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Original Article

Evaluation of Pentoxifylline in the Prevention of Contrast-Induced Nephropathy in Patients Undergoing Primary Percutaneous Coronary Intervention

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ABSTRACT

Background: As percutaneous coronary intervention (PCI) technologies confer increasing patient advantage, the use of iodinated contrast media for diagnostic and interventional procedures is increased. Although contrast media obstacles are transient and mild, contrast-induced nephropathy (CIN) negatively affects long-term patient mortality. PCI creates a high-risk condition for the incidence of CIN even in patients with a normal renal function. Pentoxifylline (PTX) with a variety of mechanisms may prevent CIN. We sought to assess the positive effect of PTX administration at the beginning prior to contrast media use to 24 hours after PCI to prevent CIN in patients with STEMI.

Methods: In this double-blind, single-center, clinical trial, we randomly assigned 296 consecutive patients to the control group (n=148) without PTX and the case group (n=148) with PTX 400 mg/tid at the time of hospitalization to 24 hours after the procedure. Serum creatinine was measured before and 48 hours after the procedure. The occurrence of CIN within 48 hours was our end point. CIN was defined as a 0.5 mg/dL increase or more in serum creatinine or a 25% increase or more above baseline serum creatinine.

Results: A total of 296 patients were enrolled in this trial and were randomly assigned to receive either primary PCI plus PTX or only primary PCI. Out of 148 patients who received PTX, only 12.2% were seen to have CIN incidence (>0.5 mg/dL or a 25% increase in the Cr level); however, the difference between the 2 groups regarding CIN was not significant (P=0.4). Out of the 296 patients, only 20 were found to have chronic kidney disease (CKD) (CKD was defined as baseline Cr>1.5); and of those patients, 3 (15%) showed CIN incidence. Nevertheless, the difference between the 2 groups regarding CIN incidence was not significant (P=0.7). The regression test showed that between all confounding factors in the 2 groups of PTX positive and negative, sex and ejection fraction had positive effects on the rise in the Cr level and, consequently, the incidence of CIN (95% CI: 1.60 to 30.85; P=0.01 and 95% CI: 0.92 to 1; P=0.05).

Conclusions: Administration of oral PTX to patients with increased risk for CIN scheduled for primary PCI may not reduce the Cr level and thus the occurrence of CIN. Given the higher prevalence of hypotension in the patients without PTX, higher prevalence of CKD in the patients without PTX, and absence of significant difference between the 2 groups regarding the incidence of CIN, PTX had no preventive effect on CIN occurrence in STEMI.

Among all factors influencing CIN occurrence, sex and ejection fraction had positive effects on the rise in the Cr level. ***(Iranian Heart Journal 2015; 16(4): 28-34)***

Keywords ■ Contrast media ■ Primary PCI ■ Contrast-induced nephropathy■ Pentoxifylline

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Advanced growth in the capacity of computed tomography (CT) images and the efficacy of PCI has developed the utilization of techniques; consequently, the number of the patients who receive contrast media (CM) has increased.[1-5] Complications concomitant with CM range from mild symptoms to life-threatening reactions such as hypotension, cardiovascular events, and renal dysfunction. Although most common adverse events are transient, contrast-induced nephropathy (CIN) can have some serious long-term consequences.[6] These possible complications should be considered if renal function is not assessed. The association between complications and CM administration may not be obvious.

CIN is commonly distinct as an acute renal failure occurring within 48 hours of exposure to an intravenous contrast that is not attributable to other causes.[7] CIN, which is either >25% increase in baseline serum creatinine or >0.5 mg/dL increase in serum creatinine above baseline creatinine during 48 hours of exposure, is the most common description.[8]

Pentoxifylline (PTX) is a methylxanthine derivative agent with numerous hematological attributes. It has been recently introduced for CIN prevention inasmuch as it develops oxygen delivery to the ischemic tissue by treating peripheral vascular disease and has anti-inflammatory properties that can reduce nitric oxide deterioration.[7] In septic shock, intravenous PTX has been indicated to reduce the serum level of some inflammatory cytokines.[9] Conversely, the oral absorption of PTX is near complete; the plasma level peaks about 2 to 3 hours after drug absorption and with a variety of mechanisms may prevent CIN.[9] PCI provides a high-risk condition for the incidence of CIN even in patients with normal renal function.[9] In the current study, we hypothesized that the oral administration of PTX at the beginning prior to CM use (usual dose of 400 mg/tid) to 24 hours afterward could help CIN prevention in patients with STEMI.

