Avicenna Journal of Phytomedicine (AJP)

Original Research Article

Evaluation of the preventive effect of intravenous trans-sodium crocetinate followed by oral crocetin on contrast-induced nephropathy in patients with chronic kidney disease undergoing coronary angioplasty: A randomized placebo-controlled triple-blind clinical trial

Sofia Salari[1], AmirHooshang Mohammadpour[1,2], Arash Gholoobi[3,*], Vahid Ghavami[4], Javad Ramezani[3], Ali Eshraghi[3] , Hossein Hosseinzadeh[2,5,*]

[1]*Department of Clinical Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*
[2]*Pharmaceutical Sciences Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*
[3]*Department of Cardiovascular Diseases, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[4]*Department of Biostatistics, Social Determinants of Health Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*
[5]*Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*

Article history:
Received: Apr 17, 2025
Received in revised form: Jul 16, 2025
Accepted: Jul 17, 2025
Epub ahead of print

**** Corresponding Author:***
Tel: +985131801193
Fax: +985138823251
GholoobiA@mums.ac.ir
hosseinzadehh@mums.ac.ir

Keywords:
Saffron
Trans sodium crocetinate
Percutaneous coronary intervention
Contrast-induced nephropathy

Abstract

Objective: Contrast media (CM) can potentially cause nephropathy. Trans-sodium crocetinate (TSC) has shown promising antioxidant and anti-inflammatory properties in animal studies. This research sought to assess TSC efficacy in contrast-induced nephropathy (CIN) prevention.

Materials and Methods: A randomized triple-blind trial involving 130 patients undergoing elective PCI (percutaneous coronary intervention) was conducted. Participants received either TSC (0.5 mg/kg) before the procedure, followed by crocetin tablets thrice daily for five days to evaluate its impact on CIN occurrence, or a placebo. The primary outcome was the occurrence of CIN, with secondary outcomes including blood urea nitrogen (BUN), serum creatinine (SCr), glomerular filtration rate (GFR), C-reactive protein (CRP), urine albumin-to-creatinine ratio (ACR), and prooxidant-antioxidant balance (PAB) test in a 5-day follow-up.

Results: The study's primary outcome revealed a significantly lower CIN prevalence in the TSC group (7.7%) compared to the placebo group (24.6%) ($p = 0.009$). Secondary outcomes showing significant inter-group differences included BUN ($p<0.001$), GFR ($p<0.05$), CRP ($p<0.001$), ACR ($p<0.05$), and PAB test ($p<0.05$). However, SCr and adverse effects did not differ significantly between the groups.

Conclusion: TSC demonstrated its ability to impede nephrotoxic processes and significantly reduce CIN incidence. Additional clinical studies are required to further validate the beneficial effects in this context.

Please cite this paper as:
Salari S, Mohammadpour A.H, Gholoobi A, Ghavami V, Ramezani J, Eshraghi A, Hosseinzadeh H. Evaluation of preventive effect of intravenous trans-sodium crocetinate on contrast-induced nephropathy in patients with chronic kidney disease undergoing coronary angioplasty: A randomized placebo-controlled triple-blind clinical trial. Avicenna J Phytomed, 2025. Epub ahead of print.

Introduction

Contrast media (CM) in imaging may lead to contrast-induced nephropathy (CIN), the third significant cause of acute kidney injury (AKI), indicated by a rise in serum creatinine (SCr) levels (at least 25% or an increase of 0.5 mg/dl from baseline) within 48 to 72 hr post-contrast administration. SCr levels typically peak on days 3 to 5 and can develop for up to a week. The prevalence of CIN varies greatly based on risk factors and reaches up to 40% (Li and Wang, 2024). Optimized hydration therapy efficiently prevents CIN, but no effective treatment exists (van der Molen et al. 2018).

Contrast media (CM) administration affects kidney tissues via direct, indirect, and oxidative stress-related mechanisms, with renal blood circulation modifications and elevated ROS (reactive oxygen species) during ischemia contributing to nephrotoxicity (Caiazza et al. 2014).

Optimized hydration therapy has been proposed as the most convenient and cost-effective way to prevent CIN. Regrettably, there is currently no defined treatment for CIN. Several randomized clinical trials (RCTs) and meta-analyses have studied different medications like N-acetylcysteine, statins and vitamin C, but there is no definitive proof that they can lower the risk of CIN (van der Molen et al., 2018). Current options for treating CIN are quite limited.

Trans-sodium crocetin (TSC), derived from saffron (*Crocus sativus* L.) crocetin, exhibits enhanced bioavailability and therapeutic effects. TSC has been shown to enhance oxygen diffusion (Gainer et al. 2005; Stennett et al. 2006), reduce inflammation and diminish oxidative stress through free radical scavenging (Rajabian et al., 2024). Additionally, TSC influences autophagy and apoptosis, showcasing its potential in various health applications (Naraki et al. 2024; Rajabian et al. 2023).

The use of TSC alongside crocetin, a more soluble synthetic derivative of crocetin in water, allows a higher initial dose to be quickly administered to the individual and helps to prevent destructive mechanism due CM injection immediately after TSC injection immediately after TSC injection (reducing hypoxic and inflammatory effects from CM in animal and cellular studies) (Shah et al. 2021).

Considering the absence of *in vivo* studies, this trial specifically investigates TSC's impact on CIN in PCI (percutaneous coronary intervention) patients with no previous similar trial.

Materials and Methods

Chemicals

TSC vial and Crocetin tablets (concentrated solution for infusion, 20 mg/mL), placebo vial (sodium chloride 0.9% powder for injection), and placebo tablets were manufactured by Dr. Rajabi Pharmaceutical Laboratory (Mashhad, Iran).

Study design

This randomized, single-center, triple-blind, placebo-controlled study was conducted from September 2022 to February 2023 in Imam Reza Hospital, Mashhad, Iran (the participants, the clinicians administering the treatment, and the analysts were blinded to the group assignment). This study was registered in the Iranian Clinical Trials Registry (registration number IRCT20081019001369N8) and approved by the Internal Review Board and Ethics Committee of University of Medical Sciences (IR.MUMS.REC.1400.308).

Patient selection

A total of 130 patients were informed about the study and they provided written consent. The inclusion criteria were as follows: (1) age over 18 years, (2) admitted for non-primary PCI (PCI performed more than 2 hr after admission), (3) Glomerular filtration rate (GFR) < 90 ml/min.1.73m^2 prior to angioplasty, (4) Mehran score (Mehran et al. 2021) ≥ 6, (5) administration of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers

(ARBs) along with a high dose of rosuvastatin for at least one month before PCI, (6) SCr level fluctuation of no more than 15% during the three days preceding angioplasty, (7) hydration for four hours prior to angioplasty, (8) no history of AKI in the past six months (defined as an increase of 0.3 mg/dl within the last four weeks) or kidney transplantation, (9) ability to provide informed consent and agree to comply with all study visits and requirements, (10) the absence of end-stage renal disease requiring hemodialysis before angioplasty, (11) the absence of comorbidities such as prior CIN, multiple myeloma, or thromboembolic disease, and (12) no history of nephrotoxic drug administration, including cyclosporine, aminoglycosides, or cisplatin within two days before angioplasty and specific medications such as N-acetylcysteine, vitamin C, mannitol, theophylline, or dopamine in the past two weeks, as well as routine use of warfarin. Additional criteria included (13) the absence of active tumors, (14) no exposure to CM in the prior two weeks, and (15) the absence of cardiogenic shock.

