Pentoxifylline and prevention of contrast-induced nephropathy: Is it efficient in patients with myocardial infarction undergoing coronary angioplasty?

Ali Eshraghi[(1)], Roya Naranji-Sani[(2)], Hourak Pourzand[(3)], Mohammad Vojdanparast[(4)], Negar Morovatfar[(5)], Javad Ramezani[(1)], Ramin Khamene-Bagheri[(1)], Pouya Nezafati[(6)]

Original Article

Abstract

BACKGROUND: Contrast-induced nephropathy (CIN) is a major concern following procedures with applying iodinated contrast media. The basis prevention of CIN is hydration and to avoid hypovolemia. We aimed to evaluate the efficacy of pentoxifylline (PTX) for the prevention of CIN in patients with myocardial infarction (MI) undergoing coronary angioplasty.

METHODS: This prospective, single-blind, randomized clinical trial study was performed on 175 (127 men) of MI patients undergoing routine treatment. Patients were assigned randomly to the control (n = 84) and study groups (n = 91). In our study group, patients received 400 mg/3 times a day from 24 hours before to 24 hours after coronary angiography. In addition, before the procedure and after 48 hours from the procedure, serum creatinine was measured.

RESULTS: CIN occurred in 14 patients (8.0%); 8 controls (9.5%) and 6 patients (6.6%) in the PTX group (P = 0.475) showing PTX to have no significant effect on CIN [P = 0.750, odds ratio = 0.82 (confidence interval = 0.24-2.8)] though a significantly different volume of contrast was used between the groups (231.29 ± 105.10 mm^3 and 190.88 ± 75.82 mm^3; P = 0.005, respectively).

CONCLUSION: There was no significantly different occurrence of CIN on patients with MI, undergoing coronary angioplasty, but its relatively lower rate in PTX group would recommend the prophylactic oral use of PTX for CIN prevention.

Keywords: Pentoxifylline, Myocardial Infarction, Contrast Media, Angioplasty, Nephropathy, Creatinine

Date of submission: 1 Jan 2016, ***Date of acceptance:*** 6 Aug 2016

Introduction

Coronary angioplasty as a non-surgical procedure is widely used in patients with known indications, and the contrast dye is used to guidewires through the vessels. A known side effect in performing this procedure occurs by means of contrast-induced nephropathy (CIN), which is the third leading cause of new onset renal failure in hospitalized patients. CIN is defined as a > 25% increase in baseline serum creatinine or > 0.5 mg/dl absolute increase in serum creatinine above baseline within 48 hours of exposure.[1] CIN is recognized as one of the complications of contrast media after coronary angiography and angioplasty.[1-4] Its incidence ranges from 2% to 50% in low- and high-risk populations, respectively.[5] Moreover, CIN incidence is 13% in non-diabetic patients and 20% in diabetics.[1]

Morbidity, mortality, length of hospitalization, and risk of progression toward end-stage renal disease are increased due to CIN. Dialysis is needed

1- Assistant Professor, Atherosclerosis Prevention Research Center AND Department of Cardiology, Imam Reza School of Medicine, Imam Reza Hospital, Mashhad, University of Medical Sciences, Mashhad, Iran
2- Resident, Department of Cardiology, Imam Reza School of Medicine, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
3- Associate Professor, Atherosclerosis Prevention Research Center AND Department of Cardiology, Imam Reza School of Medicine, Imam Reza Hospital, Mashhad, University of Medical Sciences, Mashhad, Iran
4- Cardiologist, Atherosclerosis Prevention Research Center, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
5- Assistant Professor, Imam Reza Clinical Research Units, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
6- General Practitioner, Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medicine Sciences, Isfahan, Iran
Correspondence to: Hourak Pourzand, Email: pourzandh@mums.ac.ir

for about 1% of CIN patients and remains permanent in half of these patients.[1,5-9] There are some risk factors in developing this complication including, volume and type of contrast media, underlying diseases such as chronic kidney disease, diabetes mellitus, and congestive heart failure, and also individual factors such as sex, advanced age, anemia, and reduced effective circulation volume;[10] CIN pathophysiological mechanism is believed to be related to the changes in renal hemodynamics and damages on tubular cells caused by free radicals or direct toxic effect of the contrast media.[11]

A recent agent in preventing CIN is pentoxifylline (PTX), a methylxanthine derivative with multiple hematologic properties.[11] According to some of its anti-inflammatory properties, PTX is commonly used to treat peripheral vascular diseases. Furthermore, there is evidence that PTX reduces nitric oxide deterioration and scavenging of free radical. However, beneficial effects of PTX in CIN are not fully showed in trials, especially in patients undergoing angioplasty.