METHODS

Study Populations

In the present clinical trial, 296 patients (236 male and 60 female; age >20 y) with STEMI who underwent primary PCI in our tertiary research center between 2013 and 2015 and were considered for emergency coronary angiography and intervention and were candidated for primary PCI were enrolled. A history of taking CM within the previous 10 days and N-acetylcysteine use was considered the exclusion criterion. The patients were divided into 2 groups: those who underwent PCI and did not receive PTX and those who received PTX in addition to their routine drugs. All the patients gave informed written consent before entering the study. The study protocol was approved by the institutional ethics committee. Age, sex, diabetes mellitus, hyperlipidemia, hypertension, hypotension, intravenous contrast volume, use of intra-aortic balloon pump, and chronic kidney disease (CKD) were considered as the study variables.

Study Protocol

In this prospective, randomized, double-blind, clinical trial, 296 patients were randomly assigned to the control group (n=148) with routine treatment and no PTX and the study group (n=148) with routine treatment and PTX (400 mg/tid) from the initiation of the study to 24 hours after the procedure; no placebo was administered. Controls were selected randomly out of the patients who came to our hospital and underwent primary PCI and who did not receive PTX, and the cases were selected from the cases that underwent primary PCI and received PTX. The study and control groups had the same routine preparation protocol for angioplasty as hydration before and after angioplasty with normal saline (1-1.5 cc/kg), which was administered at the start of the study to 12 hours after the procedure.

In all the patients, baseline serum creatinine was measured using Beckman Coulter-SYNCHRON CX®5 PRO Clinical System before angioplasty. One sample serum creatinine was obtained 48 hours after the procedure in all the patients. Measurements were all made in a single center-based laboratory, and the laboratory staff was blinded to the study protocol and serum samples. The choice of the type of CM was left to the interventional cardiologist performing the procedure.

The coronary angioplasty procedures were carried out using the iso-osmolar nonionic CM, iodixanol (Vesipaque 320, GE Healthcare, Cork, Ireland) or iopromide (Ultravist 300, Schering AG, Germany).The primary end point of the study was the occurrence of CIN, which was defined as an increase in serum creatinine level of 0.5 mg/dL or a 25% increase over the baseline creatinine level over a 2-day period after exposure to CM.

Statistical Analysis

The continuous data are expressed as means ± standard deviations and they were compared between the 2 groups using the Student *t*-test. The categorical data are expressed as numbers and percentages and they were compared via the chi-square test. The Mann–Whitney U test was employed to assess the Cr level between the 2 groups. The regression linear test was used to remove the confounding effect of the variables. A P value <0.05 was considered significant. The data were analyzed using SPSS software 13.0 (SPSS Inc. Chicago, Illinois, U.S.A.).

RESULTS

A total of 296 patients were enrolled in this trial and were randomly assigned to receive either routine treatment plus PTX (n=148, 117 [79.1%] male; P=0.7) or only routine treatment (n=148). Out of the 148 patients who received PTX, 65 (43.9%) had hypertension (P=0.7), 43 (29.1%) had dyslipidemia (P=0.3), 10 (6.8%) had hypotension (P=0.04), and 49 (33.1%) had diabetes mellitus (P>0.99). All the demographic data and clinical findings are depicted in Table 1 and Table 2.

Table 1. Patients' demographic data

Risk factors	Pentoxifylline- (n=148)	Pentoxifylline+ (n=148)	P Value
Age			
Sex Female	58.2±12.5	58.4±10	0.89
Male	119(80.4%)	117(79.1%)	0.77
DLP	51(34.5%)	43(29.1%)	0.31
HTN	68(45.9%)	65(43.92%)	0.04
FH	20(13.5%)	30(20.3%)	0.12
DM	49(33.1%)	49(33.1%)	0.99

Abbreviations: DLP, Dyslipidemia; HTN, Hypertension; FH, Familial history; DM, Diabetes mellitus; CS, Cigarette smoking P<0.05 was considered the level of significance.

