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Original Article

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The Effects of Pentoxifylline on Contrast-Induced Nephropathy Reduction in Patients Undergoing Percutaneous Coronary Intervention

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ABSTRACT

Objective: Contrast-induced nephropathy is one of the most common adverse consequences of contrast media use. The purpose of this study was to investigate the efficacy of pentoxifylline to prevent contrast-induced nephropathy in patients undergoing percutaneous coronary intervention.
Methods: This prospective, single-blind, quasi-experimental study was performed on 68 patients with ST-elevation myocardial infarction who were admitted for percutaneous coronary intervention at Imam Ali Hospital, affiliated with Kermanshah university of medical science (KUMS), Kermanshah province, Iran. Patients were assigned randomly to the control (n = 34) and pentoxifylline (n = 34) groups. Normal saline 0.9% at 0.5-1 mL/kg/h was prescribed from 12 hours before to 12 hours after angioplasty. Pentoxifylline was prescribed at a dose of 400 mg 3 times per day from 24 hours before to 48 hours after angioplasty. Serum creatinine level was measured for both groups at the time of referral and after 72 hours of angioplasty. Independent samples *t*-tests, chi-square test, and Fisher's exact test were used to assess the differences between groups.
Results: No significant difference was found between the 2 groups regarding demographic and baseline clinical characteristics. The mean serum creatinine level (time of referral) was 1.52 ± 0.11 mg/dL and 1.55 ± 0.14 mg/dL in pentoxifylline and control groups, respectively (P = .999). Seventy-two hours after angiography, the mean serum creatinine level was 1.54 ± 0.13 mg/dL and 1.56 ± 0.17 mg/dL in pentoxifylline and control groups, respectively (P = .999). We found that contrast-induced nephropathy occurred in 7 patients (10.3%); 4 controls (11.8%), and 3 patients (8.8%) in the pentoxifylline group, which was not significantly different between the 2 groups (P = .690).
Conclusion: The findings of the current study showed that oral administration of pentoxifylline to patients at higher risk for developing contrast-induced nephropathy undergoing coronary angioplasty may decrease the occurrence of contrast-induced nephropathy, but this decrease is not statistically significant.
Keywords: angioplasty, CIN, contrast, nephropathy, PCI, Pentoxifylline

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INTRODUCTION

Cardiovascular diseases (CVDs) are the most common cause of death and disability across the world. Despite rapid diagnostic and therapeutic advances, one-third of patients with myocardial infarction still die, and two-thirds of those who survive are never fully recovered and do not return to normal life. Moreover, CVDs impose a huge cost on the health systems; however, it is one of the most preventable noncommunicable diseases.[1] The prevalence of coronary artery disease (CAD) has significantly increased due to lifestyle changes, such as reduced physical activity and increased calorie intake.[2] Coronary artery disease is a chronic process that begins from young age and progresses gradually. Main risk factors for CAD include family history, smoking, diabetes, hypertension, high blood lipids, sedentary lifestyle, aging, gender, and obesity.[3]

Percutaneous coronary intervention (PCI) is one of the treatment procedures for CAD patients. Nowadays, this procedure is widely used to treat CAD.[4] Percutaneous coronary intervention refers to all coronary interventions performed by catheterization under fluoroscopic guidance that increase the diameter of the coronary artery and its blood flow (such as balloon angioplasty or stenting).[5] After elective PCI, an increase in the level of kidney markers is observed, even when the procedure is uncomplicated. Studies have indicated that increasing the level of heart markers is associated with an increased risk of cardiac events, such as death at the follow-up stage.[6,7]

