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Evaluation of Pediatric Liver Transplantation-Related Artery Complications Using Intra-Operative Multi-Parameter Ultrasonography

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Background: This article discusses the value of using multi-parameter evaluation of intra-operative ultrasonography in evaluating pediatric liver transplantation-related arterial complications.

Material/Methods: Sixty-eight children receiving a liver transplant underwent intraoperative ultrasonography for monitoring of artery hemodynamics. The ultrasonic measurement parameters included the diameters of the hepatic artery (HA) of the donor and anastomotic stoma, peak systolic velocity (PSV), resistance index (RI), acceleration time (SAT), and blood flow volume.

Results: After being treated immediately using surgery or other means, blood flow returned to normal in 8 cases, and did not in 3 cases, of whom 2 experienced postoperative HAT. There was a significant difference in HA diameter of the donor, anastomotic stoma diameter, PSV, RI, SAT, and blood flow volume before and after treatment of the donor in the complications group. Postoperative complications occurred in 7 of 68 recipients, including the 2 cases exhibiting complications during the surgery (complication group) and 5 without complications during the surgery (no complication group). There was a statistically significant difference ($P<0.05$) between the 2 groups in intraoperative ultrasonography parameters of HA diameter, anastomotic stoma diameter, RI, and blood flow volume.

Conclusions Through intraoperative multi-parameter ultrasonic measurement, a definite diagnosis of hepatic artery complications can be made in liver transplantation patients. HA diameter of the donor, anastomotic stoma diameter, PSV, RI, SAT, and blood flow volume are important in assessing intraoperative artery complications.

MeSH Keywords: **Liver Transplantation • Pediatrics • Ultrasonography**

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Background

Pediatric liver transplantation (PLT) has become an effective, definitive, and universally accepted treatment for terminal liver diseases [1]. However, because of small transplant size, thin hepatic artery, unmatched arterial diameter between the donor and the recipient, and difficult anastomotic technique, it easily causes hepatic artery complications. In the surgery, surgeons often evaluate the artery blood flow by observing the arterial pulse and touching the artery oscillation, based on their experiences. Doppler ultrasonography is the preferred non-invasive technique to evaluate the arterial blood flow after liver transplantation. As shown in previous studies, RI, SAT, and tardus-parvus waveform are usually used for diagnosis of hepatic artery stenosis and thrombosis [2], but few studies have explored whether they could be used to evaluate hepatic artery complications by intraoperative ultrasonography and assess the artery blood flow in PLT.

Material and Methods

Data collection

From May 2007 to August 2015, 68 PLTs were performed in 67 patients (37 males and 30 females) in our center, including 1 case of secondary liver transplantation. These recipients had a mean age of 35.3 months (range 4 to 144 months), 47.1% (32/68) were aged <12 months. The mean height was 87.1±26.7cm and average weight was 14.1±9.7 kg; 50% (34/68) weighed <10 kg, had a transplant weight of 280.5±88.9 g, and a ratio of graft weight to recipient weight (GRWR%) >1%.

Preoperative primary diseases were as follows: congenital biliary atresia in 43 cases (43/67, 64.2%), congenital hepatic fibrosis in 5, Wilson's disease in 4, cholestatic liver disease in 3, hepatoblastoma in 3, Caroli's disease in 3, Budd-Chiari syndrome in 2, liver cirrhosis in 1, citrullinemia in 1, Langerhans's cell histocytosis in 1, and glycogen storage disease in 1.

Relatives donated 58 livers (58/68, 85.3%), including 7 right lobe, 7 left lobe, and 44 left lateral lobe; 10 livers were from brain-dead donors (10/68, 14.7%), including 4 whole liver transplantations, 5 split transplantations of the left lateral lobe, and 1 reduced-size liver transplantation.

Apparatus and method

Ultrasonic instrument: We used an α 7 Ultrasound System from Aloka with 9132T intraoperative probe (5–10 MHz) and 9133 probe (2–6 MHz), and an S3000 Ultrasound System from Siemens with 18L6 probe (6–18 MHz), and 6C1 probe (1–6 MHz).

