International Pharmacy Acta. 2021;4(1):e11
Clinical Research Article
OPEN ACCESS
ISSN: 2645-3266

The Effects of Oral Pentoxifylline on the Prevention of Contrast-Induced Nephropathy in Patients with Chronic Kidney Disease and Normal Renal Function: A Randomized Clinical Trial

Fatemeh Yasari[a], Farah Naghashzadeh[b], Saghar Barati[c] , Farzaneh Dastan[a,c,*]

a. Chronic Respiratory Diseases Research Center (CRDRC), National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran.
b. Lung Transplantation Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran.
c. Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Article Info:
Received: July 2021
Accepted: October 2021
Published online: October 2021

*** Corresponding Author:**
Farzaneh Dastan
Email:
fzh.dastan@gmail.com

Abstract:

Introduction: Finding preventive methods for Contrast-Induced Nephropathy (CIN) is essential for reducing the burden of complications. In this context, anti-oxidant agents such as pentoxifylline can be viable options. This study aimed to determine the effects of oral pentoxifylline on the prevention of contrast induced nephropathy in patients undergoing angiography.

Methods and Results: In this randomized clinical trial 96 patients with chronic kidney disease (CKD) and 96 subjects with normal renal function were included and randomly assigned to receive either pentoxifylline or placebo. The Incidence of CIN was determined and compared between the groups. The incidence of CIN in healthy subjects receiving pentoxifylline or placebo was 4 (8.3%) and 2 (4.16%), respectively. (P-value = 1). The incidence of CIN in patients with CKD in the pentoxifylline and placebo group was 5 (10.41%) and 12 (25%) respectively. (P-value = 0.58).

Conclusion: According to the obtained results, there was no difference between patients with CKD and those with normal renal function in terms of the pentoxifylline effects on the prevention of Contrast Induced Nephropathy.

Keywords: Pentoxifylline; Angiography; Contrast-Induced Nephropathy; Prevention

Please Cite this article as: Yasari F., Naghashzadeh F., Barati S., Dastan F. The Effects of Oral Pentoxifylline on the Prevention of Contrast-Induced Nephropathy in Patients with Chronic Kidney Disease and Normal Renal Function: A Randomized Clinical Trial. Int. Pharm. Acta. 2021;4(1):e11
DOI: https://doi.org/10.22037/ipa.v4i1.35349

1. Introduction

Contrast-Induced Nephropathy (CIN) is the most frequent cause of acute renal failure in hospitalized patients. Previous reports indicated that CIN occurs in 4 to 20% of patients following intra-arterial administration after coronary angiography (29). It has become the third common cause of iatrogenic acute renal failure due to the growing use of contrast in recent diagnostic procedures, pushing individuals to an increased risk of death. Furthermore, CIN leads to increased? risk of morbidity and higher hospitalization costs (1-4).

Pentoxifylline (PTX), categorized as one of the Phosphodiesterase 4 (PDE4) inhibitors, reduces platelet aggregation and fibrinogen, affecting neutrophils and inflammatory mediators. In addition, this substance is an antioxidant and a lipid peroxidation reducer that may prevent the aforementioned type of nephropathy (5).

The contrasts, especially Iodine-containing types, are important factors in renal tubular damage and Acute Tubular Necrosis (ATN), occurring mostly in a vast number of medical conditions such as diabetes mellitus, Chronic Kidney Disease (CKD), Congestive Heart Failure (CHF), fluid loss, hypotension (6-9), and multiple myeloma (10-15). Studies have pointed to the higher risk of CIN occurring in the primary Percutaneous Coronary Intervention (PCI) (16, 17). Some researchers have focused on inflammatory biomarkers, such as C-reactive Protein (CRP), to find a direct correlation with CIN (18-20).

Few studies have evaluated the protective effects of PTX against CIN (21, 22). Firouzi et al. illustrated this effect during angioplasty and concluded no beneficial effects. Busch and Eshraghi et al. raised the issue of protective effects of PTX in angiography in 2013 and 2016 and recommended administering CIN preventive oral medications in high-risk patients. (24, 25) These effects were confirmed by Yang et al. in 2015 in China on animals. (26) On the contrary, having studied 199 patients, Yavari et al. found no significant protective effect of PTX on CIN reported in 2014 (27).
The current study aimed to compare the protective effects of PTX on CIN in patients with or without CKD when administered before angiography.