Furthermore, contrast-induced nephropathy (CIN) is one of the most common preventable causes of acute kidney injury (AKI).[8] Acute kidney injury increases the mortality rate in affected patients.[9] Acute kidney injury caused by contrast media is an important issue in patients with CADs, and CVD risk factors make these patients more susceptible to AKI caused by the contrast media. Coronary angiography and PCI are the most common cardiac interventions worldwide. With the increase in PCI procedures, the incidence of CIN has also been increased.[10] Contrast-induced nephropathy is usually defined as a 25% increase or more in serum creatinine level compared to the basal level or an absolute increase of 0.5 mg/dL or more in serum creatinine level compared to the baseline, within 48 hours after the contrast injection.[9] The incidence of CIN in patients undergoing PCI varies from 2% to more than 50%.[11] Its incidence was 13% in patients without diabetes and 20% in patients with diabetes after PCI.[12] About 1% of patients with CIN require dialysis.[11,13,14] The pathophysiological mechanism of CIN is believed to be related to the changes in kidney circulatory status, damages on tubular cells caused by free radicals, or the direct toxic effect of the contrast agents.[15,16] The presence of chronic kidney disease, diabetes mellitus, congestive heart failure, male sex, advanced age, anemia, and volume and type of contrast media may increase the chance of CIN by 50%.[17]

Pentoxifylline (PTX), a derivative of methyl xanthine, is a vasodilator.[16] It is effective in reducing proteinuria of diabetic nephropathy by inhibiting tumor necrosis factor alpha (TNF-α),[18,19] which can slow the process of diabetic nephropathy.[20] Pentoxifylline is commonly used to treat peripheral vascular diseases due to its anti-inflammatory properties. Pentoxifylline decreases the deterioration of nitric oxide and the inhibition of free radicals. Since oxidative stress is a major contributor to CIN, considering the anti-inflammatory and antioxidant effects of PTX, we hypothesized that its usage before contrast media use may be effective in preventing CIN. The potential beneficial effects of PTX in preventing CIN are not fully shown in previous studies, especially in patients undergoing PCI. The purpose of this study was to investigate the efficacy of PTX to prevent CIN in patients undergoing PCI.

MAIN POINTS

- Short-term prophylaxis with PTX does not seem to prevent CIN in patients at higher risk for developing CIN who undergo PCI.
- We suggest conducting a future study with a larger sample size of patients and investigating the possible short- and long-term usage of PTX, which would help to better understand the effect of supplementing PTX to routine CIN preventive measures.

METHODS

Patient Population and Design

This was a prospective, single-blind, quasi-experimental study that was conducted at Imam Ali Cardiovascular Hospital affiliated with Kermanshah university of medical science (KUMS), Kermanshah province, Iran. Imam Ali Cardiovascular Hospital is the main cardiovascular center in the west of Iran. Imam Ali Cardiovascular Hospital serves about 2 million patients (inpatients and outpatients) annually and provides advanced cardiovascular services.

Patients with ST-elevation myocardial infarction (STEMI) who were admitted for PCI at Imam Ali Hospital, between June 20, 2018, and October 20, 2018, were included in this study. Based on coronary angiography (CAG) reports, these elective cases were recommended for PCI. Also, all procedures were performed by a single interventional cardiologist. Inclusion criteria were adult (above 18 years old) patients with STEMI who had serum creatinine more than 1.4 mg/dL (high-risk population). Patients were excluded from the study if they had a history of heart failure, severe kidney failure [estimated glomerular filtration rate (GFR) less than 30 mL/min], undergoing dialysis, contrast media usage in the previous 14 days, pulmonary edema, multiple myeloma, uncontrolled hypertension, or sensitivity to PTX, or if they were using nonsteroidal anti-inflammatory medicines (NSAIDs) or nephrotoxic drugs, pregnant, or breastfeeding. Actually, all patients had a serum creatinine of more than 1.4 mg/dL, such that they were at the initial phase of stage 1 CKD (kidney damage with normal kidney function). Patients who used renin–angiotensin–system blocker and sodium–glucose-linked cotransporter inhibitors stopped these drugs before PCI. During PCI, their blood pressure was controlled. No complication was observed during PCI. Contrast volume administered ranged from 100 to 200 cc, with a mean of 136.00 ± 56.67. We did not check the urine output and proteinuria.

