Iodinated Contrast Media in Pediatric Cardiac Angiography
Nephrotoxic risk evaluation

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Contrast agents are among the most frequently used drugs in medical practice. The aim of our study was to evaluate the incidence of complications associated with the use of different contrast agents in an angiography lab dedicated to pediatric patients with congenital heart disease. Between June 2015 and December 2017, 166 patients with congenital heart disease were diagnosed and/or treated in the angiography lab. Of these patients, 38 were excluded because they did not require contrast substance administration. As interventional procedures we performed pulmonary valvular dilatation in 17 cases (10.2%), stent implantation in coarctation of the aorta in 9 cases (5.4%), PDA closure in 62 cases (37.3%), atrial septal defect (ASD) closure in 36 patients (including patients without contrast agent's administration) (21.7%). In the group of 129 patients who received contrast agents, the median age was 5.8 years (range 0.1-19 years) and median weight 22.8 kg (range 2.8-72 kg). Average consumption of contrast media per procedure was 79 ml/procedure (range 5 - 400 mL) and 4.3 mL/kg (range 0.4 - 22.7). We used iomeprol (24%), iohexol (8.5%), iopromide (67.4%). No contrast related complications are reported in this group. In conclusion, the contrast agents we used seem to be safe and are not associated with renal complications.

Keywords: contrast-induced nephropathy, contrast-induced acute kidney injury, nephrotoxicity, contrast media, congenital heart disease, cardiac angiography

Contrast agents (CA) are commonly used in medical practice to increase the visibility of anatomical structures using substances which have the property to absorb the X-ray [1]. They have the chemical structure derived either from iodine, barium sulfate or gadolinium. They do not emit radiation, unlike radiopharmaceuticals used in nuclear medicine. Intravascular administration for angiographic purpose uses exclusively iodine compounds. The iodine contrast agents are organic compounds, monomers or dimers, with a benzenic structure and a variable content of iodine. CA differ between themselves by their ionic or non-ionic, monomeric or dimeric structure, iodine content, osmolarity and viscosity (table 1).

Administration of intravascular chemical compounds is associated with numerous adverse effects. Of these, the risk of nephrotoxicity and, implicitly, the occurrence of contrast-induced nephropathy (CIN) or nephrogenic systemic fibrosis (NSF) are the most important [1]. The drug-induced nephrotoxicity is well-known in medical literature and is related to the use of the nonsteroidal anti-inflammatory drugs, cyclosporine, aminoglycosides, cisplatin [2]. The risks for nephrotoxicity are less frequent in children than in adults. CA are contraindicated in patients with allergy, impaired renal function, thyrotoxicosis [1].

Experimental part

The aim of our study was to study the incidence of complications associated with the use of different CA in an angiography lab dedicated to pediatric patients with congenital heart disease (CHD). CHD is present in 7-8‰ of the children and some of them may beneficiate from an interventional procedure for complete diagnosis or treatment [3-5].

An informed consent regarding the risk of the procedure and the risks of contrast agent administration was obtained from the parents or from the custodians of the patients.

For the descriptive statistical analysis, we used the Excell Data Analysis Tool. We calculated the median, the mean value ± standard deviation.

Between June 2015 and December 2017, 166 patients with CHD were diagnosed and/or treated in the angiography lab, 102 females and 64 males. This is a longitudinal retrospective study on a 31 months period. Of these patients, 38 were excluded because they did not require contrast substance administration, the procedure being cardiac catheterization with the study of pulmonary resistance, Rashkind atrioseptectomy, or the simple closure procedure for atrial septal defect under transesophageal echocardiographic guidance. Of the remaining 128, 29 were cardiac diagnostic catheterization for either pulmonary vascular resistance study in Eisenmenger physiology associated with ventricular septal defects (VSD), atrioventricular septal defects, patent ductus arteriosus (PDA), univentricular heart, coronary angiography or for diagnose of coronary fistula, tetralogy of Fallot, coarctation of the aorta, abnormal partial systemic or pulmonary venous return, aorticopulmonary collaterals in pulmonary atresia with VSD.

As interventional procedures we performed pulmonary valvular dilatation in 17 cases (10.2%), stent implantation in coarctation of the aorta in 9 cases (5.4%), PDA closure in 62 cases (37.3%), atrial septal defect (ASD) closure in 36 patients (including patients without CA administration) (21.7%).