2. Materials & Methods

2.1. Subjects and grouping

Through a randomized clinical trial, patients with chronic stable angina who were candidates for coronary angiography were divided into two groups regarding the presence of CKD or not.
The group of CKD included angiography candidates with Glomerular Filtration Rate (GFR) between 30-65 ml/min who were referred to Dr. Masih Daneshvari Hospital. Non-CKD patients consisted of individuals with creatinine clearance of greater than 65 ml/min. The creatinine clearance was calculated based on Cockcroft-Gault formula. The inclusion criteria consisted of patient with ischemic heart disease who were candidates for coronary angiography with creatinine clearance of greater than 30 ml/min. The patients with creatinine clearance lower than 30 ml/min or patients under hemodialysis were excluded from the study. The control group included angiography candidates with normal renal function. Each group was further subcategorized into two subgroups: (a) the control group who received 1cc/kg/h normal saline and (b) the interventional group who received 400 mg oral PTX three times a day the day before coronary angiography. The contrast used in the trial was iodixanol (Visipaque®) and the volume used in the setting was 30-50 cc. Patients with acute infectious diseases, uncompensated acute heart failure, and known blood disorders as well as the ones currently receiving chemotherapy and dialysis were excluded.

2.2. Demographics and laboratory variables

All the participants were asked to provide their medical background and demographic information through a specially designed questionnaire. Then, the investigators explained the aims and the process of the study before handing out personal consent forms.
Laboratory parameters including Blood Urea Nitrogen (BUN), serum Creatinine (Cr), Complete Blood count (CBC), CRP, serum albumin, and urinalysis (U/A) were assessed upon admission and 24 hours after angiography. The patients' creatinine clearance was calculated using Cockroft-Gault equation.
Serum Cr and serum protein/creatinine ratio were evaluated the day before angiography, immediately after the procedure and also, 24 hours later.

2.3. Outcome measure

The main outcome of the study was to evaluate the incidence of CIN between the two groups and subgroups based on kidney disease improving global outcomes (KDIGO) criteria (30). CIN was defined as an elevation of serum creatinine (Scr) of more than 25% or ≥0.5 mg/dl (44 µmol/l) from baseline within 48 h after excluding other factors that may cause nephropathy, such as hypotension and urinary obstruction (30).

2.4. Statistical analysis

Data were analyzed by SPSS 25. The indicators of mean and standard deviations were reported as the central indices for quantitative variables while absolute and relative frequencies were reported for qualitative parameters using Chi-Square and Fisher's exact tests, respectively. The significance level was considered when P-value was < 0.05 and the confidence interval (CI) was 95% to attain the study power of 0.8.

2.5. Ethics

The current study was registered on "IRCT.ir" under the code: IRCT20161219031464N4, after being approved by the Ethics Committee of "NRITLD", coded IR.SBMU.NRITLD.REC.1399.039. In line with the Declaration of Helsinki, all the participants gave their written informed consents upon being informed of the aim and importance of the present study. Patients were allowed to quit the study of their own volition.

3. Results

In total, 192 patients including 96 with CKD and 96 with healthy kidney were included in the study. Table 1 shows the Gender status of the patients.

Table 1. Gender status of the patients.

Kidney Function		Gender		Total N (%)
		Male n (%)	Female n (%)	
Normal	Pentoxifylline	33 (68.8%)	15 (31.3%)	48 (100%)
	Control	25 (52.1%)	23 (47.9%)	48(100%)
CKD	Pentoxifylline	30 (62.5%)	18 (37.5%)	48(100%)
	Control	32 (66.7%)	16 (33.3%)	48(100%)

Table 2 shows age status of the patients. Age distribution was quite close in all of the groups showing no statistical difference in age between healthy and CKD groups.

Table 2. Age status of the patients.

Kidney Function		Age (year) Mean±SD
Normal	Pentoxifylline	56.21 ± 10.88
	Control	56.35 ± 10.66
CKD	Pentoxifylline	59.96 ± 9.17
	Control	63.15 ± 10.86

The history of diabetes mellitus, hypertension, and chronic heart failure in all the participants was evaluated. Data are presented in table 3.

Table 3. Past medical history of the patients.