In view of a previous study on the risk of CIN,[21] we calculated the sample size of the study as 34 in each group, considering a confidence level of 95%.

$$n = \frac{\left(z_{\alpha/2}\sqrt{2\bar{p}\bar{q}} + z_{\beta}\sqrt{p_1q_1 + p_2q_2}\right)^2}{\left(p_1 - p_2\right)^2} \simeq 34$$

Study Protocol

Sixty-eight eligible patients were included in this study and assigned to 1 of the 2 groups by a computer-generated randomization program, and assignments were placed in opaque envelopes. After opening the envelopes, patients were assigned to one of the medication or control groups. Patients were allocated randomly to the control (n = 34) and PTX groups (n = 34).

In the current study, no placebo was prescribed for the control group. Routine preparation for PCI, including hydration with normal saline before and after the angioplasty, was prescribed for both groups before and after angioplasty. Normal saline 0.9% at 0.5-1 mL/kg/h was prescribed from 12 hours before to 12 hours after angioplasty. Pentoxifylline was prescribed at a dose of 400 mg 3 times per day from 24 hours before to 48 hours after angioplasty. All patients received the same contrast media, Visipaque (iso-osmolar nonionic contrast media iodixanol) 320 manufactured by GE Healthcare (Cork, Ireland).

Medications with known nephrotoxic effects, including metformin and NSAIDs, were stopped from 24 hours before to 72 hours after angioplasty. Serum creatinine level and GFR were measured for both groups at the time of referral and after 72 hours of angioplasty. The present study was single blind, so laboratory staffs who measured the serum creatinine were blinded to the treatment condition of the patients.

End Points

Our primary end point was a 25% increase or more in serum creatinine from baseline levels or an absolute increase of 0.5 mg/dL or more in serum creatinine compared to baseline, within 72 hours after exposure to contrast media.

Instrument and Data Collection

Data were collected by a physician. A valid checklist was used for data gathering. The checklist was developed and verified by expert opinions comprising 2 cardiologists and 1 statistician. The collected data included demographic characteristics (e.g., age), clinical history (e.g., diabetes mellitus), and serum creatinine level at the time of referral and after 72 hours of angioplasty.

Statistical Methods

Data analysis was performed using the Statistical Package for the Social Sciences version 21.0. (IBM SPSS Corp.; Armonk, NY, USA). Quantitative variables (e.g., age) were described using mean (SD) and categorical variables were expressed as frequencies (percentages). Quantitative data were evaluated if normally distributed in each group using the Kolmogorov–Smirnov test. Differences between groups were assessed using independent *t*-tests for continuous and normally distributed variables and chi-square or Fisher's exact tests for categorical variables. We assessed the association between CIN and diabetes mellitus using multivariable logistic regression models. Odds ratios (ORs) and 95% CIs were calculated. A *P*-value <.05 was considered statistically significant.

Table 1. Baseline Clinical Characteristics of Enrolled Patients

Characteristic	Control Group (*n* = 34)	PTX Group (*n* = 34)	*P*
Age, years	60.88 ± 9.76	59.97 ± 9.96	.704*
BMI, kg/m^2	25.35 ± 4.41	26.58 ± 5.11	.292*
Male	20 (58.8)	21 (61.8)	.804**
Diabetes mellitus	7 (20.6)	6 (17.6)	.757***
Hypertension	4 (11.8)	6 (17.6)	.493**
History of smoking	4 (11.8)	2 (5.9)	.392**
Hypercholesterolemia	10 (29.4)	9 (26.5)	.787**
Hb (mg/dL)	13.69 ± 1.92	12.99 ± 1.86	.131*
FBS (mg/dL)	120.59 ± 21.93	125.45 ± 28.36	.432*
LDL (mg/dL)	95.23 ± 19.41	97.65 ± 21.78	.630*
HDL (mg/dL)	36.12 ± 6.98	37.41 ± 9.02	.512*
TG (mg/dL)	125.98 ± 40.78	129.11 ± 41.19	.753*
CK-MB (units/L)	19.25 ± 3.44	19.40 ± 4.15	.871*
BUN (mg/dL)	40.48 ± 15.45	41.54 ± 18.48	.798*
Troponin I (ng/mL)	0.80 ± 0.21	0.75 ± 0.13	.999*
EF (%)	48.15 ± 19.78	47.48 ± 19.14	.887
ESR (mm/h)	18.71 ± 6.14	17.69 ± 6.66	.513*
Aspirin user	20 (58.8)	20 (58.8)	1**
ACE inhibitor users	13 (38.2)	11 (32.3)	.611**
ARB users	21 (61.8)	20 (58.8)	.804**
Beta-blocker user	8 (23.5)	9 (26.5)	.780**
Statin users	23 (67.6)	22 (64.7)	.797**

