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Cystatin C as biomarker of contrast-induced nephropathy in pediatric cardiac angiography

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Background/aim: The purpose of this study is to find the frequency of contrast-induced nephropathy (CIN) and to show the risk factors in the development of CIN and the diagnostic utility of serum cystatin C (CysC) and serum and urine neutrophil gelatinase-associated lipocalin (NGAL) during childhood following cardiac angiography.

Materials and methods: In this prospective study, we studied 46 children with congenital heart disease. The levels of serum creatinine, serum CysC, and serum NGAL were measured at 4, 24, and 48 h, while levels of urine NGAL and urine creatinine were measured at 4 to 8 and 48 h following cardiac angiography.

Results: According to serum creatinine levels, with a cutoff value of 4.1 mL/kg for development of CIN, sensitivity, specificity, area under the receiver-operating characteristic curve, and positive likelihood ratio were calculated as 69%, 70%, 0.67, and 2.29, respectively. The levels of serum CysC and serum creatinine significantly increased at 4, 24, and 48 h after the application of the contrast agent.

Conclusion: The results of this study show that according to the definition of CIN, the incidence of CIN is significantly increased in pediatric patients with congenital heart disease. Moreover, the results support that serum CysC levels may allow the detection of CIN after cardiac angiography, like serum creatinine in present study.

Key words: Cardiac angiography, contrast media, creatinine, cystatin C, lipocalin, nephropathy

1. Introduction

The administration of radiographic contrast agents remains an important cause of hospital-acquired acute renal failure, which contributes to morbidity and mortality during hospitalization, prolongs hospital stay, and increases the incidence of chronic end-stage renal disease and costs of health care (1–5). In pediatric studies, the acute renal damage induced by nephrotoxins is estimated to have been 17%, half of which was reported to result from cardiac angiography (6). Twelve percent of acute renal failures were shown to be induced by the use of contrast media (3). Therefore, in all intervention contrast media used, risks for nephropathy should be evaluated and necessary precautions should be taken for the patients.

In recent studies, cystatin C (CysC) and neutrophil gelatinase-associated lipocalin (NGAL) were defined as determining the renal damage risk (7,8). It has been shown that, in diagnosing contrast-induced nephropathy (CIN), the level of serum CysC in the first 24–48 h and the serum and urine NGAL levels in the first 4 h have seen to have increased (9–12).

In this study, we aimed to evaluate the incidence and risk factors for CIN in children undergoing cardiac angiography, and the role of serum CysC and serum and urine NGAL levels in early diagnosis of CIN.

2. Materials and methods

2.1. Study population

This study was conducted within a period of 18 months on 13 healthy children whose physical examination was found to be within normal limits and on 46 subsequent patients with congenital heart disease, whose diagnostic cardiac angiographies were carried out in the Pediatric Cardiology Department of the Medical Faculty of Gazi

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University. Prior to this study, which was prepared in compliance with the Declaration of Helsinki and supported by the Scientific Research Projects Unit at Gazi University with the permission of the local ethics council, informed consent was obtained from the parents of the children.

The age, sex, body weight, body height, body surface area, medication history, cyanosis, systolic and diastolic blood pressure, and echocardiographic left ventricular ejection fraction of the patients were recorded 24 h prior to the angiography procedure. Blood samples for complete blood count, urea, creatinine, serum CysC level, and serum NGAL level and urine samples for urine specific gravity, urine creatinine level, and urine NGAL level were taken. Glomerular filtration rate was calculated. Oral feeding was stopped while intravenous hydration (1500–2000 mL m^{-2} day^{-1}) was started 4–8 h prior to the procedure. Intravenous hydration with isotonic saline solution was continued for 24 h after the procedure.

Standing height (cm) was measured to the nearest 0.1 cm using a Harpenden fixed stadiometer. Body weight (kg) was observed on a SECA balance scale to the nearest 0.1 kg, with subjects dressed in underwear. The body surface area was calculated using the DuBois formula (13). Blood pressure was measured with a standard clinical sphygmomanometer (ERKA, Germany) from the right arm after a 5-min rest in the supine position, using a stethoscope placed over the brachial artery pulse, proximal and medial to the cubital fossa, and below the bottom edge of the cuff (i.e. 2 cm above the cubital fossa). The cuff used was appropriate for the size of the child's upper right arm (14). Transthoracic echocardiography was examined with ViVid 7 Pro (General Electric Medical Systems, USA) and 5- and 7-MHz transducers, according to the recommendations of Task Force of the Pediatric Council of the American Society of Echocardiography (15).