Results and discussions

In the group of 129 patients who received the CA for angiography in CHD, the median age was 5.8 years (range 0.1-19 years) and median weight 22.8 kg (range 2.8-72 kg). 20% of the children were less than 1-year-old. Average consumption of contrast media per procedure was 79 mL/procedure (range 5 - 400 mL) and 4.3 mL/kg (range 0.4 -

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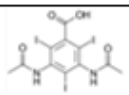
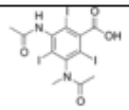
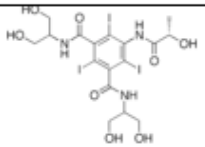
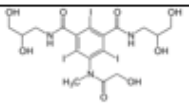
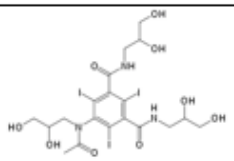
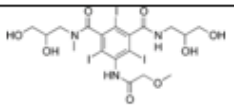
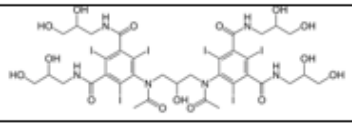
Radiocontrast	Composition		Iodine content	Osmolarity		Ionic/non-ionic
Diatrizoate (Renografin, Hypaque 50, urografin)	Monomer, $C_{11}H_9I_3N_2O_4$		300 mgl/dl	1550	high	ionic
Metrizoat (Isopaque 370)	Monomer, $C_{12}H_{11}I_3N_2O_4$		370 mgl/dl	2100	high	ionic
Iopamidol (Isovue 370)	Monomer, $C_{17}H_{22}I_3N_3O_8$		370 mgl/dl	796	low	Non-ionic
Iomeprol (Iomeron 400)	Monomer, $C_{17}H_{22}I_3N_3O_8$		400 mgl/dl	726	low	Non-ionic
Iohexol (Omnipaque 350)	Monomer, $C_{19}H_{26}I_3N_3O_9$		350 mgl/dl	884	low	Non-ionic
Iopromide (Ultravist 370)	Monomer, $C_{18}H_{24}I_3N_3O_8$		370 mgl/dl	774	low	Non-ionic
Iodixanol (Visipaque 320)	Dimer, $C_{35}H_{44}I_6N_6O_{15}$		320 mgl/dl	290	low	Non-ionic

Table 1
CHEMICAL PROPERTIES OF THE MOST COMMONLY USED IODINATED RADIOCONTRAST AGENTS

22.7). The recommended dose for iv contrast administration is 2 mL/kg [6].

Average consumption of contrast media per procedure was 79 ml/procedure (range 5 - 400 mL) and 4.3 mL/kg (range 0.4 -22.7). We used iomeprol (24%), iohexol (8.5%), iopromide (67.4%). All these contrast media were non-ionic monomers with low osmolality. In our 129 patients group, no contrast-related nephropathy case is reported. Postintervention we evaluate the renal function (by checking serum creatinine in 48 h) in patients identified as high risk regarding the volume of CA administration or the cardiovascular status, but randomly for the others as well. No child had a preexisting renal disease.

Contrast media administration is associated with important risks. The most feared are the life-threatening complications, such as cardiac arrest related to cardiac arrhythmia, stroke, anaphylactic reaction. All complications that might be related with contrast media administration are presented in table 2. Contrast-induced nephropathy (CIN) is also associated with contrast media administration. Usually, CIN is defined by an increase in serum creatinine by 0.5 mg/dL, or a relative increase, by >25%, compared with the initial value in 2-3 days period after contrast agent administration, in absence of other cause of acute kidney injury [1,7]. After 7 days from the initial increase, the level of serum creatinine starts to decrease and returns to normal in the second week. In children, a fixed value of the serum creatinine is less expressive on the risk of CIN comparative to the glomerular rate filtration (GRF).

The prevalence of CIN in adults varies between 1-50%, depending on the selected group [7]. Contrast-induced acute kidney injury was reported between 3-25% in adults and in 10% of the children evaluated [8]. It is directly linked with associated risk factors, such as medical history of chronic kidney disease or diabetes, factors that might have cytotoxic effect at the kidney level, or might influence the renal perfusion. Those are anemia, low cardiac output, hypotension with hemodynamic instability, hypo-albuminemia or higher amount of contrast agents, high-osmolality contrast media, multiple administration of contrast media within 72 h, concomitant use of nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs, cyclosporine, aminoglycosides, cisplatin [7]. In a group of 140 neonates receiving contrast media, both iodinated and gadolinium derivates, no change in the GFR were registered, during 45 days with six evaluations of the creatinine and GFR calculation during this period [9].

Regarding the amount of contrast administration, CA volume overload is a risk factor. In adults, it was considered that for each 100 mL CA there is 12% increase risk for nephropathy [10]. A formula that might be also applied to children concerning the maximum amount of contrast administration is 5mL X [body weight (kg)/serum creatinine (micromoles per liter):88.4]. Over this volume, there is a 12-fold increase in the risk of hemodialysis [10]. In our study, the average consumption was 4.3 mL CA/kg body weight, which is below the maximum dose. There were cases which received over this dose. For these cases we evaluate the renal function by checking the serum creatinine level at 48 h and in all patients, there were normal values. All patients in our study received IV hydration pre and postintervention at 100 mL/kg/24 h (80 mL/kg/24 h if liquid restriction regimen was applied) either saline or 5% dextrose, followed by oral hydration at 24 h from the procedure as a preventive method. It is to mention that the osmolality of the saline solution is 308 mOsm/L, while the osmolality of the 5% dextrose is 277 mOsm/L and if there are no contraindications (diabetes mellitus) the 5% dextrose solution might be administered as well especially in fasting children pre or post general anesthesia.

