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REVIEW

Current status of contrast-induced nephropathy and nephrogenic systemic fibrosis in children

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Introduction

Iodinated and gadolinium contrast agents are being increasingly used for CT and MRI examinations in paediatric patients, particularly for cardiovascular studies [1–5]. These agents are among the most frequently used medications due to dramatic increase in the number of imaging studies.

Estimated GFR versus creatinine and renal function

Serum creatinine level allows crude estimation of renal function; therefore, estimated glomerular filtration rate (GFR) is being increasingly used for renal function evaluation [6–9]. In paediatric patients the upper level of creatinine changes from the newborn period to teenagers and GFR can be calculated by the Schwarz equation [10]. Calculation of estimated GFR instead of serum creatinine is critical for deciding contrast agent administration. Estimated GFR can be calculated by knowing the patient's age, sex and weight. Chronic renal failure is divided into five groups based on the GFR: grade I, 90–120 ml/min; grade 2, 60–89 ml/min; grade 3, 30–59 ml/min; grade 4, 15–29 ml/min; grade 5, 0–14 ml/min. Patients with grade 4 and 5 usually undergo dialysis.

Contraindications to iodinated contrast agents

Major contraindications are allergy, impaired renal function and thyrotoxicosis [7, 9]. Also, diabetic patients using metformin should discontinue use of this drug 48 h before contrast medium administration to reduce the risk of lactic acidosis. Previously, patients with phaeochromocytoma were to not receive iodinated contrast agents. Current evidence differs following publication of a study in 2007 that demonstrated that it is safe to use non-ionic iodinated contrast media in patients with phaeochromocytoma [11].

Contraindications to gadolinium contrast agents

Major contraindications are allergy and patients undergoing dialysis. Gadolinium is a relatively safe agent with only one mortality recorded in the literature [8]. Also, it is important to know that certain contrast agents (gadodiamide and gadoversetamide) can cause spurious hypocalcaemia due to rapid chelation in vitro that interferes with laboratory methods measuring serum calcium [12, 13].

Contrast medium economy and contrast medium volume reduction strategies for CT and MRI

Contrast medium economy is becoming important for the reduction of contrast material volume, particularly in patients with impaired renal function. The lowest volume of contrast agent should be used to be on the safe side for contrast-induced nephropathy (CIN) and nephrogenic systemic fibrosis (NSF) in risk groups, and repeat examinations should be avoided within 48 h. Contrast medium volume can be decreased to half for abdominal and chest CT in such patients. Also, contrast medium injection rate can be decreased for CT and MR angiographic examinations, which may result in decreased opacification of arteries, but diagnostic images may still be obtained. Also,

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fast scanning MDCT systems and saline injection with a dual syringe injector can be used to decrease required contrast medium volume [14–16]. Moreover, in patients who will undergo multiple CT studies, CT studies of different body regions can be combined. Thus, a single contrast agent injection can be performed in trauma patients and patients with malignant tumours, which would lead to decreased contrast medium volume [17].

For CT angiography studies, contrast medium volume can be decreased by increasing table speed or decreasing the injection rate. For MR angiography and MRI studies, the dose can be decreased to 0.05 mmol/kg and diagnostic images can still be obtained [18, 19]. Also, for MR angiography, higher field strength MR scanners, faster sequences or unenhanced MR angiography techniques can be used [18].

Contrast-induced nephropathy

CIN is defined as an increase of creatinine level above 25% of baseline or 0.5 mg/dl within the following 3 days after contrast medium administration [9, 20]. Creatinine increases within 1–7 days and usually returns to baseline at 7–14 days. Permanent kidney damage rarely develops in these patients. CIN is thought to develop secondary to vasoconstriction in the outer medulla of the kidney, which may lead to acute tubular necrosis [21]. CIN is negligible in patients with normal renal function, and hydration of the patient is the most important preventive measure [7, 9]. Most of the studies concerning CIN were undertaken on patients who underwent cardiac catheterization or arterial catheter angiography. There are only a few studies assessing CIN in patients who received iodinated contrast agents intravenously [7, 22, 23]. Newhouse et al [22] and Bruce et al. [23] recently published two articles questioning the definition of CIN because fluctuations of creatinine level (that can be regarded as CIN) were noted in patients who underwent unenhanced CT studies. Therefore large studies are needed to understand the effects of intravenously administered iodinated contrast agents with a control group. Risk factors should be asked to patients who will undergo contrast enhanced CT studies to prevent development of CIN [24].

Nephrogenic systemic fibrosis

NSF is a rare debilitating systemic disease, resembling scleroderma, associated with gadolinium agents which can cause mortality [25–34]. Approximately 400–500 NSF patients have been reported after approximately 150 million gadolinium injections. Although the first case was diagnosed in 1997, the entity was not first described until 2000 [26]. The association between NSF and gadolinium agents was documented in 2006 [27]. Most of the affected patients were patients undergoing dialysis [25–34]. He most commonly reported gadolinium agent associated with NSF is gadodiamide (Omniscan, GE Healthcare, St. Giles, UK) followed by gadoversetamide (Optimark, Covidien/Mallinckrodt, St. Louis, MO), gadolinium-DTPA (Magnevist, Schering Pharma AG, Berlin, Germany) and gadoteridol (Prohance, Bracco Altana, Konstanz, Germany) [29]. Proposed risk factors are dialysis patients with GFR below 30 ml/min, high-dose gadolinium, proinflammatory conditions, acute renal failure, postoperative state, and hyperphosphataemia [25–34]. Interestingly, European and FDA guidelines differ for gadolinium use in risk groups [29]. In patients at high risk for NSF (patients with GFR <30 ml/min), the European guidelines do not recommend use of any gadolinium agents and in patients with GFR of 30–60 ml/min gadolinium agents that have been reported to be associated with NSF are not recommended [29]. FDA guidelines announced black-box warning for the use of all gadolinium agents in patients with GFR <30 ml/min [7, 8]. There is insufficient evidence regarding the development of NSF in patients with normal renal function.

Several factors (transmethylation, dechelation, instability, chemical structure of gadolinium agents) have been proposed for NSF development that are based on higher prevalence of NSF in patients, who received gadodiamide [29]. However, most of the proposed factors rely on in vitro studies and further research is needed to understand the pathophysiology of NSF.

The effects of gadolinium in children is not clear [35]. Two paediatric patients with NSF have been reported by Jain et al. [36] in 2004, and in 2007 the same authors [37] realized that these patients underwent MR angiography with gadolinium agents.

Although there is no consensus on the treatment of NSF, several treatments have been tried, but with no conclusive benefit [7, 8, 38–43]. Haemodialysis can be protective, but peritoneal dialysis is not recommended for the prevention of NSF [7, 8].

Gadolinium as an alternative CT contrast agent to iodine

Gadolinium has been used as an alternative to iodine in patients with impaired renal function [44]. However, this paradigm has changed after the recognition of NSF. Today, the only indication for gadolinium in CT is patients with iodine allergy.

Conflicts of interest The authors have declared that there are no conflicts of interest.

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