2.2. Study design

Blood samples were drawn from the antecubital vein in all subjects. For the serum urea and creatinine levels, Abbott ARCHITECT c16000 and assay kits were used (Abbott, USA). The glomerular filtration rate (with respect to the reference interval of 60–169 mL min^{-1} 1.73 m^{-2}) was calculated using the Schwartz formula (16). The blood count, from blood taken into tubes with special lids including potassium ethylene diamine tetraacetic acid, was conducted using the CELL-DYN Sapphire and CELL-DYN 3700 models of Abbott. The urine specific gravity (with respect to the reference interval of 1002–1030) was evaluated using the Roche Combur10 Test and Miditron M. Serum NGAL levels (with respect to the reference interval of 19.99–148.94 ng/mL) and urine NGAL levels were examined with a fully automated ALISEI ELISA device (SEAC Diagnostics, Italy) using the commercial ELISA human lipocalin-2/NGAL kit (Biovendor Research and Diagnostic Products, Czech Republic). Urine creatinine measurements were conducted using original Olympus kits in an Olympus AU400 immunoanalyzer (Japan). Serum CysC levels (with respect to the reference interval of 0.53–0.95 mg/L) were determined using a nephelometer produced by Siemens (BN II System, Germany) with Siemens N Latex Cystatin C Kits.

Cardiac angiography procedures were initiated with sedation and local anesthesia with strict aseptic preparation of the skin. The sheaths were percutaneously inserted into the femoral vein and artery. Pressure records and blood samples were taken from each location of the heart and vessels via appropriate cardiac catheters. After administering contrast media injections, angiograms were taken, nephrograms having been recorded. Iopromide (769 mg/mL Ultravist-370, IV flacon, Schering German Pharmaceutical Company) was intravenously used as a contrast medium with nonionic low osmolarity. The amount of the contrast medium during the procedure, fluoroscopy time, and oxygen saturations of the patients were all recorded. Blood samples were taken at the end of 4, 24, and 48 h for serum creatinine, serum CysC, and serum NGAL levels. Urine samples were taken at 4–8 h and at the end of 48 h for urine NGAL and urine creatinine levels. Serum creatinine, serum CysC, and serum and urine NGAL levels were also taken into account in the healthy children in the control group as well.

For the diagnosis of CIN, ≥25% relative increase or an absolute increase of ≥0.5 mg/dL in serum creatinine from baseline value at 48 to 72 h after exposure to contrast media when alternative explanations for renal impairment or kidney failure had been excluded was used (2–4).

2.3. Statistical analyses

SPSS, 16.01 for Windows (SPSS Inc., USA) was used for statistical analyses. All data were reported as mean ± standard deviation. In comparing the patient and control group data, the Mann–Whitney U test, a nonparametric test, was used; for the data for the 2 dependent groups, the Wilcoxon signed-rank test (Kruskal–Wallis analysis was used; and for the data having more than 2 dependent group parameters, the Friedman repeated measures analysis of variance (ANOVA) test was used for evaluations. Having completed the Friedman ANOVA, the Wilcoxon signed-rank test with Bonferroni correction was implemented in order to show from which group the statistical discrepancy had stemmed. When the general significance level was regarded as <0.05, the P-value, considered statistically significant in correlations with more than 2 variables, was acquired by dividing the value into the number of the groups compared ($P < 0.05$/number of the groups compared). In comparing the ratios of the groups, the chi-square test was implemented. For multivariate analysis of CIN risk factors, backward stepwise logistic regression analysis was used. To

measure the sensitivity and specificity for contrast medium volume for development of CIN, receiver-operating characteristic (ROC) curves were generated and the area under the curve (AUC) calculated. An AUC of 0.5 is not accepted as a risk factor, whereas a value of 1.0 signifies a perfect cutoff volume of contrast medium. P values of less than 0.05 were considered statistically significant.

