COMPARISON OF DIFFERENT AGENTS ON RADIOGRAPHIC CONTRAST AGENT INDUCED NEPHROPATHY

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Aim: Nephropathy induced by contrast media (CM) still a problem in clinical practice and a variety of therapeutic interventions have been used in an attempt to prevent radiocontrast-induced nephropathy. However most of the published reports are placebo controlled studies and especially in patients with pre-existing renal insufficiency. Therefore, in this study we wanted to investigate and to compare the efficacy of not only one agent, but also N-acetylcysteine, theophylline, nifedipine and misoprostol in the prevention of RCIN in subjects without renal insufficiency.

Methods: We studied 97 non-diabetic patients without pre-existing renal insufficiency who received 100 ml low osmolar CM, Iomeprol or Iopamidol. Patients were randomized to five groups; Group S; only saline hydration (SH) used control group, group N; SH plus N-acetylcysteine, group M; SH plus misoprostol, Group N; SH plus nifedipine and Group T; SH plus theophylline. Patients were treated for three days and received 2000 ml saline i.v. each day. Serum creatinine and creatinine clearance were measured before and three days after CM application.

Results: We were able to observe RCIN in four patients in group T and one patient in group NAC. Serum creatinine level increased after administration of radiocontrast agent in group M and T.

Conclusion: We did not only observe any no additional advantage in administration of N-acetylcysteine (NAC), theophylline, nifedipine and misoprostol to SH alone in the prevention of RCIN but also an adverse effect of theophylline. Therefore, further studies with much more patients were included are necessary.

Key words: Misoprostol; n-acetylcysteine; nifedipine; radio contrast nephropathy; theophylline

INTRODUCTION

Radiocontrast agents are used frequently for several diagnostic applications due to development in imaging technologies and radiocontrast-induced nephropathy (RCIN) is seen at an increasing rate in clinical practice. Despite the development of low or iso-osmolar contrast media, renal failure induced by these agents has remained an important clinical problem (1). RCIN remains a common cause of renal failure in patients undergoing radiocontrast study and is currently the third leading cause of hospital-acquired renal failure (2-4). In addition, it is associated with significant in-hospital and long-term morbidity and mortality, and increases the costs of medical care by at least extending the hospital stay (5,6). Therefore, prevention of RCIN is essentially important in view of improving morbidity, mortality and also in ensuring good clinical outcomes.

In recent published reports a variety of therapeutic interventions, including saline hydration (7-9), calcium channel antagonist (Nifedipine) (10), adenosin receptor antagonist theophylline (11,12), N-acetylcysteine (NAC) (13,14) and misoprostol (15) administration have been employed to prevent radiocontrast-induced nephropathy. However, the recent published reports have been focused on to investigate the efficacy of different agents, are placebo controlled studies (7-14). Moreover, there is no report comparing different agents in the prevention of RCIN in patients without renal insufficiency. Therefore, in this study

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Table 1. Clinical characteristics and baseline laboratory parameters of the patients.

Parameters	S (n:20)	NAC (n:20)	M (n:20)	T (n:20)	N (n:17)	p
Age (years)	58.2±11.3	62.0±15.8	56.5±13.0	56.3±13.0	60.1±10.7	0.33
Male/Female	15/5	11/9	9/11	11/9	8/9	0.54
Serum BUN, mg/dL	19.1±11.5	19.8±8.9	22.3±13.6	19.5±7.7	20.0±7.2	0.87
Serum creatinine, mg/dL	0.88±0.23	0.78±0.19	0.85±0.19	0.84±0.27	0.87±0.17	0.85
Serum sodium, mEq/L	139.2±4.9	139.1±2.79	137.7±3.91	137.3±3.93	138.7±3.96	0.43
Serum potassium, mEq/L	4.16±0.49	4.25±0.50	4.13±0.53	4.55±0.68	4.11±0.74	0.24
Cr clearance, ml/min	89.3±36.9	100.6±39.6	95.1±31.0	113.4±42.3	90.2±35.1	0.55

S; only saline hydration used group, NAC; saline hydration plus N-acetylcysteine used group, M; saline hydration plus misoprostol used group, T; saline hydration plus theophylline used group , N; saline hydration plus nifedipine used group. Parametric values were expressed as means ± SD. Kruskal-Wallis Test was used to compare all groups.

we wanted to investigate and to compare the efficacy of not only one agent, but also N-acetylcysteine, theophylline, nifedipine and misoprostol in the prevention of RCIN in subjects without renal insufficiency.

MATERIAL AND METHODS
Study cohort

In this prospective randomized controlled study we wanted to investigate the efficacy of different four agents including N-acetylcysteine (NAC), theophylline (T), nifedipine (N) and misoprostol (M) in the prevention of RCIN, in those beneficial effects have been shown recently. In addition, we wanted to compare their effects in the prevention of RCIN with saline hydration alone.