Exclusion criteria included: (1) pregnancy, lactation, or childbearing potential; (2) history of allergy to medication; (3) instability during angioplasty (systolic blood pressure < 95 mmHg, cardiogenic shock, or pulmonary edema); (4) being receipt of investigational medicinal products within the last 30 days; (5) diagnosis of an active tumor during the study; and (6) patient unwillingness to continue participating in the study.

Randomization and blinding

The study's randomization employed a block method with constant sizes, assigning 130 volunteers to placebo (P) or trans sodium crocetinate (TSC) using a block method at a 1:1 ratio. Each participant received a unique 4-digit ID. To maintain concealment, indistinguishable vials were prepared, with TSC and placebo appearing identical.

Intervention groups and outcomes

Hospitalized patients undergoing PCI received five-day drug treatment; characteristics, past drug/medical history, and blood samples were documented. Patient candidates for the PCI meeting study criteria were randomly assigned to TSC or placebo. TSC (0.5 mg/kg) or placebo was injected before angioplasty with iohexol (Visodix® 320 mg/20 ml). Post-PCI, crocetin (7.5 mg) tablets were added to one group's standard treatment thrice daily, for five days. The other group was similarly given placebo tablets thrice daily for 5 days. Blood samples were collected before and on the 1st day after the PCI to evaluate pro-oxidant-antioxidant balance (PAB) biomarkers of oxidative stress. These samples were kept in a -20 °C freezer after centrifugation at 2500 rpm for 15 minutes at room temperature, then evaluated by the ELISA reader (Hiperion, Germany) using the method described in the literature (Alamdari et al. 2008). Also, Complete blood count (CBC), electrolytes, C-reactive protein (CRP), Venous blood gas (VBG), and liver, kidney, and muscular profiles, and urinary parameters were reassessed on days 1 and 5 by Autoanalyzer BT3500 (Biotecnica, Italy) (Figure 1).

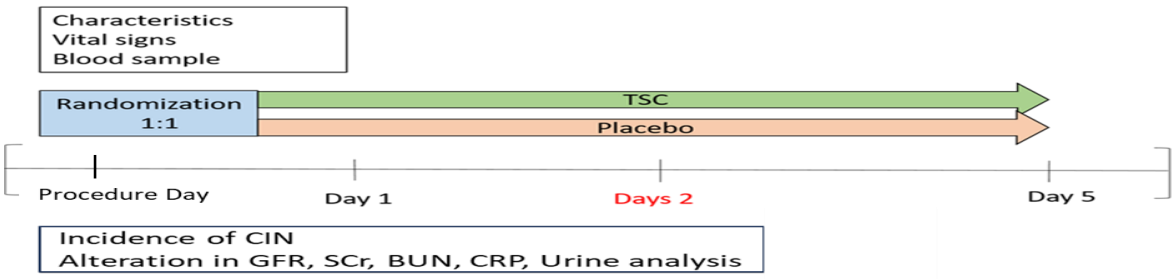

Figure 1. Study outline, procedure day is the day PCI was performed

The primary outcome was assessed by measuring the incidence of CIN. Additionally, according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines, stage 1 AKI is characterized by an increase in SCr of ≥0.3 mg/dL (≥ 26.5 mmol/L) within 48 hr or a rise of 1.5 to 1.9 times the baseline level within 7 days (Khwaja 2012).

Secondary outcomes included the impact of TSC on GFR by the Chronic Kidney Disease Epidemiology Collaboration formula 2021 (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) formulas (Khwaja 2012), SCr, blood urea nitrogen (BUN), CRP, urine analysis and PAB. These measurements were taken at baseline and on days 1 and 5 post-treatment.

Statistical analyzing

According to previous research, 20% of patients undergoing PCI develop CIN within three days (Zhang et al. 2020). Sample size calculated with a power of 80% ($Z_{1-\beta}$ = 0.84) and a 5% type I error rate ($Z_{1-\alpha/2} = 1.96$), the required sample size to detect an absolute decrease of 15% (d = 0.15) in the incidence of CIN episodes by a clinician's opinion, considering a projected dropout rate of 10%, was determined to be 65 subjects in each group.

Descriptive statistics summarized data, using measures of central tendency and dispersion. Normality was tested via the Shapiro-Wilk test. Data is presented as means± SD or median (IQR) for continuous and percentages for categorical variables. Comparative analyses utilized t-tests, Mann-Whitney U, chi-square, Fisher's exact, and paired tests, with SPSS version 25 at a 0.05 significance level.

Results

Patients characteristics

In the study, 644 patients were screened; 514 patients failed in the screening process, mainly due to unmet criteria (52.7%) or declining participation (43.4%). Ultimately, 130 patients were enrolled, divided equally into TSC and placebo groups (Figure 2).

No significant differences were noted in baseline parameters (Tables 1 and 2), except for contrast volume, history of Coronary artery bypass graft (CABG) and Body mass index (BMI) that needed to be adjusted for analysis.

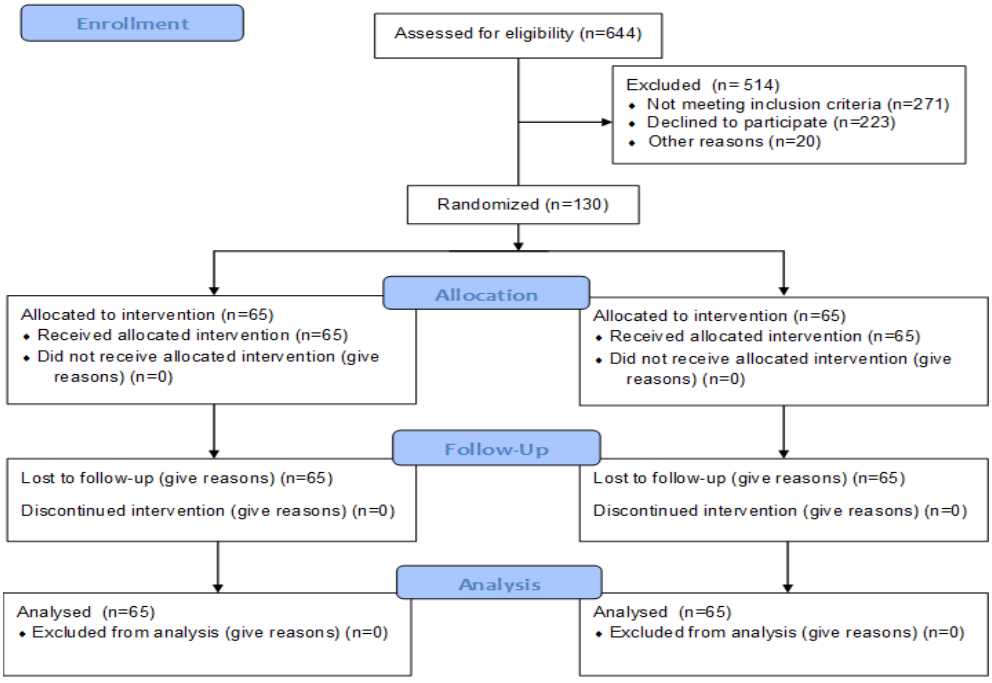

Figure 2. Consort diagram

Table 1. Comparison of baseline clinical characteristics between the TSC and placebo groups

