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Renal Protection for Coronary Angiography in Advanced Renal Failure Patients by Prophylactic Hemodialysis

A Randomized Controlled Trial

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Objectives We performed a study to determine whether prophylactic hemodialysis reduces contrast nephropathy (CN) after coronary angiography in advanced renal failure patients.

Background Pre-existing renal failure is the greatest risk factor for CN. Hemodialysis can effectively remove contrast media, but its effect upon preventing CN is still uncertain.

Methods Eighty-two patients with chronic renal failure, referred for coronary angiography, were assigned randomly to receive either normal saline intravenously and prophylactic hemodialysis (dialysis group; n = 42) or fluid supplement only (control group; n = 40).

Results Prophylactic hemodialysis lessened the decrease in creatinine clearance within 72 h in the dialysis group (0.4 ± 0.9 ml/min/1.73 m^2 vs. 2.2 ± 2.8 ml/min/1.73 m^2; $p < 0.001$). Compared with the dialysis group, the serum creatinine concentrations in the control group were significantly higher at day 4 (6.3 ± 2.3 mg/dl vs. 5.1 ± 1.3 mg/dl; $p = 0.010$) and at peak level (6.7 ± 2.7 mg/dl vs. 5.3 ± 1.5 mg/dl; $p = 0.005$). Temporary renal replacement therapy was required in 35% of the control patients and in 2% of the dialysis group ($p < 0.001$). Thirteen percent of the control patients, but none of the dialysis patients, required long-term dialysis after discharge ($p = 0.018$). For the patients not requiring chronic dialysis, 13 patients in the control group (37%) and 2 in the dialysis group (5%) had an increase in serum creatinine concentration at discharge of more than 1 mg/dl from baseline ($p < 0.001$).

Conclusions Prophylactic hemodialysis is effective in improving renal outcome in chronic renal failure patients undergoing coronary angiography. (J Am Coll Cardiol 2007;50:1015–20) © 2007 by the American College of Cardiology Foundation

Contrast nephropathy (CN) is a major complication after coronary intervention and is the third leading cause of hospital-acquired acute renal failure (1–4). Because preexisting renal dysfunction is the most important risk factor (1–4), the incidence of acute renal shutdown after coronary angiography (CAG) is quite high in patients with chronic renal failure. It has been reported that when serum creatinine (Cr) levels are >4.5 mg/dl, the likelihood of CN approaches 100% for diabetic patients and 60% for nondiabetic patients (5–7). When CN occurs in these high-risk patients, this could cause temporary renal deterioration or lead to permanent end-stage renal disease (ESRD) necessitating chronic dialysis.

Several interventions have been used to prevent CN, but only fluid supplements, low-osmolality contrast, a double dose of N-acetylcysteine, and reducing the dose of the contrast agent have been shown to be effective (8–15). These strategies were mainly investigated in the general population or in patients with mild renal insufficiency; methods for preventing CN in advanced renal failure patients remain unknown. Additionally, excessive fluid supplement is barely tolerated in patients with renal failure, especially when they have poor heart function.

Contrast media are excreted mainly by glomerular filtration. The elimination is slow in patients with chronic renal failure; therefore, it would make these vulnerable patients

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Abbreviations and Acronyms

CAG = coronary angiography
CN = contrast nephropathy
Cr = serum creatinine
CrCl = creatinine clearance
ESRD = end-stage renal disease

exposed to contrast media longer. It is known that contrast media can be effectively removed from the blood of patients with chronic renal failure by hemodialysis even faster than by kidney in normal subjects (16). Hemodialysis after contrast media exposure is hypothesized to be helpful in lessening CN. Therefore, we performed a prospective, randomized control trial to examine the efficacy of prophylactic hemodialysis in the prevention of CN in patients with advanced renal failure undergoing coronary procedures.

