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Pentoxifylline for the prevention of contrast-induced nephropathy in diabetic patients undergoing angioplasty: a randomized controlled trial

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Abstract

Objectives Contrast-induced nephropathy (CIN) is one of the most important complications of contrast media. We aimed to evaluate the preventive effects of pentoxifylline (PTX) on CIN in diabetic patients undergoing angioplasty using cystatin C.

Materials and methods The present study was a randomized clinical trial, which was investigated the impact of PTX in the prevention of CIN among 90 diabetic patients undergoing the angioplasty using cystatin C as a novel biomarker of renal injury. The patients randomly were allocated 1:1 into the intervention and the control groups. The intervention group received a total of 1200 mg PTX orally before the angioplasty. The serum level of cystatin C and creatinine was measured at baseline and 24 h after the procedure.

Results The incidence of CIN was 8.9% in the PTX group vs. 6.7% in the control group ($p=1.00$). The baseline level of cystatin C was 1.31 ± 0.39 mg/L in the PTX group and 1.24 ± 0.42 mg/L in the control group ($p=0.561$). After angioplasty, the level of cystatin C was increased to 1.33 ± 0.61 in PTX group and to 1.31 ± 0.47 in the control group but was not statistically significant. The similar pattern was also seen in the level of serum creatinine.

Conclusions The results of this study did not support the potential benefit of PTX in the prevention of CIN in diabetic patients undergoing angioplasty.

Keywords Angioplasty · Contrast-induced nephropathy (CIN) · Pentoxifylline · Diabetes

Introduction

Contrast-induced nephropathy (CIN) is one of the important complications of contrast media (CM), which causes hospital-acquired acute kidney injury (AKI) and results in morbidity and mortality [1, 2]. CIN is indicated by a progressive increase (> 25% increase in serum creatinine (SCr) from baseline or an absolute increase of > 0.5 mg/dL in SCr value) in SCr following 48–72 h administration of CM. The incidence of CIN was reported from 0.5 to 50% depending on the presence of the known risk factors [1, 2].

The major risk factors for CIN include chronic kidney disease (CKD), volume depletion, diabetes mellitus, congestive heart failure (CHF), and the large volume of contrast agent [1, 2]. The major mechanisms appear to be responsible for CIN including vasoconstriction, renal medulla hypoxia, cytotoxic damage to renal tubules by the production of oxygen free radicals, and transient obstruction of the renal tubules with the deposit of CM [1, 2].

Pentoxifylline (PTX), a methylxanthine derivative, is a non-selective phosphodiesterase inhibitor (PDEI) that shows the potential cardiovascular benefits [3, 4]. PTX principally inhibits phosphodiesterase (PDE) activity and therefore increases cyclic adenosine monophosphate (cAMP) level and in the periphery causes vasodilation. The increase in cAMP at the site of red blood cells (RBCs) membrane results in RBCs flexibility improves blood hemorheological properties and reduces blood viscosity. On the platelet membrane, cAMP inhibits platelet aggregation as well as platelet adhesion to the vessels walls [3–5].

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PTX shows the anti-inflammatory properties by reducing inflammatory cytokines levels such as TNF-α, IL-1, IL-6, and IL-8 [3, 4, 6]. In addition, PTX is a well-established antioxidant drug with an effective hydroxyl radical scavenger property [7–11]. In one study on the rat, PTX reduced oxidative renal tissue damage induced by streptozotocin [11]. Several studies also confirmed the protective role of PTX in ischemia–reperfusion injury [12–15].

Based on the evidence, cystatin C is a better biomarker for early detection of acute kidney injury and estimates better glomerular filtration rate (GFR) than the serum creatinine (SCr). SCr is produced from muscle cells, and several factors such as age, gender, race, weight, and drugs (steroids, cimetidine, and cotrimoxazole) affect its concentration, while cystatin C produces by the blood cells and is not significantly influenced by several factors such as age, sex, muscle mass, diet, and race [16, 17].

The purpose of this investigation was to evaluate the effect of PTX in the prevention of CIN in diabetic patients undergoing angioplasty. To the best of our knowledge, this is the first study that measures cystatin C as a biomarker of kidney damage for evaluation of the effect of PTX on the prevention of CIN.

Methods

Ethics

This study was approved by the ethics committee of the university then was registered in the WHO clinical trials registry platform with ID: IRCT201603038307N14. This investigation was done based on the Declaration of Helsinki that is a statement of ethical principles to provide guidance to physicians and other participants in medical researches involving human subjects [18].