Past medical history		Kidney function		Total n (%)
		Normal n (%)	CKD n (%)	
DM	PTX	12 (12.5)	32 (33.3)	44 (45.8)
	Control	20 (20.8)	30 (31.2)	50 (54.2)
HTN	PTX	12 (12.5)	22 (22.9)	34 (35.4)
	Control	19 (19.8)	22 (22.9)	41 (42.7)
CHF	PTX	5 (5.2)	5 (5.2)	10 (10.4)
	Control	10 (10.4)	12 (12.5)	22 (22.9)

DM: Diabetes Mellitus, HTN: Hypertension, CHF: Congestive Heart Failure;

The incidence of contrast-induced nephropathy was finally compared between different groups (Table 4). The results of the Chi-square test revealed no significant difference between them.

Table 4. The incidence of contrast-induced nephropathy between groups.

Kidney Function		Incidence of Contrast Induced Nephropathy n(%)	Total n (%)	P-Value
Normal	Pentoxifylline	4 (8.3%)	48 (100%)	1.00
	Control	2 (4.2%)	48(100%)	
CKD	Pentoxifylline	5 (10.4%)	48(100%)	0.58
	Control	12 (25.0%)	48(100%)	

4. Discussion

Our study did not show any statistically significant differences in the incidence of Contrast-Induced Nephropathy among pentoxifylline users and controls. The present study attempted to compare the occurrence rate of CIN after pentoxifylline administration in the groups with and without kidney failure and evaluated the risk involved under normal and abnormal kidney function in the process of angiography. The rate of CIN was almost the same in patients with healthy kidneys, while controls had a slightly higher rate of CIN than the individuals who took PTX.

Given the globally growing body demand for angiography and the increasing prevalence of renal failure, it is necessary to focus on the risk of contrast-induced nephropathy, even in patients with normal kidney function. Pentoxifylline, as an anti-inflammatory and antioxidant medication, may still prevent the occurrence of CIN despite no strong confirmation throughout the current study. There are only a few studies that have assessed the role of PTX in this regard. (21, 22) Firouzi et al. suggested employing the beneficial role of PTX in preventing CIN after angiography despite scant evidence. (23)

A year later, Busch et al. explained that the occurrence of CIN was obviously reduced among patients with low risk of complications (24); however, we found no significant difference in this regard. On the contrary, working on Myocardial Infarction (MI) cases in 2016, Eshraghi et al. disclosed a relatively lower occurrence of CIN after angioplasty when PTX was previously administered to evaluate the preventive effects of PTX for CIN. (25) The difference in findings may result from different doses of PTX and/or the frequencies of known risk factors or comorbidities between the studies.

In Ireland, a review article by Ahmad et al. in 2018 confirmed the reduced risk of CIN due to the anti-inflammatory and antioxidant effects of PTX (5). Our study showed a need for greater research on the matter, especially with different doses, and also, considering many other risk factors for the evaluation.

Similar to our process, Yavari et al. (2014) studied 199 candidates of angiography in Iran and found no significant effect of PTX on CIN prevention (27), while Yang et al. confirmed the effect of this medication on animals in China in 2015 (26).

Through a review article published in 2017, Chen et al. found that despite anti-inflammatory, anti-proliferative, and anti-fibrotic effects of several medical conditions and given imperfect methodologies and sample sizes, there was no supportive evidence for reno-protective benefits in terms of PTX yet (28).

5. Conclusion

The present study could not confirm the preventive effects of oral PTX against contrast-induced nephropathy after angiography. However, more studies should be conducted with different doses to ensure its positive results on animals. Greater focus should be dedicated to more accurate monitoring of CIN risk factors as well as demographic, clinical, and paraclinical parameters that may affect the occurrence of CIN and the effectiveness of PTX in this regard.

Abbreviations

CIN, Contrast-Induced Nephropathy
PTX, Pentoxifylline
PDE4, Phosphodiesterase 4
ATN, Acute Tubular Necrosis
CKD, Chronic Kidney Disease
CHF, Congestive Heart Failure
PCI, Percutaneous Coronary Intervention
CRP, C-reactive Protein
GFR, Glomerular Filtration Rate
BUN, Blood Urea Nitrogen
Cr, Creatinine
CBC, Complete Blood count
U/A, Urinalysis
CI, Confidence Interval
MI, Myocardial Infarction

Acknowledgements

This study was approved and supported by Shahid Beheshti University of medical sciences.

Conflict of interest

None.

Funding/ Support

None.