		Placebo(n=65)	TSC(n=65)	p-Value
Age (year) ¥		63 [16]	64 [18]	>0.05‡
Male gender [n (%)]		35 (54)	43 (66)	>0.05¶
BMI (kg/m^2) ¥		23.65 [3.9]	23.5 [5.3]	0.049‡
Medical history				
DM2 [n (%)]		28 (43.1%)	35 (53.8%)	>0.05¶
Hypertension [n (%)]		39 (60.0%)	34 (52.3%)	>0.05¶
IHD [n (%)]		45 (69.2%)	38 (58.5%)	>0.05¶
HF [n (%)]		54 (83.1%)	53 (81.5%)	>0.05¶
CABG [n (%)]		8 (12.3%)	1 (1.5%)	0.033γ
HLP [n (%)]		21 (32.3%)	20 (30.8%)	>0.05¶
Anemia [n (%)]		20 (30.8%)	15 (23.1%)	>0.05¶
LVEF (%)		45 [19]	45 [20]	>0.05‡
Mehran risk group				
Low (≤5)		0(0%)	0(0%)	>0.05γ
Medium (6–10)		45(69.2%)	44(67.7%)	
High (11–15)		18 (27.7%)	21 (32.3%)	
Very high (≥16)		2 (3.1%)	0(0.0%)	
Mehran score in groups		8.5 [6]	9 [4]	>0.05‡
Social history				
Smoking or Tobacco		17 (26.1%)	14 (21.5%)	>0.05¶
Alcohol /Opioid		33 (50.7%)	31 (47.6%)	>0.05γ
Drug history				
Antiplatelet [n (%)]		55 (84.6%)	57 (87.7%)	>0.05¶
Anticoagulant [n (%)]		9 (13.8%)	8 (12.3%)	>0.05¶
Statin [n (%)]		65 (100.0%)	65 (100.0%)	>0.05¶
ACEi/ARB/ARNI [n (%)]		65 (100%)	65 (100%)	>0.05¶
Empagliflozin [n (%)]		14 (21.5%)	13 (20%)	>0.05¶
β-blocker [n (%)]		48 (73.8%)	41 (63.1%)	>0.05¶
MRA [n (%)]		14 (21.5%)	17 (26.1%)	>0.05¶
Insulin [n (%)]		0 (0%)	3 (4.6%)	>0.05γ
Metformin [n (%)]		16 (24.6%)	16 (24.6%)	>0.05¶
Vital sign				
HR (beats/minutes) ¥		83 [18]	87 [14]	>0.05‡
SaO2 (%) ¥		61.5 [36]	67 [26.2]	>0.05‡
MAP (mmHg) ¥		80 [30]	81.5 [12]	>0.05‡
Blood Laboratory data				
WBC (10^3/µl) ß		8.13±2.10	9.13±2.93	>0.05$
Neutrophil (%) ß		63.79±10.03	66.48±10.59	>0.05$
Lymphocyte (%) ß		28.49±8.74	26.01±10.07	>0.05$
RBC (10^3/µl) ß		4.93±0.68	5.04 ± 0.58	>0.05$
Hemoglobin (g/dl) ß		13.39±1.77	13.86±1.88	>0.05$
Platelet (10^3/µl) ¥		187 [125.50]	236 [189]	>0.05‡
AST (U/L) ¥		17 [5.75]	2 [3.75]	>0.05‡
ALT (U/L) ¥		17 [9.25]	25 [6.5]	>0.05‡
Amylase (U/L) ¥		38 [12.75]	29.5 [21.50]	>0.05‡
Urea (mg/dl) ¥		38 [12.75]	29.5 [21.50]	>0.05‡
Creatinine (mg/dl) ¥		1.15 [0.48]	1.1 [0.18]	>0.05‡
GFR (ml/min)	CKD-EPI ¥	64.5 [28.50]	63 [16]	>0.05‡
	MDRD ¥	50.30 [18.90]	59.7 [16.33]	>0.05‡
Mehran score ¥		8.5 [6]	9 [4]	>0.05‡
CPK (U/L) ¥		118.45 [140.63]	78 [77.93]	>0.05‡
LDH (U/L) ¥		345 [157.20]	357.5 [201.75]	>0.05‡
Sodium (mEq/dL) ¥		136.5 [8.50]	140 [3]	>0.05‡
CRP (mg/L) ¥		2 [2.33]	0.8 [2.80]	>0.05‡
INR ¥		0.96 [0.12]	0.98 [0.15]	>0.05‡
Urine Laboratory data				
Urine Albumin (mg/L) ¥		2.35 [3.52]	11.15 [14.35]	>0.05‡
Urine protein (mg/L) ¥		22.5 [37.25]	50 [68.5]	>0.05‡
Urine Cr (mg/L) ¥		570 [403.5]	860 [1037]	>0.05‡
Urine Na (mEq/L) ¥		160 [99]	151.5 [122]	>0.05‡
Urine SG ¥		1016 [10]	1020 [4.2]	>0.05‡
Urine Alb/Cr ratio (mg/g) ¥		3.3 [17.2]	10.43 [19.9]	>0.05‡

‡ Mann-Whitney U test, $ Two independent samples t-test, ¶ Chi-squared test, γ Fisher's Exact Test, ¥ Median [Intraquartile range], ß Mean ± SD. ACEi = Angiotensin-converting enzyme inhibitor; Alb/Cr = Albumin/Creatinine, ALT = Alanine aminotransferase; aPTT= activated thromboplastin clotting time; ARB = Angiotensin receptor blocker; ARNI = Angiotensin receptor/neprilysin inhibitor; AST = Aspartate aminotransferase; BMI = Body mass index; CABG = Coronary artery bypass graft; CCB = Calcium channel blocker; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration formula; CPK= Creatine phosphokinase; CRP= C-reactive protein; DM2 = type 2 diabetes mellitus; GFR= Glomerular filtration rate; HCTZ = Hydrochlorothiazide; HF = Heart failure; HR = Heart rate; IHD = Ischemic heart disease; LDH= Lactate dehydrogenase; LVEF = Left ventricular ejection fraction; MAP= Mean arterial pressure; MDRD= Modification of Diet in Renal Disease formula ; MRA = Mineralocorticoid receptor antagonist; PCI = Percutaneous coronary intervention; PT= Prothrombin time; SaO2 = O2 saturation; RBC= Red blood cell; WBC = White blood cell , SG= Specific gravity, TSC= Trans sodium crocetinate ; Placebo and TSC group both contain 65 patients. Comparing characteristics between the groups, BMI and history of CABG were significantly different, while there was no significant difference between the groups in other baseline information.

Table 2. Angiographic characteristics

PCI-related information	Placebo (n=65)	TSC(n=65)	p-value
Vessel treated			
LAD [n (%)]	38 (58.2%)	29 (44.6%)	>0.05ᵞ
LCX [n (%)]	11 (16.9%)	6 (9.2%)	
LMA [n (%)]	2 (3.1%)	2 (3.1%)	
RCA [n (%)]	10 (15.4%)	12 (18.5%)	
PDA [n (%)]	1 (1.5%)	0 (0%)	
LAD, LCX [n (%)]	2 (3.1 %)	5 (7.7%)	
LCX, RCA [n (%)]	0 (0%)	5 (7.7%)	
LAD, RCA [n (%)]	0 (0%)	2 (3.1%)	
LAD,LMA [n (%)]	0 (0%)	4 (6.2%)	
LAD, LCX, LMA [n (%)]	1 (1.5%)	0 (0%)	
Access route			
Radial [n (%)]	56 (86%)	54 (83%)	>0.05ᵞ
Femoral [n (%)]	9 (14%)	11 (16.9)	>0.05ᵞ
Volume Injections during PCI			
Hydration volume (ml)	500 [0]	500 [250]	>0.05‡
Contrast volume (ml)	150 [50]	125 [50]	0.004‡

‡ Mann-Whitney U test, $ Two independent samples t-test, ¶ Chi-squared test, γ Fisher's Exact Test. LAD= Left anterior descending artery; LCX = Left circumflex artery; LMA= Left marginal artery; PDA= Posterior descending artery; RCA = Right coronary artery, TSC= Trans sodium crocetinate; Placebo and TSC groups both contain 65 patients. Comparing characteristics between groups, contrast volume was significantly different, while there was no significant difference between other information.