Methods

Participants. The study was performed between August 2003 and June 2006 in Kaohsiung Veterans General Hospital in Taiwan. Patients were considered eligible for the study if they were older than 20 years of age, had been referred for coronary angiography, and had a stable Cr concentration of more than 3.5 mg/dl with a change of <0.5 mg/dl in 1 month. Criteria for exclusion included pregnancy, lactation, intravascular administration of contrast medium within the previous 7 days, treatment with metformin or nonsteroidal anti-inflammatory drugs within the previous 48 h, exposure to nephrotoxic drugs within the previous 7 days, history of serious reactions to the contrast medium, newly diagnosed unstable diabetes, severe concomitant disease, renal transplantation, and ESRD necessitating chronic dialysis. Acetylcysteine, theophylline, dopamine, and mannitol were not used during the study. Angiotensin-converting enzyme inhibitors were allowed but were withheld on the day of radiographic investigation. The ethics committee of Kaohsiung Veterans General Hospital approved the study protocol, and all patients gave written, informed consent.

Procedures. All patients were given intravenous normal saline at 1 ml/kg/h for 6 h before and 12 h after contrast medium exposure, and then randomized to receive hemodialysis (dialysis group) or not (control group). In the dialysis group, dialysis was started as soon as technically possible after angiography, and the time interval from contrast exposure to initiation of dialysis was recorded. Hemodialysis was performed through a double-lumen intravenous femoral catheter placed before coronary angiography. The dialyzer was a high-flux polysulfone membrane (BS1.8, Toray Industries, Inc., Tokyo, Japan). The blood flow was 150 ml/min, the duration of dialysis was 4 h, and the dialysate flow was 500 ml/min. To lessen the hemodynamic changes, 200 ml normal saline priming was administered before dialysis and no fluid removal was prescribed in the dialysis group. The radiocontrast medium was nonionic iohexol (Omnipaque, GE Healthcare Technologies, Waukesha, Wisconsin), and the dose was recorded.

Follow-up. Creatinine clearance (CrCl) was measured by 24-h urine collection before and on the fourth day after coronary angiography. Additional measurements of Cr were performed in patients with acute renal failure (defined as an increase of Cr on the fourth day of more than 25% from baseline) every other day until dialysis started or renal function recovered and at discharge in all patients who did not need dialysis. Biochemical data were analyzed at a central laboratory. The primary end point was the change in CrCl between baseline and the fourth day. Secondary end points were the differences in Cr levels on the fourth day from baseline, peak Cr level during hospitalization, and Cr level at discharge. The numbers of patients with an increase in Cr level at discharge of at least 1.0 mg/dl above baseline and of patients that required emergent and permanent dialysis were also recorded. Emergent dialysis was performed if there was oliguria for more than 48 h despite the administration of more than 1,000 mg intravenous furosemide per day or if the level of serum potassium remained >6 mEq/l with or without electrocardiogram change despite the administration of oral kayexalate. Hemodialysis was discontinued when there was evidence of recovery of renal function, with the restoration of urine amount of >500 ml/day and improvement of CrCl >5 ml/min/1.73 m^2. The need for permanent dialysis was persistent with CrCl <5 ml/min/1.73 m^2.

Statistical analysis. When calculating sample size, we assumed a baseline CrCl of 12 ml/min/1.73 m^2. Assuming a decrease in the CrCl of 5 percent for the dialysis group, 20% for the control group and a common standard deviation of the decrease of 2.2 ml/min/1.73m^2; the inclusion of 34 subjects in each group allowed for a 2-sided significance level of 5% and 90% power. The data are expressed as mean ± SD or as proportions. To compare baseline variables between the 2 groups, Fisher exact test for categoric variables and Student unpaired *t* test for continuous variables were used. Changes in Cr values in the dialysis and control groups were assessed using repeated-measures analysis of covariance. Statistical analysis of the decrease in the CrCl from baseline to day 4 was performed using multiple regression. The covariates were age, gender, diagnosis of diabetes mellitus, hypertension, type of procedure, dose of contrast medium, prophylactic dialysis, and baseline CrCl. Age, contrast medium dose, and baseline CrCl were examined as continuous variables. A p value of <0.05 was considered to be of statistical significance. All calculations were computed with the aid of the SPSS 10.0 software package (SPSS Inc., Chicago, Illinois).

