CI: 0.25 to 1.27; $P > .05$).

There was no significant difference regarding

Table 3. Logistic Regression Test for Possible Predictors of CIN

Variables	OR	95% CI for OR	P
Age	0.95	0.95 - 0.99	< .05
Gender, Female vs. Male	1.26	0.55 - 2.86	> .05
FBS	0.99	0.98 - 1.00	> .05
Treatment, Curcumin vs. Placebo	0.62	0.28 - 1.35	> .05

OR, odds ratio; CI, confidence interval; FBS, fasting blood sugar

CIN in diabetic patients between placebo and curcumin group, 30.0% (OR = 0.62, 95% CI: 0.39 to 0.98) and 11.1% (OR = 2.13, 95% CI: 0.77 to 5.90); respectively ($P > .05$).

Serum creatinine level was significantly lower 24h after contrast injection in curcumin group, compared with placebo group (1.57 ± 0.70 vs. 1.72 ± 0.06 , $P < .05$), yet; 48h after injection the difference was not significant (1.74 ± 0.10 vs. 1.9 ± 0.1 , $P > .05$). In 'repeated measure analysis' no statistically significant difference was found in serum creatinine changes in diabetic patients among two treatment groups ($P > .05$).

Additional Analysis

In an additional analysis, we considered the serum creatinine change of 0.3 mg/dL as a lower threshold for CIN definition and compared the occurrence of CIN based on the new criteria between two treatment groups.

According to the lower Creatinine threshold, CIN occurred in 51 patients (39.5%); which was 41.9% (OR = 0.92, 95% CI: 0.64 to 1.31) and 37.9% (OR = 1.09, 95% CI: 0.77 to 1.54) in placebo and curcumin groups, respectively. There was no significant difference regarding CIN (with lower threshold) among two groups ($P > .05$).

DISCUSSION

In a randomized, double-blind clinical trial, the role of turmeric extract “curcumin” in reducing the incidence of contrast-induced nephropathy in patients with chronic renal failure selected for cardiac catheterization was investigated. 132 patients were randomly divided into two groups and treated with curcumin or placebo in combination with hydration to prevent the development of contrast-induced nephropathy. Demographic characteristics of patients including age and sex were not significantly different between the two groups ($P > .05$, $P > .05$; respectively), and the bias was minimal in this regard. The baseline serum creatinine level as well as the baseline estimated glomerular filtration rate (eGFR) were not significantly different in both groups ($P > .05$). Serum creatinine level increased in both groups 24h and 48h after contrast injection compared to creatinine level before intervention, while the changes in the two groups did not significantly differ ($P > .05$); in other words, curcumin compared to the placebo has no significant effect on serum creatinine level changes. The overall incidence of CIN was 27.1% (32.3% for placebo recipients and 22.7% for curcumin recipients). Clinically, the occurrence of CIN was lower in patients receiving curcumin, but this difference was not statistically significant ($P > .05$). eGFR decreased significantly in both groups 48h after contrast injection, while these changes were not significantly different between two groups ($P > .05$).

Although CIN pathophysiology is still not well defined, oxidative stress has been included in the top of the list.²⁴ Due to the direct toxic effects of contrast agents, free radicals are produced which lead to oxidative stress resulting in apoptosis in tubular and glomerular cells.²⁵ Necrotic and degenerative changes, especially in tubular cells, in CIN have been well documented in animal and human studies.²⁶ Protective methods against pathophysiological mechanisms have been studied in pre-clinical and clinical studies.²⁷⁻³⁰ Most clinical trials have tested the effects of saline, theophylline, n-acetylcysteine (NAC), sodium bicarbonate, dopamine, furosemide, mannitol, and ascorbic acid. Although the protective effects of NAC have been shown in studies, but a recent study³¹ showed that NAC in patients with at least one risk factor had no benefit in reducing CIN incidence. In a study conducted by Bribouri and colleagues which performed on patients with

