IJKD KIDNEY DISEASES

The Effect of Curcumin in Prevention of Contrast Nephropathy Following Coronary Angiography or Angioplasty in CKD Patients

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Original Paper

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Keywords. acute renal injury, curcumin, contrast nephropathy

Introduction. Contrast-induced nephropathy (CIN) is the most common cause of iatrogenic acute kidney injury, happens more commonly in patients with underlying kidney diseases. It has been shown that oxidative stress is the main mechanism of contrast nephropathy. Curcumin is suggested as an herbal antioxidant agent, thus we decided to assess the effect of curcumin in preventing this complication in patients with underlying chronic kidney disease who need coronary angiography.
Methods. We conducted double blind, placebo-controlled clinical trial in 60 moderate to severe CKD patients who underwent coronary angiography or angioplasty. Adjusted dose of Iodixanol was used as contrast agent in all of them. Curcumin or placebo administered orally, 1.5 g daily from 2 days before procedure to 3 days after it. CIN was defined by an increased serum creatinine ≥ 0.3 mg/dL or an increase to ≥ 1.5 times of the baseline within 48 hours after procedure.
Results. CIN occurred in 12 (20%) of patients, 5 (16.7%) in Curcumin group and 7 (23.3%) in placebo group (OR = 0.56, 95% CI = 0.18 to 2.36; $P > .05$). Serum Creatinine was increased after 72 hours of intervention from 1.65 ± 0.26 mg/dL to 1.79 ± 0.33 mg/dL in Curcumin group and from 1.61 ± 0.23 mg/dL to 1.86 ± 0.35 in placebo group. No significant difference was seen between the mean increase of serum creatinine in two groups (difference of 0.006 mg/dL, 95% CI = - 0.06 to 0.08; $P > .05$).
Conclusion. Prophylactic oral Curcumin could not show protective effects on CIN in high-risk patients who have undergone coronary procedures.

IJKD 2019;13:304-9
www.ijkd.org

INTRODUCTION

CIN is the most common etiology of iatrogenic AKI[1] and one of the leading causes of mortality in hospitalized patients with AKI.[2] Although the incidence of CIN in patients with normal kidney function is low, roughly 1-2%; it is estimated to be much more higher in patients with underlying kidney diseases, nearly 25%.[3] In recent years it is appeared the incidence of CIN is enhancing as the imaging and interventional procedures have been developed.[4] Despite the use of many prophylactic therapies such as hydration with isotonic saline, N-acethyl cysteine; sodium bicarbonate, etc only intravenous isotonic saline is approved in practice. It should be noted that intravenous isotonic low-osmolar contrast agents also is recommended in

all patients.[5] Many studies have been designed to find a method to prevent or even decrease its severity. Although the pathophysiology of CIN is not completely obvious, it is suggested that oxidative stress due to free radicals, and renal vasoconstriction have main roles in kidney tubular hypoxia especially in outer medullary region that tubular cells are strongly active and oxygen consumer, consequently CIN is developed.[6] Based on this theory various drugs and complementary medicine with antioxidant property such as vitamin C,[7-8] vitamin E,[9] statins,[1] prostaglandins,[1] trimetazidine[10] are used in trials for CIN prevention. In this study we tried to evaluate the effect of curcumin in prevention of CIN in CKD patients. Curcumin which is an active component of spice herb curcuma longa or turmeric, accounts for only 5% of this spice. Curcuma commonly used as a spice in foods and traditional Asian medicine. It is proven that curcumin has anti-inflammatory and anti-oxidant effects.[11,12] We selected moderate to severe CKD patients due to their kidney damage can contribute to less auto regulatory capacity in the renal tubules and vasculature systems.[7] Based on previous studies it is reported that in patients with GFR < 60, CIN risk following cardiac angioplasty increased to more than 50%.[13]

MATERIALS AND METHODS

A total of 65 CKD patients with stable renal function and serum creatinine > 1.2 mg/dL or GFR between 15 to 60 mL/min (stage 3 to 4) who were candidate for cardiac angiography or angioplasty due to stable angina pectoris or non ST elevated MI enrolled in study. They randomized to receive curcumin or placebo. Patients with ESRD, AKI, cardiogenic shock, severe CHF, history of taking radio contrast in the last 3 months, or using medications such as N-acetyl cystein, vitamin C, dopamin, theophylin, manitol, and warfarine in the last 2 weeks were excluded. 60 patients completed the study (30 patients in each group). Randomization was performed using a computer-generated random allocation list. Patients were randomly assigned 1:1 in intervention and control groups. The randomization scheme is shown in Figure.

