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THE EFFECTS OF CONTRAST MEDIA ON RENAL FUNCTION IN CHILDREN: COMPARISON OF IONIC AND NON-IONIC AGENTS*

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SUMMARY: Buyan N, Arab M, Hasanoğlu E, Gökçora N, Ercan S. (Nephrology Unit, Department of Pediatrics, and Departments of Nuclear Medicine and Pharmacology, Gazi University Faculty of Medicine, Ankara, Turkey). The effects of contrast media on renal function in children. Comparison of ionic and non-ionic agents. Turk J Pediatr 1995; 37: 305-313.

Nephrotoxicity is a common side effect of intravascular contrast media (CM). Although nephrotoxicity of ionic CM has been widely demonstrated, recent studies suggest that newer and more costly non-ionic agents are no less nephrotoxic.

We studied the hemodynamic, hematologic and nephrotoxic effects of CM prospectively in 38 patients (ages six months-16 years) with or without risk factors predisposing to nephropathy and compared ionic and non-ionic CM. We performed intravenous urography (IU) with an ionic CM, sodium meglumine diatrizoate (n = 18) and a non-ionic CM, iohexol (n = 20). The patients were divided into three groups according to glomerular filtration rate (GFR) [GFR ≤ 50 (n = 9), 50-80 (n = 13), ≥ 80 ml/min/1.73m^2 (n = 26)]. Eleven patients had risk factors for nephropathy. Blood pressure, heart rate, ECG, urine and blood samples were obtained 24 hours and one hour before as well as one, 24, and 48 hours after CM infusion. Although a significant increase was found in urine specific gravity, protein/creatinine ratios and serum Na and creatinine levels, the increased levels were within normal limits. We observed a significant reduction in Hb and Htc and urinary prostaglandin E_1 levels. Many of the changes observed in the urine and serum values after the use of CM were minor, insignificant and transient, later returning to their initial values. The GFR levels, the presence of risk factors and the use of ionic vs. non-ionic CM had no effect on the results. The elevated urinary basal beta-2-microglobulin levels further increased after CM infusion in patients with low GFRs.

It was concluded that non-ionic CM was not superior to ionic CM in patients with GFRs greater than 50 ml/min regardless of predisposing risk factors. One of the non-invasive radiological methods is advised instead of IU in patients with low GFRs.
Key words: contrast nephropathy, ionic contrast media, non-ionic contrast media, beta-2-microglobulin, intravenous urography.

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Contrast nephropathy (CN) is defined as acute toxic nephropathy due to radiographic contrast media (CM)[1].

Recently, it has been shown that CN is not common in patients with normal renal function, but occurs more frequently in patients with renal impairment (RI), especially due to diabetic nephropathy. Although nephrotoxicity of ionic, high-osmolar CM has been widely demonstrated, recent studies suggest that newer and more costly non-ionic, low-osmolar agents are no less nephrotoxic than standard preparations, especially in high-risk patients with RI and/or diabetic nephropathy[2-6].

The aim of this prospective study was to evaluate and compare the hemodynamic, hematologic and nephrotoxic effects of an ionic conventional CM with a non-ionic low-osmolar CM in patients with or without risk factors predisposing to nephropathy, since low-osmolar CM is 10 to 20 times more expensive than high-osmolar CM[1,7].