Ninety-seven eligible patients receiving 100 ml non-ionic low osmolar radiocontrast agents Iomeprol 61.25 g/100 ml or Iopamidol 61.25 g/100 ml during diagnostic computed tomography were included into the study. Patients with diabetes mellitus, chronic renal failure, uncontrolled hypertension (systolic blood pressure was higher than 160 mmHg and/or diastolic blood pressure was higher than 100 mmHg) or hypotension (systolic blood pressure was lower than 90 mmHg), pregnancy, end-stage renal disease, renal transplantation, presence of dialysis history or contrast agent sensitivity and nephrotoxic drug usage including non-steroid anti-inflammatory drugs, aminoglycoside etc. were excluded. The study protocol was approved by the local ethical committee and all patients were included to the study after the written informed consent obtained from each volunteer.

RCIN definition

The guidelines on administering RCM provided by the European Society of Urogenital Radiology have shown that the elevation of serum creatinine (SCr) by ≥0.5 mg/dL or ≥25% within 3 days of RCM injection is defined as radiocontrast nephropathy (16). Thus, many investigators have employed either one or both as the criteria of radiocontrast nephropathy. Similarly, RCIN was defined as an elevation of serum creatinine by 0.5 mg/dL or ≥25% within three days of RCA injection in present study.

Randomization and study protocol

Except nifedipine used group, all groups comprised twenty patients and total 97 patients were randomized to 5 groups according to the following procedure;
Group S : 2000 ml 0.9% saline hydration alone, intra-venous (i.v.).
Group NAC : 2000 ml 0.9% saline hydration plus 600 mg/day NAC p.o.,
Group M : 2000 ml 0.9% saline hydration plus 400 mg/day misoprostol p.o.,
Group T : 2000 ml 0.9% saline hydration plus 200 mg/day theophylline p.o.,
Group N : 2000 ml 0.9% saline hydration plus 30 mg/day nifedipine p.o.

All patients were studied on an in-patient basis. All patients were treated for three days (pre-procedure, procedure and following day). Patients received hydration with 0.9% 2000 ml saline intravenously starting at least 24 hours before the application of radio-contrast agent and continued until 24 hours after. All patients

Table 2. Changes in serum creatinine and creatinine clearance between groups.

	Serum creatinine (mg/dL) Baseline	Serum creatinine (mg/dL) After treatment	p
Group S	0.88±0.23	0.87±0.24	0.70
Group NAC	0.78±0.19	0.80±0.17	0.70
Group M	0.85±0.19	0.91±0.24	0.02
Group T	0.84±0.27	1.03±0.38	0.005
Group N	0.87±0.17	0.85±0.25	0.25
	Creatinine clearance (ml/min) Baseline	Creatinine clearance (ml/min) After treatment	
Group S	89.3±36.9	83.1±31.3	0.55
Group NAC	100.6±39.6	98.1±42.9	0.91
Group M	95.1±31.0	85.9±31.0	0.24
Group T	113.4±42.3	81.5±31.7	0.09
Group N	90.2±35.1	104.8±26.0	0.12

S; only saline hydration used group, NAC; saline hydration plus N-acetylcysteine used group, M; saline hydration plus misoprostol used group, T; saline hydration plus theophylline used group , N; saline hydration plus nifedipine used group. Wilcoxon rank test was used determine in changes between baseline and after treatment values.

were randomized to receive one of the following agents; theophylline (200 mg a day in the morning, Teokap SR, Nobel, Istanbul, TURKEY), N-acetylcysteine (600 mg a day in the morning, Asist, ADEKA, Istanbul, TURKEY), nifedipine (30 mg a day in the morning, Adalat crono, BAYER, Istanbul, TURKEY) or misoprostol (200 mg twice a day, Cytotec®-Searle-Ali Raif, ISTANBUL, TURKEY). All blood samples for routine laboratory parameters were drawn from antecubital vein.

Clinical characteristics and measurements

Each patient's clinical and demographic characteristics were recorded at the beginning of the study. Serum creatinine, blood urea nitrogen (BUN), plasma sodium, potassium levels and creatinine clearance were measured at both pre-procedure day and three days after contrast media application. All measurements were performed by standard methods at Süleyman Demirel University laboratories. Each group was compared with only saline hydration used control group to obtain additive and/or adverse effect of the agent in the prevention of RCIN. In addition the ratio of changes in serum creatinine and creatinine clearance were compared.

Statistical Analysis

Parametric values were expressed as means ± SD. P value <0.05 was considered statistically significant. Kruskal-Wallis Test was used to compare groups. Comparison of two groups was done by Mann-Whitney U test.