All patients signed a consent form before entering the study.

Study design

This research is a prospective, randomized, single-blind, controlled trial that was performed at the Shahid Madani Heart Center, the largest hospital in the northwest of Iran for cardiovascular disorders, from 2016-06 to 2017-01 for a 6-month period.

Patients

The current study was performed on 90 diabetic patients with ischemic heart disease over 18 years old that were referred to the hospital for the angioplasty. The inclusion criteria of the study were all type 2 diabetics' patients ages between 18 and 80 years old undergoing the angioplasty and completing the consent form. The exclusion criteria were the patients with hepatic failure (Child-Pugh stage B and C), patients with renal impairment (SCr above 2.5 mg/dL, or GFR < 30 mL/min/1.73 m^2 or undergoing dialysis), pregnant and lactating women, uncontrolled autoimmune and inflammatory diseases, cancer, severe infection, use of nephrotoxic medications (such as non-steroidal anti-inflammatory drugs, aminoglycosides, etc.), contraindication for use of PTX and lack of consent to participate in the study.

Sample size calculation

Based on Rahman et al. study [19], the incidence of CIN in diabetic patients following the angioplasty was reported 36.8%. To reduce this risk to 10% (the incidence rate of CIN in non-diabetic patients with cardiovascular disease) with the power of 80% and alpha = 0.05 and 95% confidence interval 38 patients in each group will be needed to show a significant result.

Study protocols

The patients were allocated 1:1 into the PTX-treated group ($n = 45$) and the control group ($n = 45$) according to a systematic randomization computer-generated list by an independent medical staff who was not involved in the study. The intervention group received a 1200-mg dose of PTX orally (3 tablets, 400 mg) 2–4 h before the angioplasty based on the time to peak of PTX plus the standard treatment. In the control group, patients received the standard treatment included aspirin 325 mg and clopidogrel 300 mg orally plus weight-adjusted intravenous heparin with a target activated clotting time of 250–350 s. All patients in both groups received 150 ± 20 mL of the contrast medium iodixanol (visipaque™ 320, GE Healthcare, Cork, Ireland) during the angioplasty.

The prophylaxis protocol of contrast-induced nephropathy (CIN) was performed in both group, which included the infusion of 0.5–1 mL/kg/h normal saline 12 h before and after the angioplasty plus 154 meq/L sodium bicarbonate in dextrose 5% (3 mL/kg/h) before and after the angioplasty plus oral 600 mg *N*-acetyl cysteine twice daily before and after the procedure.

All angioplasty procedures were performed based on the standard method by the expert interventional cardiologists. All catheterization staffs were blinded to the study. In all patients, serum cystatin C and SCr levels were measured before and 24 h after the procedure. Patients' demographic information including age, sex, weight, body mass index, drug history, laboratory data, and positive family history of cardiovascular disease was recorded in a data collecting forms.

Blood sampling

The serum samples were prepared by centrifugation of the clotted blood samples. In order to estimate the incidence of CIN, the cystatin C and SCr levels were measured at baseline (before giving PTX) and 24 h after the angioplasty.

End-point outcome

The primary end-point of the study was the incidence of CIN, defined as an increase (> 25% or > 0.5 mg/dL) in cystatin C or serum creatinine 24 h after the contrast media infusion.

Statistical analysis

The statistical analysis was carried out in IBM, SPSS version 23.0 (SPSS, Inc. Chicago, IL, USA). The Kolmogorov–Smirnov test was checked to evaluate the normal distribution of data. In order to frequency analysis, the Chi-square test or the Fisher's exact test was implemented. The mean ± standard deviation (SD) was used for showing the continuous data. Continuous variables were compared between the two groups by using the independent *t* test. The paired sample *t* test was implemented to compare the means before and after the intervention in each group. A p value < 0.05 was considered significant.

Results

Demographic and clinical data

During the study period, 90 patients were allocated with 1:1 ratio to the intervention group ($n = 45$) and the control group ($n = 45$). Nine patients in the control group and 5 patients in the intervention group were excluded after follow-up. Finally, 76 patients (PTX group = 40, control group = 36) were entered the analysis (see Fig. 1). Demographic and clinical data for the PTX and the control groups are shown in Table 1. No significant difference was found between the two groups regarding age, sex, weight, ejection fraction, past medical and medication history, and smoking.

