

Incidence of contrast nephropathy in patients receiving comprehensive intravenous and oral volume supplementation

Christian Mueller^{a, b}, Peter Seidensticker^c, Heinz J. Buettner^b, André P. Perruchoud^a, Daniel Staub^a, Andreas Christ^a, Gerd Buerkle^b

^a University Hospital of Basel, Switzerland

^b Heart Centre Bad Krozingen, Germany

^c Schering AG, Berlin, Germany

Summary

Background: Contrast-induced nephropathy (CIN) remains a major complication of percutaneous coronary interventions (PCI) and a common cause of acute renal failure. The most effective preventive strategy is unknown.

Objectives: This study sought to estimate the incidence of CIN in patients receiving comprehensive intravenous and oral volume supplementation for PCI during which iopromide (Ultravist 370, Schering, Berlin, Germany) was used.

Methods: We prospectively studied the development of CIN in 425 consecutive patients undergoing PCI, applying comprehensive intravenous and oral hydration in all patients. Baseline renal function was assessed by calculating the glomerular filtration rate (GFR) with the use of the abbreviated Modification of Diet in Renal Disease Study equation. CIN was defined as an increase in serum creatinine of at least 0.5 mg/dl (44 mmol/l) within 48 hours.

Results: Mean patients' age (mean \pm SD) was 64

\pm 10 years. A total of 133/425 patients (31%) were 70 years or older, 107 (25%) were women, 70 (16%) were diabetics, 218 (51%) had prior myocardial infarction, and 43 (10%) underwent PCI for an acute ST-segment elevation myocardial infarction. Mean GFR was 89 ml/min/1.73 m². Glomerular filtration rate was below 60 ml/min/1.73 m² in 43 patients (10%). During PCI 226 \pm 80 ml of iopromide were used. With the comprehensive hydration strategy used, CIN developed in only 6 of 425 (1.4%; 95% confidence interval 0.5–3.1%) patients. No patient required dialysis.

Conclusions: Applying the combination of intravenous and oral volume supplementation results in a very low incidence of CIN following PCI. Hydration remains the cornerstone for the prevention of CIN.

Key words: volume supplementation; renal failure; contrast media

Introduction

The administration of radiographic contrast agents remains an important cause of hospital-acquired acute renal failure, which contributes to morbidity and mortality during hospitalisation, as well as costs of health care [1–5]. The most effective preventive strategy is unknown.

A variety of approaches have been suggested for the prevention of contrast-induced nephropathy (CIN) including volume supplementation, furosemide, mannitol, dopamine, fenoldopam, aminophylline, theophylline, atrial natriuretic peptide, acetylcysteine, prostaglandin E₁, iso-os-

molar contrast agents, and captopril [6–20]. However, only volume supplementation is uniformly accepted and used in clinical practice. Unfortunately, the combination of intravenous and oral volume supplementation has neither been used in most of these studies, nor is it currently applied in most centres.

We prospectively estimated the incidence of CIN in patients receiving comprehensive intravenous and oral volume supplementation for percutaneous coronary intervention (PCI) using iopromide.

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Methods

Patients and coronary angioplasty procedure

Patients scheduled for elective or emergency PCI were included in this study. Endstage renal failure on regular haemodialysis, cardiogenic shock and mechanical ventilation were exclusion criteria. In addition, patients who underwent coronary artery bypass grafting or repeat catheterisation within 48 hours of PCI were excluded from further analysis. PCI was performed by standard technique via the femoral artery. This report is based on the subgroup of patients included in a large randomised trial in which the procedures were performed with iopromide (Ultravist 370, Schering, Berlin, Germany), a low-osmolar, monomeric, nonionic contrast agent [21]. Acetylcysteine and theophylline were not used in this study. No changes in medication were allowed during the study period. This study was carried out according to the principles of the Declaration of Helsinki and approved by the institutional review board. Written informed consent was obtained from all participating patients.

Volume supplementation regimens

Patients were randomly assigned to receive hydration with either 0.9% saline (isotonic), or 0.45% saline plus 5% glucose (half-isotonic). The hydration started with an infusion rate of 1 ml/kg of body weight per hour at 8 a.m. on the day of PCI. As the time of PCI was different among patients, the amount of fluids received prior to PCI and after PCI differed among the patients. The randomisation of the intravenous solutions refers to the previous trial and was not performed for the purpose of this study [21]. In addition, patients were persistently encouraged to drink plenty of fluids (tea, mineral water). Tea was provided to all patients in their room (500 ml), and in the post-PCI unit (at least 1000 ml) oral fluid intake was maximally encouraged. In patients undergoing emergency PCI, no protocol-defined pre-hydration could be given. However, the subgroup of patients with acute coronary syndromes received a 500 ml crystalloidal (ringer) infusion as their standard medical care already before admission to the hos-

pital. The assigned infusion was started immediately at arrival in the catheter laboratory. The infusion rate during PCI was adjusted to clinical conditions by the operator. 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