renal failure, it was shown that NAC + bicarbonate prevents CIN better than saline + NAC or saline + ascorbic acid.³² In another study in this regard, which was performed on renal failure patients, protective effects of ascorbic acid were shown.³³ In a meta-analysis that was conducted in 2008 and 40 clinical trials,³⁴ according to the results, only the administration of NAC or theophylline was more beneficial than saline hydration, while furosemide has been associated with increased risk for CIN. In most studies, hydration with saline 0.9% resulted in a significant reduction in the risk of CIN, and the efficacy of another method along with saline is still unclear. In the recent study, Habib M *et al.*³⁵ also compared the protective effects of NAC, NAC + ascorbic acid and placebo with normal saline hydration, which showed the protective effects of NAC with high doses (1200 mg in three doses). As in the study of Martin B *et al.*³⁶ the administration of NAC and ascorbic acid in patients undergoing cardiac catheterization with high risk of CIN, who received low osmolality contrast, did not have a significant protective and preventive effect. Waseem and colleagues³⁷ have shown protective effects of turmeric extract against cisplatin-induced nephropathy. Ueki *et al.* Also measured TNF-alpha levels, as an inflammatory index, and showed protective effects of curcumin against cisplatin-induced nephropathy.³⁸ Kumaravel *et al.*³⁷ also found that curcumin had inhibitory activity in cancer cells. In the case of cyclosporine, it has also been shown that curcumin has a protective effect against apoptosis.⁴⁰ In a study by Dian *et al.*⁴¹ on contrast-induced nephropathy (CIN), the study groups were evaluated for the activity of homozygous-1 and apoptosis, and it was shown that curcumin had a protective effect against CIN. In an animal study carried out by Buyuklu *et al.*⁴² the protective effect of curcumin against CIN was demonstrated in experimental models. Creatinine is the most important indicator used in the diagnosis of CIN in the clinic. Previous studies have shown that serum levels of urea and creatinine increase significantly in CIN.^{30,43} In the present study, serum creatinine level was significantly increased 48 hours after contrast injection. Although the incidence of CIN in the curcumin group was lower (22% compared to 32% in the placebo group), this difference was not significant and thus the curcumin did not have a significant protective effect. This finding is not

consistent with the findings of Buyuklu *et al.*⁴² even though their study was an animal study, in which CIN was developed for mice, and then the effect of curcumin was measured on biochemical parameters as well as urea and creatinine levels. In other studies, the protective effects of curcumin in diabetic nephropathy have been shown in which most effects were described associated with its antioxidant effects, which can reduce oxidative stress effects of free radicals.^{10,18} Glucose-lowering effects of curcumin have also been reported in streptozotocin (STZ) and STZ-nicotinamide-induced diabetic rats.⁴⁴ Therefore, it seems that the protective effects of curcumin on diabetic nephropathy and contrast-induced nephropathy are different. Given the fact that diabetic nephropathy may have affect the results of our study, we run analysis in diabetic patients separately. The results showed insignificant protective effects of curcumin against CIN in diabetic patients compared to none diabetic patients. Fasting blood sugar had also no effect on final analysis, according to logistic regression test.

Despite the precise randomization, which results in unimportance difference in baseline characteristics of two groups, our study has a number of limitations. First, the trial was a single-center study with a relatively small sample size, which can impress our results. In addition, only patients with renal insufficiency were included, which may limit the generalizability of the study results. Finally, the follow up period was 48 hours, while long-term follow up may provide more information on the effectiveness of such preventive measures. In our study, we use lipophilic form of curcumin, which have low gastrointestinal absorption. Possibly use of nanomicelles form of curcumin has more gastrointestinal absorption and effect.

CONCLUSION

According to the findings, although curcumin reduced the incidence of contrast-induced nephropathy, this difference was not statistically significant. It seems that, like other antioxidant substances studied in previous studies, such as N-acetyl cysteine, ascorbic acid and theophylline, although curcumin can reduce apoptosis and oxidative stress at cellular level, but in patients with a high risk for CIN, such as patients with renal insufficiency, it does not produce more protective effects than hydration with normal saline. Further

studies with larger sample size are recommended.

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