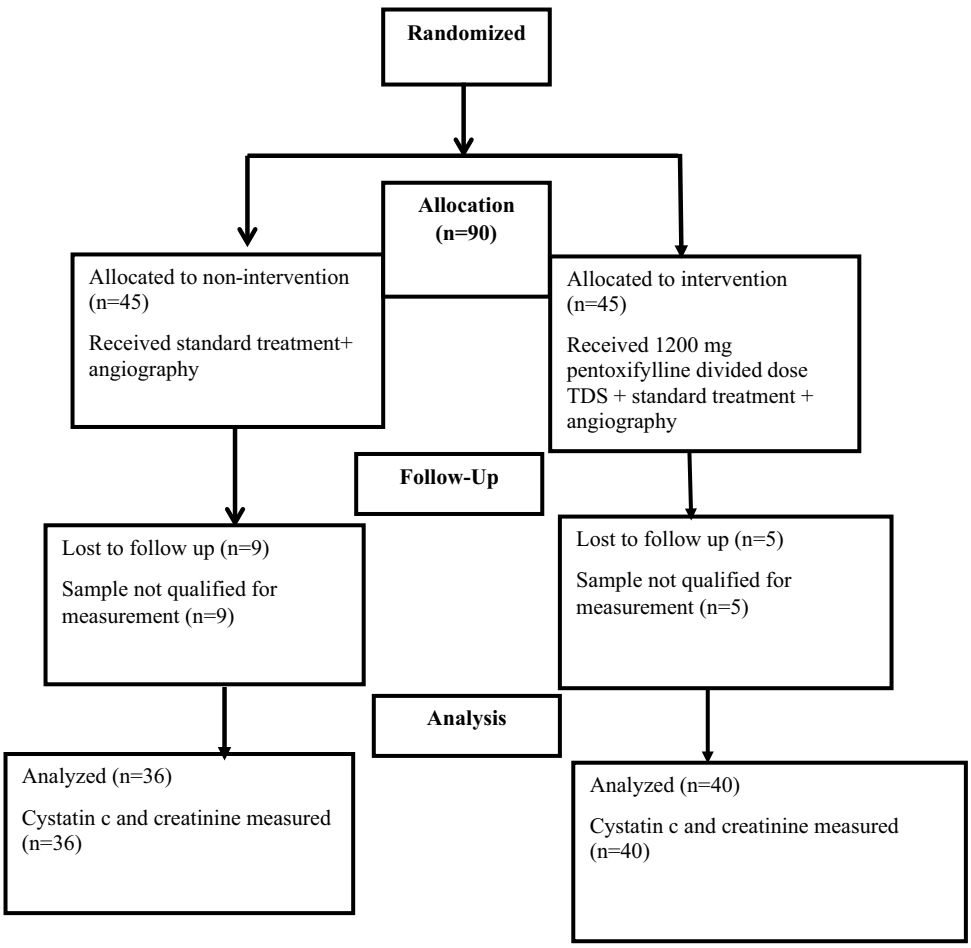

Fig. 1 CONSORT flow diagram of the study

Table 1 Demographic and clinical data of the study groups

Variables	PTX group ($n=40$)	Control group ($n=36$)	p value
Age (years)	62.9 ± 10.0	58.3 ± 7.3	0.184
Sex (male), *n* (%)	16 (35.5%)	23 (51.1%)	0.101
Weight (kg), mean ± SD	77.9 ± 10.8	79.1 ± 12.5	0.630
BMI (kg/m^2), mean ± SD	29.4 ± 4.1	28.7 ± 4.2	0.423
EF (%)	46.0 ± 9.0	45.4 ± 8.9	0.769
Hypertension, *n* (%)	27 (67.5%)	23 (63.9%)	0.740
Dyslipidemia, *n* (%)	13 (32.5%)	14 (38.9%)	0.561
CVA, *n* (%)	3 (7.5%)	1 (2.8%)	0.340
COPD, *n* (%)	4 (10%)	1 (2.8%)	0.369
Positive family history of cardiovascular disease, *n* (%)	5 (12.5%)	8 (22.2%)	0.261
Smoking, *n* (%)	9 (22.5%)	12 (33.3%)	0.292
Drug history, *n* (%)			
β-Blocker	12 (30%)	10 (27.8%)	0.831
ACEI	2 (5.5%)	2 (5.55%)	1.00
ARB	2 (5.5%)	7 (19.4%)	0.076
Metformin	16 (40%)	16 (44.4%)	0.695
Sulfonylurea	8 (20%)	7 (19.4%)	0.952
Insulin	4 (10%)	6 (16.7%)	0.391
Nitrate	2 (5%)	3 (8.3%)	1.000
Aspirin	8 (20%)	10 (27.7%)	0.426
Diuretics	10 (25%)	12 (33.3%)	0.831
Statins	7 (17.5%)	7 (19.4%)	0.827
CCBs	2 (5%)	2 (5.5%)	1.000
Incidence of CIN, *n* (%)	4 (8.9%)	3 (6.7%)	1.000