Material and Methods

Thirty-eight children between the ages of six months and 16 years (mean 7.6 years) who underwent intravenous urography (IU) between August 1991 and November 1992 were studied. They were divided into three groups according to creatinine clearance [Group A: glomerular filtration rate (GFR) $\leq$ 50 (n = 9), Group B: GFR = 50-80 (n = 13), Group C: GFR $\geq$ 80 ml/min/1.73 m^2 (n = 16)] and each group was stratified into either low-risk (n = 27) or high risk (n = 11) groups based on the presence of risk factors reported previously for predisposition to nephropathy. GFR was determined from the creatinine clearance using the formula: creatinine clearance (ml/min per 1.73 m^2) = k x height (cm)/plasma creatinine (mg/dl). "k" was calculated according to the degree of malnutrition in our patients. Patients were placed in the high-risk group if they had azotemia (Cr > 2 mg/dl), hypertension, DIDMOAD syndrome, solitary kidney with RI, or nephrotic syndrome. Eighteen patients were examined with an ionic CM, sodium meglumine diatrizoate (Urografin, 76% Shering AG, Berlin, Germany) while the remaining 20 received a non-ionic CM, iohexol (Omnipaque, Nycomed, Oslo, Norway) (Table I).Each patient received CM at a dose of 1 ml/kg body weight intravenously (i.v) within 10 minutes through a catheter inserted into an antecubital vein. Food was restricted three to 12 hours prior to the CM infusion depending on the patient's age. Patients were given i.v. fluids before IU as a clinical precaution to minimize nephrotoxicity.

IU was necessary in the diagnostic evaluation of all patients for symptoms possibly related to urologic abnormality.

Patients were excluded from the study if they had a history of: 1) adverse reaction to any medicine, 2) coagulopathy, 3) plasma creatinine higher than 3 mg/dl, 4) electrolyte or fluid imbalance, 5) previous contrast agent administration, 6) nephrotoxic antibiotic therapy.

Table I: Primary Diseases of the Patients

GFR ml/min per 1.73 m²			Grokup A (n = 9) ≤ 50	Group B (n = 13) 50-80	Group C (n = 16) ≥ 80
High-Risk Group (n = 11)	Na-meglumine diatrizoate	n = 7	Group = 1 – VUR – Hydronephrosis – Hydronephrosis	Group = 2 – DIDMOAD Syn.	Group = 3 – Hypertension – Hypertension – Hypertension
	Iohexol	n = 4	Group = 4 – Renal agenesis (UL) – Nephrolithiasis	Group = 5 – Nephrotic Syn. – Renal agenesis (UL)	Group = 6
Low-Risk Group (n = 27)	Na-meglumine diatrizoate	n = 11	Group = 7 – Hydronephrosis – Nephrocalcinosis	Group = 8 – Recurrent UTI – Hydronephrosis – Urolithiasis renal agenesis (UL) – Urolithiasis	Group = 9 – Hematuria – Hematuria – Rhabdomyosarcoma – Hematuria – Recurrent UTI
	Iohexol	n = 16	Group = 10 – Urolithiasis – Multiple congenital abnormalities	Group = 11 – Multiple congenital abnormalities – Neuroblastoma – Recurrent (UTI) – Urolithiasis – Urolithiasis – Hematuria	Group = 12 – Horseshoe kidney – Urolithiasis – Recurrent UTI – Urolithiasis – Recurrent UTI – VUR – Hematuria – Hematuria

VUR = Vesico ureteral reflux
UTI = Urinary tract infection
UL = Unilateral

Blood and urine samples were obtained 24 hours and one hour before, as well as one, 24 and 48 hours after CM infusion (Fig. 1). Blood pressure, heart rate and ECG patterns were recorded at set times established according to the pharmacokinetic characteristics of ionic and non-ionic CM (Table II).