Spargias et al.[12] found that the parenteral use of PTX in patients with septic shock could reduce the serum levels of some inflammatory cytokines. Furthermore, plasma level of PTX peaks within 2-3 hours after drug ingestion and its oral absorption is nearly complete.

Due to the anti-inflammatory and antioxidant effects of PTX, we hypothesized that its oral administration before contrast media use might be effective in preventing CIN. The purpose of this study is to investigate the efficacy of PTX to prevent CIN in patients with myocardial infarction (MI) who are subjected for coronary angioplasty.

Materials and Methods

In view of other trials on risk of nephropathy and CIN prevention,[13] we calculated sample size of study as 87 in each group considering the significance level of 0.05 to evaluate the efficacy of PTX on prevention of CIN.

Patients with ST elevation MI and above 18 years of age who referred for emergency angioplasty to the Interventional Cardiology Department at Imam Reza Hospital, between October 2013 and July 2014, were enrolled into this study. All procedures were performed by a single interventional cardiologist.

Exclusion criteria were serum creatinine more than 1.5 mg/dl, heart failure, history of end-stage renal failure or being on dialysis, use of N-acetylcysteine, theophylline, aminoglycosides, and non-steroidal anti-inflammatory medicines, and intravenous contrast media administration within the last 2 days. Besides, patients with pulmonary edema, multiple myeloma, and uncontrolled hypertension were excluded from the study. This study protocol was approved by Ethics Committee of Mashhad University of Medical Sciences and conforms to the standards currently applied by the Iranian Registry of Clinical Trial (IRCT2014092819316N1). Written informed consent was obtained from all patients.

This was a prospective, single-blind, randomized clinical trial study. The patients were randomly allocated to treatment (PTX) or control group. Paraclinical tests were done in a single hospital laboratory, and laboratory personnel were blinded to the study protocol.

In this study, no placebo was administered for the control group. Similar routine preparation for angioplasty, including hydration with normal saline before and after the protocol, was received in both groups before and after the protocol.

Normal saline 1-1.5 cc/kg was administered from 6 hours before to 6 hours after procedure. PTX was administrated at a dose of 400 mg 3 times a day from referral day until 24 hours after the procedure in the treatment group.

Serum creatinine level was measured for both groups in referral time and after 48 hours of protocol. Serum creatinine was measured with Beckman Coulter SYNCHRON CX5® PRO Clinical System during study protocol.

Iso-osmolar nonionic contrast media iodixanol (Vesipaque 320, GE Healthcare, Cork, Ireland) was used for performing coronary angioplasties. Mehran et al.[14] introduced a risk prediction score for the development of CIN which we used this to predict the risk of CIN in all patients. Our primary end point was considered as either a minimum of 0.5 mg/dl or 25% increase in serum creatinine above the baseline, 48 hours after exposure to contrast media, which we defined as the occurrence of CIN.

The data were analyzed using SPSS software for Windows (version 16, SPSS Inc., Chicago, IL, USA). Normality distribution of quantitative data was checked by Kolmogorov–Smirnov test. Continuous data were expressed as mean ± standard deviation. The Chi-square test was applied for comparison of qualitative data between the two groups. Quantitative data were checked if normality distributed in each group using the Kolmogorov–Smirnov test. Then, the independent sample t-test or Mann–Whitney U-test was applied for comparison of data between the two

groups. Logistic regression was used to control of effect of sex, age, history of hypertension, smoking, diabetes history, and contrast volume on CIN occurrence. All significance tests were two-tailed. $P < 0.050$ considered as significant level.

Results

In this study, we recruited a total of 175 patients (127 men and 48 women); 91 patients received PTX, and 84 were in the control group (Figure 1). The demographic data and some paraclinical characteristics are presented in table 1. Besides the history of hypertension and the level of hematocrit which were significantly higher in the PTX group than control group (52% vs. 32%; P = 0.020, 43.0 ± 6.7 vs. 41.0 ± 6.6; P = 0.020, respectively), no significant difference was found between the two groups regarding age, sex, body mass index, and biochemical markers including high-density lipoprotein, low-density lipoprotein, and triglyceride.

