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Incidence of Contrast-Induced Nephropathy with Volume Supplementation – Insights from a Large Cohort

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Key Words
Volume supplementation · Renal failure · Contrast media

Abstract
Objective: The present study was performed to determine the effect of combined intravenous and oral volume supplementation on the incidence of contrast-induced nephropathy (CIN) in patients undergoing percutaneous coronary intervention (PCI). ***Subjects and Methods:*** Consecutive patients (n = 958) receiving iomeprol 350 during PCI were evaluated prospectively for the development of CIN. All patients received protocol-defined intravenous and oral volume supplementation. CIN was defined as an increase in serum creatinine of at least 44 μmol/l within 48 h. ***Results:*** Of the 958 patients enrolled in the study, 147 (15%) were diabetic and 107 (11%) had stage III renal disease. The average baseline glomerular filtration rate was 88 ± 25 ml/min/1.73 m^2. During the intervention an average of 238 ± 86 ml of contrast medium was administered. CIN developed in 13 of 958 (1.4%; 95% confidence interval 0.6–2.1%) patients. The incidence of CIN was low even in predefined risk subgroups (women: 2.4%, diabetics: 2.7%, patients with stage III kidney disease: 6.5%). ***Conclusions:*** The incidence of CIN is low when preprocedural fluid volume supplementation is used.

Introduction

Contrast-induced nephropathy (CIN) is the third leading cause of hospital-acquired acute renal failure, contributing not only to increased morbidity and mortality during hospitalization, but also to higher overall costs of health care [1–6]. The risk factors for CIN are related to patient characteristics, ranging from the severity of the underlying renal disease and cardiovascular performance, to the characteristics of the procedure itself, and to the quantity of contrast agent administered. Unfortunately, despite being a major concern, the most effective strategy for the prevention of CIN is unknown.

Although numerous preventive strategies involving the administration of furosemide, mannitol, dopamine, fenoldopam, atrial natriuretic peptide, and prostaglandin E_1 have been examined in randomized clinical trials, none have been found to be totally effective [7–12]. Likewise, results for acetylcysteine, theophylline, and captopril have been controversial [13–18]. Despite ongoing studies to establish the value of pharmacologic prevention, at present only volume supplementation is uniformly accepted and used in clinical practice [19–23]. Unfortunately, little has yet been reported on the most effective approach to volume supplementation. In particular, details such as the timing and rate of infusion and the respective value of intravenous and oral volume supplementation are not well defined. A combination of intra-

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Table 1. Baseline clinical characteristics

Baseline characteristics	Patients (n = 958)	
	n	%
Aged ≥70 years	321	34
Female sex	247	26
Diabetes mellitus	147	15
Smoking	298	31
Arterial hypertension	612	64
Previous myocardial infarction	462	48
Acute myocardial infarction	71	7
Emergency procedures	550	57
Number of diseased vessels		
1	346	36
2	273	29
3	339	35
Left ventricular ejection fraction (EF)		
EF ≥ 60%	422	44
45% ≤ EF < 60%	389	41
30% ≤ EF < 45%	124	13
EF < 30%	23	2

venous and oral volume supplementation has not generally been used in published studies.

The present study was performed to determine the value of combined intravenous and oral volume supplementation on the incidence of CIN in patients undergoing percutaneous coronary intervention (PCI).

Methods

Patients

Consecutive patients scheduled for elective or emergency PCI were enrolled in a prospective cohort study. Two different intravenous infusions schemes were used during the observational period [21]. Patients with end-stage renal failure on regular hemodialysis or with cardiogenic shock and mechanical ventilation were excluded. Similarly, patients with coronary artery bypass grafting or who were undergoing repeat catheterization within 48 h of PCI were excluded from analysis.

All patients received iomeprol 350 (Imeron, Bracco Altana Pharma, Germany), a low-osmolar, monomeric, nonionic contrast agent. PCI was performed via the femoral artery in all patients using a standard technique.