Primary endpoint

Comparison of CIN between groups

Among these 130 patients, 21 developed CIN. Patients were evaluated for AKI (Figure 3) and CIN (Figure 4). Table 3 details the primary outcome values.

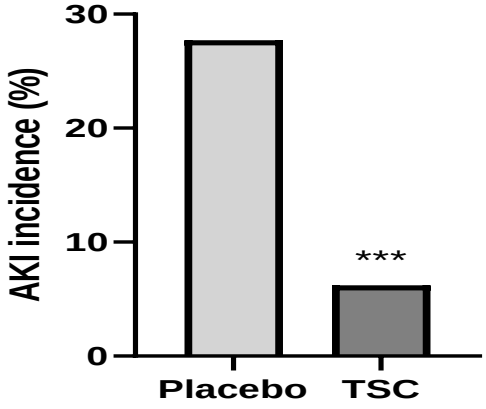

Figure 3. Comparison of stage 1 AKI between the TSC and the placebo group during a 5-day follow-up. A significant reduction in AKI incidence was observed in the TSC group (***p<0.001). AKI= Acute kidney injury, TSC=Trans sodium crocetinate

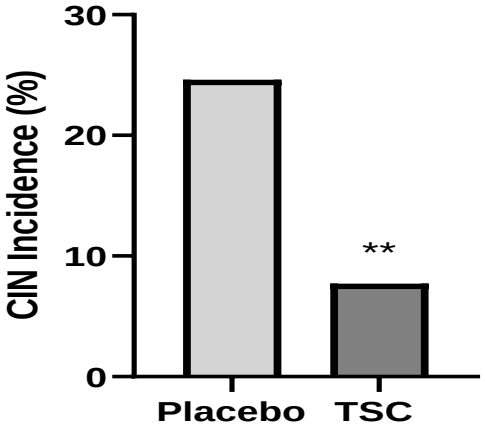

Figure 4. Comparison of CIN occurrence between the TSC and the placebo group during a 5-day follow-up. A significant reduction in CIN occurrence was observed in the TSC group (**p<0.01). CIN=Contrast-induced nephropathy, TSC = Trans sodium crocetinate

Table 3. Frequency of CIN and AKI in patients undergoing PCI in the TSC and placebo groups

	With CIN	Without CIN	With AKI stage 1	Without AKI stage 1
TSC [n (%)]	5 (7.7)	60 (92.3)	4 (6.2)	61 (93.8)
Placebo [n (%)]	16 (24.6)	49 (75.4)	18 (27.7)	47 (72.3)
Total [n (%)]	21 (16.1)	109 (83.9)	22 (16.9)	108 (83.1)
p value	0.009¶		0.001¶	

Chi-squared test. AKI = Acute kidney injury, CIN = Contrast induced nephropathy, PCI= Percutaneous coronary intervention; TSC = Trans sodium crocetinate; Placebo and TSC groups both contain 65 patients. A significant reduction of AKI and CIN was seen in the TSC group.

Comparison of the incidence of CIN between the groups based on risk factors

The CIN incidence was similar between the diabetics and non-diabetics groups (Table 4). Moreover, in those with moderate Mehran scores, CIN occurrence was significantly higher in the placebo group (p = 0.010). Albeit in high/very high Mehran scores, no significant difference was noted between the placebo and TSC group. Furthermore, CIN was notably higher in the placebo group than the TSC group in patients with heart failure (p=0.015).

The TSC group showed increased CIN with contrast under 200 ml versus placebo (p=0.009), but not with volumes over 200 ml.

Univariate analysis indicated significant differences between CIN and non-CIN groups concerning CABG history, contrast volume, and BMI (p=0.033, p=0.004, and p=0.049, respectively). Additionally, multivariable logistic regression identified the use of TSC as the only predictor of CIN following PCI (Table 5).

Table 4. Frequency of DM in patients undergoing PCI in the TSC and placebo groups

	CIN with DM	CIN without DM	p value
TSC group [n (%)]	3 (4.6)	2 (3)	>0.05$^{\gamma}$
Placebo group [n (%)]	7 (10.7)	9 (13.8)	>0.05¶

Chi-squared test, γ Fisher's exact test. There was no significant difference in the incidence of CIN between patients with/without diabetes (DM). CIN = Contrast induced nephropathy; DM= Diabetes; PCI= Percutaneous coronary intervention; TSC = Trans sodium crocetinate

Table 5. Multiple logistic regression analysis predicting the effect of TSC on CIN, adjusted for BMI, Contrast volume and CABG history

	coefficient	SE	Wald	df	p-value	odds ratio
TSC	-1.587	0.600	7.000	1	0.008	0.205
CABG	0.241	0.821	0.086	1	0.769	1.272
BMI	-0.233	0.107	4.753	1	0.029	0.792
Contrast volume	0.000	0.004	0.004	1	0.949	1.000
Constant	4.432	2.620	2.720	1	0.099	75.222

BMI = Body mass index, CABG = Coronary artery bypass graft, CIN= Contrast-induced nephropathy, TSC = Trans sodium crocetinate. Multiple logistic regression was conducted and BMI was reported with significant p-values.

Comparison of BUN and SCr between groups

The study revealed a significant decrease in BUN levels in both groups, with the TSC group showing a more substantial reduction compared to the placebo group (p<0.001 for TSC; and p=0.002 for placebo). Both groups exhibited a notable decline in BUN from day 0/1 to day 5. Also, a significant difference was noted on day 1 between the groups (p<0.001, Figure 5). The analysis revealed a decrease in SCr levels in the TSC group versus an increase in the placebo group. However, Figure 6 showed no significant differences in SCr levels between the groups during the study, with fluctuations in renal biomarkers detailed in Table 6.

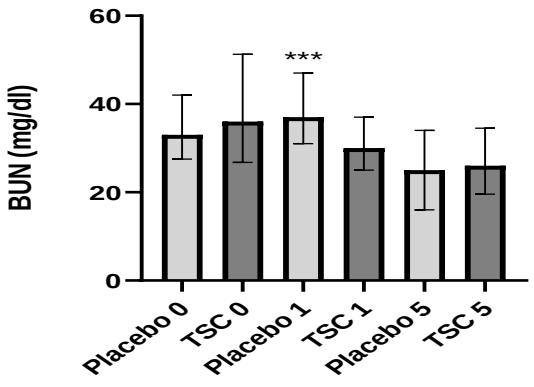

Figure 5. Comparison of the BUN level between TSC and placebo. A significant reduction of BUN was seen in the TSC group on the 1st day after PCI (***p<0.001). TSC/Placebo 0: level in baseline, TSC/ placebo 1: level on the 1st day of treatment, TSC/ placebo 5: level on the 5th day of treatment. BUN= Blood urea nitrogen, TSC = Trans sodium crocetinate