Patients in both groups received curcumin or placebo capsules 500 mg three times a day from two days before procedure to three days after. For all patients normal saline serum 1 mL/kg/h were infused from 12 hours before to 12 hours after angiography. The iodixanol was used as contrast agent in all procedures, which is a nonionic iso-osmolar agent. In patients who had angiography and angioplasty the average of contrast agent dosage were 50 and 300 mL, respectively.

Kidney function was evaluated by assessment of serum creatinine before and then in second and third days after angiography. Urinary NGAL (neutrophil gelatinase-associated lipocalin) test was also measured by enzyme-linked immunosorbent assay 24 hours after procedure. CIN was defined if serum creatinine was increased more than 0.3 mg/dL daily or an increase to ≥ 1.5 times of the baseline within 48 hours after procedure. Urinary NGAL more than 5000 ng/mL was considered to be suggestive of CIN.

Statistical Methods

The data was analyzed by SPSS version 18.0. All data was presented as the mean ± standard deviation (SD). Chi-square test or Fisher exact tests were used to compare qualitative variables. Differences between groups were compared with independent t test and ANOVA test. *P* value less than .05 was considered statistically significant.

All patients accept to enter the study and signed informed consents. The study was approved by Ethics committee of Mashhad university of medical sciences (number = T4835, code = 941656). It is also approved by Iranian registry of clinical trials with ID code: 487 (IRCT138706261256N1).

RESULTS

Of 65 patients who entered the study, 60 patients completed it. Mean preprocidural serum creatinine was 1.63 ± 0.24 mg/dL. The basic characteristic data is reported in Table 1. Before procedure, there was no significant difference between two groups. Although the percent of patients in curcumin group who received coronary angiography were higher than coronary angioplasty, the difference was not significant (*P* > .05). In the control group the percent of both angiography and angioplasty procedure was equal.

The contrast volume used was different in two procedures, nearly 50 and 300 mL in angiography and angioplasty respectively, the total volume of