Methods: Ultrasonography was performed immediately after completing all vascular anastomoses, to observe the hepatic artery blood flow. We placed the probe on the surface of the liver, with a small amount of saline as the lubricant. Next, we carefully looked for the portal vein under the conditions of gray-scale ultrasonography (the gray-scale value was adjusted to the level at which the images were clear without background noise), which was taken a reference for carefully seeking the hepatic vein. The instrument was set first at the color ultrasonography mode to observe the arterial blood flow, and then at the pulse Doppler mode to adjust the color gain and the scale of velocity to appropriate levels, in order to observe the hepatic artery frequency spectrum form and blood flow. Then, the probe was placed on the porta hepatis while an appropriate amount of saline was added into the abdominal cavity as the acoustic window for observation of the inner diameter of anastomotic stoma and the blood flow. If the color Doppler ultrasonography images were unsatisfactory, E-flow imaging technique or vascular enhancement technology (VET) equipped with the instrument was used for re-test.

Hepatic artery measurement parameters included: the diameters of the hepatic artery of the donor and anastomotic stoma (mm), peak systolic velocity (PSV, cm/s), resistance index (RI), acceleration time (SAT s), blood flow volume (ml/min100g liver), and spectrum waveforms.

Judgment of hepatic artery complications

All intraoperative ultrasonographies were completed by the same professional sonographer, who had ultrasonic experience in liver transplantation. In detection of hepatic artery anastomotic stenosis, high-frequency ultrasonography displays the anastomotic conditions, the diameter of the donor segment/anastomotic stoma ≥2, and the intrahepatic artery shows tardus-parvus waveform (RI <0.5, SAT >80 msec). In detection of hepatic artery thrombosis, no blood flow signal is found in the hepatic artery and/or arterial blood flow is reduced significantly, or gray-scale ultrasonography showed solid intraluminal thrombus echo. In detection of hepatic artery spasm, the hepatic artery spectrum shows tardus-parvus waveforms and returns to normal after infusion with lidocaine or papaverine. In detection of poor hepatic artery blood flow, the color images show dark intraluminal blood flow, PSV <25 cm/s, and reduced significantly blood flow volume. In detection of hepatic artery dissection, gray-scale ultrasonography displays the medial membrane separation in the artery, and the failure of color intraluminal arterial blood flow in filling onto the arterial wall.

Treatments of intraoperative complications

All complications were managed through consultation between the surgeon and the sonographers to determine whether the

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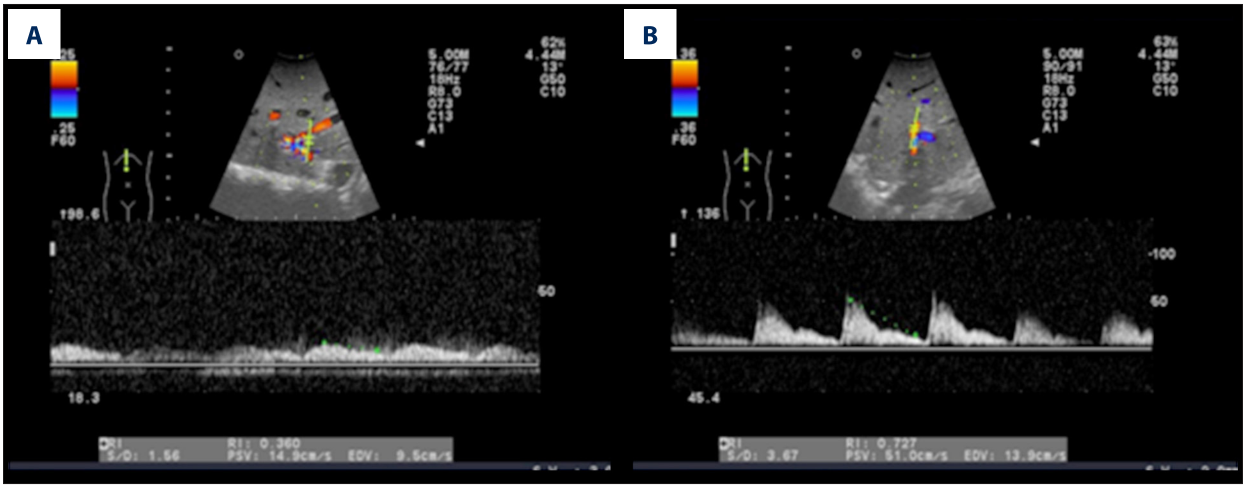

Figure 1. Ultrasonography performed for a 6-year-old child using Aloka α 7 during liver transplantation. (**A**) Hepatic artery spasm and ramus communicans arteriae were displayed on spectral Doppler; (**B**) Hepatic artery blood flow spectrum returned to normal after relieving spasm by immersing in lidocaine.

