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Contrast-enhanced ultrasound with SonoVue in the evaluation of postoperative complications in pediatric liver transplant recipients

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KEYWORDS

Split liver;
Pediatric liver
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sonography.

Abstract *Purpose:* To evaluate the utility of contrast-enhanced sonography in the study of pediatric liver transplant recipients and its potential impact in reducing the need for invasive diagnostic procedures.

Materials and methods: From October 2002 to December 2003 we performed routine color Doppler ultrasound and contrast-enhanced ultrasound studies on 30 pediatric patients who had undergone liver transplantation. Findings indicative of complications were confirmed with invasive studies (angiography, computed tomography, and PTC).

Results: Contrast-enhanced sonography correctly identified four of the five cases of hepatic artery thrombosis and all those involving the portal ($n = 6$) and hepatic vein ($n = 3$) thrombosis. It failed to identify one case of hepatic artery thrombosis characterized by collateral circulation arising from the phrenic artery and the single case of hepatic artery stenosis. The latter was more evident on color Doppler, which revealed a typical *tardus parvus* waveform. The use of contrast offered no significant advantages in the study of biliary complications although it did provide better visualization of bile leaks.

Conclusions: Contrast-enhanced sonography improves diagnostic confidence and reduces the need for more invasive imaging studies in the postoperative follow-up of pediatric liver transplant recipients.

Sommario *Scopo:* Valutare l'utilità dell'ecografia con mezzo di contrasto (Mdc) ecografico di II generazione nel paziente pediatrico trapiantato di fegato, in particolare al fine di ridurre il ricorso a metodiche diagnostiche invasive.

Materiali e metodi: Dall'ottobre 2002 al dicembre 2003, in 30 pazienti pediatriche sottoposti a trapianto di fegato è stato eseguito esame eco-contrastografico a completamento dell'esame eco-color-Doppler di routine. Nel caso di esame indicativo per complicità si è proceduto all'esecuzione di un successivo esame invasivo di conferma (angiografia, TC, PTC).

Risultati: L'esame ecografico con Mdc ha correttamente identificato 4 trombosi dell'arteria epatica su 5 casi, tutti i casi di trombosi portale (6) e delle vene sovraepatiche (3), mentre

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ha fornito dati falsamente negativi in un caso di trombosi dell'arteria epatica, ricanalizzata da rami provenienti dall'arteria frenica, e nell'unico caso di stenosi anastomotica dell'arteria epatica della nostra casistica, nel quale è stato indicativo il pattern "tardus parvus" osservato all'esame eco-Doppler. Nel caso delle complicanze biliari l'esame eco-contrastografico non ha apportato significativi vantaggi, se non una migliore definizione dei margini e dell'estensione delle raccolte biliari post-intervento.

Conclusioni: L'esame ecografico con Mdc è metodica in grado di incrementare la confidenza diagnostica dell'operatore, consentendo una riduzione al ricorso ad esami radiologici invasivi; ciò è particolarmente importante nel caso di pazienti a rischio, quali i bambini sottoposti a trapianto epatico.

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Introduction

Liver transplantation is the treatment of choice for adults and children with otherwise untreatable forms of chronic or acute liver disease. Its success is the result of progressive improvement of surgical techniques and immunosuppressive regimens for the prevention of transplant rejection [1,2]. Among pediatric patients, over 90% of all liver transplants are prompted by the existence of cholestatic disease (Table 1) or congenital metabolic deficits; other less common causes are metabolic liver disease, cystic fibrosis, and certain types of liver tumors (in most cases, hepatoblastoma and hepatocellular carcinoma) [3]. The scarcity of cadaver organs has led to the development of the so-called split-liver surgical techniques, which allows the surgeon to obtain two functioning units from a single cadaver or living-donor organ. In general, the right lobe is reserved for an adult recipient while part of the left lobe (segments II, III, and sometimes IV, depending on the size of the recipient) is destined for a child [4].