Authors' ORCIDs

Farzaneh Dastan:
https://orcid.org/0000-0001-7253-4333

References

1. Caixeta A, Mehran R. Evidence-based management of patients undergoing PCI: contrast-induced acute kidney injury. *Catheter Cardiovasc Interv* 2010; 75: S15-20.
2. Narula A, Mehran R, Weisz G, Dangas GD, Yu J, Ge´ne´reux P, et al. Contrast-induced acute kidney injury after primary percutaneous coro- nary intervention: results from the HORIZONS-AMI substudy. Eur Heart J 2014; 35:1533-40.
3. McCullough PA, Adam A, Becker CR, Davidson C, Lameire N, Stacul F, et al. CIN Consensus Working Panel. Epidemiology and prognostic implications of contrast-induced nephropathy. Am J Cardiol 2006;98: 5K-13K.
4. Shaker OG, El-Shehaby A, El-Khatib M. Early diagnostic markers for contrast nephropathy in patients undergoing coronary angiography. Angiology 2010; 61(8):731-73.
5. Ahmed K, McVeigh T, Cerneviciute R, et al. Effectiveness of contrast-associated acute kidney injury prevention methods; a systematic review and network meta-analysis. BMC Nephrol. 2018 Nov 13;19(1):323.
6. Koda-kimble MA, Young, L.Y. Applied Therapeutics The clinical use of Drugs, 7th edition, USA 2001: 23-29.
7. Lasser EC. Contrast media for urography: In Pollach HM, ed. Clinical urography: An atlas and text book of Urological Imaging, Vol 1. philalelphia, pa: WB Saunders Co; 1990: 23-36.
8. Moore RD, Steinberg EP, Powe NR. Nephrotoxicity of high osmolality versus low-osmolality contrast media:randomized clinical trial. Radiology 1992; 189:649-55.
9. Parfery PS, Griffiths SM, Barrett BJ. Contrast material-induced renal failure in patient with diabetes mellitus, renal insufficiency, or both: a prospective controlled study. Negl J Med 1989; 320:143-9.
10. Pappy R, Stavrakis S, Hennebry TA, Abu-Fadel MS. Effect of statin therapy on contrast-induced nephropathy after coronary angiography: a meta-analysis. Int J Cardiol. 2011;151(3):348-53
11. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. N Engl J Med 1989; 320:143.
12. Rudnick MR, Goldfarb S, Wexler L, et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. The Iohexol Cooperative Study. Kidney Int 1995; 47:254.
13. Davidson CJ, Hlatky M, Morris KG, et al. Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization. A prospective trial. Ann Intern Med 1989; 110:119.
14. Schwab SJ, Hlatky MA, Pieper KS, et al. Contrast nephrotoxicity: a randomized controlled trial of a nonionic and an ionic radiographic contrast agent. N Engl J Med 1989; 320:149.
15. Cigarroa RG, Lange RA, Williams RH, Hillis LD. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. Am J Med 1989; 86:649.
16. Lautin EM, Freeman NJ, Schoenfeld AH, et al. Radiocontrast-associated renal dysfunction: incidence and risk factors. Am J Roentgenol 1991; 157:49.
17. Marenzi G, Lauri G, Assanelli E, et al. Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. J Am Coll Cardiol. 2004;44(9):1780-5.
18. 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.
19. Goldenberg I, Matetzky S. Nephropathy induced by contrast media: pathogenesis, risk factors and preventive strategies. CMAJ. 2005;172(11):1461-71.
20. Akcay A, Nguyen Q, Edelstein CL. Mediators of inflammation in acute kidney injury. Mediators Inflamm. 2009; 2009:137072.
21. 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
22. Tintinalli JE. Tintinalli's emergency medicine: a comprehensive study guide. 7th edition. 2011
23. 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
24. Busch SV, Jensen SE, Rosenberg J, Gögenur I J Interv Cardiol. Prevention of contrast-induced nephropathy in STEMI patients undergoing primary percutaneous coronary intervention: a systematic review. J Interv Cardiol. 2013; 26(1):97-105.
25. Eshraghi A, Naranji-Sani R. 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.
26. Yang SK, Duan SB, Pan P, Xu XQ, Liu N, Xu J. Preventive effect of pentoxifylline on contrast-induced acute kidney injury in hypercholesterolemic rats. Exp Ther Med. 2015; 9(2):384-8.
27. Yavari V, Ostovan MA, Kojuri J, et al. The preventive effect of pentoxifylline on contrast-induced nephropathy: a randomized clinical trial. Int Urol Nephrol. 2014; 46(1):41-6.
28. Chen YM, Chiang WC, Lin SL, and Tsai TJ. Therapeutic efficacy of pentoxifylline on proteinuria and renal progression: an update. Journal of Biomedical Science 2017; 24:84.