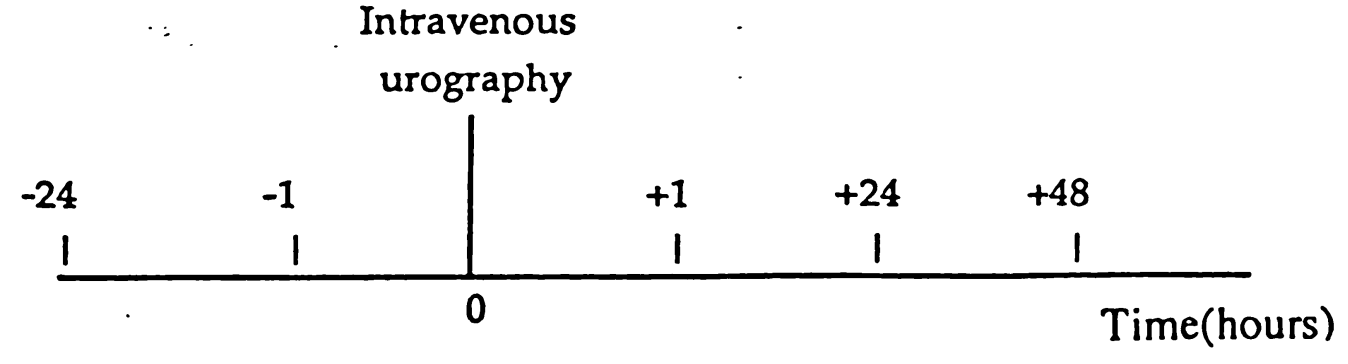

Fig. 1: Time points when plasma and urine samples were obtained.

Table II: Properties of the Selected Contrast Media

Contrast Media	Max.Urinary Excretion Time	Iodine (mg/ml)	Osmolality (mOsm/kg)	Viscosity 20 °C	Viscosity 37 °C	Na+ (mEq/L)	Disodium EDTA
Sodium meglumine	10-20 min	370	2100	13.8	8.4	190	0.4
Diatrizoate Iohexol	1 h.	350	780	23.3	10.6	Negligible	0.1

Urine specimens were analyzed for levels of creatinine, sodium (Na), potassium (K), chloride (Cl), uric acid (ua), protein, beta-2-microglobulin β_2 (M) and prostaglandin E_1 (PGE_1). Blood samples were analyzed for hemoglobin (Hb), hematocrit (Htc), blood urea nitrogen (BUN), ua, creatinine, Na, K and Cl levels.

Proteinuria, hematuria, glucosuria and urine pH were measured with a urine dipstick, urine osmolality was measured with an osmometer and urine specific gravity was measured with refractometer. All urine specimens were analyzed microscopically by a physican. Fractionated excretion of sodium (FENa), fractionated excretion of potassium (FEK), fractionated excretion of chloride (FECl), fractionated excretion of uric acid (FEua) and ratios of urinary protein to creatinine were calculated with standard formulas. Urinary β_2 M samples were alkalinized immediately after voiding with sodium hydroxide to prevent decomposition and were analyzed with an RIA kit (IEMA KIT DSL-6100, Webster, TX). Urine PGE_1 levels was measured by bioassay.

In all cases, the parents were informed and consent obtained.

Data analysis: Data were presented as mean plus or minus standard deviation. The Wilcoxon test on medians was used for statistical analysis, and intergroup significance was calculated by analysis of variance and Student's t-test.

Results

Data obtained at different times and at the same time in different groups were compared. Statistical analysis was performed in only four low-risk groups (Group = 8, 9, 11, 12) because of insufficient numbers of patients in other groups, especially those with low GFRs and high risk factors because of ethical reasons. All the results in the remaining groups were evaluated, but statistical analysis was not performed.

We observed no adverse reaction or side effect on renal function requiring treatment after the use of ionic or non-ionic CM in any group. Many of the changes observed in urine or serum values after the use of CM were minor, insignificant and transient.

No significant change in blood pressure, heart rate, ECG pattern, urinalysis, FENa levels or urine osmolality values was observed at any point in any group, regardless of risk factors or the use of ionic versus non-ionic CM. Although a

statistically significant increase in serum Na and creatinine levels was found one hour after CM infusion (in groups 8 and 9, and groups 9 and 12, respectively), the increased levels were within normal limits (Fig. 2).