For intravenous volume supplementation, roughly half of the patients (n = 494) received physiologic saline (0.9%; isotonic) while the remainder (n = 464) received 0.45% saline plus 5% glucose (half-isotonic). Infusion was performed at a rate of 1 ml/kg of body weight per hour beginning at 8 a.m. on the day of PCI. In addition, patients were encouraged to drink plenty of fluids (tea, mineral water). Tea was provided to all patients in their room prior to the PCI procedure (500 ml) and in the post-PCI unit following the procedure (1,000 ml). In patients undergoing emergency PCI, an infusion of 500 ml of crystalloid (Ringer's) solution was initiated by the paramedics as their standard medical care before admission to the hospital. In this patient subset, isotonic and half-isotonic infusions were started immediately upon arrival at the catheter laboratory. During PCI, the rate of infusion was adjusted to the clinical condition of the patient. After the procedure, volume supplementation was continued at 1 ml/kg of body weight per hour until the following morning (8 a.m.).

Follow-Up and Endpoints

Venous blood specimens were drawn on the morning before the PCI procedure, and at 24 and 48 h after the procedure for determination of the serum creatinine level. All samples were analyzed in a central laboratory using a dedicated enzymatic kit (CREA plus, Boehringer Mannheim Systems, Mannheim, Germany).

Glomerular filtration rate (GFR) was calculated for all patients on the basis of creatinine clearance using the abbreviated 'Modification of Diet in Renal Disease Study' equation [24–26] in which: GFR (in ml/min/1.73 m^2 of body surface area) = 186 × (serum creatinine in mg/dl)$^{-1.154}$ × (age in years)$^{-0.203}$ × 0.742 in female subjects × 1.210 in black subjects.

The most common definition of CIN, i.e., an increase in serum creatinine of at least 44 μmol/l (0.5 mg/dl) within 48 h, was used as the primary endpoint in this trial.

Statistical Analysis

Patients were evaluated primarily for the occurrence of CIN. Statistical analyses were performed using the SPSS/PC (version 13, SPSS Inc., Chicago, Ill., USA) software package. Discrete variables were expressed as counts, and continuous variables as means ± standard deviation (SD). Comparisons were made as appropriate using Student's t test for independent samples, the χ^2-test, and Fisher's exact test. All hypothesis testing was two-tailed at a significance level of $p < 0.05$.

Results

A total of 958 consecutive patients (mean age: 64 ± 11 years) were evaluated. A summary of patient and procedural characteristics is given in table 1. The volume of administered contrast agent was similar for all patients irrespective of the presence of stage II or stage III kidney disease (table 2). Approximately one third (n = 321) of the patient cohort was aged 70 years or older. Twenty-six percent of patients were women and 15% were diabetic. A total of 462/958 (48%) patients had a prior history of myocardial infarction and 71/958 (7%) underwent PCI for an acute ST-elevation myocardial infarction. Emergency interventions accounted for slightly more than 50% of all procedures. Almost 50% of coronary lesions were complex (lesion type B2 or C). A mean total volume of 238 ± 86 ml of iomeprol 350 was administered. None of the patients in this study received acetylcysteine or theophyl-

Table 2. Subgroup details

	All patients (n = 958)		≤ Stage I kidney disease (n = 439)		Stage II kidney disease (n = 412)		Stage III kidney disease (n = 107)	
	isotonic	half-isotonic	isotonic	half-isotonic	isotonic	half-isotonic	isotonic	half-isotonic
Isotonicity of saline	494 (52%)	464 (48%)	228 (52%)	211 (48%)	213 (52%)	199 (48%)	53 (50%)	54 (50%)
Contrast dose, ml	235 ± 81	240 ± 91	235 ± 74	235 ± 89	239 ± 89	247 ± 96	221 ± 72	236 ± 82
Serum creatinine, μmol/l								
Baseline	82 ± 27	82 ± 25	66 ± 10	66 ± 10	86 ± 12	86 ± 12	133 ± 46	129 ± 35
24 h	80 ± 26	81 ± 27	68 ± 11	68 ± 14	82 ± 15	82 ± 15	122 ± 51	126 ± 46
48 h	89 ± 34	88 ± 26	74 ± 11	73 ± 12	90 ± 19	90 ± 17	141 ± 69	133 ± 37

line and no changes in medication were allowed during the study period.