Results

A total of 3,724 patients who received coronary angiography were consecutively screened, and 318 patients had chronic renal insufficiency. Eighty-eight patients had ESRD necessitating chronic dialysis, 122 patients had Cr <3.5mg/dl, 18 patients refused to enter the study, and 90 were enrolled. They

Table 1 Clinical Characteristics of the Patients

	Dialysis Group (n = 42)	Control Group (n = 40)	p Value
Age (yrs)	65.3 ± 11.1	65.9 ± 11.2	0.780*
Male	27 (64%)	26 (65%)	0.946†
Body weight (kg)	63.7 ± 10.2	61.0 ± 10.0	0.220*
Systemic hypertension	40 (95%)	37 (93%)	0.604†
Diabetes mellitus	23 (55%)	25 (62%)	0.477†
Coronary artery disease			0.600†
Stenosis <50%	3 (7%)	1 (3%)	
Single-vessel	16 (38%)	12 (30%)	
Double-vessel	8 (19%)	10 (25%)	
Triple-vessel	15 (36%)	17 (42%)	
Prior myocardial infarction	10 (24%)	7 (18%)	0.481†
Left ventricular ejection fraction	0.45 ± 0.07	0.42 ± 0.08	0.221*
Use of ACE inhibitors	11 (26%)	11 (28%)	0.894†
Indication for CAG			0.812†
Stable angina	22 (52%)	22 (53%)	
Acute coronary syndrome	20 (48%)	18 (47%)	
Performed procedure			0.837†
Coronary angiography	19 (45%)	19 (47%)	
Percutaneous coronary intervention	22 (55%)	21 (53%)	
Volume of contrast medium (ml)	106.8 ± 44.0	108.1 ± 32.6	0.877*

Data are presented as n (%) or mean ± SD. *Student unpaired *t* test was used for the comparison between the groups. †Fisher exact test was used for the comparison between the groups.
ACE = angiotensin-converting enzyme; CAG = coronary angiogram.

were randomized into 2 groups. After excluding patients of insufficient follow-up (n = 3), receiving nonsteroid anti-inflammatory drugs (n = 2), receiving N-acetylcysteine (n = 2), and receiving another contrast examination within 48 h (n = 1), 42 receiving prophylactic hemodialysis after coronary angiography and 40 receiving fluid supplement only were included in the analyses (Table 1). The 2 groups were similar with respect to demographic and baseline clinical characteristics. Among the patients in the dialysis group, dialysis was initiated at an interval of 81 ± 32 min, ranging from 45 to 180 min, after exposure to the contrast medium.

The baseline CrCl was similar in the dialysis (13.2 ml/min/1.73 m^2) and control (12.6 ml/min/1.73 m^2) groups; however, the CrCl on the fourth day after coronary angiography in the dialysis group was significantly higher than that in the control group (Table 2). The decrease in CrCl within 72 h after the procedure was 0.4 ml/min/1.73 m^2 in the dialysis group and 2.2 ml/min/1.73 m^2 in the control group ($p < 0.001$) (Table 2).

Multiple regression analysis shows that only prophylactic dialysis and baseline CrCl were significantly associated with a change in CrCl (Table 3). The control group was significantly associated with a decrease in CrCl of 1.938 ml/min/1.73 m^2. Every 1-ml/min/1.73 m^2 decrease in baseline CrCl was significantly associated with a decrease in CrCl of 0.324 ml/min/1.73 m^2. There is no association between the change in CrCl and other risk factors such as age, gender, diabetes, hypertension, type of procedure, or dose of contrast medium.