RESULTS
Patient characteristics

Ninety-seven non-diabetic patients aged 24 to 85 years, receiving 100 ml non-ionic low-osmolar radiocontrast agents Iomeprol 61.25 g/100ml or Iopamidol 61.25 g/100ml for diagnostic application, enrolled in this study and none of the patients was excluded during the study period. Fifty-four patients (55%) were male and forty-three (45%) patients were female. The mean age was 58.5±12.9 years. None of the patients required hemodialysis and had to prolong hospital stay due to azotemia. All groups were similar for age, gender, baseline serum BUN, creatinine, sodium, potassium levels and creatinine clearance (Table 1). However in Group M and Group T, mean serum creatinine level increased after administration of radiocontrast agent. Effects of different agents on serum creatinine level and creatinine clearance are shown in Table 2. We were able to observe RCIN in four patients (20%) in group T and one patient (5%) in group NAC.

DISCUSSON

The main finding of this study is that prophylactic administration of misoprostol, nifedipine, theophylline and N-acetylcysteine do not appear to prevent radiocontrast induced declines in kidney function and has not superiority compared to saline hydration alone in a patient population without renal insufficiency. However, prophylactic theophylline administration has not only beneficial

effect but also has side effect. This finding provides clinical evidence that, as opposed to animal study (17) adenosine receptor antagonist theophylline administration has not protective effect on prevention of RCIN.

This is a single center prospective randomized study and the number of patients is also limited. In addition, we did not include patients, who had diabetes mellitus and/or renal failure that are known risk factors for the development of RCIN. However, recently published reports were placebo controlled studies and focused on to investigate the efficacy of only one agent in the prevention of RCIN. Therefore this study is the first report comparing four different agents with saline hydration alone.

RCIN is a common cause of renal failure among hospitalized patients, and is recognized complication of diagnostic and therapeutic procedures in which intravenous contrast agent is required (2-4). Many important issues remain unresolved including the pathogenesis and treatment of this problem, and the relative nephrotoxicity of different radiocontrast agents. However little is known about mechanisms underlying RCIN. Direct toxic action on renal tubular cell, decrease in renal blood flow and increased oxidative stress had been considered to be involved in the pathogenesis of RCIN (2,18). Alterations in renal haemodynamics and direct tubular toxicity are common in the pathogenesis of RCIN. However, we found that RCIN rate was higher in group T than group N in present study. Therefore, we suggested that the development of contrast-medium nephropathy is affected especially by changes in renal hemodynamics rather than the oxidative stress.

The incidence of RCIN reported in the literature that included patients with pre-existing renal function or diabetes mellitus is between 12% and 26% (2, 9, 19, 20). However among patients without risk factors lower rate has been reported (21). However, RCIN developed in 5 patients (4 in group T and one in group NAC) and the incidence of RCIN was 5% in present study. In animal model theophylline has been successfully employed to improve renal function after induction of acute renal failure (17). However in present study, RCIN incidence was 20% in group

T and addition of theophylline 200 mg/day to saline hydration, increased the serum creatinine level. Despite recent published reports in patients with renal insufficiency (14, 15), we found that theophylline have had an adverse effect on RCIN. The specific pathways by which theophylline increase serum creatinine are uncertain. It could be speculated that the different distribution of adenosine receptors in healthy kidneys compared to damaged ones or the polymorphism of the adenosine receptor gene.

Renal tubular toxic damage and vasoactive mechanisms may be directly induced by contrast medium. Specifically, reactive oxygen species have been implicated as a contributory factor in RCN. Lipid peroxidation and tubular oxidative damage presumably could lead to transient renal dysfunction. Among patients with chronic renal failure, the administration of N-acetylcysteine, a thiol-containing antioxidant, in combination with saline hydration and a nonionic, low osmolal contrast agent has protected against contrast nephropathy in some studies (22-24). In contrast to these findings, benefits from acetylcystine have not been observed in other studies (25, 26). The mechanism of RCN prevention by NAC is not clear at present. Interference with serum creatinine determination and increased tubular secretion of creatinine (27) may misleadingly suggest renal protection.

In present study we were able to observe RCIN in only one patient but there was no significantly difference between baseline and after treatment serum creatinine levels in group NAC. Therefore, we conclude that acetylcystine has not beneficial effect.

Risk factors for the RCIN have been reported previously (28-31), especially presence of diabetes mellitus and chronic renal failure appear to be the most important predictors of RCIN. The incidence of RCIN was found lower than the other studies due to patients with renal insufficiency were excluded.

In conclusion, saline hydration is the main strategy in the prevention of RCIN. We did not observe any additional advantage in administration of NAC, nifedipine and misoprostol to saline hydration in the prevention of RCIN. Moreover, we experienced adverse effect

of theophylline. Therefore, theophylline should not be used for the prevention of RCIN. However adverse effects of theophylline and misoprostol could be investigated in further studies.

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