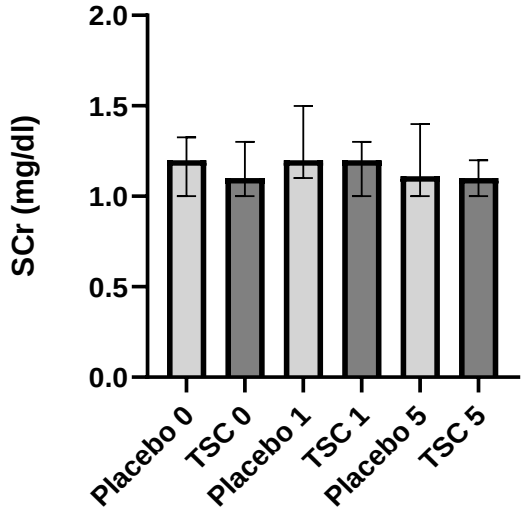

Figure 6. Comparison of SCr level between TSC and placebo. There was no significant change in SCr between the groups on follow-up. TSC/Placebo 0: level in baseline, TSC/ Placebo 1: level on the 1st day of treatment, TSC/ Placebo 5: level on the 5th day of treatment. SCr=Serum creatinine, TSC= Trans sodium crocetinate

Comparison of GFR between the groups

The results indicated a decline in GFR levels following an initial increase observed in both groups throughout the study. Notably, when applying the CKD-EPI formula, the increase in GFR at the study's end was more pronounced in the TSC group compared to the placebo group, with significant differences noted between day 1 and day 5 GFR values (p = 0.005 for 1st day, p=0.046 for 5th day). Conversely, the MDRD formula revealed significant differences in GFR values between the groups on day 1 and day 5 (p = 0.003 for the 1st day and p = 0.017 for the 5th day, Figure 7). The placebo group experienced a significant drop only on the first day (p=0.042, Table 6).

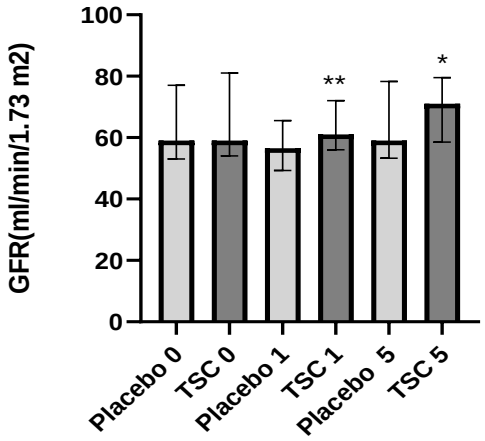

Figure 7. Comparison of GFR level with CKD-EPI between TSC and placebo. GFR significantly increased in the TSC group on days 1 and 5 after PCI. (*p<0.05, **p<0.01). TSC/Placebo 0: level in baseline, TSC/ Placebo 1: level on the 1st day of treatment, TSC/ Placebo 5: level on the 5th day of treatment. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration formula, GFR= Glomerular filtration rate, TSC = Trans sodium crocetinate

Table 6. Comparison of changes in renal biomarkers and drug adverse reactions between the TSC and placebo groups

	Placebo	**TSC**	**p-value**
Δ BUN (1-0) (mg/dl) ¥	1.5 [18.25]	0.5 [17.5]	>0.05‡
Δ BUN (5-0) (mg/dl) ß	-6.79 ± 14.98	-9.40 ± 13.48	>0.05$
Δ BUN (5-1) (mg/dl) ß	-7.19 ± 13.62	-14.39 ± 13.65	0.007$
Δ SCr (1-0) (mg/dl) ¥	0.2 [0.25]	0.0 [0.08]	0.002‡
Δ SCr (5-0) (mg/dl) ¥	0.05 [0.53]	-0.07 [0.14]	>0.05‡
Δ SCr (5-1) (mg/dl) ß	-0.14 ± 0.24	-0.29 ± 0.49	0.025$
Δ eGFR (1-0) (ml/min/) ¥	-7.5 [28.75]	0.0 [5.75]	0.042‡
Δ eGFR (5-0) (ml/min) ¥	-12 [31]	2.5 [14]	>0.05‡
Δ eGFR (5-1) (ml/min) ¥	12 [44]	2.5 [14.75]	>0.05‡
Headache [n (%)]	10 (15.8)	11 (16.9)	>0.05¶
Insomnia [n (%)]	8 (12.3)	5 (7.7)	>0.05¶
Drowsiness [n (%)]	0 (0)	0 (0)	>0.05¶
Agitation [n (%)]	0 (0)	0 (0)	>0.05¶
Fatigue [n (%)]	18 (27.6)	11 (16.9)	>0.05¶
Hypersensitivity reactions [n (%)]	0 (0)	1 (1.5)	>0.05 ¶
Nausea [n (%)]	9 (13.8)	12 (18.4)	>0.05 ¶
Vomiting [n (%)]	9 (13.8)	12 (18.4)	>0.05 ¶
Diarrhea [n (%)]	0 (0)	0 (0)	>0.05 ¶
Constipation [n (%)]	0 (0)	0 (0)	>0.05 ¶
Tremor [n (%)]	0 (0)	0 (0)	>0.05 ¶
Loss of appetite [n (%)]	0 (0)	0 (0)	>0.05 ¶
Increased appetite [n (%)]	0 (0)	0 (0)	>0.05 ¶
Rash and itching [n (%)]	8 (12.3)	8 (12.3)	>0.05 ¶

Table 6 continue

Body pain [n (%)]	0 (0)	0 (0)	>0.05 ¶
Abdominal pain [n (%)]	0 (0)	0 (0)	>0.05 ¶
Bradycardia [n (%)]	8 (12.3)	5 (7.6)	>0.05 ¶
Palpitation [n (%)]	10 (15.3)	9 (13.8)	>0.05 ¶

Δ (1-0): Difference between the day 1 after PCI and the baseline level, Δ (5-0): Difference between the day 5 after PCI and the baseline level, Δ (5-1): Difference between the day 5 after PCI and the day 1 after PCI level, ‡ Mann-Whitney U test, $ Two independent samples t-test, ¥ Median [Intraquartile range], ¶ Chi-squared test, ß Mean ± SD. BUN = Blood urea nitrogen, eGFR= estimated GFR based on CKD-EPI formula, SCr = Serum creatinine, TSC = Trans sodium crocetinate; Placebo and TSC groups both contain 65 patients. The difference in BUN values on day 1 and 5, Scr between day 1 and baseline values and day 5 and day 1 values and the difference in GFR values between day 1 and baseline values were significant. The placebo and TSC groups both had 65 patients. The difference in drug adverse reactions between the groups was not significant.

Comparison of CRP and PAB between the groups

Comparison between the groups revealed significant differences in values from day 1 and day 5 ($p<0.001$). In contrast to the TSC group, the placebo group showed a notable difference in CRP levels between baseline and day 1 ($p<0.001$, Figure 8, Table 7).

Notably, the placebo group exhibited a significant increase in PAB levels ($p=0.009$), while the TSC group had no significant change. Changes in PAB values during the study were significant between the placebo and the TSC group ($p=0.029$, Table 7).

Comparison of urine analysis between the groups

No significant urine variable differences were noted between the groups, except for a marked decrease in urine albumin-to-creatinine ratio (ACR) in the TSC group in comparison to placebo ($p=0.022$, Table 8).

Safety of TSC

TSC is well-tolerated, and adverse reactions were similar between the TSC and placebo groups (Table 6).

Effect of TSC on laboratory values

There was no statistically significant difference in laboratory data between the two groups (Table 8).