n, number; BMI, body mass index; Hb, hemoglobin; FBS, fast blood sugar; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; CK-MB, creatine kinase myocardial band; BUN, blood urea nitrogen; EF, ejection fraction; ESR, erythrocyte sedimentation rate; ARB, angiotensin receptor blockers; ACE, angiotensin-converting enzyme.
Continuous variables are expressed as mean ± SD, otherwise *n* (%).
**t*-Test; **chi-square test; ***Fisher's exact test.

Ethics

The Research Ethics Committee of the Deputy of Research, Kermanshah university of medical science (KUMS) approved the study protocol in January 2018 (Ethics No. IR. KUMS.1396.578). Further, the participants were given a participant information statement and signed a written consent form. Individual personal information was kept confidential.

RESULTS

In this study, we enrolled a total of 68 patients (41 men and 27 women); 34 patients received PTX and 34 were in the control group. The demographic characteristics and some para-clinical data are shown in Table 1. No significant differences were found between the 2 groups regarding demographic and baseline clinical characteristics.

Table 2. Level of Serum Creatinine in Referral Time, after 72 Hours of Angioplasty, and Changes (Δ) in the PTX Supplementation and Control Groups

Characteristic	Control Group (*n* = 34)	PTX Group (*n* = 34)	*P*
Cr (mg/dL) (referral time)	1.55 ± 0.14	1.52 ± 0.11	.999*
Cr (mg/dL) (72 hours after angioplasty)	1.56 ± 0.17	1.54 ± 0.13	.999*
ΔCr (mg/dL)	0.01 ± 0.08	0.02 ± 0.11	.999*
GFR (ml/min) (referral time)	69.19 ± 23.25	69.25 ± 24.29	.999*
GFR (ml/min) (72 hours after angioplasty)	67.89 ± 19.29	68.19 ± 19.46	.163*
The incidence of CIN	4 (11.8)	3 (8.8)	.690**

Cr, creatinine; GFR, glomerular filtration rate; CIN, contrast-induced nephropathy. Continuous variables are expressed as mean ± SD, otherwise *n* (%).
**t*-Test; ***chi-square test.

The mean serum creatinine level (time of referral) was 1.52 ± 0.11 mg/dL and 1.55 ± 0.14 mg/dL in PTX and control groups, respectively (*P* = .999). Seventy-two hours after PCI, the mean serum creatinine level was 1.54 ± 0.13 mg/dL and 1.56 ± 0.17 mg/dL in PTX and control groups, respectively (*P* = .999). The changes in mean serum creatinine levels before and after PCI were not significantly different between the 2 groups (*P* = .999). Mean GFR (time of referral) was 69.25 ± 24.29 (ml/min) and 69.19 ± 23.25 (ml/min) in PTX and control groups, respectively (*P* = .999). Seventy-two hours after PCI, the mean GFR was 68.19 ± 19.46 (ml/min) and 67.89 ± 19.29 (ml/min) in PTX and control groups, respectively (*P* = .163). Contrast-induced nephropathy occurred in 7 patients (10.3%) – 4 controls (11.8%) and 3 patients (8.8%) in the PTX group –which was not significantly different between the 2 groups (*P* = .690) (Table 2). Moreover, no complications due to PTX usage were reported. We did not see any patient who died or suffered from severe kidney injury needing dialysis.

