Oral *versus* intravenous hydration and renal function in diabetic patients undergoing percutaneous coronary interventions

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Abstract

Background: Contrast-induced nephropathy (CIN) is a serious complication of percutenous coronary interventions (PCI). Proper hydration reduces the risk of PCI. Wheter oral hydration is as effective as intravenous one has not been well established.

Aim: To determine the effects of oral hydration with mineral water *versus* intravenous hydration with isotonic solution (0.9% NaCl) on renal function in diabetic patients undergoing coronary angiography and angioplasty.

Methods: The study included 102 patients (age 67 ± 7.8 years, 44 female/58 male). Eligible patients (group 1 — 52 pts) were hydrated intravenously (1 mL/kg/h) 6 hours before and during 12 hours following PCI with isotonic solution (0.9% NaCl). Fifty patients (group 2) were randomised to receive oral mineral water (1 mL/kg/h) 6–12 hours before and during 12 hours following angiography or angioplasty. All patients during the procedure received contrast medium ioversol. Primary endpoint of the study was the evaluation of renal function before and 72 hours after contrast medium administration.

Results: Baseline creatinine clearance was 70.3 ± 21.22 mL/min in group 1 and 78.69 ± 19.92 mL/min in group 2 (NS). The mean volume of contrast medium was 101.1 ± 36.7 mL in group 1 and 110.4 ± 45.3 mL in group 2 (NS). At 72 hours after the procedure, creatinine clearance was 65.3 ± 23.39 mL/min in group 1 and 73.5 ± 21.94 mL/min in group 2 (NS).

Conclusions: Our study demonstrates that the oral hydration with mineral water and intravenous hydration with 0.9% NaCl have similar effects on renal function in diabetic patients undergoing coronary angiography and angioplasty.

Key words: contrast induced nephropathy, hydration

Kardiol Pol 2010; 68, 9: 1015–1020

INTRODUCTION

Contrast induced nephropathy (CIN) is defined as deterioration of renal function related to contrast media administration. It is accompanied by an increase in creatinine level of 0.5 mg/dL or more or at least 25% in relation to the baseline values [1]. The increase of creatinine levels is detectable at 24 hours after the exposure to contrast media, peaks at 3–5 days and normalises after 10–14 days [2]. Pathogenesis of nephropathy is related to direct toxic effect of contrast media on the tubular epithelial cells and results directly from haemodynamic disturbances of the renal blood flow. Renal tubules are less prone to injury when iso-osmotic contrast medium is used as compared to low-osmolality contrast media. It has been demonstrated that the effects of intravascular contrast administration on renal blood flow were biphasic. Initial vasodilatation turns into longer lasting phase of reduced renal blood flow as a result of vasoconstriction and changes in O_2 supply. Moreover, the release of endogenous factors such as endothelin, adenosine, free radicals, Ca^{2+} ions, additionally reduce renal perfusion. Eventually, renal blood flow is reduced and renal excretion is impaired [3].

The incidence of CIN in the general population is 1–6% and the rates related to angiography tend to be higher than the rates related to intravenous injection of contrast media. In high risk populations, e.g. in patients with diabetic nephropathy, these rates are as high as 40–50% [4]. In a study by

Manske et al. [5], the incidence of CIN in patients with diabetic nephropathy was studied in relation to the level of contrast exposure and a significant increase of creatinine concentration was found in 50% of these patients. Similarly, in a prospective study of 1196 patients, Rudnick et al. [6] demonstrated that CIN developed in 40.8% of patients with renal insufficiency and diabetes, as compared to 8.4% in patients with neither diabetes nor renal disease. The CIN develops more frequently in patients with creatinine clearance of < 60 mL/min, after intra-aortic balloon pumping, after urgent coronary angioplasty procedures, in patients with chronic heart failure, arterial hypertension, peripheral vascular disease and in patients in whom > 260 mL of contrast media were used [7].

The CIN is often completely asymptomatic. Alternatively, in rare cases (1% patients) it leads to acute non-inflammatory renal insufficiency requiring dialysis. Transient acute renal insufficiency usually resolves spontaneously within 7–14 days [8].

In-hospital mortality rates are significantly higher in patients who develop CIN. Based on large patient group analyses, it was shown that these rates were 22% to 34%, whereas in controls, these rates were between 1.4% and 7%. Also, the mortality rate in CIN patients requiring dialysis was higher than in CIN patients not requiring such therapy (35.7% *vs* 7.1%). Fatal complications were related to cardiac events, gastrointestinal bleeding and sepsis [9].