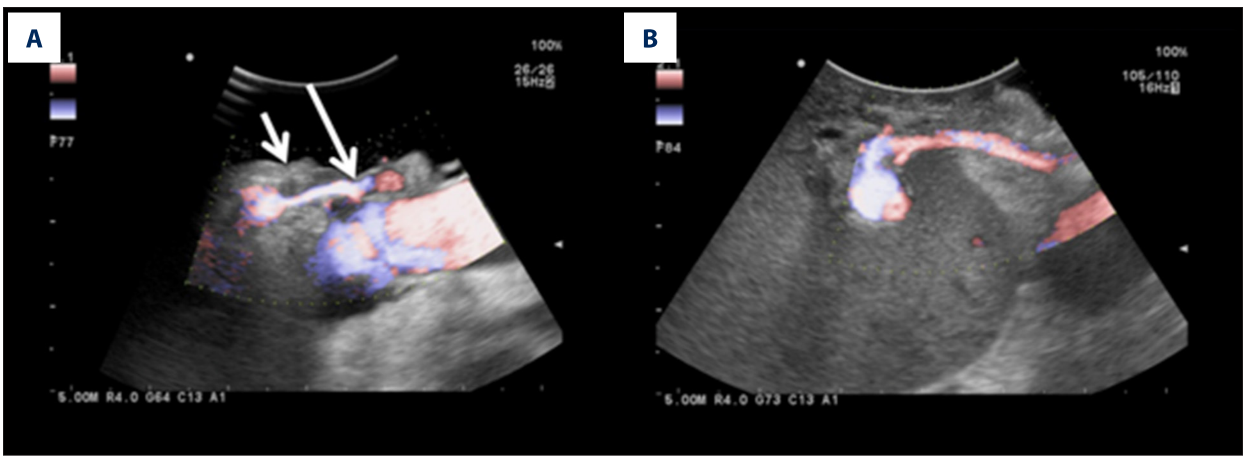

Figure 2. Aortic dissection above the anastomotic stoma of hepatic artery in a 1.5-year-old child shown by ultrasonography with Aloka α 7. (**A**) Anastomosed artery stoma (longer arrow) and dissection site (shorter arrow). In E-flow mode, endarterium was separated from adventitia, and the intraluminal blood flow in the artery failed to reach the wall, and a filling defect existed between blood flow and the wall of the artery; (**B**) After arterial reconstruction, aortic dissection disappeared and the blood flow returned to normal.

patient should undergo surgical reconstruction, be treated with drugs, or not be treated.

Statistical analysis

We used the SPSS18.0 statistical analysis program. Mean ±SD or median was used for comparison of measurement data, along with the paired Wilcoxon signed ranks test.

Ethicality statement

All the surgeries for the donors and recipients were approved by the Ethics Committee of our hospital before the surgery (2007-39-J2), and the informed consent forms were signed.

Results

Eleven recipients were diagnosed with hepatic artery complications by intraoperative ultrasonography, including 3 with HAT, 5 with arterial spasms (Figure 1), 1 with aortic dissection (Figure 2), 1 with suspected arterial dissection combined with ramus communicans arteriae, and 1 with poor artery blood flow. After immediate treatment using surgical reconstruction or other methods, 8 patients returned to normal, but the other 3 did not, in whom 2 showed postoperative HAT. Details of complications are shown in Table 1. Z values for HA diameter of the donor, anastomotic stoma diameter, PSV, and blood flow volume before and after treatment in the complications group (11 patients totally) were −2.39, −2.53, −2.93, and −2.93,

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Table 1. Surgical methods, intraoperative ultrasonography parameters, surgical treatments, and prognosis in 11 recipients.

