



Prophylactic Effect of Theophylline in Renal Contrast Nephropathy after Coronary Angiography

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Abstract

Background: Contrast nephropathy will increase mortality up to 30% following angiographic procedures. Adenosine is a crucial mediator of contrast-induced nephropathy. The purpose of this study was to investigate whether the adenosine antagonist Theophylline reduces the incidence of CN after coronary angiography.

Methods: In this randomized, double-blind, placebo-controlled clinical trial study, carried out from February 2004 to September 2005 at the Fatemeh Zahra Hospital, 70 patients who were undergoing coronary angiography were divided into two groups. Case group (n=35) received oral Theophylline 200 mg bid. 24 h before and for 48 h after angiography. The control group (n=35) received placebo. Serum Na⁺, K⁺, blood urea nitrogen (BUN), creatinine, glomerular filtration rate (GFR) were measured before and after angiography.

Results: In the case group there were no significant change in serum creatinine (0.90±0.7 vs. 0.92±0.3 mg/dl), BUN (17.76±7.8 vs. 19.35±9.6 mg/dl), GFR (83.01±26.7 vs. 81.36±24.9 ml/min) Na⁺ (139.08±3.6 vs. 138.54±2.7 mEq/l) and K⁺ (4.30±0.4 vs. 4.19±0.3 mEq/l). In the control group, there was a significant fall in GFR after angiography (86.10±34.8 vs. 80.7±30.4 ml/min, P=0.03). Following angiography, there were no significant difference in serum creatinine, BUN, GFR, Na⁺ and K⁺ level between the two groups. None of the patients in either group faced contrast induced nephropathy.

Conclusion: Theophylline does not appear to add a protective role in preventing against contrast induced nephropathy in patients undergoing angiographic procedures.

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Introduction

Contrast-induced nephropathy (CN) is an important cause of renal failure and is related to greater mortality and morbidity rates and health care costs.¹ It is the third leading cause of ARF in hospitalized patients.² The incidence of CN, varies from 0 to 23% in patients undergoing cardiac catheterization and angiography, depending on the definition of CN used and the risk profile of the patient population included in the study.³ CN increases mortality up to 30% following angiographic procedures.⁴ Usually, CN is defined as a rise in serum creatinine of 25%, or 50% of the baseline value, and appears to be the result of a synergistic combination of direct tubular

epithelial cell toxicity and alterations in renal hemodynamics with renal modularly ischemia.⁵ Although the mediators of these changes are still not very clearly defined, but alterations in the metabolism of prostaglandins, nitric oxide, endothelin, and adenosine may play a role. Various preventive strategies have been employed to reduce the incidence of CN, which include administration of intravenous fluids, furosemide, mannitol, low-dose dopamine, atrial natriuretic peptide (ANP), and calcium-channel blockers.⁶⁻¹⁵ However, the results of most studies are conflicting, and more evidence is required before any therapeutic measures can be recommended for routine

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use. Since adenosine may have a role in the pathogenesis of CN, hence an adenosine antagonist (Theophylline) has been investigated as a means for reducing the risk of CN.^{12, 16-18} However; data on use of oral Theophylline for this purpose is scant and inconsistent. The purpose of this prospective study was to determine whether alterations in renal function after administration of radio contrast agents can be prevented by oral Theophylline.

Methods

This study was a randomized, double-blind, placebo-controlled clinical trial about the role of Theophylline in contrast induced nephropathy as compared with placebo. The study was carried out from February 2004 to September 2005 at the Fatemeh Zahra Hospital, affiliated with Mazandaran University of Medical Sciences, Iran. The study protocol was approved by the institutional ethics Committee and informed written consent was obtained from all the patients under study.

Patients

Patients were the Iranian male and female living in southern coastline of the Caspian Sea who met the inclusion criteria of the study. We prospectively studied 70 consecutive patients who were referring to the Institute for coronary angiography. All of them were at high risk of CN (had at least one of the following factors: age>65 years, diabetes mellitus, history congestive heart failure, recent use of NSAIDs or ACE inhibitors or amino glycoside drugs). Exclusion criteria included, pre-existing renal failure with serum creatinine 3.0 mg/dl, maintenance dialysis, a history of acute myocardial infarction, left ventricular ejection fraction (EF) <25%, allergy to contrast media, pregnancy, diuretic therapy and using of Theophylline until one week before angiography.