Complications that arise during the transplantation procedure may require additional surgery, and in some cases, even a new transplant. The post-transplantation follow-up is thus of fundamental importance. It is based on daily ultrasound (US) and color Doppler studies during the immediate postoperative period. If abnormalities emerge, additional studies are needed, more complex and invasive

examinations like computed tomography or angiography that requires assisted sedation and exposure to high doses of ionizing radiation. The recently developed ultrasound contrast agents can be helpful in the detection of vascular and biliary complications, reducing the need for more invasive diagnostic studies [5]. Therefore, we investigated the role of second generation contrast-enhanced ultrasonography as an adjunct in the postoperative follow-up of pediatric liver transplant recipients.

Materials and methods

Between October 2002 and December 2003, a total of 44 liver transplantations were performed on 40 pediatric patients in our hospitals (Ospedali Riuniti di Bergamo). The procedures included 34 split-graft transplants (comprising segments II–III, $n = 31$, or segments II–IV, $n = 3$) and 10 whole-liver transplants. The patients (21 boys and 19 girls) ranged in age from 2 months to 10 years (mean: 2 years). Weights ranged from 3 to 30 kg (mean: 8 kg). Thirty-one of the children were suffering from biliary atresia, five had Alagille syndrome, and the others had hemolytic–uremic syndrome, cystic fibrosis, Bayer disease, and hepatic hypoplasia.

Immediately after surgery, all patients underwent color Doppler US studies. In 30 patients, clinical and/or sonographic signs were suggestive of possible vascular/biliary complications. In these cases, a second US examination was done with the second generation contrast agent SonoVue® (Bracco, City, State). If the results of the contrast-enhanced US study were also indicative of complications and the clinical picture warranted additional studies, the patient was re-examined with more invasive methods. Otherwise, routine follow-up was continued.

The US examinations were carried out by three radiologists with experience in the contrast-enhanced and non-enhanced sonographic study of adult and pediatric liver transplant recipients. Three different scanners were used (ATL HDI 5000, Technos Esaote, and Sequoia Siemens), each equipped with dedicated software for contrast-enhanced studies. SonoVue was administered by intravenous bolus at a maximum dose of 0.5 ml (up to three injections). When possible, the examination was recorded on a VHS cassette or optical magnetic disk.

In all cases, informed consent to the use of the contrast agent was obtained from the child's parents. Administration of SonoVue was not associated with any immediate or long-term side effects.

Results

The 44 transplantation procedures were associated with 14 vascular complications: four cases of hepatic arterial thrombosis (28%), one of hepatic arterial stenosis (7%), six cases of portal vein thrombosis (43%) and three cases

Tab. 1 Most frequent cholestatic diseases leading to pediatric liver transplantation

Cholestatic disease

Extrahepatic disease

Biliary atresia

Intrahepatic disease

Idiopathic

Idiopathic neonatal hepatitis

Persistent intrahepatic cholestasis

Arteriohepatic dysplasia (Alagille syndrome)

Nonsyndromic paucity of intrahepatic bile ducts

Progressive familial intrahepatic cholestasis

Byler disease

Anatomic

Congenital hepatic fibrosis

Caroli disease

of hepatic vein thrombosis (22%). All of the arterial complications were confirmed by angiography. All five cases of arterial thrombosis (in four patients) required retransplantation. The single case of hepatic arterial stenosis was resolved by surgical revision of the anastomosis. Four of the six cases of portal vein thrombosis were confirmed (by CT in two cases, by portography in two others), and the other two continued routine follow-up. In two cases of hepatic vein thrombosis, the patient was managed with US follow-up alone, which revealed spontaneous recanalization of the vein in both cases. In the third case, the thrombosis was confirmed by means of angiography and treated with percutaneous transluminal angioplasty (PTA). None of the patients developed portal vein stenosis.

Biliary-tract complications included four anastomotic strictures and 12 biliary leaks (11 located along the surgical section and one in the hilar region). All of the strictures were successfully treated with percutaneous cholangiography with bilioplasty. Seven of the perihepatic leaks required US-guided drainage, and the other four resolved spontaneously.

Discussion

Despite the refinement and standardization of surgical techniques and the availability of effective immunosuppressive drug therapy, liver transplantation is still frequently associated with life-threatening complications, which are caused by multiple factors related to the patient's poor state of health and the complexity of the surgical procedure itself. The complications can be insidious and nonspecific, and diagnostic imaging plays a fundamental role in their diagnosis and characterization. The most common are transplant rejection, vascular stenosis or thrombosis, bile-duct obstruction and bile leaks, hemorrhage, infarction, and abscess formation. Early diagnosis is of crucial importance: prompt treatment (surgical or interventional radiology) can prevent irreversible

damage, which can jeopardize the transplant or even the patient's life.