Vesipaque was the type of contrast media used both in the control and PTX groups.

Statistical analysis showed that there was a significant difference between volume of contrast used (P = 0.005). We found that CIN occurred in 14 patients (8%); 8 controls (9.5%) and 6 patients (6.6%) in the PTX group, which was not significantly different between the two groups (P = 0.475) (Table 1).

Regression analysis by backward method with CIN as dependent variable and sex, age, history of hypertension, smoking, diabetes history, and contrast volume as independent variables showed that none of them had significant independent effects on CIN occurrence across the two groups of study. Mean level of hematocrit had nearly significance effect [P = 0.051, odds ratio (OR) = 0.92 (confidence interval (CI) = 0.85-1.00)]. Moreover, the use of PTX had no significant effect on CIN occurrence [P = 0.750, OR = 0.82 (CI = 0.24-2.8)] (Table 2).

Our studied patients did not require any renal replacement therapy; moreover, there was not any hospital mortality in the control and PTX groups.

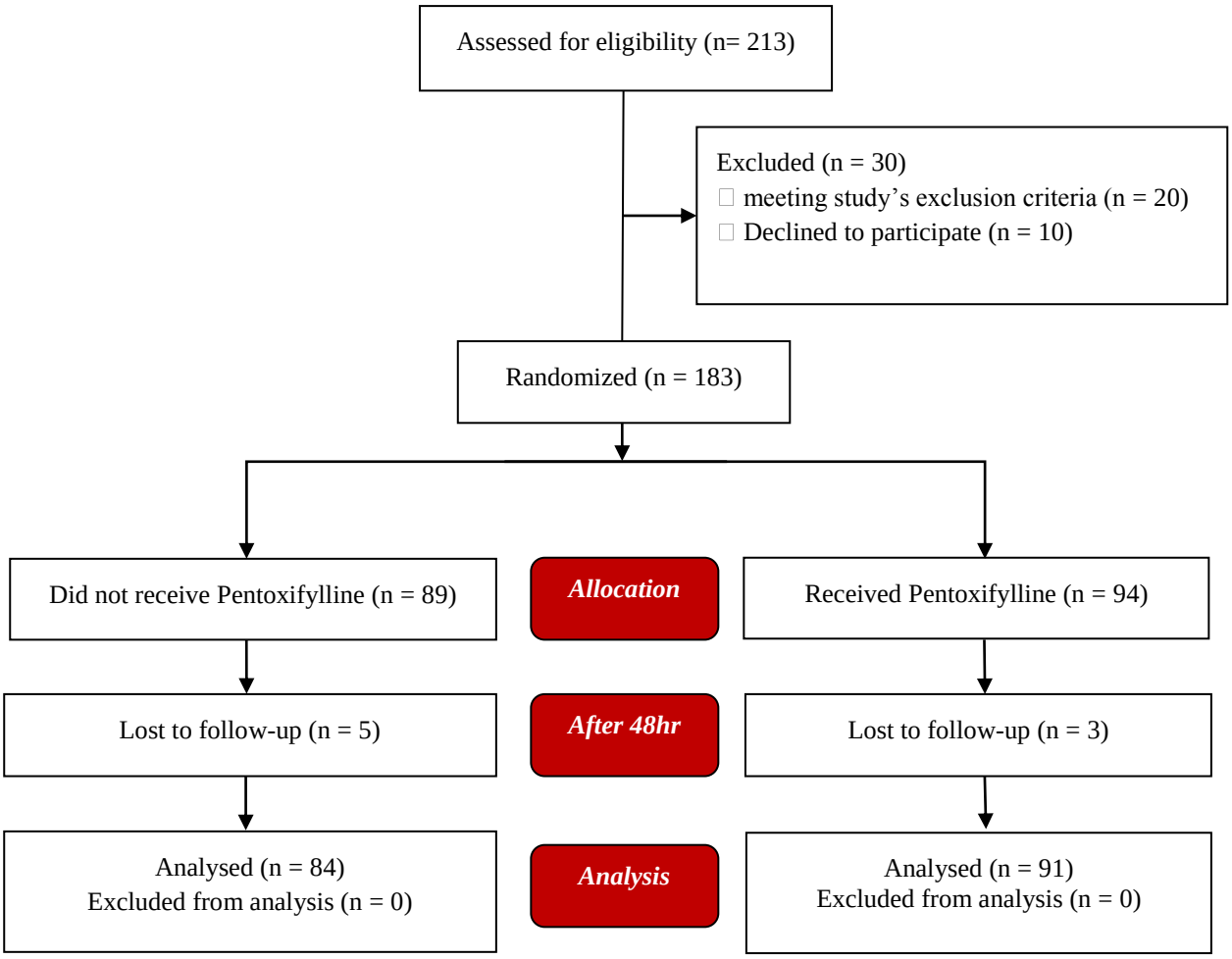

Figure 1. Flowchart of the study

Table 1. Demographic, clinical, and laboratory data of patients in the two groups