Table 3 provides the results of the ORs and 95% CI of CIN according to diabetes mellitus. After adjusting model 1, model 2, and model 3, diabetes mellitus had no effect on the increased OR of CIN in both groups.

DISCUSSION

For many years, PTX, as a methyl xanthine-derivative drug, has been used for the treatment of peripheral vascular disease. Also, PTX, as a strong suppressor of TNF-α secretion, has been used for human and animal inflammatory diseases.[22] Moreover, Yang et al[23] indicated that PTX could effectively decrease kidney injury induced by contrast media in hypercholesterolemic rats. Groesdonk et al[24] showed that PTX could reduce the kidney injury induced by *Escherichia coli* in a model of isolated perfused rat kidney. Furthermore, 3 studies have specifically illustrated the protective effects of PTX in preventing gentamicin nephrotoxicity in animal models.[25-27] The aim of this study was to evaluate the efficacy of PTX in reducing CIN in patients undergoing PCI at Imam Ali Hospital affiliated with KUMS. Pentoxifylline was prescribed at a dose of 400 mg 3 times per day from 24 hours before to 48 hours after angioplasty for a group of patients, and the outcomes were compared with the control group. Serum creatinine level was measured at the time of referral and after 72 hours of angioplasty. Our patients' demographic and baseline clinical characteristics were similar in the 2 groups. Although CIN incidence was less in the group with prophylactic oral PTX (8.8% vs. 11.8), this difference was not significantly significant (*P* = .690). In the present study, we did not find that PTX can significantly reduce the incidence of CIN in a high-risk group of patients who underwent coronary angioplasty.

Our findings are in accordance with some previous studies. Of note, all studies have measured serum creatinine as the biomarker of kidney injury. Similarly, Firouzi et al[28] in 2012 found that PTX could decrease, though not significantly, the incidence of CIN in patients undergoing PCI. Yavari et al[14] in 2014 found that short-term prophylaxis with PTX does not seem to reduce CIN in patients undergoing PCI. However, PTX may decrease long-term mortality, which was not included in our study design. It is probable that long-term prophylaxis with PTX is successful in preventing CIN. For example, an animal study performed by Han et al[29] reported that the anti-inflammatory effects of PTX were revealed after 4 weeks of taking the drug. Roozbeh et al[30] in 2010 and Badri et al[31] in 2011 demonstrated that PTX could significantly decrease proteinuria in patients with diabetes. It may be assumed that PTX is more effective in this subset of patients.

Table 3. The Univariate and Multiple Logistic Regression for Evaluation of Association Between CIN and Diabetes Mellitus by Adjusted Important Predictors

	Control Group				PTX Group			
Variables	Crude, OR (95% CI)	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)	Crude, OR (95% CI)	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Diabetes mellitus	1.12 (0.92, 1.49)	1.15 (0.95, 1.66)	1.18 (0.96, 1.72)	1.24 (0.93, 1.65)	1.10 (0.86, 1.32)	1.09 (0.84, 1.44)	1.04 (0.79, 1.32)	1.14 (0.87, 1.57)

Model 1, adjusted by sex, age, BMI, history of smoking, and hypercholesterolemia; Model 2, model 1 + adjusted by Hb, FBS, LDL, HDL, TG, CK-MB, BUN, troponin I, EF, ESR, aspirin users, ACE inhibitor users, ARB users, beta-blocker users, and statin users; Model 3, model 1 + model 2 + adjusted by hypertension.
PTX, pentoxifylline; OR, odds ratio; BMI, body mass index; Hb, hemoglobin; FBS, fast blood sugar; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; CK-MB, creatine kinase myocardial band; BUN, blood urea nitrogen; EF, ejection fraction; ESR, erythrocyte sedimentation rate; ARB, angiotensin receptor blockers; ACE, angiotensin-converting enzyme.