The mean baseline renal function as assessed by calculating GFR was 88 ± 25 ml/min/1.73 m^2. Stage II kidney disease (GFR 60–90 ml/min/1.73 m^2) was present in 412 patients (43%), while stage III kidney disease (GFR below 60 ml/min/1.73 m^2) was present in 107 (11%) patients (table 2).

Overall, CIN developed in 13 (1.4%; 95% confidence interval 0.6–2.1%) of the 958 patients evaluated (table 3). The incidence of CIN was significantly higher in patients aged 70 years or older compared with patients younger than 70 years of age (2.5 vs. 0.8%, p = 0.040; fig. 1). We observed no statistical difference between the occurrence of CIN in the isotonic and half-isotonic hydration groups (1.0 vs. 1.7%). A low incidence of CIN was observed even in established predefined risk subgroups including women (2.4%), diabetics (2.7%), and patients with stage III kidney disease (6.5%).

Overall, 2 patients (0.2%) received dialysis during the hospitalization period. Neither of the events was a direct consequence of CIN, although both events were related to the PCI procedure. One 70-year-old female patient with mild chronic renal insufficiency and mitral regurgitation developed pulmonary edema during coronary angioplasty that required treatment with dialysis. The other patient, a 77-year-old male with severe chronic renal insufficiency, had already undergone a shunt operation in the preceding week and was scheduled to begin chronic dialysis in 4 weeks. The operator elected to leave the arterial sheath in place for acute dialysis after coronary angiography and PCI had been performed. During the follow-up period no additional patients required subsequent chronic dialysis.

Table 3. Incidence of CIN in patients (n = 958) undergoing PCI

	Patients	95% CI
Overall CIN	13 (1.4)	0.6–2.1
CIN subgroups		
Men (n = 711)	7 (1.0)	0.3–1.7
Women (n = 247)	6 (2.4)	0.5–4.4
Age <70 years (n = 637)	5 (0.8)	0–1.5
CIN Age ≥70 years (n = 321)	8 (2.5)	0.8–4.2
Nondiabetics (n = 811)	9 (1.1)	0.4–1.8
Diabetics (n = 147)	4 (2.7)	0.1–5.1
GFR ≥60 ml/min/1.73 m^2 (n = 851)	6 (0.7)	0.1–1.3
GFR <60 ml/min/1.73 m^2 (n = 107)	7 (6.5)	1.8–11.3

CIN was defined as an increase in serum creatinine of at least 44 μmol/l within 48 h. Number and percent (in parentheses) of patients are given. CI = Confidence interval.

Discussion

The results of the large prospective cohort study confirm that the combined use of intravenous and oral volume supplementation results in a very low incidence of CIN. The overall incidence of CIN in this cohort was only 1.4%. This is considerably lower than values reported previously in similar patient populations [1–20]. For example, an incidence of 3.3% has recently been reported in a retrospective analysis of the Mayo Clinic PCI registry [6]. Particularly noteworthy in the present study was an overall incidence of CIN of only 6.5% in patients with stage III kidney disease (a GFR below 60 ml/min/1.73m^2). The results presented herein support previously published re-

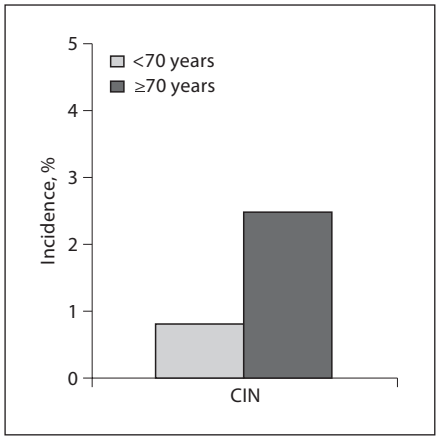

Fig. 1. Incidence of CIN in patients.