A venous blood specimen for serum creatinine was drawn in the morning before, as well as 24 and 48 hours after PCI. All samples were analysed in a central laboratory with the use of an enzymatic kit (CREA plus, Boehringer Mannheim systems, Mannheim, Germany). The glomerular filtration rate (GFR) is the best measure of overall kidney function [26]. We calculated GFR with the use of the abbreviated Modification of Diet in Renal Disease Study equation [21, 22]:

$$\text{GFR (in ml/min/1.73 m}^2 \text{ of body-surface-area)} = 186 \times (\text{serum creatinine in mg/dl})^{-1.154} \times (\text{age in years})^{-0.203} \times 0.742 \text{ in female subjects} \times 1.210 \text{ in black subjects.}$$

This equation is based on data from Levey et al. on 1628 subjects with 558 in the validation set [21, 22]. The most common definition of CIN, an increase in serum creatinine concentration of at least 0.5 mg/dl (44 $\mu\text{mol/l}$) within 48 hours, was used as the primary endpoint in this trial.

Statistical analysis

The primary analysis assessed the incidence of CIN. The statistical analyses were performed using the SPSS/PC (version 11.5, SPSS Inc., USA) and SAS (version 8.2) software packages. Discrete variables were expressed as counts, continuous variables as means \pm SD. Comparisons were made using t-test for independent samples, chi-square test, and Fisher's exact test as appropriate. All hypothesis testing was two-tailed.

Results

Baseline patient characteristics and procedural details

A total of 425 consecutive patients (107 women and 318 men) scheduled for elective or emergency PCI could be evaluated for the development of CIN (table 1). Mean patients' age (mean \pm SD) was 64 \pm 10 years. A total of 133/425 patients (31%) were 70 years or older, 107 (25%) were women, 70 (16%) were diabetics, 218 (51%) had prior myocardial infarction, and 43 (10%) underwent PCI for an acute myocardial infarction. About 50% of coronary lesions were complex (lesion type B2 or C). Emergency interventions accounted for slightly more than 50% of all procedures. For intravenous volume supplementation, isotonic and hypotonic infusions were each used in about half of the patients. During PCI 226 \pm 80 ml of iopromide as 370 mg I/ml solution was used corresponding to 84 \pm 30 g of iodine.

Baseline renal function as assessed by calculating GFR was 89 ml/min/1.73 m² (mean). GFR was below 60 ml/min/1.73 m² in 43 (10%) of patients. Mean baseline serum creatinine was 0.91 mg/dl.

Contrast-induced nephropathy

With the comprehensive hydration strategy used, CIN, defined as an increase in serum creatinine concentration of at least 0.5 mg/dl (44 $\mu\text{mol/l}$) within 48 hours, developed in only 6 of 425 (1.4%; 95% confidence interval 0.5–3.1%) patients (table 2). The incidence of CIN was very low even in several predefined risk subgroups including women (3.7%), elderly patients (2.3%), diabetics (2.9%), and patients with stage III kidney disease and a GFR below 60 ml/min/1.73 m² (4.7%). No patient required dialysis.

Table 1

Baseline clinical, angiographic and procedural characteristics.

		n = 425
Age; mean (SD)		64 (10)
Female sex; no. (%)		107 (25)
Diabetes mellitus; no. (%)		70 (16)
Smoking; no. (%)		136 (33)
Arterial hypertension; no. (%)		261 (62)
Previous myocardial infarction; no. (%)		218 (51)
Acute ST-elevation myocardial infarction; no. (%)		43 (10)
No. of vessels with >50% stenosis; no. (%)	1	149 (35)
	2	118 (28)
	3	158 (37)
Left ventricular ejection fraction (EF); no. (%)		
EF ≥60%		173 (41)
45% ≥EF <60%		180 (42)
30% ≤EF <45%		60 (14)
EF <30%		12 (3)
Lesion type*; no. (%)	A	14 (3)
	B1	197 (46)
	B2	155 (37)
	C	59 (14)
Emergency procedures**; no. (%)		240 (57)
Procedure time in min; mean (SD)		58 (28)
Contrast volume in ml; mean (SD)		226 (80)
Isotonic hydration; no. (%)		191 (45)
IV fluids during procedure in ml; mean (SD)		336 (141)

* American Heart Association/American College of Cardiology classification. A total of 21 patients (5%) underwent percutaneous coronary intervention of a saphenous vein graft lesion.