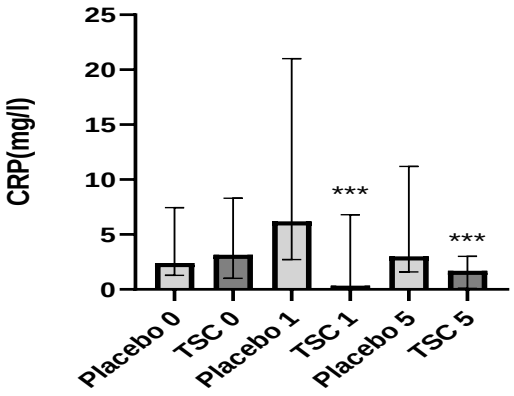

Figure 8. Comparison of CRP between TSC and placebo. CRP levels significantly decreased in the TSC group on the 1st and 5th days post-procedure (***$p<0.001$). TSC/Placebo 0: level in baseline, TSC/ Placebo 1: level on the 1st day of treatment, TSC/ Placebo 5: level on the 5th day of treatment. CRP= C-reactive protein, TSC = Trans sodium crocetinate

Table 7. PAB results at pre-and post-PCI times in the TSC and placebo group

	Placebo	**TSC**	**p value between groups**
Before PCI ¥ (HKunit)	159.13 [63.22]	140.7 [78.8]	>0.05‡
After PCI ¥ (HK unit)	167.5 [51.41]	150.04 [64.15]	>0.05‡
Within groups	p= 0.009*	p= 0.599*	-
Δ PAB ¥	4.52 [32.63]	0.86 [24.39]	0.029‡

‡ Mann-Whitney U test, * Wilcoxon assay, ¥ Median [Intraquartile range], **Δ** PAB **=** Difference between the day 1 after PCI and the baseline level. PAB = Prooxidant–antioxidant balance; PCI= percutaneous coronary intervention; TSC = Trans sodium crocetinate; Δ PAB= Difference between the day 1 after PCI and the baseline level of PAB value; Placebo and TSC groups both contain 65 patients. The difference in PAB values between day 1 and baseline values was significant.

Table 8. Comparison of laboratory data between the TSC and placebo groups

	Placebo Day 1	TSC Day 1	p-value	Placebo day 5	TSC day 5	p-value
Blood laboratory data						
WBC (103/µl) ß	9.73±2.17	9.89±2.93	>0.05$	7.81±1.91	8.17±2.14	>0.05$
Neutrophil (%) ¥	65.6 [15.15]	74.9 [6.38]	>0.05‡	61.45±9.59	65.23±9.08	>0.05‡
Lymphocyte (%) ¥ ß	24.65±6.74	22.43±7.54	>0.05$	58.5 [21.38]	66 [10.08]	>0.05$
RBC (103/µl) ß	4.97±0.71	4.93±0.55	>0.05$	4.97±0.71	4.93±0.55	>0.05$
Hemoglobin (mg/dl) ß ¥	13.40 [3.5]	12.70 [1.55]	>0.05‡	13.38±1.77	13.35±1.72	>0.05$
Platelet (103/µl) ¥	215 [115.50]	213 [117]	>0.05‡	213.50 [77.25]	222.50 [130.50]	>0.05‡
AST (U/L) ¥	18.5 [12.50]	28 [14]	>0.05‡	18 [7]	21 [8.50]	>0.05‡
ALT (U/L) ¥	15.5 [9.50]	24.5 [15.25]	>0.05‡	25 [8]	26 [10.50]	>0.05‡
Amylase	57.7 ± 25.7	48.9 ± 25.2	>0.05‡	47.3 ± 21	61 ± 24	>0.05‡
BUN (mg/dl) ¥	34 [14.75]	32 [25.5]	<0.001‡	26.5 [22.75]	22.5 [13.4]	>0.05‡
Creatinine (mg/dl) ¥	1.30 [0.45]	1.10 [0.25]	>0.05‡	1.20 [0.45]	1.02 [0.12]	>0.05‡
GFR CKD-EPI ¥	55 [26.25]	65 [12.75]	0.005‡	56.5 [24.5]	62 [28.25]	0.046‡
(ml/min) MDRD ¥	50.05 [17.65]	60.80 [11.15]	0.003‡	52.45 [20.80]	64 [26.57]	0.017‡
CPK (U/L) ¥	167 [277.75]	100.50 [107.25]	>0.05‡	151 [122.50]	61.50 [59.50]	>0.05‡
LDH (U/L) ¥	344 [189]	335.50 [188]	>0.05‡	301 [156]	280.5 [141.5]	>0.05‡
Sodium (mEq/dl) ¥	137.5 [2.5]	136.5 [7.5]	>0.05‡	135 [3]	136 [3.5]	>0.05‡
CRP (mg/L) ¥	4 [6.92]	1.25 [2.8]	<0.001‡	2.95 [1.73]	1 [3.93]	<0.001‡
INR ¥	0.94 [0.17]	0.99 [0.09]	>0.05‡	1 [0.06]	1 [0.03]	>0.05‡
Urine laboratory data						
Urine albumin mg/L) ¥	8.75 [12.43]	13.25 [28.55]	>0.05‡	8.20 [20.63]	13.25 [16.02]	>0.05‡
Urine protein (mg/L) ¥	40 [49.75]	145 [187.5]	>0.05‡	35 [176.23]	45.3 [125.75]	>0.05‡
Urine creatinine (mg/L) ¥	860 [1003.75]	720 [2152]	>0.05‡	851.5 [794.40]	781.5 [448.25]	>0.05‡
Urine Na (mEq/L) ¥	135.15 [112.90]	158 [51.50]	>0.05‡	121.60 [119.15]	106 [151]	>0.05‡
Urine SG ¥	1022.50 [11.75]	1025 [11.75]	>0.05‡	1207.5 [8.75]	1021 [16.75]	>0.05‡
Urine Alb/Cr ratio (mg/g) ¥	6.5 [29.80]	10 [18.43]	>0.05‡	12.16 [39.15]	17.88 [21.95]	0.022‡
Vital signs						
HR (beat/minutes) ß	86.89±13.37	85.97±11.93	>0.05$	-	-	-
SaO2 (%) ¥	64.35 [19.30]	69.80 [31.38]	>0.05‡	-	-	-
MAP (mmHg) ¥	76.50 [15]	70.50 [15]	>0.05‡	-	-	-

‡ Mann-Whitney U test, $ Two independent samples t-test, ¶ Chi-squared test, γ Fisher's exact test, ¥ Median [Intraquartile range], ß Mean ± SD. Alb/Cr = Albumin/Creatinine, ALT = Alanine aminotransferase; aPTT= activated thromboplastin clotting time; AST = Aspartate aminotransferase; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration formula; CPK= Creatine phosphokinase; CRP= C-reactive protein; GFR= Glomerular filtration rate; HR = Heart rate; LDH= Lactate dehydrogenase; MAP= Mean arterial pressure; MDRD= Modification of Diet in Renal Disease formula; PCI = Percutaneous coronary intervention; PT= Prothrombin time; SaO2 = O2 saturation; RBC= Red blood cell; WBC = White blood cell, SG= Specific gravity, TSC= Trans sodium crocetinate; Placebo and TSC group both had 65 patients; Vital signs were measured before PCI and on the 1st day after PCI. Comparing laboratory values and vital signs between the groups showed that there was no significant difference in information except for BUN of the 1st day, GFR values of the 1st and 5th day, CRP of the 1st and 5th day and Urine Alb/Cr ratio of the 5th day between the groups.