	Surgical methods	Age	Sex	Diseases	Abnormal IOUS parameters	IOUS diagnosis	Treatment methods	IOUS findings after treatment	Outcomes
1	Brain death donor Split transplantation of the left lateral lobe	18	Male	Biliary atresia	No blood flow signal in the hepatic artery	HAT	Thrombolysis and re- anastomosis of	Return to normal	Good prognosis
2	Relative donor Transplantation of the left lobe	108	Female	Budd-Chiari syndrome	Tardus-parvus waveform	Arterial spasm	Immersed in lidocaine	Return to normal	Good prognosis
3	Relative donor Transplantation of the left lobe	110	Female	Kayser's disease	No blood flow signal in the hepatic artery	HAT	Re-anastomosis	PSV 21.0 cm/s RI 0.45 Blood flow volume 15.1 ml/min/100 g	Relapse of HAT
4	Brain death donor Transplantation of the left lateral lobe	7	Female	Biliary atresia	PSV 6.5 cm/s; diameter 1.3 mm; blood flow volume 1.6 ml/min/100 g	Poor blood flow	Re-anastomosis	Return to normal	Good prognosis
5	Relative donor Transplantation of the left lateral lobe	46	Male	Biliary atresia	PSV 18.7 cm/s; intraductal blood flow filling defect of the artery, blood flow volume 15.6 ml/min/G	Aortic dissection	Arterial bypass Re- anastomosis	Return to normal	Good prognosis
6	Relative donor, transplantation of the left lateral lobe	8	Male	Biliary atresia	Tardus-parvus waveform	Arterial spasm	Immersed in lidocaine	Return to normal	Good prognosis
7	Brain death donor II, III and partial IV segment	10	Female	Biliary atresia	Tardus-parvus waveform	Arterial spasm	Immersed in lidocaine	Return to normal	Good prognosis
8	Relative donor Transplantation of the left lateral lobe	109	Male	Biliary atresia	SAT138 msec, 16.1 ml/min/100 g	Arterial spasm	Immersed in lidocaine	Return to normal	Good prognosis
9	Relative donor Transplantation of the left lateral lobe	11	Female	Biliary atresia	Tardus-parvus waveform	Arterial spasm	Immersed in lidocaine	Return to normal	Good prognosis
10	Relative donor Right lobe (not containing the middle)	11	Male	Biliary atresia	No blood flow signal in the hepatic artery	HAT	Intraoperative thrombectomy, re-anastomosis	Return to normal	Good prognosis
11	Brain death donor Transplantation of the left lateral lobe	12	Male	Biliary atresia	Poor blood flow of the left artery in the liver; showing a "工"-shaped communicating between the left artery and the middle artery in the liver	Suspected arterial dissection of the middle lobe combined with ramus communicans arteriae between the left artery and the middle artery in the liver, poor blood flow	After re-repair the stump of the middle artery of the liver, the blood flow of the left artery of the liver was improved slightly	The ramus communicans arteriae still existed, but the blood flow of the left artery of the liver was improved slightly	Relapse of HAT

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Table 2. Surgical methods, intraoperative ultrasonography parameters, surgical treatments, and prognosis in 5 PLT recipients of the complications group.

n	Surgical methods	Age	Sex	Diseases	Postoperative complications	Occurrence time	Treatment methods	Intraoperative abnormal parameters of arterial blood flow	Prognosis
1	Relative donor transplantation of the left lateral lobe	5	Male	Biliary atresia	HAT with intrahepatic multiple necrotic lesions	7 d after surgery	Thrombolysis using the surgery, vascular remodeling	None	Surgical reconstruction, re-embolism, and collateral hepatic artery formation
2	Relative donor transplantation of the left lateral lobe	5	Female	Progressive familial cholestasis disease	HAT	23 d after surgery	The second liver transplantation due to hepatonecrosis and biliary complication	None	Good
3	Brain death donor whole liver transplantation	12	Male	Biliary atresia	HAT in the right artery of the liver with intrahepatic multiple abscess and biloma	30 d after surgery	Catheter drainage for abscess	None	Collateral artery formation
4	Brain death donor whole liver transplantation	132	Female	Biliary atresia	HAT with intrahepatic multiple necrotic lesions and biloma	24 d after surgery	Catheter drainage for necrotic lesions and biloma	None	Biliary complication, which was recovering.
5	Brain death donor whole liver transplantation	11	Female	Biliary atresia	HAT with intrahepatic multiple necrotic lesions and biloma	3 d after surgery	Catheter drainage for necrotic lesions and biloma	RI 0.44 SAT 96 ms blood flow 16.7 ml/min/100 g	Collateral artery formation Good prognosis

Table 3. Intraoperative ultrasonography parameters in the postoperative complications group and postoperative no complications group ($\bar{\chi}$ ±SD).