3. Results

Forty-six patients (18 males and 28 females) using contrast media whose median age was 3 years (2 months to 16 years) and 13 healthy children (6 males and 7 females) whose median age was 6 years (9 months to 13 years) were studied. In the patients, the medians of weight, height, and body surface area were found 14.5 kg, 95 cm, and 0.61 m^2, respectively. In the controls, these were 18 kg, 110 cm, and 0.70 m^2, respectively.

The clinic and laboratory data are summarized in Table 1. There was no significant difference ($P > 0.05$) in blood pressures; urine specific gravity; serum creatinine; glomerular filtration rate; serum CysC, serum NGAL, and urine NGAL levels; or urine NGAL/urine creatinine ratio between the patients and healthy children. Furthermore, anaphylactic reaction, acute renal failure, morbidity, and mortality were not observed in the patients.

Sixteen subjects who received cardiac angiography with contrast media and who developed CIN (≥25% increase in serum creatinine from baseline value) and 30 children with no CIN were compared in terms of risk factors (Table 2). No significant difference was found between the groups in this comparison ($P > 0.05$). The risk factors for CIN were then evaluated with backward stepwise logistic regression analysis (Table 3), but these factors were not independent risk factors. The diagnoses of the patients are shown in Table 4.

A cutoff volume of contrast media was found as 4.1 mL/kg in the patients with CIN. The sensitivity, specificity, negative predictivity, and positive predictivity of the cutoff volume were calculated as 69%, 70%, 51%, and 50%, respectively. The AUC of ROC curves and positive likelihood ratio were found as 0.67 (range: 0.51 to 0.84) and 2.29 for the cutoff volume of contrast media.

The nephrotoxicity findings in the patients with and without CIN are compared in Table 5. The serum creatinine and CysC levels at all measurement times were within normal ranges. However, serum creatinine and serum CysC levels in the subjects with CIN after the procedure at 4, 24, and 48 h were statistically found to be significantly high in comparison to the values prior to angiography ($P < 0.05$), whereas no significant difference was found in other comparisons ($P > 0.05$).

4. Discussion

CIN is typically defined as an increase in serum creatinine by either ≥0.5 mg/dL or by ≥25% from baseline within the first 2–3 days after contrast administration (2,4). In line with this definition, in 16 of the subjects who underwent cardiac angiography (34.7%) in our study, the basal serum creatinine level was found to have increased by 25% or more. In 3 of these patients (6.5%), an increase of 50% or more in creatinine levels were observed. However, serum creatinine levels did not increase by higher than 0.5 mg/dL from baseline levels in the patients. After the angiography, we found significantly high levels of serum creatinine and serum CysC at 4, 24, and 48 h compared to the values prior to the procedure in the patients diagnosed with CIN.

Despite the fact that there are no comprehensive studies done on CIN in large pediatric patient groups, it is known that CIN is the third most widespread reason for acute renal cases developing in hospitals, with 12% of contrast

Table 1. Comparisons of basal clinical and laboratory findings between the groups.

Characteristics	Patients (n = 46)	Controls (n = 13)	P-value[a]
Systolic blood pressure, mmHg	92.5 (60–140)	90 (70–110)	0.27
Diastolic blood pressure, mmHg	60 (40–80)	50 (40–70)	0.55
Urine specific gravity	1010 (1005–1035)	1010 (1005–1020)	0.43
Serum creatinine, mg/dL	0.45 (0.31–0.79)	0.48 (0.36–0.72)	0.17
GFR, mL min^{-1} 1.73 m^{-2}	120 ± 35.9	113 ± 25.2	0.55
Serum cystatin C, mg/L	0.56 (0.3–1.1)	0.55 (0.4–0.8)	0.93
Serum NGAL, ng/mL	32.0 (1.9–226)	35.1 (18.3–90.3)	0.15
Urine NGAL, ng/mL	2.5 (0.6–67.1)	1.8 (0.6–16.4)	0.12
Urine NGAL/urine creatinine, ng/mg	3.9 (1.2–47.6)	3.2 (0.8–49.8)	0.29

[a]: Mann–Whitney U test; $P < 0.05$.
GFR: glomerular filtration rate; NGAL: neutrophil gelatinase-associated lipocalin.