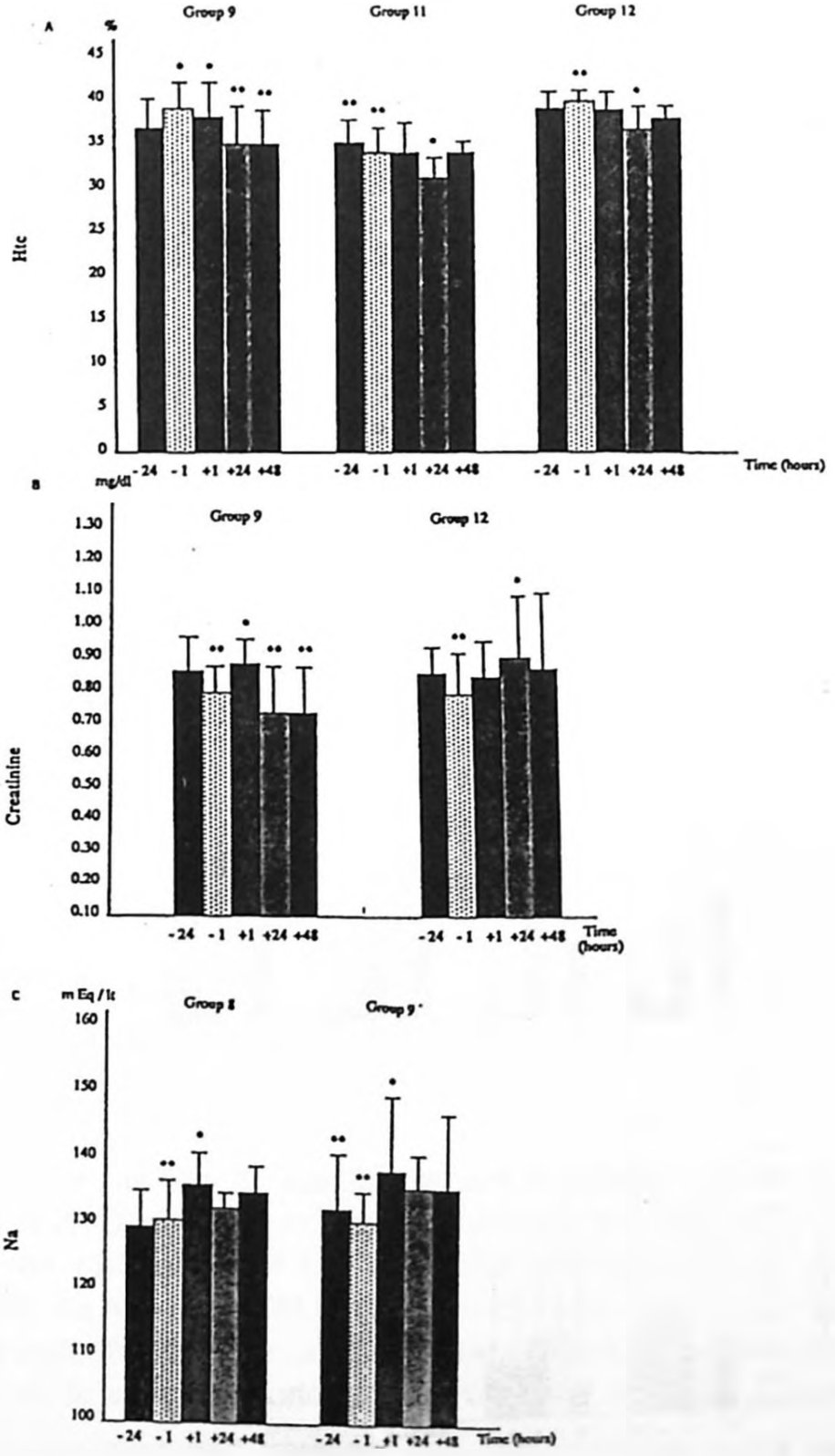

Fig. 2: Changes in hematocrit (A), serum creatinine (B) and serum sodium levels (C) before and after contrast media infusion in different groups. Only the groups with significant differences were included. * < 0.05 vs. ** for each group. Values given as mean ± SD.

We observed a significant reduction in Hb and Htc levels at +24 and +48 hours in group 9 and at +24 hours in groups 11 and 12 ($p < 0.05$) (Fig. 2).

Urine specific gravity increased one hour after CM infusion in all groups and was statistically significant in groups 8, 9, 11 and 12 ($p < 0.05$) (Fig. 3). A decrease in urinary PGE_1 levels was found at different times after CM infusion in all groups ($p < 0.05$ in groups 8, 9, 11 and 12) (Fig. 3) A significant increase was observed in the urine protein / creatinine ratio at +24 hours in group 9 and at + one hour in group 12 ($p < 0.05$) (Fig. 3).