Figure 1 shows the time course of renal function in the 2 groups. In the control group, the mean Cr concentration increased significantly after coronary angiography and maintained higher than baseline values at hospital discharge in those patients who did not need permanent dialysis. After angiography in the dialysis group, the Cr concentrations were slightly increased on day 4 (4.9 ± 1.3 mg/dl vs. 5.1 ± 1.3 mg/dl; p = 0.06) but were significantly increased only at peak value (5.3 ± 1.5 mg/dl; p = 0.008). No significant changes from baseline values in renal function were observed at discharge (5.1 ± 1.3 mg/dl). The renal function of patients in the dialysis group was better preserved over the whole course after CAG compared with the control group.

One patient (2%) in the dialysis group and 14 patients (35%) in the control group required temporary dialysis after CAG ($p < 0.001$) (Fig. 2) during hospitalization. The length of time between contrast exposure and initiation of dialysis was 5 ± 3 days (range 1 to 13 days). Ten of the patients recovered and stopped hemodialysis within 3 weeks (range 1 to 21 days). No patients in the dialysis group, but 5 in the control group (13%), required maintenance dialysis after discharge (number needed to treat [NNT] 8; p = 0.018). For the patients who did not require chronic dialysis, the mean Cr level at discharge was higher, but not significantly, in the control group than in the dialysis group (5.9 ± 2.5 mg/dl vs. 5.1 ± 1.4 mg/dl; p = 0.113). However, 18 patients in the control group (45%), but only 2 in the dialysis group (5%), had permanent renal damage with an increase in Cr concentration greater than 1 mg/dl or required permanent dialysis after discharge (risk ratio 2.80, 95% confidence interval 1.24 to 4.35, NNT 2.5; $p < 0.001$). The length of hospital stay was considerably shorter in the dialysis group compared to that in the control group (6 ± 3 days vs. 13 ± 18 days; p = 0.017).

No major complications were associated with the dialysis or the catheter in the dialysis group. Only 1 patient developed minor bleeding from the puncture site of the femoral catheter; the bleeding stopped easily after removal of catheter and there was no need for a blood transfusion.

Table 2 Changes in Renal Function From Baseline to Day 4 (Mean ± SD)

	Dialysis Group (n = 42)	Control Group (n = 40)	p Value
Baseline plasma creatinine (mg/dl)	4.9 ± 1.3	4.9 ± 1.6	0.936
Baseline creatinine clearance (ml/min/1.73 m^2)	13.2 ± 3.6	12.6 ± 4.4	0.528
Day 4 creatinine clearance (ml/min/1.73 m^2)	12.8 ± 3.5	10.4 ± 4.4	0.008
Change in creatinine clearance from baseline to day 4 (ml/min/1.73 m^2)	−0.4 ± 0.8	−2.2 ± 2.8	0.001

Student unpaired *t* test was used for the comparison between the groups.

Table 3 Factors Associated With Change in Creatinine Clearance From Baseline to Day 4 for All Patients (R^2 = 0.260)

	Unstandardized Coefficient B	Standardized Coefficient B	95% Confidence Interval	p Value
Age (1-yr increase)	0.001	0.001	−0.043 to 0.043	0.991
Male	0.645	0.140	−0.465 to 1.755	0.251
Diabetes mellitus	−0.169	−0.038	−1.206 to 0.868	0.746
Hypertension	−0.241	−0.026	−2.310 to 1.827	0.817
PCI	0.203	0.499	−0.791 to 1.197	0.685
Dose of contrast medium (1-ml increase)	−0.003	−0.040	−0.015 to 0.010	0.716
Prophylactic dialysis	1.938	0.440	1.040 to 2.837	<0.001
Baseline creatinine clearance (1-ml/min/1.73 m^2 increase)	0.324	0.180	0.042 to 0.318	0.011

PCI = percutaneous coronary intervention.