Table 2. Clinical and procedural findings according to pentoxifylline administration

Risk factors	Pentoxifylline – (n=148)	Pentoxifylline + (n=138)	P Value
Hypotension	2(3%)	10 (6.8%)	0.04
IABP	2(1.4%)	4(2.7%)	0.6
LVEF<40%	61(41.2%)	65(43.9%)	0.63
CHF	11(7.4%)	11(7.4%)	0.99
Anemia	26(17.6%)	23(15.5%)	0.63
Contrast volume	240±99	240±91	0.31
CKD	10(6.8%)	3(2%)	0.04

Abbreviations: IABP, Intra-aortic balloon pump; CHF, Congestive heart failure; LVEF, Left ventricular ejection fraction; CKD, Chronic kidney disease
P<0.05 was considered the level of significance.

Out of the 148 patients who received PTX, only 18 (12.2%) were seen to have CIN incidence (Cr level >0.5 mg/dL or a rise >25%); however, the difference between the 2 groups regarding CIN was not significant. Out of the 148 patients who did not receive PTX, 22 (14.9%) showed CIN incidence (P=0.4) (Table 3).

Table 3. Occurrence of CIN according to the total Cr level (>0.5 mg/dL and a 25% rise)

± PTX	CIN + Total	CIN – Total	P Value
	Cr≥0.5 mg/dL Cr≥25%	Cr <0.5 Cr<25%	
Without PTX n=148	22 (14.9%)	126 (85.1%)	0.4
With PTX n=138	18 (12.2%)	130 (87.2%)	

Abbreviations: PTX, Pentoxifylline; CIN, Contrast-induced nephropathy
P<0.05 was considered the level of significance.

Out of the 296 patients, 256 (86.5%) showed no CIN incidence, defined as CIN total (0.5≤CIN or 25%≤CIN) and only 40 patients were found with CIN incidence. Out of the 296 patients, only 20 were found to have CKD (CKD were defined as baseline CR >1.5); and of those patients, 3 (15%) showed CIN incidence. The difference, however, between the 2 groups concerning CIN incidence was not significant (P=0.7). Out of the 276 patients who were CKD negative (Cr level <1.5), 239 (86.6%) did not show CIN incidence (Table 4).

Table 4. Occurrence of CKD according to the Cr level (≥1.5)

± CKD	CIN+ Total	CIN – Total	P Value
	Cr≥0.5 mg/dL Cr≥25%	Cr <0.5 Cr<25%	
CKD +	3(15%)	17(85%)	0.8
CKD -	37(13.4%)	239(86.6%)	

Abbreviations: CKD, Chronic kidney disease; PTX, Pentoxifylline

The regression model showed that between all the confounding factors in the 2 groups, sex and ejection fraction had positive effects on the rise in the Cr level and consequently the incidence of CIN (95% CI: 1.60 to 30.85; P=0.01 and 95% CI: 0.92 to 1; P=0.05).

DISCUSSION

PTX can be effective in preventing CIN given its anti-inflammatory, antioxidant, and circulatory properties. There are a few animal studies concerning the renoprotective effect of PTX in contrast nephropathy. A few human studies for the evaluation of the renopreventive effect of PTX in contrast nephropathy have been reported.[7,13] Our study is one of the few studies conducted hitherto on the effects of PTX on CIN.