Table 2. Comparisons of risk factors of contrast-induced nephropathy in the patients.

Risk factors	No CIN (n = 30)	CIN (n = 16)	P-value[a]
Number of patients with drug use	4 (13.3%)	2 (12.5%)	1.00[b]
Number of patients with cyanosis	4 (13.3%)	5 (31.3%)	0.24[b]
Number of patients with anemia	7 (23.3%)	7 (43.8%)	0.19[b]
Mean ± SD of hemoglobin, g/dL	12.3 ± 1.2	12.2 ± 1.8	0.77
Mean ± SD of hematocrit, %	36.7 ± 3.4	36.6 ± 4.3	0.99
Median of ejection fraction, %	71.5 (25–81)	72 (62–85)	0.74
Median of contrast media volume, mL	57.5 (20–165)	58 (10–153)	0.91
Mean ± SD of contrast media volume, mL/kg	3.7 ± 2.0	5.0 ± 2.3	0.06
Mean ± SD of fluoroscopy time, min	15.2 ± 9.7	16.0 ± 7.9	0.79
Median of serum urea, mg/dL	12 (5–24)	11.5 (7–17)	0.37
Mean ± SD of serum urea/serum creatinine	26.0 ± 6.9	29.1 ± 9.1	0.21

[a]: Mann-Whitney U test, [b]: chi-square test; $P < 0.05$.
CIN: contrast-induced nephropathy; SD: standard deviation.

Table 3. Multivariate risk factors analysis for the development of contrast induced nephropathy.

Risk factors	P-value	Odds ratio [95% confidence interval]
Cyanosis	0.30	0.1 [0.05–0.7]
Anemia	0.13	0.2 [0.05–0.9]
Contrast media volume, mL/kg	0.06	0.3 [0.1–0.9]
Fluoroscopy time, min	0.22	0.1 [0.03–0.8]
Serum urea/serum creatinine	0.09	–0.2 [0.05–0.8]

Table 4. Main diagnoses of the patients.

Main diagnoses	No CIN (n = 30)	CIN (n = 16)
Ventricular septal defect	7	5
Patent ductus arteriosus	6	1
Aortic valve stenosis	2	3
Atrial septal defect	2	2
Tetralogy of Fallot	2	2
Coarctation of aorta	4	-
Transposition of great arteries	2	1
Dilated cardiomyopathy	2	-
Double outlet of right ventricle	2	-
Primary pulmonary hypertension	1	1
Corrected transposition of great arteries	-	1

CIN: contrast-induced nephropathy.

Table 5. Comparisons of laboratory findings in the patients without and with contrast induced nephropathy.

Indicators of nephrotoxicity	No CIN (n = 30)	CIN (n = 16)	P-value[a]
Serum creatinine (mg/dL)			
Before angiography	0.43 (0.32–0.79)	0.38 (0.31–0.67)	0.87
After 4 h	0.48 (0.34–0.79)	0.49 (0.31–0.73)[c]	0.92
After 24 h	0.48 (0.35–0.83)	0.47 (0.34–0.83)[c]	0.52
After 48 h	0.47 (0.35–0.77)	0.46 (0.36–0.94)[c]	0.73
P[b]	0.18	<0.01	
Serum cystatin C (mg/L)			
Before angiography	0.54 (0.3–1.11)	0.58 (0.3–0.80)	0.96
After 4 h	0.61 (0.3–0.91)	0.64 (0.5–0.97)[c]	0.25
After 24 h	0.58 (0.3–1.02)	0.62 (0.4–0.90)[c]	0.13
After 48 h	0.62 (0.33–1.03)	0.65 (0.3–0.90)[c]	0.54
P[b]	0.06	<0.01	
Serum NGAL (ng/mL)			
Before angiography	26.4 (1.9–226)	23.2 (5.3–40.8)	0.71
After 4 h	26.6 (4.4–214)	28.9 (3.6–153)	0.12
After 24 h	24.4 (1.7–195)	24.0 (5.8–48.6)	0.29
After 48 h	27.6 (4.7–91.2)	22.5 (2.3–41.1)	0.09
P[b]	0.11	0.87	
Urine NGAL (ng/mL)			
Before angiography	4.1 (0.6–67.1)	5.1 (0.6–64.1)	0.97
After 4–8 h	2.2 (0.6–27.4)	2.3 (0.6–104)	0.87
After 48 h	2.8 (0.6–74.5)	6.3 (0.5–56.6)	0.08
P[b]	0.185	0.174	
Urine NGAL/urine creatinine (ng/mg)			
Before angiography	5.6 (1.2–476)	13.9 (1.3–62.6)	0.26
After 4–8 h	8.2 (0.8–850)	20 (1.5–271)	0.33
After 48 h	5.5 (0.8–123)	18.9 (1.3–420)	0.11
P[b]	0.301	0.829	