Discussion

Patients with chronic renal failure are prone to atherosclerotic cardiovascular diseases (17), and renal dysfunction accounts for the greatest risk factor in developing CN after CAG. Once CN occurred, 36% to 60% of these high-risk patients required emergent dialysis, and the hospital stay was prolonged to an average of 17 days (18,19). Of these patients, 28% to 33% did not recover and needed maintenance dialysis. Therefore, the cardiologist usually has to make a difficult choice between alleviating coronary syndromes by coronary intervention and the risk of acute renal failure in patients with pre-existing renal dysfunction. Based on the present results, prophylactic hemodialysis immediately after CAG appears to be an effective and safe strategy to improve renal outcome in patients with advanced renal failure who need CAG.

Some may argue that either the Cr level or CrCl could represent the glomerular filtration rate (GFR) only at a steady state. Because it is the change in GFR rather than the absolute GFR level that we wanted to measure, and because the change in Cr level reflects the change in GFR faithfully, we chose the changes in Cr level and CrCl to evaluate the change in renal function after CAG in the present study. The only pitfall was that the Cr level in the dialysis group would be artificially lower immediately after prophylactic hemodialysis. According to an earlier study (20), Cr levels in the dialysis group would catch up with baseline levels and the levels in the control group within 3 days. Therefore, we used the changes in Cr level or CrCl of day 4 from baseline to express the change in GFR. Besides, using our secondary end points, including the number of patients who needed either temporary or long-term dialysis after CAG and the changes in Cr level at discharge, prophylactic hemodialysis after CAG also showed significantly better results in the dialysis group.

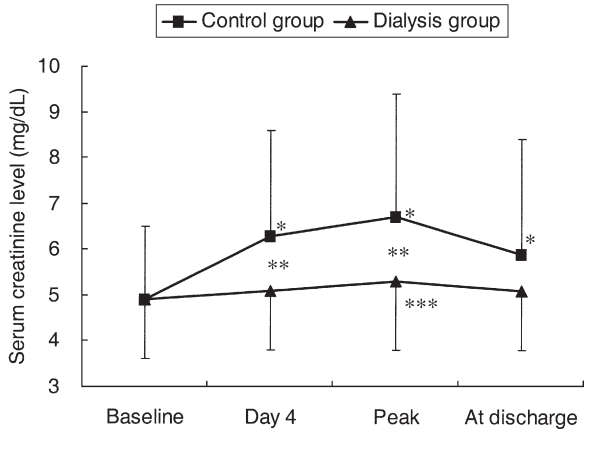

Figure 1 Cr Levels Before Coronary Angiography, on Day 4, at Peak Value, and at Hospital Discharge

Changes in serum creatinine (Cr) values in the dialysis and control groups were assessed using repeated-measures analysis of covariance. Multiple comparisons with the Bonferroni *t* test were used for the comparisons between and within groups. For the interaction between time and treatment in terms of the Cr level, F statistic = 22.9 ($p < 0.001$). Changes from baseline in the Cr level were significant at the peak value in the dialysis group (***$p = 0.008$) and on day 4, at the peak value, and at discharge in the control group (*$p < 0.001$); the difference between the 2 groups was significant on day 4 and at peak value (**$p = 0.010$ on day 4; $p = 0.005$ at peak value).