A major problem after CM-required procedures is CIN, which is generally characterized as either an absolute increase in serum creatinine (SCr) concentration of 0.5

mg/dL (44.2 l mol/L) or a relative rise >5% from baseline.[14,15] CIN typically and clinically manifests within 3 days of CM administration, peaks within 3 to 5 days, and returns to its baseline level within 10 to 21 days.[16] Nevertheless, in some cases, sustained or permanent nephropathy occurs. It is recommended that SCr measurements be continued for >48 hours after exposure to CM to monitor for CIN.[17]

In a trial, CKD was defined as SCr>1.5 mg/dL and was also the strongest predictor of all-cause mortality. An analysis of more than 130,000 elderly post-MI patients found that 1-year survival was increasingly reduced as creatinine clearance declined.[18]

In an investigation, CKD was compared with normal renal function at baseline level in patients with acute myocardial infarction who underwent PCI and was related to an obvious increase in the mortality rate over a 30-day period (7.5% vs. 0.8%; P<0.0001) and at 1 year (12.7% vs. 2.4%; P<0.0001);[19] nevertheless, the additional burden of CIN in patients undergoing PCI with previously compromised renal function apparently increases the risk of adverse outcomes.

Patients undergoing PCI with pre-existing renal dysfunction are at increased risk for adverse outcomes in comparison to those with a normal renal function.[18] The present study showed that the incidence of CIN was 13.5%, which is almost similar to the rate reported by the previous studies. CIN incidence was reported 1-13% in elective PCI or 19% in the Marenzi study.[20] The incidence of CIN in primary PCI in our study showed that there was no significant increase in CIN after STEMI. We think that this is because of better preventive management in 12-hour hydration in our center, which is a high-volume and referral center for primary PCI with optimal arrangements for primary PCI, which results in the earlier reperfusion of occluded vessels and less hemodynamic burden of myocardial infarction.

The overall incidence of CIN in the control group of a previous study was 13.69%,[13] which is comparable to previous reports in an unselected population[8] and less than the CIN incidence in our study.

In the current study, out of the 148 patients who received PTX, only 10 (6.84%) had hypotension and there was a significant relationship between the 2 groups apropos hypotension (P=0.04). Nonetheless, due to the small sample size, it was only seen in a small group of our study population. In a study by Firouzi et al.[13] in patients who underwent angioplasty, it was shown that the oral use of PTX could be recommended for CIN prevention and that it had prophylactic effects, although no statistically significant protective effect was documented. The result of their study was in accordance with our investigation. In the present study, out of the 148 patients who did not receive PTX, only 22 (14.9%) showed CIN incidence (P=0.4). Therefore, the administration of PTX had no statistically significant effects. Out of the 296 patients, only 40 were found to have CIN incidence. Out of the 296 patients, only 20 were found to have CKD (CKD were defined as baseline Cr >1.5); and of those patients, 3 (15%) showed CIN incidence (P=0.7).

The regression test revealed that between all the confounding factors in the 2 groups, sex, and ejection fraction had positive effects on the rise in the Cr level and, thus, the incidence of CIN (P=0.01 and P=0.05, respectively). The difference between the present study and the other investigations regarding the beneficial effect of PTX in the prevention of CIN incidence may be due to the different sizes of the study populations. Our results demonstrated that PTX was a useful drug in the prevention of the negative effects of CM and that it had no preventive effects on the alteration in the Cr level and, consequently, CIN incidence.

Limitations

The most important limitation of this small and short-term trial study is the lack of sample-size calculation, which resulted in estimating the small sample size on the basis of other similar trials. We suggest that larger studies be conducted on the effect of PTX.

CONCLUSIONS

The present clinical trial utilized PTX for CIN prevention and the results suggested that the administration of oral PTX to patients with a high risk of CIN scheduled for angioplasty might not reduce the Cr level and, thus, the occurrence of CIN. Given the higher prevalence of hypotension in the PTX-negative group, higher prevalence of CKD in the patients without PTX, and the absence of a significant difference between the 2 groups regarding the incidence of CIN, PTX had no preventive effects on CIN occurrence in STEMI. Among all the factors influencing CIN occurrence, sex and ejection fraction had positive effects on the rise in the Cr level and, thus, the occurrence of CIN.

Suggestion

Measures before, during, and after the use of CM that reduce the incidence of CIN such as discontinuation of nephrotoxic medications, adequate hydration, and use of appropriate volumes and types of CM should be considered in all patients with renal insufficiency or with other risk factors for CIN. Larger trials or studies in higher-risk patients may shed further light on the protective effect of PTX in CIN.