[a]: Comparisons of the patients without and with CIN, Mann–Whitney U test; $P < 0.05$.
[b]: Comparisons between hours in the patients without or with CIN, Friedman repeated measures ANOVA; $P < 0.05$.
[c]: Statistically significant difference between values prior to the angiography, Bonferroni corrected Wilcoxon sign test; $P < 0.05/4 = 0.0125$.
CIN: contrast-induced nephropathy; NGAL: neutrophil gelatinase-associated lipocalin.

media use in all acute renal failure cases, as well (3,6,12). Furthermore, CIN is known to have ranked third in causes of mortality in postrenal failure acquired in hospitals (5). However, today pediatric angiography patients can be discharged within 24–48 h, with no CIN-induced mortality or morbidity being expected or reported (12).

In the studies reporting postprocedural serum creatinine follow-ups in pediatric angiography patients, the patient groups were monitored for from 48 h to 2 weeks (9,12,17–20). Hirch et al. regarded a 50% or greater increase in basal serum creatinine levels as significant and found that 12% their patients developed CIN (9). Sagy et al. showed that, in the pediatric patients with cardiac angiography, left ventricular volume overload was observed, and that, in those suffering from right-to-left shunt congenital heart disease with clinical left-sided

heart failure, serum creatinine and uric acid levels rose to a considerable extent (17). However, in other studies (18–21), no change was observed in the serum creatinine levels after having implemented the procedure. In our study, it has been shown that risk factors are not effective in terms of CIN development. However, in the patients diagnosed with CIN, it has been observed that creatinine levels substantially increased 4 h after the cardiac angiography, and this increase was determined to be still in progress at 48 h, as well. This finding supports the idea that creatinine, independent of risk factors, is effective in diagnosing CIN.

Kavukçu et al. administered iopromide, in a maximum dose of 5 mL/kg with low osmolarity contrast media, to 19 children with congenital heart disease. In these patients, no significant difference was observed in the levels of serum creatinine, creatinine clearance, plasma uric acid, plasma osmolarity, urine osmolarity, fractional excretion of sodium, and urine N-acetyl-β-(D)-glucosaminidase prior to and 48 h after angiography (20). As reported by Noyan et al., in 17 cyanotic and 18 acyanotic children with congenital heart disease, nonionic low osmolarity iopamidol administration did not lead to CIN development (19). In the subjects under 1 year of age and in those administered more than 5 mL/kg of contrast medium, the levels of urine N-acetyl-β-(D)-glucosaminidase, β2-microglobulin, and α1-microglobulin were found to be remarkably high 12 h after the procedure, and these values were determined to have returned to normal in the next 2 weeks, as well, by Niboshi et al. (18). In our study, however, when comparing the subjects with and without CIN, the baseline levels of nephrotoxicity biomarkers were seen to have fallen short in anticipating the CIN risk. Furthermore, in the patients diagnosed with CIN, no significant difference was observed in serum NGAL levels, urine NGAL levels, and urine NGAL/urine creatinine ratio when compared to the values prior to the procedure. On the other hand, serum CysC levels increased substantially 4 h after cardiac angiography, and this increase was found to still persist at 48 h. This finding has led us to assume that in CIN diagnosis and follow-ups, serum CysC is more effective than NGAL.