Immediately after the transplant, the patient should have daily color Doppler US studies. The vascular and biliary anastomoses should be carefully examined and the graft zone explored for fluid collections (bile, blood, or serum) and abscesses, which are most commonly found along the cut edge of the liver. If the US examination is positive or there is strong clinical evidence of vascular complications, more invasive imaging studies are called for CT, MRI, or even angiography. The complexity of liver transplant surgery is related to the high number of anastomoses that have to be created (Fig. 1), and this also explains the high rate of technical and functional problems that arise during the postoperative period, as well as the vascular and biliary complications [6].

Vascular complications are more common in pediatric transplant recipients due to the smaller caliber of the vessels, but their frequency varies widely from series to series (2–25%). They should be suspected when the patient presents signs of liver failure, bile leakage, abdominal hemorrhage, or septicemia [6,7].

Thrombosis of the hepatic artery is the most serious vascular complication. It carries a high rate of mortality (50–58%), and retransplantation is necessary in 60% of all cases. It requires immediate surgical thrombectomy. This complication is more common in pediatric liver transplant recipients (9–42% versus 4–12% among adults), for reasons related primarily to the surgical technique [6,8]. If it occurs early (within the first 30 days after transplantation), it can lead to acute hepatic ischemia. The result is diffuse parenchymal damage with areas of necrosis and parenchymal infarcts in the non-perfused areas. The picture may be additionally complicated by abscess formation, bile-duct necrosis with leakage or intraparenchymal collections of bile (bilomas), and in some cases rejection and massive liver-cell necrosis.

Spontaneous neovascularization is rare in adults but less so in children: the development of collateral circulation arising from the superior mesenteric artery (through the

Fig. 1 Representation of the arterial, venous, and biliary anastomoses in a split-liver graft (segments II–III).

Fig. 2 (a) During the examination with SonoVue, the absence of enhancement within the lumen of the hepatic artery was suggestive of thrombosis, which was subsequently confirmed on angiography (b).

rich vascularization of the Roux-en-Y jejunal loop) or from the splenic and gastroduodenal arteries eliminates the symptoms of thrombosis and delays the need for emergency retransplantation, and this justifies a longer period of patient monitoring [9,10].

In most cases, the suspicion of hepatic artery thrombosis is first raised by the absence of flow signals on color Doppler US. This examination has a sensitivity of 92–96% for the detection of hepatic artery thrombosis in the general population of liver transplant recipients [1,6,11]. Compared with that of an adult patient, this examination is associated with certain difficulties in infants and children, who are generally less cooperative. In addition, if the child has a split-liver transplant, uncertainties can also arise as a result of the modified anatomy of the organ.

If the artery cannot be reliably identified with color Doppler, contrast-enhanced US should be able to reveal its entire intrahepatic course. If not, there is a high probability that the artery is indeed thrombosed (Fig. 2a,b) [5,12]. In five of the patients from our series, hepatic arteries that could not be identified on the preliminary examination were clearly observed on the contrast-enhanced US. This eliminated the need for angiographic confirmation, which is still the gold standard in these cases [13]. In one case, however, the contrast study also failed to identify the presence of arterial thrombosis due to the presence of collaterals arising for the most part from the phrenic artery, as subsequently demonstrated by angiography (Fig. 3).

The reported frequency of hepatic artery stenosis varies from 3% to 11%. In most cases (70%) it occurs at the level of the anastomosis although all segments of the artery are at risk. Left untreated, significant stenosis slows blood flow and increases the risk for thrombosis. It can also lead to ischemia with liver failure, bile-duct stenosis, sepsis, and even loss of the graft [6,14]. Anastomotic stenosis typically occurs in an extrahepatic segment of the artery that is difficult to explore. However, it should be suspected when a *tardus parvus* Doppler signal (Fig. 4a) is observed at the level of an intrahepatic segment of the artery [15]. A false-negative finding in our series was caused by a case of hepatic artery stenosis: the color-Doppler exam revealed a *tardus parvus*

pattern, and the hepatic artery was normally visualized after contrast enhancement. Stenosis was also suggested by the presence of hypovascularized areas within the hepatic parenchyma, which were indicative of arterial damage (Fig. 4b). Angiography confirmed the presence of stenosis, and the patient underwent surgery for revision of the arterial anastomosis, which was successful.