	Complication group	No complication group	P value
Donor HA	2.07±0.31	2.82±0.55	0.001
HA anastomotic stoma	2.16±0.34	2.70±0.54	0.012
PSV	40.16±11.67	54.11±22.82	0.177
RI	0.58±0.10	0.71±0.11	0.012
SAT	50.86±32.05	40.73±24.75	0.472
Blood flow volume	28.06±11.51	49.17±29.66	0.036

with the corresponding *P* values being 0.017, 0.012, 0.003, and 0.003, respectively. In this group (8 cases after excluding 3 cases of HAT), the RI median before and after treatment was 0.48 and 0.69, respectively, while the SAT median was 117 ms and 28.5 ms, respectively. Z value was –2.52 and –2.52, respectively, and the corresponding value was 0.012 and 0.012, respectively. $P<0.05$ for all 6 parameters suggested statistically significant differences in HA diameter, anastomotic stoma diameter, PSV, RI, SAT, and blood flow before and after treatment. Fifty-seven PLT recipients did not experience any intraoperative complications, of whom 5 had postoperative complications. See Table 2 for details.

A total of 7 of 68 recipients had postoperative complications, which were all HAT. Through analysis of intraoperative ultrasonography parameters in the postoperative complications

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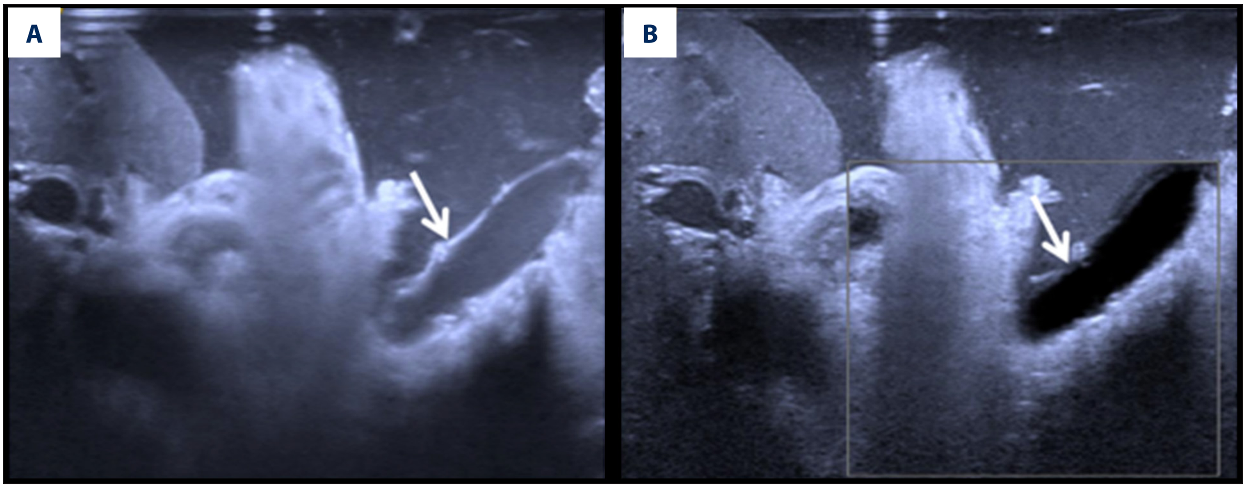

Figure 3. The anastomotic stoma of hepatic artery in an 8-year-old child using a Siemens S3000 device. Normal saline was filled around the hepatic artery. (**A**) Ordinary gray-scale ultrasonography showed the anastomotic stoma of hepatic artery (white arrow); (**B**) VET displayed the anastomotic stoma of hepatic artery (white arrow).

group and non-complications group, we found statistically significant differences in HA diameter, anastomotic stoma diameter, RI, and blood flow volume between the 2 groups ($P<0.05$) (Table 3), and there were not statistically significant differences in PSV and SAT ($P>0.05$). Median age of the 7 patients in the complications group was 12 months, and there were five younger than 12 months. Median age of the 61 patients in the non-complications group was 20 months. The Mann-Whitney U test was used to compare the median age between the 2 groups, and the results showed that there was no significant difference (P>0.05).

Discussion

After over 40 years of development, orthotopic liver transplantation has become the preferred treatment for children with end-stage liver disease, but there is still a huge technical challenge for pediatric liver transplantation recipients with lower body weight [3,4]; this is because children have their own particular characteristics and difficulties in liver transplantation compared with adults. First, pediatric intra-abdominal volume is small, and a matched liver is difficult to obtain; hence, living donor liver transplantation from the relatives or split liver transplantation is generally used. Second, the vascular diameters often do not match between the donor and the recipient, especially arteries; moreover, difficult anastomosis and higher postoperative complications exist. In the present study, through intraoperative multi-parameter ultrasonography measurement used to determine whether the arteries were unblocked and suffered from complications, as well as consultation with the surgeon during the surgery and timely treatment, the postoperative arterial complications were reduced effectively and the survival of the transplant could be ensured.