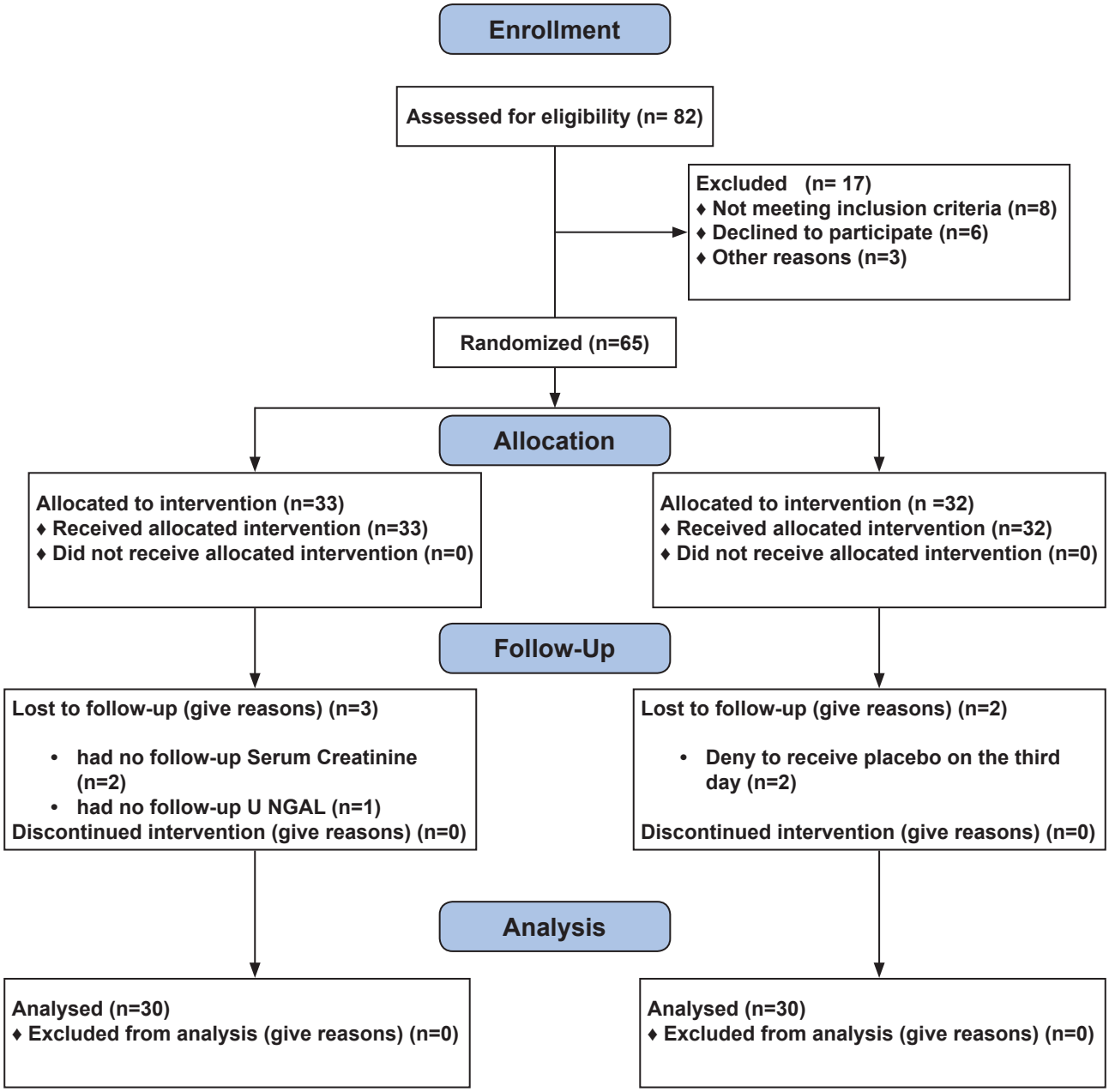

Figure. It shows the randomization scheme of the patients.

contrast media was comparable in both groups and there was no significant difference between them. The mean of used contrast volume was 158.3 mL.

CIN was occurred in both groups totally in 12 (20%) of patients, as in curcumin group 5 (16.7%) of patients and in placebo group 7 (23.3%) of them had more than 25% increase in baseline serum creatinine levels (OR = 0.56, 95% CI = 0.18 to 2.36; $P > .05$). There was no significant difference between them ($P > .05$). Increment in Serum Creatinine level after angiography was similar in both groups; details are shown in Table 2.

Serum creatinine was increased after 72 hours of intervention from 1.65 ± 0.26 mg/dL to 1.79 ± 0.33 mg/dL in curcumin group and from 1.61 ± 0.23 mg/dL to 1.86 ± 0.35 in placebo group. There was no significant difference between the mean increase in serum creatinine concentration in the placebo group and curcumin group (difference of 0.006 mg/dL, 95% CI = -0.06 to 0.08; $P > .05$).

We also checked urinary NGAL level in all patients at first day after angiography. Urinary

Table 1. Basic Characteristics Data of the Two Groups

	Curcumin Group (n = 30)	Placebo Group (n = 30)	*P*
Age, years	60.9 ± 10.3	66.6 ± 12	> .05
Male/Female	18/12	17/13	> .05
Education			
Graduate	5	5	
Under Graduate	25	25	> .05
Diabetes Mellitus	13	12	> .05
Smoking	9	10	> .05
BMI, kg/m^2	26.74 ± 2.99	25.48 ± 2.5	> .05
Base Serum Creatinine, mg/dL	1.65 ± 0.26	1.61 ± 0.23	> .05
GFR (MDRD), mL/min	47.04 ± 8.18	47.54 ± 8.32	> .05
Family History of Kidney Disease	7/23	5/25	> .05
Angigraphy/Angioplasty	19/11	15/15	> .05
Urinary NGAL	4124.87 ± 3623.43	3871.13 ± 2734.60	> .05

Table 2. Changes in Serum Creatinine Level After Angiography

	Curcumin Group	Placebo Group	*P*
Second Day	1.79 ± 0.27	1.76 ± 0.3	> .05
Third Day	1.79 ± 0.33	1.86 ± 0.35	> .05

NGAL level was significantly higher in patients with AKI (2862.98 ± 1855.94 vs. 8538.08 ± 3404.55, $P < .001$). Its level in each group did not reach any significant difference ($P > .05$).

We compared clinical and procedural characteristics of patients with and without CIN in Table 3, which shows patients with CIN; were more often male, older with higher BMI, with more diabetes mellitus history but none of these characters reached statistical significance. There was no difference regarding gender and smoking history. As it is predicted serum creatinine level, creatinine clearance and urinary NGAL were significantly higher in AKI group ($P < .001$).