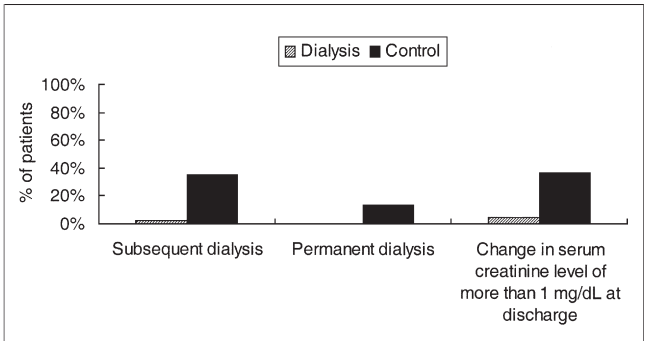

Figure 2 Renal Outcomes of Dialysis and Control Groups

The **bars** show significantly different percentages of dialysis and control patients who needed subsequent dialysis (2% vs. 35%; $p < 0.001$), patients who needed permanent dialysis (0 vs. 13%; $p = 0.018$), and those with an increase in serum creatinine level between baseline and discharge of at least 1.0 mg/dl (5% vs. 37%; $p < 0.001$). Fisher exact test was used for the comparison between the groups.

The underlying mechanism of CN is not clear. A reduction in renal perfusion caused by a direct effect of the contrast medium on the kidney and toxic effects on the tubular cells are generally accepted as the main factors in the pathogenesis of CN (21). In patients with renal insufficiency, delayed excretion of the contrast medium has led to concerns about increased toxicity after CAG. Although the concentration of the contrast medium can be effectively reduced by hemodialysis within short periods (22–25), the effect of prophylactic hemodialysis in preventing CN addressed in earlier studies is still controversial (20,26). Different doses of contrast media, small sample sizes, and variations in residual renal function might be causes of bias. Moreover, nephrotoxicity due to dialysis per se has been linked with the activation of inflammatory reactions by the dialyzer and the induction of hypovolemia and hypotension during dialysis. It is possible that the nephrotoxic effect of hemodialysis might have offset the beneficial effect of the removal of the contrast medium. In the present study, all of the possible nephrotoxic factors were eliminated.

The overwhelming positive effect of our study may be due to the high-risk population we chose; all of our patients had a residual CrCl of <25 ml/min/1.73 m^2, which made the kidney very vulnerable to any further injury. Thus, the rapid removal of nephrotoxic contrast agents by hemodialysis was dramatically shown to be of great benefit. Considering that hemodialysis is an invasive procedure—although we cannot clearly indicate the critical level of residual CrCl at which prophylactic hemodialysis will be beneficial from the results of the present study—we strongly suggest that patients with a CrCl of <25 ml/min/1.73 m^2 receive prophylactic hemodialysis after CAG to prevent permanent renal injury. Because the incidence of permanent renal injury in the dialysis group was very low (2 of 42 patients), there was no significant association between exposure time to the contrast medium and renal injury (data not shown). We were not able to ascertain how long after the exposure time to the contrast medium the prophylactic hemodialysis would still be effective. From our study, it was speculated that starting prophylactic hemodialysis within 180 min after exposure might be acceptable when low-dose contrast media (<150 ml) are used.

The present study is designed to examine the preventive effect of hemodialysis in advanced renal failure patients after CAG. Because the dose of contrast medium of diagnostic computer tomography is usually <150 ml and the procedure is normally <180 min, it is reasonable to apply our results to this population who need receive diagnostic computerized tomography.

In contrast to hemodialysis, continuous venovenous hemofiltration (CVVH) before and after CAG has also been proposed as being effective in preventing CN (27,28). Considering the relatively high cost and time-consuming nature of this procedure, the limited availability of beds in intensive care units, the lengthy immobilization of patients, and the pharmacokinetics of contrast media during dialysis (25), hemodialysis might be more practicable than CVVH to prevent CN after CAG.

Study limitations. Our study was not blinded. The potential effective strategies to prevent CN had been implemented in both groups, including fluid supplement, low-osmolality contrast media, and a lower dose of contrast agents, and there was still shown to be a significant benefit of prophylactic hemodialysis. However, the influence of the double dose of N-acetylcysteine and hemodialysis to prevent CN requires further investigation.

Conclusions

Our findings suggest that prophylactic hemodialysis in patients with advanced chronic renal failure undergoing coronary angiography reduces the intensity of acute renal deterioration due to contrast medium exposure, shortens hospital stay, and improves renal outcome.

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