The most important preventive measures that can reduce the risk of CIN include: (1) identifying high risk patients as the most important step towards decrease of the incidence of CIN; (2) withdrawal of potentially nephrotoxic drugs 24 hours before contrast administration; (3) adequate hydration with 0.9% NaCl or 1.4% $NaHCO_3$ solution; (4) reduction of contrast amount used and administration of the low-osmolality media; (5) haemodialysis and haemofiltration. It was shown that haemodialysis effectively eliminates contrast media with no effect on the incidence of CIN. On the other hand, haemofiltration effectively prevents deterioration of the renal function resulting from CIN, and (6) attempts at pharmacological prophylaxis with calcium channel blockers, dopamine, atrial natriuretic peptide, N-acetylcysteine, fenoldopam, prostaglandin PGE1, endothelin receptor antagonists turned out to be ineffective, so currently these agents are not recommended for prevention of CIN [10–25].

The aim of the study was the assessment of clinical feasibility and effectiveness of oral hydration with neutral liquid and intravenous hydration with 0.9% NaCl in the prevention of renal function impairment after exposure to contrast media in patients with diabetes undergoing elective invasive procedures — coronary angiography and coronary angioplasty.

METHODS
Patients
One hundred and two patients (44 women and 58 men) with cardiovascular disease and diabetes were included in the study. All patients underwent coronary angiography and/or angioplasty using low-osmolality contrast agent Ioversol, and had comorbidities that increase the risk of CIN, such as history of chronic kidney disease, creatinine level > 1.3 mg/dL, heart failure, hypertension and peripheral arterial disease.

Exclusion criteria were as follows: contraindications for invasive procedures, pregnancy or breast-feeding, symptoms and signs of infection, antibiotic treatment, participation in other studies within the preceding 30 days, history of hypersensivity to contrast agents, comorbid cancer and acute renal failure of alternative aetiology.

Type of hydration
Patients were randomly included into one of two groups:
— group 1 — 52 patients hydrated intravenously with isotonic 0.9% NaCl solution. Intravenous infusion of isotonic 0.9% NaCl at 1 mL/kg/h was started 6 hours prior to the procedure and continued up to 12 hours post-procedurally;
— group 2 — 50 patients hydrated orally. Weight-adjusted quantity of neutral fluid (commercially available still mineral water or boiled water) was administered at 1 mL/kg/h between 12 and 6 hours before the procedure and continued up to 12 hours post-procedurally. In patients with heart failure the volume of fluid was reduced to 50% of the calculated values.

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Biochemical workup
For biochemical and haematological workup, 20 mL of blood was taken from cubital vein, 6–8 hours prior to the procedure and after 72 hours. In cases of CIN diagnosis, additional blood tests were done in subsequent days of hospitalisation depending on clinical indications, until renal function parameters were normalised. Blood samples were taken for peripheral blood morphology (haemoglobin, haematocrite, white cell count and platelet count), fasting blood glucose, creatinine and urea concentration as well as natrium and potassium levels.

Prior to invasive cardiovascular procedure, either therapeutic or diagnostic, and after considering inclusion and exclusion criteria for participation in the study, patients were given written information in order to obtain their informed consent. Then, a detailed history was taken including coexisting diseases, symptoms of ischaemia for the assessment of the severity of coronary artery disease, and physical examination was performed. Next, additional biochemical tests and resting electrocardiogram were done. Creatinine clearance was measured according to the Cockroft and Gault formula.

Statistical analysis
The results are presented as mean ± SD. Differences between analysed variables were assessed using Student t-test. A p value < 0.05 was considered significant.

Table 1. Comparison of the patient groups

	Group 1 (n = 52)	Group 2 (n = 50)	P
Age [years]	67.3 ± 7.76	63.7 ± 7.82	NS
Body mass index [kg/m²]	31.71 ± 4.762	30.52 ± 4.97	NS
Systolic blood pressure [mm Hg]	134.8 ± 24.03	141.5 ± 20.68	NS
Diastolic blood pressure [mm Hg]	76.8 ± 13.59	80.9 ± 12.96	NS
Fasting glucose [mg/dL]	125.6 ± 22.75	130.4 ± 34.23	NS
Haemoglobin [g%]	13.22 ± 1.59	14.01 ± 1.37	NS
Contrast volume [mL]	101.1 ± 36.62	110.4 ± 65.28	NS
Fluid volume [mL]	1597.7 ± 225.97	1662.7 ± 338.72	NS

Numerical values are presented as means ± standard deviation.

Table 2. Renal function parameters and electrolyte balance — baseline values

	Group 1	Group 2	P
Creatinine [mg/dL]	1.235 ± 0.4454	1.172 ± 0.3872	NS
Creatinine clearance [mL/min]	70.33 ± 21.215	78.69 ± 19.919	NS
Urea [mg/dL]	49.01 ± 23.54	44.95 ± 13.58	NS
Uric acid [mg/dL]	6.15 ± 2.116	6.03 ± 1.793	NS
Na$^+$ [mmol/L]	139.2 ± 1.95	138.7 ± 2.83	NS
K$^+$ [mmol/L]	4.60 ± 0.575	4.39 ± 0.477	NS

Numerical values are presented as means ± standard deviation.