Some previous studies excluded patients with a creatinine level of more than 1.5 mg/dL (i.e., patients at higher risk for developing CIN), so the low incidence of CIN in their studies was predictable. A systematic review by Busch et al[11] in 2013 indicated that the incidence of CIN is significantly lower in low- to moderate-risk patients after PCI. Eshraghi et al[12] in 2016 evaluated the effectiveness of PTX in preventing CIN following PCI, but they excluded patients with a creatinine level of more than 1.5 mg/dL; so they reported a low incidence of CIN in both groups. On the other hand, we only enrolled patients with a creatinine level of more than 1.4 mg/dL. However, we observed that the incidence of CIN was also low in these patients who were at higher risk for developing CIN. In the current study, the incidence of CIN in patients at higher risk for developing CIN was almost similar to studies that enrolled low- to moderate-risk patients. The lower incidence of CIN in our study may be because we control the urine output and provide adequate hydration before and after PCI as the standard practice in our hospital. Among the prophylactic strategies for CIN, hydration is one of the best proven ways to reduce nephropathy.[32]

Furthermore, we found the incidence of CIN was 8.8% and 11.8% for the PTX and control groups, respectively. These were reported to be 6.6% and 9.5% for the PTX and control groups, respectively, in the study by Eshraghi et al[12] in 2016. Firouzi et al[28] in 2011 reported that the incidence of CIN was 8.5% and 13.6% for the PTX and control groups, respectively. Barzi et al[33] in 2019 demonstrated that CIN occurred in 5.5% and 7.3% patients of PTX and control groups, respectively. Yavari et al[14] in 2014 reported that the overall incidence of CIN was 6.2% in the PTX group vs. 5.9% in the control group. Aslanabadi et al[34] in 2019 indicated that the incidence of CIN was 8.9% in the PTX group vs. 6.7% in the control group. The different incidence rate of CIN between studies may be due to the type and volume of contrast usage, the procedure which was performed (coronary angiography or angioplasty), the patients' baseline characteristics and the clinical profile (e.g., creatinine level at the time of referral), and other routine measures to prevent CIN.

Limitation

One of the limitations of our study was using serum creatinine level to diagnose CIN. Based on the previous studies, an absolute increase in serum creatinine is a good criterion for the distinction of CIN.[35,36] Serum creatinine raises slowly, and it takes at least 72 hours to indicate nephropathy; however, using other biomarkers of kidney function such as cystatin C, which increase more rapidly in AKI, are better to detect nephropathy and allow a more precise estimate of CIN.[37] As it was a single-center study, the generalizability of our results may have been decreased. The present study has other limitations, including that it was not a double-blind, placebo-controlled trial. Additionally, all patients were hydrated according to the hospital routine protocol for a PCI procedure, but the exact amount of fluid prescribed and the patient's urine output after the PCI were not evaluated; therefore, the association between patient's hydration and CIN incidence cannot be rejected.

CONCLUSION

The findings of the current study showed that short-term prophylaxis with PTX does not seem to prevent CIN in patients at higher risk for developing CIN who undergo PCI. We suggest conducting a future study with a larger sample size of patients and investigate the possible short- and long-term usage of PTX, which would help to better understand the effect of supplementing PTX to routine CIN preventive measures. Moreover, adding PTX to *N*-acetylcysteine and their synergistic effects in reducing CIN should also be evaluated. Likewise, we suggest conducting a future study that evaluates the effect of PTX on CIN by measuring cystatin C levels instead of serum creatinine.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Kermanshah university of medical science (KUMS) University, (Date: January 2018 Decision No: 1396.578).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer reviewed.

Author Contributions: Concept – M.R.; Design – M.R.; Supervision – M.R.; Materials – R.H.M.; Data Collection and/or Processing – T.R.; Analysis and/or Interpretation – N.S.; Literature Review – N.M.; Writing – M.S.; Critical Review – M.R., R.H.M., N.S., M.S., T.R., N.M.

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