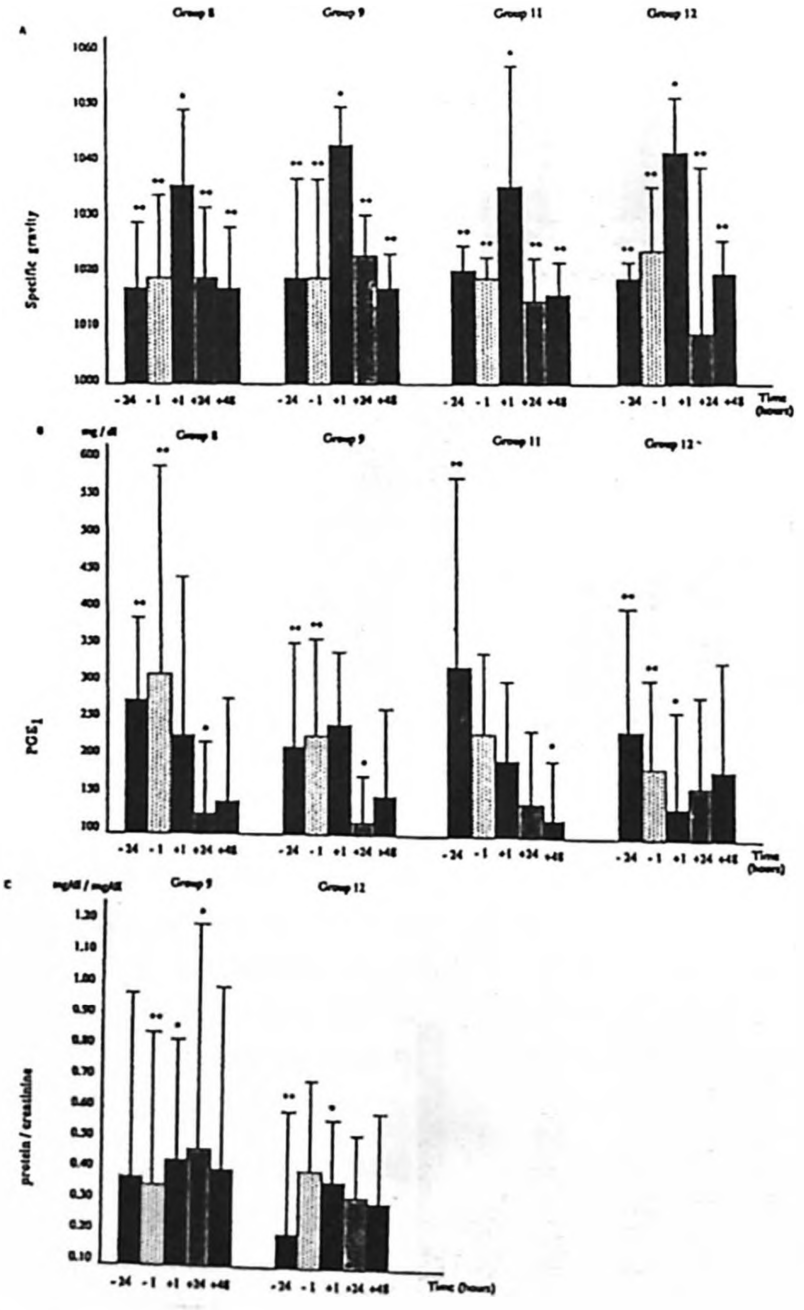

Fig. 3: Changes in urine specific gravity (A), urinary PGE_1 levels (B) and urine protein / creatinine ratios (C) before and after contrast media infusion in different groups. Only the groups with significant differences were included. * < 0.05 vs. ** for each group. Values given as mean ± SD.

We observed insignificant and transient increases in BUN, serum K, Cl, uric acid, FEK, FECl and FEua values, and insignificant decreases in creatinine clearance at some points in different groups after CM infusion, regardless of risk factors and the use of ionic versus non-ionic CM ($p > 0.05$).