** Emergency interventions were defined as percutaneous coronary interventions in patients with an acute coronary syndrome requiring revascularisation within 24 hours. Of these, 10% had persistent ST-segment elevations in the electrocardiogram.

Table 2

Contrast-induced nephropathy.

		n = 425
Contrast nephropathy, N (%)*		6 (1.4)
<i>Subgroups:</i>		
CIN in men (n = 318)		2 (0.6)
CIN in women (n = 107)		4 (3.7)
CIN with isotonic hydration (n = 191)		0
CIN with half-isotonic hydration (n = 234)		6 (2.6)
CIN with age <70 years (n = 292)		3 (1.0)
CIN with age ≥70 years (n = 133)		3 (2.3)
CIN in nondiabetics (n = 355)		4 (1.1)
CIN in diabetics (n = 70)		2 (2.9)
CIN with GFR ≥60 ml/min/1.73 m ² (n = 382)		4 (1.0)
CIN with GFR <60 ml/min/1.73 m ² (n = 43)		2 (4.7)
mean GFR 50 ml/min/1.73 m ² mean creatinine 1.43 mg/dl 11 (26%) with diabetes		

GFR denotes glomerular filtration rate.

To convert values for serum creatinine to micromoles per litre, multiply by 88.4.

* Contrast-induced nephropathy (CIN) was defined as an increase in serum creatinine of at least 0.5 mg/dl within 48 hours

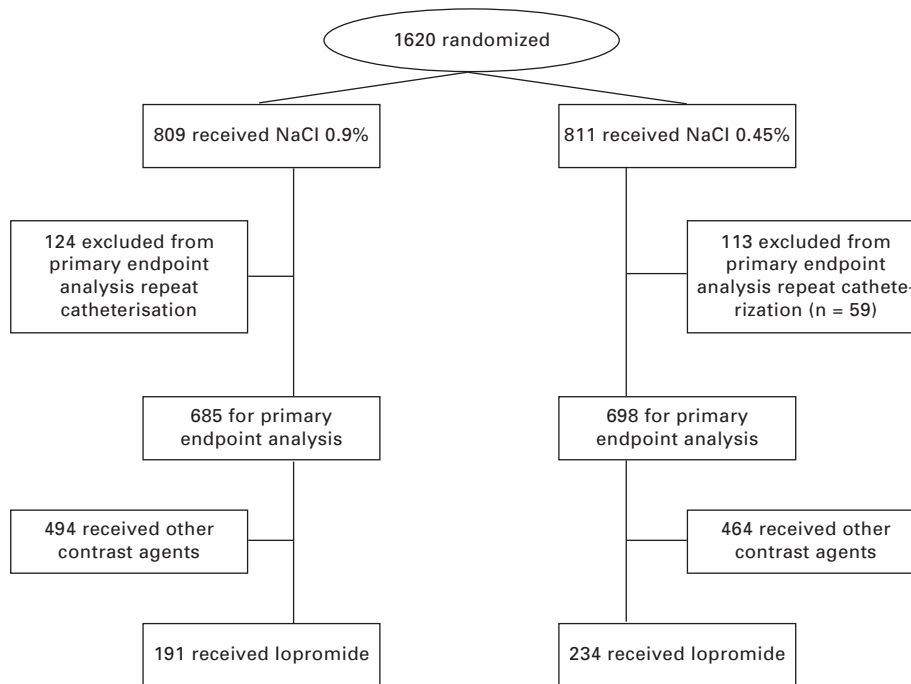
Discussion

In this prospective study of a consecutive moderate-risk cohort we found that the combined use of intravenous and oral volume supplementation results in a very low incidence of CIN. The incidence in this series was 1.4%, which is lower than previously reported in similar patient populations [4–20]. In an unselected patient population undergoing coronary angiography the incidence was 14.5% [4]. The incidence of CIN in the subgroup of patients with a GFR below 60 ml/min/1.73 m² was 4.7% in this study as compared to 24.0% and 7.7% in recent trials [8, 11]. Although differences in baseline characteristics may partly account for the lower incidence of CIN in our study, it is important to note that the comprehensive use of intravenous and oral volume supplementation seems to provide a safe, simple, effective, and inexpensive strategy for the prevention of CIN. This finding is supported by a recent study showing a reduction in CIN from 34.6% to 3.7% with the use of intravenous saline volume supplementation [24]. Interestingly, CIN could effectively be prevented also

in patients undergoing emergency intervention. This is a very important point, since data about the optimal management in this setting are sparse. Moreover, it supports the concept that post-catheterisation hydration is an integral part of this preventive measure [24].