Table 3. Renal function parameters and electrolyte levels at 72 hours after procedure

	Group 1	Group 2	P
Creatinine [mg/dL]	1.346 ± 0.4826	1.235 ± 0.4421	NS
Creatinine clearance [mL/min]	65.63 ± 23.389	73.50 ± 21.947	NS
Urea [mg/dL]	55.62 ± 30.886	53.09 ± 17.093	NS
Uric acid [mg/dL]	6.34 ± 2.493	6.22 ± 1.815	NS
Na$^+$ [mmol/L]	140.2 ± 2.02	138.8 ± 2.55	NS
K$^+$ [mmol/L]	4.39 ± 0.421	4.317 ± 0.417	NS

Numerical values are presented as means ± standard deviation.

Table 4. Renal function parameters at baseline and at 72 hours after procedure

	Creatinine clearance at baseline [mL/min]	Creatinine clearance at 72 h [mL/min]	P
Group 1	70.33 ± 21.215	65.63 ± 23.389	NS
Group 2	78.69 ± 19.919	73.50 ± 21.947	NS

Numerical values are presented as means ± standard deviation.

RESULTS

No significant between-group differences in the study parameters were found, as shown in Table 1. Baseline renal function parameters as well as Na$^+$ and K$^+$ levels were similar in both study groups. Patients included in our study had reduced filtration rates at baseline, as shown in Table 2.

Between-group differences in creatinine and creatinine clearance, urea and uric acid concentration as well as Na$^+$ and K$^+$ levels at 72 hours post-procedurally were not significant (Table 3). Contrast agents caused renal function impairment in both groups, however mean creatinine clearance was similar (Table 4). In 3 (5.77%) patients from group 1 and in 2 (4%) patients from group 2 biochemical indices of CIN were identified. None of the patients required dialysis due to impaired renal function. None of the two methods of CIN prevention influenced ion parameters. Serum

sodium and potassium levels were similar to baseline values in both groups.

DISCUSSION

Adequate hydration before and after contrast administration improves renal blood flow and glomerular filtration, and this can help reverse the negative hemodynamic conditions leading to the development of CIN. According to the guidelines of the American College of Radiology (ACR), hydration with 0.45% or 0.9% NaCl at a dosage of 100 mL/h is recommended, beginning 6–12 hours prior to and continued for 4–12 hours after contrast administration. As demonstrated by Bartolomew et al. [7] and Gruberg et al. [9], the amount of contrast used is an independent risk factor of CIN development. According to some experts, the amount of contrast higher than 300 mL, or — according to others — higher than 400 mL, is an independent risk factor of CIN in patients with normal serum creatinine. When baseline creatinine levels are 1.5–3.0 mg/dL, the amount of contrast used should not exceed 150 mL and it should not exceed 100 mL when baseline creatinine is > 3 mg/dL. Metaanalysis by Barrett and Carlisle [14] showed that high-osmolality contrast agents usage increases the risk of CIN development as compared to low-osmolality agents.

The measures of CIN prevention used in our study in the selected group of diabetic patients, i.e. administration of low-osmolality contrast agents and adequate hydration are widely used in clinical practice and have been shown effective by objective measures [11, 12]. In our study intravenous injection of 0.9% NaCl was used, as its effectiveness in CIN prevention was higher than that of 0.45% NaCl [25]. There are data in favour of greater effectiveness of intravenous aqueous solution of sodium bicarbonate in comparison to 0.9% NaCl [16], but we have chosen the latter due to its confirmed effectiveness and wide availability. In order to obtain homogenous and comparable groups we did not use any other pharmacological agents that might have protective effect on glomerular filtration, e.g. acetylcysteine. The contrast agent used in our study, Ioversol, belongs to a group of non-ionic and low-osmolality contrast agents, but there are studies reporting greater effectiveness of the iso-osmotic contrast agent, iodixanol, in the prevention of CIN [26].

In our study, patients undergoing invasive procedures requiring contrast administration were in the group of higher risk of CIN development due to coexistent diabetes and reduced baseline creatinine clearance. Adequate hydration, either oral or intravenous, failed to completely prevent the adverse effect of contrast administration — creatinine clearance values were decreased 3 days after the procedure. Similar results were reported by Garcia-Ruiz et al. [27]. They used oral hydration in patients with chronic kidney disease undergoing spiral computed tomography with intravenous contrast agent iopromide. It should be mentioned, however, that the hydration protocol used by Garcia-Ruiz et al. [27] differed from our protocol, which followed the recommendations of the ACR [13, 16]. A limitation of our study, and of many studies, is the relatively small patient group. When interpreting our results it should be kept in mind that to note significant differences in creatinine clearance values, groups of several hundred patients should be analysed.