Variables	Control group (n = 84)	PTX group (n = 91)	P
Age (mean ± SD)	57.90 ± 14.27	60.46 ± 14.03	0.270
Height (cm) (mean ± SD)	165.00 ± 15.10	167.38 ± 8.70	0.679
Weight (kg) (mean ± SD)	71.72 ± 15.61	72.53 ± 13.87	0.233
BMI (kg/m^2) (mean ± SD)	25.06 ± 3.13	25.35 ± 5.25	0.726
Hematocrit(mean ± SD)	42.75 ± 6.70	41.33 ± 6.60	0.020
Hemoglobin (mean ± SD)	14.25 ± 1.83	13.60 ± 2.34	0.051
HDL (mean ± SD)	37.43 ± 13.76	40.25 ± 26.01	0.430
LDL (mean ± SD)	113.20 ± 44.10	113.20 ± 39.42	0.997
TG (mean ± SD)	127.90 ± 78.37	113.10 ± 59.08	0.216
Volume of contrast use mm^3 (mean ± SD)	231.29 ± 105.10	190.88 ± 75.82	0.005
Baseline creatinine (mg/dl) (mean ± SD)	1.12 ±0.26	1.147 ±0.424	0.670
Creatinine after procedure (mg/dl) (mean ± SD)	1.21 ± 0.36	1.214 ± 0.425	0.990
Difference in creatinine (mg/dl) (mean ± SD)	0.09 ± 0.02	0.066 ± 0.011	0.380
Sex (male) [n (%)]	66 (79.0)	61 (67.0)	0.087
Diabetes [n (%)]	29 (35.0)	41 (45.0)	0.076
Hypertension [n (%)]	27 (32.0)	47 (52.0)	0.024
Incidence of CIN [n (%)]	8 (9.5)	6 (6.6)	0.475

BMI: Body mass index; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglyceride; CIN: Contrast-induced nephropathy; PTX: Pentoxifylline; SD: Standard deviation

Table 2. Regression analysis showing the effect of multiple variables on contrast-induced nephropathy CIN) occurrence after administrating pentoxifylline (PTX)

Variables	OR (95% CI)	P
Sex	0.695 (0.19-2.59)	0.588
Age	1.019 (0.98-1.07)	0.399
Hypertension	0.586 (0.18-1.96)	0.386
Diabetes history	0.830 (0.17-4.00)	0.817
Hematocrit	0.924 (0.85-1.00)	0.051
Smoking	1.437 (0.33-6.26)	0.629
Baseline creatinine	0.304 (0.042-2.19)	0.237
Volume of contrast use	1.005 (0.99-1.01)	0.083
PTX use	0.822 (0.24-2.78)	0.750

OR: Odds ratio; CI: Confidence interval; PTX: Pentoxifylline

Discussion

The key finding of this study is that although CIN occurrence was shown to be less in the group with prophylactic oral PTX, this reduction was not significantly different (P = 0.475). There is not any animal study about the preventive effect of PTX in CIN. However, there is only one clinical study about this preventive effect by Firouzi et al. in 2012.[15] Similarly, they also found that PTX could reduce, though not significantly, the occurrence of CIN in patients undergoing angioplasty.

Our study was single blind, and laboratory staffs that measured the serum creatinine were blinded to the treatment status of the patients. Our patients' demographic data and baseline risk factors for CIN were similar in the two groups, except for the significantly higher prevalence of hypertension and hematocrit in the PTX group. There was a significant difference in volume of Vesipaque between control and PTX group; however, this was not correlated significantly with the occurrence of CIN which could be the result of selecting patients with normal renal function in this study.