sults [22] and suggest that the combined use of intravenous and oral volume supplementation provides a safe, simple, effective, and inexpensive strategy for the prevention of CIN. Furthermore, our data confirm the findings of recent studies suggesting that age is a major risk factor for CIN [16, 27].

Approximately 30 years ago it was documented that hypovolemia accentuates the risk of CIN [28]. The incidence was higher in summer and when patients were prevented from drinking before excretory urograms in order to maximize the concentration of contrast medium in the urinary tract. Observations comparing hydrated patients with historical controls first provided evidence that a fluid load might prevent CIN [27, 29–31]. In 1994, these data were supported by a controlled study, primarily undertaken to investigate the value of mannitol and furosemide administration [7]. In a randomized controlled study of 78 patients with mild to moderate renal insufficiency, saline administration (0.45% saline over 24 h starting 12 h before administration of contrast medium) alone was more effective than the combination of volume supplementation with mannitol or furosemide [7]. Recently, three randomized studies have specifically examined the effectiveness of intravenous volume supplementation [22, 23, 32]. Trivedi et al. [22] randomized 53 patients on the day prior to scheduled elective cardiac catheterization to one of two groups: group 1 (n = 27) received normal saline for 24 h (at a rate of 1 ml/kg/h) beginning 12 h prior to scheduled catheterization, while the patients of group 2 (n = 26) were allowed unrestricted oral fluids. The incidence of acute renal failure was significantly lower in group 1 (1 out of 27; 3.7%) than in group 2 (9 out of 26, 34.6%; p = 0.005 for comparison between groups; relative risk 0.11, 95% confidence interval 0.02–0.79). Bader et al. [23] randomized 39 patients with normal renal function, who were due to undergo an angiographic procedure with at least 80 ml of low osmolar contrast medium, to one of two volume supplementation regimens: group 1, volume expansion with 300 ml saline during contrast medium administration (n = 20); group 2, intravenous administration of at least 2,000 ml saline within 12 h before and after contrast medium application (n = 19). Patients in group 1 showed a significantly higher decline in GFR (ΔGFR = 35 ml/min/1.73 m^2) compared to patients in group 2, who received the intravenous prehydration regimen (ΔGFR = 18 ml/min/1.73 m^2; $p < 0.05$). In the third study, Krasuski et al. [32] randomized 63 patients with moderate renal insufficiency who were scheduled for elective cardiac catheterization to two groups to receive either overnight hydration (n = 26) with intravenous 5% dextrose in 0.45% saline (infused at 1 ml/kg/h beginning at least 12 h before the procedure) or bolus hydration (n = 37) at the time of the procedure (250 ml of 0.9% saline administered over 20 min). After the procedure all patients were encouraged to take in oral fluids and received intravenous 5% dextrose in 0.45% saline at 1 ml/kg/h for 12 h. Although no overall change in serum creatinine was seen at 24 or 48 h after the procedure, 4 out of 37 (10.8%) patients who received bolus hydration developed CIN compared with 0 out of 26 (0.0%) patients who received overnight hydration.

It is important to note that volume expansion performed only during exposure to the contrast agent appears insufficient in itself to prevent renal damage [23, 32]. Whether the use of sodium bicarbonate allows shorter infusion periods has to be examined in future studies [33].