The issue of different forms of hydration has been addressed in only a few studies and these were chiefly studies of chronic kidney disease patients, who could be easily identified as such. Taylor et al. [28], in a small group of 36 patients and Dussol et al. [29], in a group of 312 patients with chronic kidney disease, have demonstrated comparable effectiveness of oral and intravenous hydration. Conversely, Trivedi et al. [30] showed higher effectiveness of intravenous hydration as compared to oral hydration. It should be underlined, however, that this study was carried out in a small group of 53 patients and in the oral hydration group patients were given fluids and their intake was uncontrolled. The CIN incidence (18.1%) reported by these authors was much higher than the rates published in the literature.

In the literature to date we did not find any comparison of the effectiveness of different intravenous and oral hydration protocols for CIN prevention in high risk patients with diabetes.

CONCLUSIONS

No significant between-group differences were observed in renal function parameters in patients with diabetes undergoing cardiovascular invasive procedures in whom oral hydration was used as compared to patients hydrated intravenously. These results need to be verified in a large study of several hundred patients.

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Ocena porównawcza wpływu nawodnienia doustnego płynami obojętnymi i nawodnienia dożylnego 0,9% roztworem NaCl na funkcję nerek u chorych na cukrzycę poddanych kardiologicznym procedurom inwazyjnym

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Streszczenie

Wstęp: Nefropatia indukowana kontrastem (NIK) bywa istotnym powikłaniem procedur angiograficznych. Zalecanym sposobem jej prewencji jest nawodnienie z zastosowaniem izotonicznego roztworu chlorku sodu. Chorzy na cukrzycę należą do grupy zwiększonego ryzyka wystąpienia NIK.

Cel: Celem pracy było określenie wpływu na funkcję nerek doustnego nawodnienia wodą mineralną w porównaniu z nawodnieniem dożylnym izotonicznym roztworem chlorku sodu (0,9% NaCl) w grupie chorych na cukrzycę poddanych elektywnym zabiegom koronarografii i angioplastyki wieńcowej. Pierwotnym punktem końcowym badania była ocena funkcji nerek określana klirensem kreatyniny (wg wzoru Cockroft-Gault) przed ekspozycją na środek kontrastowy w trakcie procedury inwazyjnej i 72 godziny po niej. Oceniano także zachowanie stężenia mocznika, kwasu moczowego oraz gospodarki jonowej (Na$^+$, K$^+$).

Metody: Badanie było prospektywne, randomizowane, jednoośrodkowe i objęło 102 pacjentów (śr. wiek 67 ± 7,8 roku, 44 kobiet/58 mężczyzn). Kolejnych 52 chorych (grupa 1) było nawadnianych dożylnie 0,9% NaCl (1 ml/kg/h) 6 godzin przed i 12 godzin po zabiegu koronarografii i/lub koronaroplastyki, a następnych 50 osób nawodniono drogą doustną wodą mineralną (1 ml/kg/h) między 12 i 6 godziną przed procedurą inwazyjną oraz 12 godzin po jej zakończeniu. Wszyscy pacjenci w trakcie koronarografii i/lub koronaroplastyki otrzymywali niejonowy, niskoosmolarny środek kontrastowy Ioversol (Optiray 350 – Tyco HEATHCARE).

Wyniki: Wyjściowy klirens kreatyniny w grupie 1 i 2 wynosił odpowiednio 70,30 ± 21,22 ml/min i 78,69 ± 19,92 ml/min (p = NS). Średnia objętość podanego środka kontrastowego wynosiła w grupie 1 i 2 odpowiednio 101,1 ± 36,7 ml i 110,4 ± ± 45,3 ml (p = NS). W 72. godzinie od zabiegu klirens kreatyniny w grupie 1 i 2 wynosił odpowiednio 65,3 ± 23,39 ml/min i 73,5 ± 21,94 ml/min (p = NS). Podobnie nie zaobserwowano istotnych statystycznie różnic w stężeniu w surowicy: mocznika, kwasu moczowego, sodu i potasu.

Wnioski: Wykazano, że zarówno doustne nawodnienie wodą mineralną, jak i nawodnienie dożylne izotonicznym roztworem chlorku sodu podobnie wpływa na funkcję nerek u chorych z cukrzycą poddanych kardiologicznym procedurom inwazyjnym. Nawodnienie doustne chroni funkcję nerek bez ryzyka działań niepożądanych przy równocześnie niższych kosztach.

Słowa kluczowe: funkcja nerek, nefropatia indukowana kontrastem, nawodnienie

Kardiol Pol 2010; 68, 9: 1015–1020