Hepatic artery complications are the most serious after hepatic transplantation, with the incidence in children being 3 to 4 times that in adults [5]. The values reported by different transplantation centers wary widely, but are generally 7.2% to 14.3% [6,7]. Insufficient arterial blood flow may cause transplant ischemia and dysfunction, biliary necrosis, biliary fistula, bile duct abscess, and even hepatic failure in severe cases [8]. All these seriously affect the survival of the transplants and recipients. According to the opinions of some scholars, hepatic artery complication is the only significant factor affecting the prognosis, and shows a higher risk in infants aged <12 months [9].

In the present study, 47% of recipients were under the age of 1 year, and 50% had body weight <10 kg. In this study, there were 7 children who developed HAT after surgeries, among which 5 were under 12 months of age. A study has reported that infants and children with lower body weight have significantly more postoperative complications, and their survival rates are obviously lower [10]. Complications after liver transplantation are variable and nontypical in their clinical features, so it is very difficult to achieve timely and early diagnosis. Therefore, some scholars suggested that the recipients with a higher risk for complications should be given intraoperative ultrasonography screening, especially for pediatric recipients [11].

Intraoperative ultrasonography was performed for measurement of hepatic arterial blood flow parameters to quickly evaluate whether the arterial blood supply was insufficient, thus excluding the cause during the surgery [12]. It was reported that the postoperative survival rates of HAT recipients detected by ultrasonography who were shown to have the evidence of successful reconstruction were obviously higher than those of the failures [13]. Hence, measures such as high-quality artery

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anastomosis technique, intraoperative implementing of ultrasonography, and timely treatment of intraoperative hepatic artery complications could effectively decrease postoperative artery complications.

There are fewer reports concerning arterial blood flow parameters in PLT. Also, there is controversy about evaluating them in adult liver transplantation. The measurement of intraoperative artery complication parameters and the evaluation indicators are inconsistent among transplantation centers. This study evaluated multiple parameters, including the hepatic artery diameters of the donor, anastomotic diameter, PSV, RI, SAT, and blood flow volume of the hepatic artery.

The predication standards of ultrasonic parameters for hepatic artery complications during and after the liver transplantation are controversial, as most studies focused on the diagnosis of postoperative complications, and those involving the intraoperative complications receive less attention. Generally, scholars believe that disappeared blood flow of the hepatic artery, reduced RI, prolonged SAT, and tardus-parvus waveform are the major evidence for predicting hepatic artery stenosis and thrombosis using ultrasonography [14]. In addition, we also pay attention to thrombogenesis from intraoperative hypotension-induced decrease of arterial blood flow, as well as false-positive results of ultrasonography at the early postoperative phase due to intraoperative edema and spasm in the hepatic artery [15]. Some scholars reported that SAT and tardus-parvus waveforms were associated with stenosis, but RI was not related to PSV; the sensitivity, specificity, and negative predictive values of Doppler ultrasonography were 60.0%, 73.7%, and 84.9% using tardus-parvus waveform as the evaluation factor, and 40.0%, 83.6%, and 80.9%, respectively, with prolonged SAT [16]. In diagnosing stenosis or thrombosis, tardus-parvus waveform is more reliable than SAT, but its diagnostic accuracy is not as high as that of postoperative ultrasonography. According to the results, RI <0.50 and SAT >80 ms can be indicative of abnormality in the hepatic artery, called tardus-parvus waveform [17]. Nevertheless, there are more controversies about criteria for determining abnormal PSV, varying from 30cm/s to 50cm/s [10,16,17].