BMI body mass index, *EF* ejection fraction, *CVA* cerebrovascular accident, *COPD* chronic obstructive pulmonary disease, *ACEI* angiotensin-converting-enzyme inhibitor, *ARB* angiotensin receptor blocker, *CCBs* calcium channel blockers, *CIN* contrast-induced nephropathy, *SD* standard deviation

Contrast induced nephropathy and Cystatin C level

According to the statistical analysis, CIN occurred in 7 patients (9.2%) included 4 patients (8.9%) in the PTX group, and 3 patients in the control group (6.7%) that was not statistically significant ($p=1.00$). The baseline level of cystatin C was 1.31 ± 0.39 mg/L in the PTX group and 1.24 ± 0.42 mg/L in the control group ($p=0.561$). After angioplasty, the level of cystatin C was increased to 1.33 ± 0.61 in PTX group and to 1.31 ± 0.47 in the control group but was not statistically significant (Tables 2, 3).

Table 2 Changes in SCr, GFR and serum Cystatin C values between the groups before and after the angioplasty

	PTX group	Control group	*P*
Baseline SCr, (mg/dL)	1.02 ± 0.19	1.01 ± 0.17	0.912
SCr after procedure, (mg/dL)	1.17 ± 0.28	1.12 ± 0.19	0.337
SCr mean difference	0.11 ± 0.14	0.15 ± 0.11	0.127
Baseline GFR (mL/min)	81.0 ± 21.2	79.6 ± 17.8	0.784
GFR after procedure (mL/min)	74.0 ± 19.0	75.2 ± 17.3	0.460
GFR mean difference	− 6.98 ± 2.7	− 4.41 ± 1.1	0.001
Patients with GFR 30–60 at baseline, *n* (%)	2 (5)	4 (11.1)	0.414
Patients with GFR 30–60 after procedure, *n* (%)	9 (22.5)	6 (16.6)	0.872
Baseline serum cystatin C, (mg/L)	1.31 ± 0.39	1.24 ± 0.42	0.516
Serum cystatin C after procedure, (mg/L)	1.33 ± 0.61	1.31 ± 0.47	0.906
Serum cystatin C, Mean difference	0.04 ± 0.59	0.07 ± 0.29	0.864

SCr serum creatinine, *GFR* glomerular filtration rate

Table 3 Changes in SCr, GFR and serum cystatin C values within the groups before and after the angioplasty

	Baseline	After the angioplasty	*p*
SCr, (mg/dL), PTX group	1.02 ± 0.19	1.17 ± 0.28	0.001
SCr, (mg/dL), Control group	1.01 ± 0.17	1.12 ± 0.19	0.016
GFR (mL/min), PTX group	81.0 ± 21.2	74.0 ± 19.0	0.001
GFR (mL/min), Control group	79.6 ± 17.8	75.2 ± 17.3	0.029
Serum cystatin C, (mg/L), PTX group	1.31 ± 0.39	1.33 ± 0.61	0.673
Serum cystatin C, (mg/L), Control group	1.24 ± 0.42	1.31 ± 0.47	0.244

SCr serum creatinine, *GFR* glomerular filtration rate, *PTX* pentoxifylline

Serum creatinine level and clearance of creatinine

The baseline SCr levels were 1.02 ± 0.19 mg dL in the intervention group and were 1.01 ± 0.17 mg/dL in the control group ($p = 0.912$). After the procedure, SCr level increased to 1.17 ± 0.28 mg/dL in PTX group and 1.12 ± 0.19 mg/dL in the control group, which was not statistically significant ($p = 0.337$). In each group, the rise of SCr level was significant when compared with their baseline values (1.17 ± 0.28 mg/dL; $p < 0.001$ in the PTX group, and 1.12 ± 0.19 mg/dL; $p = 0.01$ in the control group). After the procedure, the clearance of creatinine significantly decreased in both the PTX and in the control groups when compared to their baseline values (74.0 ± 19.0 mL/min; $p < 0.001$ and 75.2 ± 17.3 mL/min; $p = 0.029$, respectively) that are presented in Tables 2 and 3.