Study Procedures

Prior to angiography, in all patients, the serum level of Na⁺ and K⁺ (Medica, USA), blood urea nitrogen (BUN) and creatinine (CIBA-Corning, USA) was measured. Glomerular

filtration rate (GFR) was calculated using Cockcroft-Gault formula.¹⁹ The patients were randomly divided in two groups as following: case group (*n*=35), who underwent routine coronary angiography, and received oral Theophylline (pharmashimi, Iran) 200 mg bid. 24 hours pre to 48 hours post angiography. Control group (*n*=35), received placebo (prepared in pharmacology institute of Mazandaran University of Medical Science) with the same procedure. The placebo was prepared in identical size and color packages. The Two groups matched for age and diabetes mellitus. In addition, all patients received intravenous normal saline (1 ml/kg/h) commencing 12 hours before and continued for 12 hours after the procedure. Coronary angiography was performed using a high-osmolar contrast medium, 100 cc of 76% Urografin (Schering AG, Berlin, Germany). All laboratory tests were repeated 72 hours after angiography. All of the follow up evaluations and laboratory tests were done by individuals who were blind to the Theophylline and control groups.

Statistical analysis

Statistical analysis of all the qualitative results of this study was done by chi-square test. All data are expressed as mean±SD. The significance of a difference between two groups was calculated using independent t-test with *P* < 0.05 used as the significant level.

Results

A total of 70 patients entered this study according to the inclusion criteria and were randomly allocated in either Theophylline (21 male and 14 female, mean age 62.1±9 years) or control group (22 male and 13 female, mean age 61.3±10 years). There was no difference between the groups in terms of mean age. Prior to angiography, the two groups had comparable serum creatinine (0.90±0.7 mg/dl in Theophylline group vs. 0.93±0.3 mg/dl in control group) and BUN (17.76±7.8 vs. 19.04±10.9 mg/dl). There were no significant differences in serum creatinine and BUN. There were also no significant differences in serum Na⁺ (139.08±3.6 vs. 140.02±3.5) and K⁺ (4.3±0.4 vs. 4.3±0.5). The mean GFR as estimated by the plasma method was also not significantly different between the two groups (83.01±26.7 vs. 86.10±34.8 ml/min) (Table 1).

Table 1. Baseline parameters in the case and the control groups*

	Control group	Theophylline group	P value
Age (years)	61.3±10	62.1±9	P<0.05
Diabetes mellitus	n=19 (54%)	n=18 (51%)	P<0.05
Serum creatinine (mg/dl)	0.93±0.3	0.90±0.7	NS
BUN (mg/dl)	19.04±10.9	17.76±7.8	NS
Serum sodium (mEq/l)	140.02±3.5	139.08±3.6	NS
Serum potassium (mEq/l)	4.30±0.5	4.30±0.4	NS
GFR (ml/min)	86.10±34.8	83.01±26.7	NS

BUN, Blood Urea Nitrogen; GFR, Glomerular Filtration Rate; NS, Non Significant

* Data are stated as mean ± SD



Following angiography, there were no significant differences in serum creatinine concentrations (0.92±0.3 mg/dl in Theophylline group vs. 0.96±0.3 mg/dl in control group) and BUN levels (19.35±9.6 vs. 20.35±9.2 mg/dl). The mean GFR did not differ significantly, either (81.36±24.9 vs. 80.70±30.4 ml/min). Mean of serum Na⁺ (138.54±2.7 vs. 139.58±3.3) and K⁺ (4.19±0.3 vs. 4.29±0.6) were also similar in the two groups. On the other hand, there were no significant changes

in serum creatinine concentrations, BUN, Na⁺ and K⁺ levels in the Theophylline group after angiography. The mean GFR did not change significantly in this group as compared with pre-angiographic values. In contrast, in the control group, there was a significant fall in GFR following angiography (86.10±34.8 vs. 80.7±30.4 ml/min, *P*=0.03) (Table 2). None of the patients in either group faced contrast induced nephropathy (more than a 25% rise in serum creatinine).