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REFERENCES

1. de Feyter P, Mollet NR, Cademartiri F, Nieman K, Pattynama P. MS-CT coronary imaging. J Interv Cardiol 2003; **16**: 465–8.

2. Schoepf UJ, Becker CR, Ohnesorge BM, Yucel EK. CT of coronary artery disease. Radiology 2004; **232**: 18–37.

3. American Heart Association. Heart Disease and Stroke Statistics: 2004. p 1–52.

4. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003; **349**:1315–23.

5. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: The TAXUS-IV trial. Circulation. 2004; **109**:1942–47.

6. Thomsen HS, Morcos SK. Management of acute adverse reactions to contrast media. Eur Radiol 2004; **14**: 476–481.

7. Roozbeh J, Jahromi AH, Sharifian M, Pakfetrat M, Afsharinia R. Protective Effect Of Pentoxifylline on Contrast Induced Nephropathy. Saudi Journal Of Kidney Disease And Transplantation.2008; 985-6

8. McCullough P MD. Renal Complication of Contrast Media. IN King Spencer B Interventional Cardiology, 1st edition, China, McGeraw-Hill ,2007,chapter 23

9. Staudinger T, Presterl E, Graninger W, Locker GJ, Knapp S, Laczika K et al. Influence of pentoxifylline on cytokine levels and

inflammatory pa rameters in septic shock. Intensive Care Med. 1996; **22**(9):888-93

10. Ferrario F, Barone MT, Landoni G, Genderini A, Heidemperger M, Trezzi M, et al. Acetylcysteine and non-ionic isosmolar contrast-induced nephropathy-a randomized controlled study Nephrology Dialysis Transplantation 2009; **24**(10) : 3103-7

11. Huber W, Eckel F, Hennig M, Rosenbrock H, Wacker A, Saur D, et al. Prophylaxis of Contrast Material–induced Nephropathy in Patients in Intensive Care: Acetylcysteine, Theophylline, or Both? A Randomized Study; Radiology 2006; **239**:793-804

12. Boscheri A, Weinbrenner C, Botzek B, Reynen K, Kuhlisch E, Strasser RH. Failure of ascorbic acid to prevent contrast-media induced nephropathy in patients with renal dysfunction. Clin Nephrol. 2007; **68**(5):279-86.

13. Firouzi A; Eshraghi A; Shakerian F; Sanati HR; Salehi N; Zahedmehr A et al. Efficacy of pentoxifylline in prevention of contrast-induced nephropathy in angioplasty patients. Int Urol Nephrol. 2012; **44**(4):1145-9

14. McCullough PA, Sandberg KR. Epidemiology of contrastinduced nephropathy. Rev Cardiovasc Med. 2003; 4 (Suppl. 5): S3–S9.

15. Morcos SK. Contrast nephrotoxicity and iso-osmolar contrast agents: Implications of nephric. Clin Radiol 2004; 59:297.

16. Gleeson T, O'Dwyer J, Bulugahapitiya S, Foley D. Contrastinduced nephropathy. Br J Cardiol (Acute Interv Cardiol). 2004; **11**:AIC 53–AIC 61.

17. Gami AS, Garovic VD. Contrast nephropathy after coronary angiography. Mayo Clin Proc. 2004; **79**:211–219.

18. Szczech LA, Best PJ, Crowley E, Brooks MM, Berger PB, Bittner V, Gersh BJ, Jones R, Califf RM, Ting HH, et al. Outcomes of patients with chronic renal insufficiency in the bypass angioplasty revascularization investigation. Circulation 2002;105: 2253–2258.

19. Sadeghi HM, Stone GW, Grines CL, Mehran R, Dixon SR, Lansky AJ, et al. Impact of renal insufficiency in patients undergoing primary angioplasty for acute myocardial infarction. Circulation 2003;**108**: 2769–75.

20. Marenzi G1, Lauri G, Assanelli E, Campodonico J, De Metrio M, Marana I, et al. Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. J Am Coll Cardiol. 2004; **44**(9):1780-5.