Discussion

This study was the first randomized controlled trial that assessed the effect of pentoxifylline on CIN by measuring cystatin C. Based on the results of present study, PTX could not reduce the incidence of CIN when compared to the control group.

Studies of PTX for the prevention of CIN

The preventive effect of PTX in the prevention of CIN has been evaluated by some studies, and all of them failed to show a significant role. Of note, all studies have measured serum Cr as the biomarker of renal injury [20–22].

In one randomized clinical study conducted by Yavari et al. between April 2011 and February 2012, 199 patients with elective percutaneous coronary intervention (PCI) were randomized in the two groups to receive saline or saline plus PTX 400 mg orally three times a day for 48 h. Serum creatinine was measured 24 h before and 48 h after the procedure [20]. The overall incidence of CIN was 6% that was similar in both group (6.2% in the PTX group vs. 5.9% in the hydration group, $p = 0.92$) as well as no significant change in serum creatinine was seen between the groups [20].

In the prospective, randomized, single-blind, single-centre clinical study by Firouzi et al., 268 angioplasty patients were randomized to the control group with the standard treatment and the study group with the standard treatment and PTX 400 mg three times in day one day before and after the coronary angioplasty [21]. To evaluate CIN, serum creatinine was measured before and 48 h after the procedure. The overall rate of CIN following the angioplasty was 11.1% (13.7% in the control group, and 8.5% in the study group), but the difference was not statistically significant ($p = 0.17$). Moreover, no case of mortality and the need for hemodialysis was seen between the groups [21].

Finally, Eshraghi et al. in a single-blind, randomized clinical study on 175 MI patients undergoing PCI, the patients were allocated to the control ($n = 84$), and the intervention groups ($n = 91$) [22]. In the intervention group, patients received PTX 400 mg/3 times a day one day before and after PCI. Serum creatinine was measured at baseline and 48 h after PCI. In general, CIN occurred in 8% of all patients included 9.5% in the control group, and 6.6% in the PTX group ($p = 0.47$) [22].

Comparison with the previous studies

In our study, the overall incidence of CIN following PCI was 9.2% that is comparable with the previous studies (6%, 11.1%, and 8%) [20–22]. Like the other previous studies, our study failed to show the significant effect of PTX in the prevention of CIN. However, our study was dissimilar to the previous studies concerning some major risk factors for CIN such as volume of contrast media, population of hypertensive, and diabetic patients [20–22]. One of the key differences between our study and the previous studies is the use of cystatin C in the diagnosis of CIN.

Based on recent data, Cystatin C is superior to serum creatinine in the early detection of kidney injury following PCI [23]. It was shown that cystatin C reaches its peak value just 24 h after PCI, while serum creatinine is still normal [24]. Moreover, in the chronic kidney disease patients, the higher level of cystatin C is associated with cardiovascular mortality and morbidity [25].

The present finding of the study may be partially explained by the following reasons. First, the clear dose and time of administration of PTX for the prevention of CIN following PCI have not been identified because of the limited number of studies. Extended pre-treatment period or increased loading doses of PTX may lead to the better results. Therefore, more studies are needed to find out the precise timing and dosing of PTX in the prevention of CIN following PCI. Second, the non-significant result of this study may be explained by the limited sample size of the study. On the other hand, the present study had a pilot nature that was conducted to explore the effect of PTX in the prevention of CIN by measuring the more sensitive biomarker of kidney injury cystatin C. Therefore, the potential benefits of PTX could be clearly shown by the large-scale studies. Third, the probable variation between the detection limit of kits for measurement of serum cystatin may be the other factor that could affect the results of such studies.

Study limitations

The result of our study should be interpreted with caution since our current study includes some limitations. First, the sample size of present study was relatively small. Therefore, the study might be underpowered for measurement of end-point outcomes. Second, this study was not a placebo-controlled trial because of the accessibility problem and we could not use a placebo in the control group to minimize the potential treatment bias. Therefore, multi-centre double-blind, placebo-control studies with a larger population are recommended for future studies.

Third, we had time and cost restrictions; therefore, we could not extend the measurement time of cystatin C to 72 h after angioplasty. Fourth, our protocol for the prevention of CIN included use of hydration, bicarbonate, and NAC while the current guidelines recommend fluid therapy as a prevention strategy for CIN.

Conclusion

The results of this study did not support the potential benefit of PTX in the prevention of CIN in diabetic patients undergoing the angioplasty. Larger studies are recommended to investigate the effect of PTX in the prevention of CIN.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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