Discussion

This triple-blind, randomized, placebo-controlled trial aimed to evaluate the effect of TSC on CIN in elective PCI patients. Due to TSC's short half-life (15 minutes) and CIN potential duration of up to 5 days, along with the impracticality of hospitalizing patients for daily TSC injections, the study used TSC injection with oral crocetin, a quick-absorbing natural supplement with a half-life of 7.5 hr. Although crocetin and TSC both possess antioxidant qualities, TSC's specific oxygen-enhancing mechanisms provide distinct benefits in hypoxic scenarios such as CIN (Shah et al. 2021). Conducting clinical and preclinical studies to compare

monotherapy and combination therapies appears to be a logical subsequent step.

The study found a 16.1% overall CIN incidence, with TSC reducing it to 7.7% during elective PCI versus 24.6% in placebo ($p = 0.009$). Administration of a single dose of IV TSC, following 5 days of crocetin oral tablet, was particularly effective for moderate Mehran score patients but had a limited impact on high-risk categories. TSC-crocetin administration lowered BUN and CRP, improved ACR, and maintained GFR and prevented an increase in PAB values, but SCr lacked consistency, questioning TSC-crocetin efficacy. However, it is unclear whether the effects noted in the trial are due to TSC, crocetin or a combination of both.

CIN causes are still insufficiently investigated despite increasing interventions with CM in diagnostic and therapeutic fields. Grasping the mechanism engaged in CIN is essential for enhancing patient outcomes. CM administration affects kidney tissues via direct, indirect, and oxidative stress pathways (McCullough 2008). Altering renal blood flow through indirect mechanisms and excess mitochondrial ROS during ischemia and hypoxia contribute significantly to CM nephrotoxicity (Caiazza et al. 2014; Heyman et al. 1991). This excess causes lipid peroxidation in cell and mitochondrial membranes, mitochondrial DNA damage, pyroptosis, and apoptosis (Pisani et al. 2013).

Several compounds have been used to investigate their protective effects against CIN. Sodium Glucose cotransporter 2 (SGLT-2) inhibitors reduce oxidative stress pathways associated with CIN (Huang et al. 2022). Additionally, statins offer protection through anti-inflammatory, vasodilatory, and anti-apoptotic mechanisms (Al-Otaibi et al. 2012; Cho et al. 2020; Deng et al. 2015; Khan et al. 2019). N-acetylcysteine (NAC) shows strong antioxidant effects against CIN, but its role in preventing CIN remains unclear (de Laforcade et al. 2021). This could be a result of multiple mechanisms involved in CIN. Evaluating TSC effects on antioxidant activity and CIN incidence in PCI patients is crucial due to oxidative stress involvement.

Crocetin, a component extracted from saffron, benefits during hypoxia and oxidative inflammation (Rameshrad et al. 2018) and enhances oxygen diffusion in plasma by 25-30%, improving oxygen release from hemoglobin to tissues in rat models of acute lung injury (Shah et al. 2021).

Researchers reported TSC protective effects against nephrotoxicity from colistin and amidotrizoate, highlighting its antioxidant and anti-inflammatory properties (Naraki et al., 2024; Rajabian et al., 2024).

A trial involving 59 glioblastoma multiforme patients demonstrates TSC as a safe and effective way to combat tumor hypoxia (Gainer et al. 2017). Additionally, healthy volunteers receiving TSC experienced improved peripheral tissue oxygenation (Kankam et al. 2022). Research on COVID-19 patients showed that TSC enhances oxygen levels and is safe (Streinu-Cercel et al. 2021). Moreover, TSC improved walking distances in intermittent claudication (Mohler III et al. 2011).

This study indicates that TSC can promote antioxidant effects via the PAB assay. The lack of significant urinary findings, aside from the ACR ratio, may result from short-term fluctuations in urinary parameters, necessitating long-term evaluation for accurate assessment. Additionally, SCr, commonly used as a biomarker, is significantly altered by muscle mass, potentially leading to inaccurate estimated glomerular filtration rates in certain conditions (Delanaye et al. 2008). Moreover, the delayed response of rising in SCr limits early detection and intervention in CIN. SCr lacks sensitivity for early or subtle renal injury, as it reflects GFR changes only after significant renal damage has occurred (Gleeson et al. 2004, Goldfarb et al. 2009). Also, in patients with

preexisting renal impairment, tubular secretion of creatinine can overestimate GFR by up to 40% in at-risk patients, particularly those with chronic kidney disease (Goldfarb et al. 2009, López et al. 2021). This inconsistency leads to heterogeneity in the reported incidence rate of CIN based on SCr.

To enhance renal function assessment during CM administration, biomarkers like Neutrophil gelatinase-associated lipocalin (NGAL), Kidney injury molecule-1 (KIM-1), and serum cystatin C could be monitored for tubular dysfunction detection, especially in at-risk patients; GFR estimates are unreliable in cachexia cases (Filler and Lee 2018). Moreover, equations based on creatinine levels might overestimate GFR in people with a BMI over 30 kg/m2 because of different body composition (Sriperumbuduri et al. 2019).

Our study indicated no significant differences in urinary analysis five days post-PCI, except for the urinary ACR. As renal tubules are especially impacted by CM, assessing tubular dysfunction biomarkers in monitoring is advised, as contrast agents mainly harm tubules through inflammation and reactive oxygen species.

Our study has limitations, including the exclusion of eligible patients not previously on ACE inhibitors, Angiotensin II receptor blockers (ARBs) or statins, affecting generalizability. The small sample size, conducting the study in a single center as a limiting factor of generalizability, short follow-up period and absence of measurement of more specific biomarkers may influence results, highlighting confounding baseline characteristics.

Nonetheless, findings suggest that TSC might reduce CIN in PCI patients, necessitating further Phase III trials to investigate long-term effects and efficacy in a larger population to prevent overstating results.

The study highlights intravenous TSC and oral crocetin's protective role against CIN in PCI patients. Additionally, it helps prevent increases in BUN, CRP, and PAB assay values, while also mitigating the decline in GFR. The mechanism of action for TSC is attributed to its antioxidant properties, which reduce oxidative stress and the production of reactive ROS typically heightened by contrast media. By enhancing oxygen diffusion and minimizing cellular damage, TSC may help prevent renal tubular obstruction and apoptosis, thereby preserving kidney function during procedures associated with CIN risk. The observed safety profile further supports its consideration as a viable option for patients susceptible to CIN.

These findings suggest that TSC could be a promising therapeutic option in clinical practice, especially given the limited treatments currently available for CIN. However, further research with more specific arms of study to examine the effect of crocetin and TSC separately, as well as a longer follow-up period, is needed to validate these results and to clarify the full extent of crocetin-TSC mechanisms and benefits in Phase III and multi-center trials.

Acknowledgment

The authors are grateful to the Vice Chancellor of Research at Mashhad University of Medical Sciences in Mashhad, Iran (Grant No:991939), for financial help. This article contains information from a PhD thesis.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Funding

This work was supported by the Pharmaceutical Research Center and the Vice-Chancellor of Research at Mashhad University of Medical Sciences (Grant No: 991939).

Ethical Considerations

All procedures in this study were conducted by the Mashhad University of Medical Sciences ethical committee

(IR.MUMS.REC.1400.308). Informed consent was obtained from all individual participants included in the study.

Code of Ethics

IR.MUMS.REC.1400.308

Authors' Contributions

AmirHooshang Mohammadpour and Hossein Hosseinzadeh contributed to the study's conception and design. Sofia Salari did the patient selection, follow-up, and data collection. AmirHooshang Mohammadpour, Arash Gholoobi, Javad Ramezani, and Ali Eshraghi cooperated in the patient selection of the project. Vahid Ghavami performed statistical analysis. The first draft of the manuscript was written by Sofia Salari. AmirHooshang Mohammadpour and Hossein Hosseinzadeh revised the manuscript. The final manuscript was reviewed and approved by all authors.