Busch et al.[5] revealed that the incidence of CIN is significantly lower in low-risk population after coronary angioplasty, and as we excluded patients with creatinine level of more than 1.5 mg/dl, the low incidence of CIN in both groups was predictable. Moreover, we reported the overall incidence of CIN in the control group to be 9.5%. This was recorded 13.69% in Firouzi et al. study,[15] which was comparable to the reported incidence of CIN in unselected populations.[1]

Prophylactic oral administration of PTX showed a trend toward non-significant reduction of CIN occurrence (8 patients in control and 6 patients in PTX group). However, our two groups were not exactly comparable with each other, and after performing the logistic regression analysis, the PTX independent role in reducing CIN was found to be not significant (P = 0.750).

In our study, low rate of CIN in both groups and a non-significant difference between the groups could be due to the selection of low-to-moderate risk patients and excluding patients at higher risk. Hence, it is possible that the selection of patients

with higher risk would have shown the efficacy of PTX more prominently. In addition, adding PTX to N-acetylcysteine and its synergistic effects in preventing CIN could also be tested which might reduce the probability of CIN.

Conclusion

The authors recommend that oral administration of PTX in patients with myocardial infarction and low-to-moderate risk of CIN undergoing coronary angioplasty has a non-significant reduction effect on CIN. Performing larger trials in higher risk patients is suggested to determine the probable protective role of PTX.

Acknowledgments

The authors would like to thank all participating patients for their cooperation and for their permission to publish this article.

Conflict of Interests

Authors have no conflict of interests.

References

1. McCullough P. Renal complications of contrast media. In: King SB 3rd, Yeung AC, Editors. Interventional Cardiology. New York, NY: McGrawHill Medical; 2007.
2. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 1997; 103(5): 368-75.
3. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 2002; 105(19): 2259-64.
4. Best PJ, Lennon R, Ting HH, Bell MR, Rihal CS, Holmes DR, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. J Am Coll Cardiol 2002; 39(7): 1113-9.
5. Busch SV, Jensen SE, Rosenberg J, Gogenur I. Prevention of contrast-induced nephropathy in STEMI patients undergoing primary percutaneous coronary intervention: a systematic review. J Interv Cardiol 2013; 26(1): 97-105.
6. Pyxaras SA, Sinagra G, Mangiacapra F, Perkan A, Di Serafino L, Vitrella G, et al. Contrast-induced nephropathy in patients undergoing primary percutaneous coronary intervention without acute left ventricular ejection fraction impairment. Am Cardiol 2013; 111(5): 684-8.
7. Chiou YL, Shieh JJ, Lin CY. Blocking of Akt/NF-kappaB signaling by pentoxifylline inhibits platelet-derived growth factor-stimulated proliferation in Brown Norway rat airway smooth muscle cells. Pediatr Res 2006; 60(6): 657-62.
8. Yavari V, Ostovan MA, Kojuri J, Afshariani R, Hamidian Jahromi A, Roozbeh J, et al. The preventive effect of pentoxifylline on contrast-induced nephropathy: a randomized clinical trial. Int Urol Nephrol 2014; 46(1): 41-6.
9. Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC. Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. Ann Intern Med 2008; 148(4): 284-94.
10. Brar SS, Shen AY, Jorgensen MB, Kotlewski A, Aharonian VJ, Desai N, et al. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. JAMA 2008; 300(9): 1038-46.
11. Roozbeh J, Hamidian Jahromi A, Sharifian M, Pakfetrat M, Afshariani R. Protective effect of pentoxifylline on contrast induced nephropathy. Saudi J Kidney Dis Transpl 2008; 19(6): 985-6.
12. Spargias K, Alexopoulos E, Kyrzopoulos S, Iokovis P, Greenwood DC, Manginas A, et al. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. Circulation 2004; 110(18): 2837-42.
13. Zhang J, Fu X, Jia X, Fan X, Gu X, Li S, et al. B-type natriuretic peptide for prevention of contrast-induced nephropathy in patients with heart failure undergoing primary percutaneous coronary intervention. Acta Radiol 2010; 51(6): 641-8.
14. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol 2004; 44(7): 1393-9.
15. 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.

How to cite this article: Eshraghi A, Naranji-Sani R, Pourzand H, Vojdanparast M, Morovatfar N, Ramezani J, et al. **Pentoxifylline and prevention of contrast-induced nephropathy: Is it efficient in patients with myocardial infarction undergoing coronary angioplasty?** ARYA Atheroscler 2016; 12(5): 238-42.