In adult patients, it has been proposed that diabetes, preexisting renal insufficiency, decreased renal perfusion, and high total dose of contrast medium could be some of the risk factors for nephropathy in the use of contrast media (4,5). However, the risk factors of renal toxicity in children with cardiovascular disease by using nonionic contrast media have not been fully investigated (18). The volume of contrast media administered during the procedure, as the main modifiable risk factor, is of primary importance in the development of CIN (4). However, growing complexity of pediatric cardiac angiography inevitably causes an increased use of contrast medium per procedure and consequently enhances the risk of CIN. The correlation between the amount of contrast and the risk of CIN was documented in previous studies (5,18). Administration of nonionic low osmolarity contrast media (iopamidol, iohexol, ioversol) in cardiac angiography of 98 pediatric patients was shown to have increased the CIN risk if contrast media exceeding 5 mL/kg was administered (18). In the present study, we found that the risk of CIN increased 2.29-fold if the volume of contrast medium exceeded 4.1 mL/kg in children with congenital heart disease undergoing cardiac angiography. The sensitivity and specificity of the value were detected as 69% and 70%, respectively. Therefore, transient renal dysfunction was also associated with the dose of the contrast medium, i.e. children receiving more than 4.1 mL/kg of contrast medium showed higher levels of renal tubular functional parameters after angiography in this study. Although the tubular dysfunction was transient, the administration of large amounts of contrast medium should be avoided.

There is an agreement that adequate volume expansion prior to administration of contrast media is a major strategy in the prevention of CIN, although no randomized controlled trials directly comparing a strategy of volume expansion with no volume expansion have been carried out to date (4). Although the pathogenesis of CIN is not clearly understood, several mechanisms such as alterations in renal hemodynamics (ischemia due to vasoconstriction), direct tubular toxicity, oxidative stress, and tubular obstruction are considered to be the primary factors (4). Dilution of contrast media within the tubule lumen, reduced activation of the renin-angiotensin system due to increased delivery of sodium to the distal nephron, and minimizing of reductions in the renal production of nitric oxide caused by contrast media can contribute to the beneficial effect of volume expansion (22). Randomized studies demonstrated the positive effect of adequate hydration in reducing rates of CIN (23–25). Consequently, authors suggested adequate intravenous volume expansion with isotonic crystalloid solution for 3 to 12 h before the procedure, to be continued for 6 to 24 h to prevent development of CIN, in these patients (26). Only hydration with isotonic saline solution is accepted in general as the best way to prevent CIN in clinical practice. Although adequate hydration was assure and the volumes of contrast media and baseline creatinine levels were normal in our patients, the incidence of CIN was found to be 34.7% in our study. Therefore, we suggest that the incidence of CIN may be higher in pediatric patients with congenital heart disease than in patients with other risk factors.

4.1. Study limitations

This was a single-center study of pediatric patients with congenital heart diseases receiving contrast media during

cardiac catheterization. Therefore, the results will need to be validated in a larger population. Moreover, the present study was a cohort with normal kidney function, and it will be important to confirm these findings in documented high-risk settings such as volume depletion, concomitant nephrotoxic drug use, and preexisting kidney dysfunction.

4.2. Conclusions

In this study in which patients with cardiac angiography were taken into account, the CIN development rate was found to be 34.7%. Therefore, our findings show that the incidence of CIN is high in pediatric patients with congenital heart disease. However, these patients were asymptomatic and the course of CIN was benign. The results indicate that nonionic contrast media should also be used at minimal dosages for renal function in children with congenital heart disease, because we note that the use of nonionic contrast media leads to CIN. Especially in patients receiving more than 4.1 mL/kg of contrast media in total, we should be wary of CIN. On top of all this, in comparing the children who received cardiac angiography with the healthy ones, serum CysC, serum NGAL, and urine NGAL levels and urine NGAL/urine creatinine ratios were found to have fallen short in anticipating the CIN risk. No difference was found among the patients in terms of CIN risk factors. However, in the pediatric patients who received cardiac angiography and were diagnosed with CIN afterwards, the levels of serum creatinine and serum CysC levels were found to be higher than the ones measured prior to the procedure. Hence, it would be sufficient to follow the renal functions of the pediatric patients with cardiac angiography by monitoring their serum creatinine levels. However, more comprehensive studies into larger groups with such patients will be required for further research.

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