Contrast media	Iodinated	
	Ionic	Non-ionic
General	Asthenia, weakness	Pain, asthenia, chills, excessive thirst, hyperhidrosis, malaise, peripheral edema,
Cardiovascular	Shortness of breath, chest pain, tachycardia, Thromboembolic events with myocardial infarction and stroke	vasodilatation, vasospasm hypotension, chest pain, AVBc, VF, AF, AHT, syncope
Respiratory	Cough, asthma	Asthma, apnea, cough, dyspnea, hypoxia, pharyngeal edema, pharyngitis, PE, PHT, APE, PHT
Gastrointestinal	Nausea, vomiting, diarrhea	Nausea, vomiting, constipation, dyspepsia, abdominal pain
Renal	Hematuria, Oliguria	Renal pain, renal failure, CIN
Genitourinary	Dysuria, urinary retention	Dysuria, urinary retention, hematuria
Dermatologic	Urticaria, itching, rash	erythema, pruritus, rash, urticaria, SJS, skin discoloration, itching
Hypersensitivity	Facial edema, or of the eyelids, lips, tongue Anaphylactoid reactions	Facial edema, anaphylactoid reaction (including fatal cases), respiratory arrest, angioedema, laryngeal edema, laryngospasm, bronchospasm.
Nervous system	Convulsion, dizziness	Headache, dysgeusia, confusion, insomnia, convulsion, dizziness, cerebral ischemia, aphasia, coma, amnesia
Endocrine	Hyperthyroidism, hypothyroidism	Hyperthyroidism, thyrotoxic crisis, hypothyroidism
Metabolic		Diabetes insipidus, increased LDH, increased blood urea, increased Hb, increased WBC.
Musculoskeletal		Back pain, neck pain, arthralgia

Table 2
SIDE EFFECTS OF THE CONTRAST MEDIA

Legend: (AVBc = complete atrioventricular block, VF = ventricular fibrillation, AF = atrial fibrillation, AHT = arterial hypertension, PE = pleural effusion, PHT = pulmonary hypertension, APE = acute pulmonary edema, ARDS = acute respiratory distress syndrome, CIN = contrast-induced nephropathy, SJS = Steven Johnson syndrome, LDH = lactate dehydrogenase, Hg = haemoglobin, WBC = white blood cells).

Another presumed risk factor for contrast-induced acute kidney injury (AKI) was a short interval between contrast administration either by CT scan or by angiography and cardiothoracic bypass (CBP) surgery. This factor was analyzed in several studies. In two studies 56 neonates and 122 children with cyanotic CHD were evaluated [11,12]. In both groups, there was no association regarding the time interval between CA administration and CBP surgery. The incidence of AKI in CPB depend on the characteristics of the evaluated group and varies between 10% in children and 75% in neonates [11, 13]. Other factors are related to severe AKI in neonates, children and adults who have undergone a cardiac bypass surgery, such as longer CPB time, lower postoperative urine output, higher peak serum creatinine, infectious and hematological complications both in children and in adults [11,13-14].

Sometimes it might be too late for a retrospective diagnosis by checking serum creatinine level when more than half of the kidney function is lost. Other tests are recommended in the first 12-24 h for an active diagnosis such as cystatin C, or neutrophil gelatinase-associated lipocalin (NGAL) but they might not be available in all centers. In children, the incidence of CIN is reduced, but might be underdiagnosed due to its silent evolution [15]. Comparing with adults, there are important differences in the definition of CIN, because a fixed value for the serum creatinine is irrelevant in children. More than that, studies on CIN using other markers more sensitive and specific were performed. Cystatin C was evaluated, and a 24 h postprocedural increase of more than 10% was associated with an increased risk for CIN in children [16], especially when the administration was done in children with CHD [17]. Not only cystatin C was more sensitive for revealing the risk of CIN, but also NGAL or urine liver-type fatty acid-binding protein (L-FABP) [18]. A study on 91 children with CHD who were subjected to cardiac catheterization and angiography showed an early diagnosis of renal injury, within two hours after contrast exposure [19].

Our study has some limitations. Firstly, we report a monocentric experience in a developing center on a small number of cases. Secondly, all patients were analyzed after angiography from the clinical and hemodynamical point of view, analyzing the urine output in the following days. Evaluation of the renal function with serum creatinine at 48 h was performed in patients identified at high risk regarding the volume of CA administration or the cardiovascular status, but randomly for the others as well. Thirdly, no other more sensitive tests such as NGAL or cystatin C for evaluation after angiography were available.

Conclusions

Routinely administration of contrast media is safe as well for high-risk groups. No renal complication is reported in our group, including patients with a higher amount of contrast, neonates or patients with hemodynamic instability. No differences between the contrast media (iomeprol, iohexol, iopromide) were noticed.

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