During the preparation of this work, the author(s) used AI-assisted technologies to rephrase to reduce plagiarism and improve language and grammar. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

References

Alamdari, D. H., Ghayour-Mobarhan, M., Tavallaie, S, et al. (2008) Prooxidant–antioxidant balance as a new risk factor in patients with angiographically defined coronary artery disease. Clin Biochem 41(6): 375-380.

Al-Otaibi KE, Al Elaiwi AM, Tariq M, Al-Asmari AK (2012) Simvastatin attenuates contrast-induced nephropathy through modulation of oxidative stress, proinflammatory myeloperoxidase, and nitric oxide. Oxid Med Cell Longev 2012(1):831748

Caiazza A, Russo L, Sabbatini M, Russo D (2014) Hemodynamic and tubular changes induced by contrast media. Biomed Res Int 2014(1):578974

Cho A, Lee Y-K, Sohn SY (2020) Beneficial effect of statin on preventing contrast-induced acute kidney injury in patients with renal insufficiency: a meta-analysis. J Med 99(10):e19473

De Laforcade L, Bobot M, Bellin M-F, et al. (2021) Kidney and contrast media: Common viewpoint of the French Nephrology societies (SFNDT, FIRN, CJN) and the French Radiological Society (SFR) following ESUR guidelines. Diagn Interv Imaging 102(3):131-139

Delanaye P, Cavalier E, Radermecker RP, et al. (2008) Cystatin C or creatinine for detection of stage 3 chronic kidney disease in anorexia nervosa. Nephron Clin Pract 110(3):c158-c163

Deng J, Wu G, Yang C, Li Y, Jing Q, Han Y (2015) Rosuvastatin attenuates contrast-induced nephropathy through modulation of nitric oxide, inflammatory responses, oxidative stress and apoptosis in diabetic male rats. J Transl Med 13(1):53

Filler G, Lee M (2018) Educational review: measurement of GFR in special populations. Pediatr Nephrol 33:2037-2046

Gainer, Stennett A, Murray R (2005) The effect of trans sodium crocetinate (TSC) in a rat oleic acid model of acute lung injury. Pulm Pharmacol Ther 18(3):213-216

Gainer JL, Sheehan JP, Larner JM, Jones DR (2017) Trans sodium crocetinate with temozolomide and radiation therapy for glioblastoma multiforme. J Neurosurg 126(2):460-466

Gleeson, T. G., & Bulugahapitiya, S. (2004). Contrast-induced nephropathy. AJR 183(6): 1673-1689.

Goldfarb, S., McCullough, P. A., McDermott, J., & Gay, S. B. (2009). Contrast-induced acute kidney injury: specialty-specific protocols for interventional radiology, diagnostic computed tomography radiology, and interventional cardiology. Mayo Clin Proc 84(2):170-179.

Heyman SN, Brezis M, Epstein FH, Spokes K, Silva P, Rosen S (1991) Early renal medullary hypoxic injury from radiocontrast and indomethacin. Kidney Int 40(4):632-642

Huang X, Guo X, Yan G, et al. (2022) Dapagliflozin attenuates contrast-induced acute kidney injury by regulating the HIF-1α/HE4/NF-κB pathway. J Cardiovasc Pharmacol 79(6):904-913

Kankam M, Handley S, Galloway C, Clarke D (2022) Evaluation of Trans-Sodium Crocetinate (TSC) on Peripheral Oxygenation in Healthy Individuals Using Transcutaneous Oximetry. medRxiv:2022.01. 16.22269147

Khan SU, Khan MU, Rahman H, et al. (2019) A bayesian network meta-analysis of preventive strategies for contrast-induced nephropathy after cardiac catheterization. Cardiovasc Revasc Med 20(1):29-37

Khwaja A (2012) KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 120(4):c179-c184

Li, Y., & Wang, J. 2024. Contrast-induced acute kidney injury: a review of definition, pathogenesis, risk factors, prevention and treatment. BMC Nephrol 25(1): 140.

López, A. B., Martínez, F. G., Rodríguez, J. I., Montero-San-Martín, B., Rioja, R. G., Diez, J., & Martín-Hervás, C. (2021). Incidence of contrast-induced nephropathy after a computed tomography scan. Radiología 63(4): 307-313

McCullough PA (2008) Contrast-induced acute kidney injury. J Am Coll Cardiol 51(15):1419-1428

Mehran R, Owen R, Chiarito M, et al. (2021) A contemporary simple risk score for prediction of contrast-associated acute kidney injury after percutaneous coronary intervention: derivation and validation from an observational registry. The Lancet 398(10315):1974-1983

Mohler III ER, Gainer JL, Whitten K, Eraso LH, Thanaporn PK, Bauer T (2011) Evaluation of trans sodium crocetinate on safety and exercise performance in patients with peripheral artery disease and intermittent claudication. Vasc Med 16(5):346-353

Naraki, K., Ghasemzadeh Rahbardar, M., Razavi, B. M., Aminifar, T., Khajavi Rad, A., Amoueian, S., & Hosseinzadeh, H. 2024. The power of trans-sodium crocetinate: exploring its renoprotective effects in a rat model of colistin-induced nephrotoxicity. Naunyn Schmiedebergs Arch Pharmacol 397: 10155–10174.

Pisani A, Riccio E, Andreucci M, et al. (2013) Role of reactive oxygen species in pathogenesis of radiocontrast-induced nephropathy. Biomed Res Int 2013(1):868321

Rajabian F, Mehri S, Razavi BM, Rad AK, Rahbardar MG, Hosseinzadeh H (2023) Effect of trans-sodium crocetinate on contrast-induced cytotoxicity in HEK-293 cells. Iran J Basic Med Sci 26(2):148

Rajabian F, Razavi BM, Mehri S, et al. (2024) Evaluation of pathways involved in the protective effect of trans sodium crocetinate against contrast-induced nephropathy in rats. Naunyn Schmiedebergs Arch Pharmacol 398(5):5373-5387.

Rameshrad M, Razavi BM, Hosseinzadeh H (2018) Saffron and its derivatives, crocin, crocetin and safranal: a patent review. Expert Opin Ther Pat 28(2):147-165

Shah, H. M., Jain, A. S., Joshi, S. V., & Kharkar, P. S. (2021). Crocetin and related oxygen diffusion-enhancing compounds: Review of chemical synthesis, pharmacology, clinical development, and novel therapeutic applications. Drug Dev Res 82(7): 883-895.

Sriperumbuduri S, Dent R, Malcolm J, et al. (2019) Accurate GFR in obesity—protocol for a systematic review. Syst Rev, 8(1):147

Streinu-Cercel A, Săndulescu O, Miron VD, et al. (2021) Trans sodium crocetinate (TSC) to improve oxygenation in COVID-19. medRxiv:2021.10. 08.21264719

Van der Molen AJ, Reimer P, Dekkers IA, et al. (2018) Post-contrast acute kidney injury. Part 2: risk stratification, role of hydration and other prophylactic measures, patients taking metformin and chronic dialysis patients: Recommendations for updated ESUR Contrast Medium Safety Committee guidelines. Eur Radiol 28:2856-2869

Zhang F, Lu Z, Wang F (2020) Advances in the pathogenesis and prevention of contrast-induced nephropathy. Life Sci 259:118379