Urinary basal β_2 M values were observed at higher than normal levels and fruther increased after CM infusion in patients with low GFRs (Table III). We found no significant difference between the values obtained at the same time in different groups ($p > 0.05$) (Group 8, 9, 11 and 12).

Table III: Urinary β_2 Microglobulin Levels in Patients with Low GFRs

	β_2 Microglobulin (mg/l)				
Time Before or After CM (h)	-24	-1	+1	+24	+48
GFR ≤ 50 ml/min HO, HR (n = 3) (Group 1)	7.92 ± 14.74	8.18 ± 10.86	16.58 ± 9.24	16.49 ± 9.07	7.66 ± 10.13
GFR ≤ 50 ml/min HO, LR (n = 2) (Group 7)	0.78 ± 0.05	2.82 ± 0.6	5.18 ± 5.83	5.72 ± 9.1	2.0 ± 0
GFR ≤ 50 ml/min LO, HR (n = 2) (Group 4)	2.29 ± 2.96	9.61 ± 12.88	13.94 ± 18.82	2.08 ± 2.42	2.6 ± 0.3
GFR ≤ 50 ml/min LO, LR (n = 2) (Group 10)	0.65 ± 0.26	0.37 ± 0.22	3.4 ± 5.11	2.94 ± 3.93	1.62 ± 1.03

HR : High risk.
LR : Low risk.
LO : Low osmolality.
HO : High osmolality.
CM : Contrast media.

Discussion

The incidence of CN after IU was 55 percent in patients with RI (serum creatinine > 2 mg/dl) and 15 percent in patients without existing renal disease. In the literature, the incidence of CN after the use of ionic or non-ionic CM is controversial. As non-ionic CM is 10-20 times more expensive than conventional agents, the cost-effectiveness of CM should be evaluated carefully before making a decision as to which material should be used in which patient[1, 7-9].

In our study we observed transient and mild changes in the majority of urine and serum values after either ionic or non-ionic CM infusion in both the low-risk and high-risk groups.

It is known that an expansion in plasma volume occurs after CM infusion. In our study the reduction observed in Hb and Htc levels may be related to the osmotic effect of CM on plasma volume resulting in a rapid increase[10, 11].

The increase in the urine specific gravity observed in all groups one hour after CM infusion is secondary to the excretion of CM in high concentration in the urine[11].

Injection of CM into the renal artery was shown to cause a biphasic change in renal blood flow (RBF), and a transient vasodilation followed by a more prolonged vasoconstriction phase in experimental studies. It was concluded that the decrease observed in the urinary PGE_1 levels after either ionic or non-ionic CM infusion in all groups may be related to the reduced PGE_1 synthesis in the renal medulla secondary to the decrease in RBF. The role of prostaglandin (PG) inhibitors in clinical CN is unknown. It is recommended that all drugs known to inhibit PG synthesis should be discontinued prior to the administration of CM[12-15].

A significant increase observed in serum NA levels one hour after ionic CM infusion was found to be related to the Na content (190 mEq/L) of Na-meglumine diatrizoate. The increased Na levels were within normal limits and returned to the initial values.

In the literature, CN was defined as an elevation in the serum creatinine level of 30 percent or more over the baseline value[8]. Although we observed a significant increase in the serum creatinine levels in two groups, the increased levels were not greater than 20 percent more than basal values in any patient.

Additionally, urinary excretion of β_2 M is a widely used test of renal proximal tubular function. In the literature, there were some reports that accepted β_2 as a reliable marker for diagnosis of CN. It was concluded that the patients with RI were more sensitive to CN, since the elevated urinary basal β_2 M levels had further increased following either ionic or non-ionic CM infusion in patients with low GFRs in our study[10, 16-19].

Finally, our study showed that expensive and non-ionic CM was not superior to ionic CM in patients with GFRs greater than 50 ml/min./1.73 m^2, regardless of predisposing risk factors, since iv administration of both CM caused similar, mild and transient hematologic and nephrotoxic effects in these patients. One of the non-invasive diagnostic studies is advised instead of IU in patients with low GFRs, because these patients are more sensitive to CN.

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