This study has several limitations. First, as with all suprarenal procedures performed via the femoral artery, it is unclear to what extent atheroembolism into the renal arteries induced by catheter manipulation during catheterization contributed to the decline in renal function. Therefore, the renal damage attributable to iomeprol may be even lower than reported in this study. Second, half-isotonic rather than isotonic hydration was used in 48% of patients in the study. Because isotonic hydration is superior to half-isotonic hydration [21], again it is likely that an even lower incidence of CIN would have been observed had isotonic hydration been applied to all patients in this study. Third, comparison with historical controls invariably introduces bias due to potential differences in baseline characteristics. Additionally, this was a single-

center study. Hence, further data from multicenter studies are required to further strengthen our findings.

Although the pathogenesis of CIN is only incompletely understood, it seems to involve renal vasoconstriction, medullary hypoxia, increased red cell aggregation, and direct toxic effects on renal epithelial cells [6, 17, 19]. Accordingly, plasma volume expansion combined with concomitant suppression of the renin-angiotensin-aldosterone system, down-regulation of the tubuloglomerular feedback, dilution of the contrast agent with resulting prevention of renal cortical vasoconstriction, and avoidance of tubular obstruction has enormous theoretical appeal [17, 19]. Unfortunately, poor control of all relevant variables including intravenous and oral volume supplementation has led to widely conflicting data regarding the reported incidence of CIN and its risk factors [27]. As demonstrated in this study, the combination of intravenous and oral volume supplementation seems to be an attractive option for the vast majority of patients undergoing intravenous or intra-arterial contrast procedures. Given the fact that all alternative strategies have significant limitations, it seems of paramount importance to highlight the effectiveness of stringent volume supplementation as a baseline measure.

Conclusion

The use of combined intravenous and oral volume supplementation results in a very low incidence of CIN following PCI with iomeprol 350 in patients at moderate risk. Volume supplementation should remain the cornerstone for prevention of CIN.

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References

1 Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT: Hospital-acquired renal insufficiency: a prospective study. Am J Med 1983;74:243–248.
2 Menashe PI, Ross SA, Gottlieb JE: Acquired renal insufficiency in critically ill patients. Crit Care Med 1988;16:1106–1109.
3 Levy EM, Viscoli CM, Horwitz RI: The effect of acute renal failure on mortality: a cohort analysis. JAMA 1996;275:1489–1494.
4 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;103:368–375.
5 Gruberg L, Mintz GS, Mehran R, Gangas G, Lansky AJ, Kent KM, Pichard AD, Satler LF, Leon MB: The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J Am Coll Cardiol 2000;36:1542–1548.
6 Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN, Holmes DR Jr: Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 2002;105:2259–2264.
7 Solomon R, Werner C, Mann D, D'Elia J, Silva P: Effects of saline, mannitol, and furosemide on acute decrease in renal function induced by radiocontrast agents. N Engl J Med 1994;331:1416–1420.
8 Abizaid AS, Clark CE, Mintz GS, Dosa S, Popma JJ, Pichard AD, Satler LF, Harvey M, Kent KM, Leon MB: Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency. Am J Cardiol 1999;83:260–263.
9 Stone GW, McCullough PA, Tumlin JA, Lepor NE, Madyoon H, Murray P, Wang A, Chu AA, Schaer GL, Stevens M, Wilensky RL, O'Neill WW; CONTRAST Investigators: Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. JAMA 2003;290:2284–2291.
10 Stevens MA, McCullough PA, Tobin KJ, Speck JP, Westveer DC, Guido-Allen DA, Timmis GC, O'Neill WW: A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy. J Am Coll Cardiol 1999;33:403–411.
11 Koch JA, Plum J, Grabensee B, Mödder U, and PGE1 Study Group: Prostaglandin E1: a new agent for the prevention of renal dysfunction in high risk patients caused by radiocontrast media? Nephrol Dial Transplant 2000;15:43–49.
12 Kurnik BR, Allgren RL, Genter FC, Solomon RJ, Bates ER, Weisberg LS: Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. Am J Kidney Dis 1998;31:674–680.
13 Gupta RK, Kapoor A, Tewari S, Sinha N, Sharma RK: Captopril for prevention of contrast-induced nephropathy in diabetic patients: a randomised study. Indian Heart J 1999;51:521–526.
14 Kolonko A, Wiecek A, Kokot F: The nonselective adenosine antagonist theophylline does prevent renal dysfunction induced by radiographic contrast agents. J Nephrol 1998;11:151–156.
15 Birck R, Krzossok S, Markowetz F, Schnülle P, van der Woude FJ, Braun C: Acetylcysteine for prevention of contrast nephropathy. Lancet 2003;362:598–603.
16 Hoffmann U, Fischereder M, Küger B, Drobnik W, Krämer BK: The value of N-acetylcysteine in the prevention of radiocontrast agent-induced nephropathy seems questionable. J Am Soc Nephrol 2004;15:407–410.
17 Erley CM, Duda SH, Rehfuss D, Scholtes B, Bock J, Müller C, Osswald H, Risler T: Prevention of radiocontrast-media-induced nephropathy in patients with pre-existing renal insufficiency by hydration in combination with the adenosine antagonist theophylline. Nephrol Dial Transplant 1999;14:1146–1149.