The aetiology of CIN in humans is poorly defined but seems to include renal vasoconstriction and medullary hypoperfusion [6, 18, 19]. Accordingly, volume expansion with concomitant suppression of the renin system, down regulation of the tubuloglomerular feedback, dilution of the contrast media and thus prevention of renal cortical vasoconstriction, and avoidance of tubular obstruction has enormous theoretical appeal [24]. Poor control of all relevant variables including intravenous and oral hydration has led to the widely conflicting data that have been reported. The risk factors for CIN are related to the characteristics of the procedure itself, to the quantity of contrast agent administered, and to patient characteristics, including severity of the underlying renal disease

Figure 1
Patient flow through study.



and cardiovascular performance. 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. This approach seems to be superior to volume expansion restricted to the procedure only [24].

Four additional strategies have been proposed for selected high-risk patients: acetylcysteine [14, 17, 25], theophylline [7, 12, 18], high volume ultrafiltration [26], and the iso-osmolar contrast agent iodixanol [20, 28, 29]. Given the fact that all of these strategies have significant limitations, it seems important to highlight the effectiveness of stringent volume supplementation as a baseline measure.

Acetylcysteine, a free-radical scavenger with additional vasodilating effects, has been studied extensively with variable results [14, 17, 25]. Initial reports including a meta-analysis including 805 patients seemed promising [17]. However, more recent data seriously questions the renoprotective effect of acetylcysteine and suggests that acetylcysteine does not alter the glomerular filtration rate but causes a decrease in serum creatinine levels through another mechanism [14, 30].

Adenosine seems to be an important mediator of CIN and functions further upstream than oxygen-free radicals and antioxidants. Several clinical studies have investigated the non-selective competitive adenosine-antagonist theophylline as a prophylactic agent [7, 12, 18]. Theophylline seemed to attenuate nephrotoxicity from radiocontrast in some but not all studies. However, the hydration regimen in the positive studies was apparently suboptimal and in general lacked intravenous volume supplementation. Theophylline increases heart rate and myocardial oxygen con-

sumption. This adverse effect may be particularly detrimental in patients with acute coronary syndromes or heart failure. Unfortunately, both of these disorders are common indications for radiocontrast procedures in acutely ill patients.

In patients with severe chronic renal failure (mean serum creatinine concentration 3.1 mg/dl) who were undergoing PCI, periprocedural haemofiltration given in an intensive care unit setting appeared to be effective in preventing the deterioration of renal function due to CIN. This was associated with improved in-hospital and long-term outcomes [26]. Although haemofiltration in the intensive care unit is invasive and costly, it seems beneficial in selected very high-risk patients undergoing multiple interventions, requiring a larger volume of contrast agent than that used during simple diagnostic radiographic procedures. Recently, hydration with sodium bicarbonate has been proposed as a safe, easy and effective alternative to haemofiltration with alkalinising solutions [27].

The iso-osmolar contrast agent iodixanol has been compared with second-generation low-osmolar contrast agents in various settings [20, 28, 29]. Investigations in low-risk and moderate-risk patients with chronic renal failure without diabetes have shown that iodixanol did not reduce the incidence of CIN. However, in selected high-risk patients with both, chronic renal failure (serum creatinine concentration 1.5 to 3.5 mg/dl) and diabetes mellitus, iodixanol seemed beneficial compared to iohexol, and resulted in an incidence for CIN of 3.1%. Because of group inhomogeneities and the lack of a controlled hydration regimen in this study, further confirming research regarding this hypothesis is essential.

Limitations

First, the extent to which atheroembolism into the renal arteries during catheterisation rather than the contrast media contributed to the decline in renal function is unknown. Accordingly, iopromide may have even less toxic effect on the kidneys as estimated in our study. Second, half-isotonic rather than isotonic hydration was used in more than 50% of patients in this study. As we have shown in a previous study, isotonic hydration is superior to half-isotonic hydration. Therefore, applying isotonic hydration in all patients may result in an even lower incidence of CIN than that observed in our study [16]. Third, due to its observational design, our study cannot prove the possible complementary role of oral and intravenous volume supplementation regimens in the prevention of CIN. Fourth, the comparison with historical

controls invariably introduces bias due to potential differences in baseline characteristics.

In conclusion, the use of comprehensive intravenous and oral volume supplementation results in a low incidence of CIN following PCI using iopromide in moderate-risk patients. Volume supplementation should remain the cornerstone for prevention of CIN.

Correspondence:

Prof. Dr. Christian Mueller
Department of Internal Medicine
University Hospital
Petersgraben 4
CH-4031 Basel
E-Mail: cbmueller@ubbs.ch

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