Some of the qualitative and quantitative indicators of artery complications in PLT used by our center in this study are the same as those used by other scholars (e.g., peak velocity, resistance index, and acceleration time as the evaluation indexes), but some are different. We additionally used the diameter of the artery of the donor, anastomotic diameter, and blood flow volume of the hepatic artery. The results of this study show that aortic diameter and anastomotic diameter are associated with complications after surgeries, with more complications in patients with thinner diameters. We believe that all these parameters are associated with artery complications. Moreover, since the transplant volume in pediatric liver transplantation recipients is subject to age and body weight, they are not comparable. Referring to the calculation standard of portal blood flow volume, we corrected the blood flow volume in unit of mL/min/100 g liver. This study used 25 cm/s as the standard of PSV based on many years of experiences of the sonographer in our center, whereas other scholars used 30 cm/s to 50 cm/s; the results showed that there was no significant difference in PSV between the postoperative complications group and postoperative no complications group. Additionally, we also carefully and gently performed intraoperative ultrasonography to observe the anastomotic stoma and the peripheral arterial diameters, which became very difficult to operate due to the limitations of intra-abdominal volume, transplant placement, arterial size, and direction.

According to the results of this study, we concluded that tardus-parvus waveforms were mostly caused by artery spasm, and not closely related to stenosis and thrombosis. In 5 cases of tardus-parvus waveforms, after treatment with spasmolysis medicines, the blood flow returned to normal, and no postoperative complications were found. When intraoperative ultrasonography displays the tardus-parvus waveform, we knew that the arterial anastomotic stoma as the simple tardus-parvus waveform of non-anastomotic stenosis was associated with arterial spasm. Through postoperative ultrasonography, we rarely see the arterial anastomotic stoma. However, if the hepatic artery blood flow had abnormality early after surgery (especially tardus-parvus waveform), hepatic artery spasm, not just hepatic artery stenosis or thrombosis, should be considered. This warned us that tardus-parvus waveform detected on a single examination after surgery might not suggest HAS, so we should continue observing (if tardus-parvus waveform was observed continuously, HAS should be considered).

Domestic and foreign transplantation centers mainly use ultrasonography to measure the blood flow of the transplant after transplantation. The vast majority of scholars agree that color Doppler is the only preferred and effective examination method, and the conventional color Doppler imaging of the vessels can achieve the early detection of all vascular complications, rarely using CT or angiography [8]. Because large medical devices are inconvenient to move, and the conventional color Doppler ultrasonography might show overflowing of blood flow signal, the intraoperative imaging is completed only by ultrasonography, and small arteries cannot be measured accurately. For this reason, E-flow and vascular enhancement technology were used to monitor the arterial blood flow, which can make the display of the arterial wall and the anastomotic stoma much clearer (Figure 3)

The highly sensitive ultrasonography has a higher accuracy in diagnosis of HAT, especially intraoperative ultrasonography.

Our study team noted 3 cases of HAT during the surgery and 7 after the surgery. In case of no hepatic arterial blood flow, we can make a diagnosis of HAT, while intra-arterial thrombus is present sometimes. In the present study, the 3 cases of HAT detected intraoperatively all manifested as disappeared blood flow signal of the hepatic artery, rather than tardus-parvus waveform. At the same time, 2 cases of aortic dissection were found, of whom 1 exhibited dissection above the anastomotic stoma, which was diagnosed by E-flow technique and returned to normal blood flow after vascular reconstruction. The other showed split transplantation of the left lateral lobe, which was shown by the examination to have abnormal blood flow in the left hepatic artery and left-middle lobe communicating branch in the liver. For this child, through consultation with the surgeons, we considered that dissection of the intrahepatic artery was formed in the splitting process of the liver, and then postoperative HAT occurred.

HAT formation is relatively complex and might involve use of anticoagulants, use of special technology, selection of the donor, and technology used by the surgical team [18], and it is even more complicated in pediatric liver transplantation recipients due to their smaller arteries. To reduce the incidence of HAT, all recipients underwent arterial anastomosis performed by the same microvascular surgeon, and all intraoperative ultrasonographies were carried out by the same sonographer. There are also reports that arterial anastomosis is performed by the same surgeon in order to decrease the arterial complications in some transplantation centers [18].

Conclusions

A comprehensive evaluation through intraoperative ultrasonography of multi-parameter measurement would allow rapid evaluation of artery patency, enabling surgeons to quickly decide on appropriate measures, and thereby providing a reliable method to evaluate intraoperative arterial complications. Small arterial diameter, lower peak velocity, lower blood flow volume, lower RI, and prolonged SAT support a definite diagnosis of intraoperative arterial complications. In predicting postoperative complications, the intraoperative arterial blood flow parameters, including artery diameter, blood flow volume, and RI, are of great significance, but peak velocity and SAT are not.

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