Compared with arterial complications, those involving the portal vessels are less common, and their clinical impact is usually more limited. Portal vein thrombosis occurs in approximately 4% of all cases of pediatric liver transplantation (1–3% adults) and generally involves the site of anastomosis. In most cases, it is not associated with specific clinical manifestations, but it should be suspected if there are signs of portal hypertension (massive ascites,

Fig. 3 Angiography reveals revascularization of the occluded hepatic artery by collateral vessels arising from the phrenic artery.

Fig. 4 (a) “Tardus parvus” pattern at Doppler evaluation is indicative of stenosis. (b) Hypovascular areas of parenchyma are seen at the examination with SonoVue.

variceal hemorrhage, and splenomegaly) [16]. If the thrombosis develops gradually, it may lead to the formation of a cavernoma. In contrast, acute thrombosis of the portal vein is heralded by sudden liver failure that is similar to that is seen with hepatic artery thrombosis [6,17]. Portal

vein thrombosis can be easily diagnosed with Doppler ultrasound, and any doubts that arise can be resolved with more invasive procedures (CT, MRI, or the imaging modality of choice in cases like this, portography) [18]. In our series, all cases of thrombosis were initially suspected based on

Fig. 5 Filling defect in the portal vein at the baseline examination is manifested by (a) the absence of color signal (b) and no enhancement after SonoVue injection (c). Angiography (d) demonstrated thrombosis of the portal vein.

Fig. 6 No Doppler signal (a) and no enhancement of the right hepatic vein after SonoVue (b).

Fig. 7 At the baseline examination (a) bile leakage is shown. (b) Improved definition after SonoVue.

Fig. 8 (a) No evidence of collection. (b) After SonoVue a hilar collection is clearly seen.

Fig. 9 At the baseline examination, no abnormalities are noted in the echo structure of the spleen (a), while large ischemic areas are seen after SonoVue infusion (b).

Doppler US. Contrast enhancement revealed the absence of enhancement in the lumen of the portal vein, confirming our suspicions and allowing us to make a more confident diagnosis (Fig. 5). The same can be said for cases of hepatic vein (Fig. 6) or vena caval thrombosis.

Although surgical techniques have improved considerably, biliary-tract complications are still a significant cause of morbidity. They occur in 13–19% of all cases with a higher incidence among children (38%) [8]. For the most part, they consist in bile leaks along the cut edge of

Fig. 10 Standard (a), color-Doppler (b), and SonoVue examinations (c) show intrahepatic bile-duct dilatation caused by an anastomotic stricture, as demonstrated by cholangiography (d).

the liver and stenosis of the bile-duct anastomosis, both of which are generally managed with percutaneous interventional radiological techniques [19–21]. In the presence of biliary complications, the use of contrast enhancement did not provide any particular diagnostic advantages. However, it did provide more detailed images of cut edge and hilar leaks, one of which was recognized only in the parenchymal phase of the contrast study (Figs. 7 and 8).

There was also an extensive splenic infarct that was visualized only after infusion of the contrast agent (Fig. 9).

In conclusion, this study highlights a number of important aspects of contrast-enhanced US in the evaluation of postoperative complications in pediatric liver transplant recipients.

1. Significant increases in diagnostic certainty during the overall evaluation of the graft, the peritoneal organs, and especially the vascular structures. These advantages compensate for difficulties arising from the non-cooperation of pediatric patients, who are generally unable to hold their breath during the examination. It also increases the range of complications that can be diagnosed non-invasively and reduces the need for methods that expose the child to ionizing radiation.
2. Accurate assessment of graft vascularization with clear distinction between normally vascularized areas of the parenchyma and those that are hypoperfused (Fig. 4b).
3. Low sensitivity in the detection of arterial stenosis, which is better visualized with Doppler US.
4. Improved visualization of peri-graft collections/leaks and bile-duct dilatation secondary to anastomotic stenosis (Fig. 10).

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