Table 2. Renal parameters in the case and the control groups*

	Control group			Theophylline group		
	Before	After	P value	Before	After	P value
Serum creatinine (mg/dl)	0.93±0.3	0.96±0.3	NS	0.90±0.7	0.92±0.3	NS
BUN (mg/dl)	19.04±10.9	20.35±9.2	NS	17.76±7.8	19.35±9.6	NS
GFR (ml/min)	86.10±34.8	80.70±30.4	0.03	83.01±26.7	81.36±24.9	NS
Serum sodium (mEq/l)	140.02±3.5	139.58±3.3	NS	139.08±3.6	138.54±2.7	NS
Serum potassium (mEq/l)	4.30±0.5	4.29±0.6	NS	4.30±0.4	4.19±0.3	NS

BUN, Blood Urea Nitrogen; GFR, Glomerular Filtration Rate; NS, Non Significant

* Data are stated as mean ± SD

Discussion

Renal insufficiency presents a challenge in patients with acute coronary syndromes. Nephrotoxicity due to the administration of radio contrast agents is a common but preventable cause of acute renal failure.²⁰⁻²² Various strategies for the prevention of contrast-induced nephropathy (CN) have been studied, which had conflicting results. Adenosine has been shown to reduce renal blood flow and glomerular perfusion pressure by means of A₁-receptor-mediated renal afferent arteriolar vasoconstriction and A₂-receptor-mediated efferent arteriolar vasodilatation. The administration of contrast in human subjects is known to be associated with the production of endogenous intra renal adenosine. The vaso constrictive and potentially deleterious effects of adenosine on renal blood flow can be significantly reduced with adenosine antagonists (e.g. Theophylline) and potentiated by dipyridamole, an inhibitor of adenosine re-uptake. In this study we didn't find any result indicating the effect of Theophylline on contrast nephropathy.

A study by Kapoor *et al.* prospectively assessed the role of oral Theophylline in the prevention of contrast nephropathy after angiography and they found that, Patients who received prophylactic oral Theophylline had a significantly lower risk of contrast nephropathy as compared with the non Theophylline receivers.²³

Erley *et al.* studied the role of intravenous Theophylline (5 mg/kg) and found that, in comparison to placebo, it prevented the fall in creatinine, inulin, and para-aminohippurate clearances. However, in their cohort study,

including only 15% diabetics, there were no significant

changes in renal function in any of the patients under study.¹⁶ Abizaid *et al.* in the study comparing saline hydration, saline hydration plus dopamine, and saline hydration plus intravenous Aminophylline infusion, reported that neither dopamine nor Aminophylline reduced the incidence of CN.¹² Data on oral Theophylline in the prevention of CN is scant and contradictory. Katholi *et al.* studied the effect of 2.88 mg/kg oral Theophylline (every 12 hour, four doses) compared with placebo in the prevention of CN. They reported that although serum creatinine did not change significantly, but Theophylline completely prevented the fall in creatinine clearance within 24 hours after non-ionic contrast and reduced the level approximately in half.¹⁷ Another study, however, using 810 mg oral Theophylline, indicated that it did not offer any benefit over routine saline hydration for the prevention of CN in patients with serum creatinine 1.5 mg/dl receiving contrast media.²⁴ In our study, the increase of serum creatinine level didn't indicate contrast induced nephropathy and no patient required hemodialysis. The reason can be the exclusion of patients with moderate to severe renal failure (*Cr*≥3) from the study and the fact that all patients received adequate saline hydration. Although the difference of GFR among the two groups was not statistically significant, but estimation of GFR in the control group demonstrated a reduction, following angiography. It suggests the role of Theophylline in prevention of some functional kidney changes and contrast induced nephropathy.

We didn't observe any contrast induced nephropathy. Further studies are required to compare the efficacy of Theophylline monotherapy with that of saline hydration for

the prevention of contrast nephropathy.

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