DISCUSSION

It is suggested that Curcumin has antioxidant, anti inflammatory, and anti cancer properties.[4]

Waseem and Parvez demonstrated its protective effects on cisplatin induced nephrotoxicity.[14]

Ueki *et al.* also showed that curcumin may reduce inflammatory factors like anti TNF-alfa and ICAM-1 that are mediators of kidney damage in cisplatin induced nephrotoxicity.[15] There are studies that revealed this herbal medicine has anti cancer effects[16] and also it can protect kidneys against cyclosporine toxicity.[17]

As curcumin has anti oxidant effects in vitro and in vivo models that may be due to presence of phenolic groups in its structure that are able to bind with reactive oxygen species (ROS),[12] this study have worked on its effects on CIN.

We conducted a randomized, double-blind, placebo-controlled trial to assess the impact of curcumin on incidence of CIN in moderate CKD

Table 3. Clinical and Procedural Characteristics of Patients With and Without CIN

	With CIN (n = 12)	Without CIN (n = 48)	*P*
Male/Female	7/5 (20%)	28/20 (80%)	> .05
Diabetes Mellitus	6 (50%)	19 (39.4%)	> .05
Educated Patients (More than Diploma)	3 (25%)	7 (14.6%)	> .05
Smoking	4 (33.3%)	15 (31.2%)	> .05
Age, years	67.4 ± 13.7	62.8 ± 10.8	> .05
Body Weight, kg	26.75 ± 2.09	25.95 ± 2.95	> .05
Pre-procedure Creatinine, mg/dL	1.71 ± 0.22	1.61 ± 0.24	> .05
Pre-procedure Cr Clearance, mL/min	44.34 ± 10.50	48.03 ± 7.43	> .05
2th Day Creatinine, mg/dL	2.05 ± 0.33	1.70 ± 0.24	< .05
3th Day Creatinine, mg/dL	2.15 ± 0.33	1.74 ± 0.28	< .05
Urinary NGAL, ng/mL	8538.08 ± 3404.55	2862.98 ± 1855.94	< .001

patients after coronary angiography or angioplasty. No similar published data in human is available in media yet. There were few articles that have been evaluated curcumin effects in animal models. One of them was done by M. Buyuklu *et al.* conducted on rats. In summary, biochemical evaluation showed a significant increase in urea, creatinine, and malondialdehyde in CIN group; but these results were significantly lower in rats with CIN who received curcumin. They concluded that curcumin has protective effects in prevention of CIN in rats.[4] However based on our study, we could not reach similar results in human.

Incidence of CIN in patients with chronic kidney disease is reported to be 25%.[3]

Overall in our study, CIN was occurred in 12 (20%) of patients. Although when we compared our results with other studies such as Dvoršak's or Boscheri's who worked on effectiveness of vitamin C on prevention of CIN, the incidence of CIN was higher in ours that can be explained by higher doses of used contrast in present study (158 mL vs. 106 mL).

In this study we found less worsening of kidney function in Curcumin group but results did not reach to statistically significance level ($P > .05$). It may be due to small sample size, or less drug dosage in our patients.

Curcumin dosage in this study was 1500 mg/d, which is the recommended dosage as an over the counter drug in our country. When we compared it with used dosage in rats which curcumin was given at a dose of 200 mg/kg/d, it seems that drug dosage in rats had been more than human, about two times higher. Future studies, using higher dosage of this drug may be associated with significant effects in prevention of CIN.

Urinary NGAL that is a marker of AKI was evaluated in all patients and its level did not show any significant difference between two groups. Thus it confirmed the previous results of serum creatinine in patients with acute kidney injury.

As a matter of fact, we used commercially available curcumin that consists of three curcuminoids; about 75% of it was curcumin. This product has low solubility, low absorption from the gut, rapid metabolism and elimination. Most of it excretes without any changes from the feces.[11] Therefore, it can be revealed that for more effects we might need higher dosage of drug in the future studies.

Finally based on our study this can be claimed that with this dosage of curcumin, there was no side effect in patients with moderate to severe CKD.

CONCLUSION

We could not find any protective effect of curcumin in reducing CIN in human. However it can be due to low sample size or low dose of curcumin used in this study. For assessing its potential renoprotective effects further investigation is warranted.

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Received November 2018
Revised March 2019
Accepted July 2019