18 Huber W, Ilgmann K, Page M, Hennig M, Schweigart U, Jeschke B, Lutilsky L, Weiss W, Salmhofer H, Classen M: The effect of theophylline on contrast material-induced nephropathy in patients with chronic renal insufficiency: controlled, randomized, double-blinded study. Radiology 2003;223:772–779.
19 Mueller C: Prevention of contrast-induced nephropathy with volume supplementation. Kidney Int Suppl 2006;100:S16–S19.
20 Taylor AJ, Hotchkiss D, Morse RW, McCabe J: PREPARED: preparation for angiography in renal dysfunction: a randomized trial of inpatient versus outpatient hydration protocols for cardiac catheterization in mild to moderate renal dysfunction. Chest 1998;114:1570–1574.
21 Mueller C, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, Marsch S, Roskamm H: Prevention of contrast media-associated nephropathy: randomized comparison of two hydration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med 2002;162:329–336.
22 Trivedi HS, Moore H, Nasr S, Aggarwal K, Agrawal A, Goel P, Hewett J: A randomized prospective trial to assess the role of saline hydration on the development of contrast nephropathy. Nephron Clin Pract 2003;93:C29–C34.
23 Bader BD, Berger ED, Heede MB, Silberbaur I, Duda S, Risler T, Erley CM: What is the best hydration regimen to prevent contrast media-induced nephrotoxicity? Clin Nephrol 2004;62:1–7.
24 Levey AS: Nondiabetic kidney disease. N Engl J Med 2002;347:1505–1511.
25 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999;130:461–470.
26 National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39(suppl 1):S1–S200.
27 Maeder M, Klein M, Fehr T, Rickli H: Contrast nephropathy: review focusing on prevention. J Am Coll Cardiol 2004;44:1763–1771.
28 Anto HR, Chou SY, Porush JG, Shapiro WB: Infusion intravenous pyelography and renal function: effect of hypertonic mannitol in patients with chronic renal insufficiency. Arch Intern Med 1981;141:1652–1656.
29 Byrd L, Sherman RL: Radiocontrast-induced acute renal failure: a clinical and pathological review. Medicine 1979;58:270–279.
30 Eisenberg RL, Blank WO, Hedgock MW: Renal failure after major angiography can be avoided with hydration. Am J Radiol 1981;136:859–861.
31 Kerstein MD, Puyau FA: Value of preangiography hydration. Surgery 1984;96:919–922.
32 Krasuski RA, Beard BM, Geoghagan JD, Thompson CM, Guidera SA: Optimal timing of hydration to erase contrast-associated nephropathy: the OTHER CAN study. J Invasive Cardiol 2003;15:699–702.
33 Merten GJ, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, Bersin RM, Van Moore A, Simonton CA 3rd, Rittase RA, Norton HJ, Kennedy TP: Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. JAMA 2004;291:2328–2334.