



Prevention and treatment of new hepatitis B after living donor liver transplantation in children

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Background: This study aimed to explore the prevention and treatment of new hepatitis B in children after liver transplantation with livers positive for HBcAg and to examine the treatment of new hepatitis B.

Methods: A total of 22 children who received livers positive for HBcAg between January 2013 and December 2015 were retrospectively analyzed. After their operations, the children were given lamivudine for anti-hepatitis B virus (HBV) treatment, a hepatitis B vaccine or intermittent supplements of hepatitis B immunoglobulins to prevent recurrence of the infection, and entecavir for anti-hepatitis B treatment. The children were categorized into two groups: one group of children stopped taking lamivudine one year after operation (n=7) by themselves, while the other group did not (n=15).

Results: Of the seven children who stopped lamivudine anti-HBV treatment, six developed hepatitis B at 24.33±13.95 months after operation. Of these children, five were treated with entecavir, resulting in their HBV DNA decreasing to undetectable levels (<50 IU/mL). HBsAg turned negative in four of these patients, but in one patient it did not. The other patient with new hepatitis B continued to use lamivudine, resulting in their HBV DNA decreasing to normal levels (<50 IU/mL) but without their HBsAg turning negative. No new cases of hepatitis B were found in the 15 children who did not stop anti-HBV treatment.

Conclusions: The long-term prophylactic therapy of nucleoside analogues combined with hepatitis B immunoglobulins should be used for a long time after liver transplantation with a liver positive for HBcAg. Discontinuation of nucleoside analogues is associated with a higher risk of the new onset of hepatitis B. Entecavir has a significant effect on the treatment of postoperative new hepatitis B in children.

Keywords: Pediatric liver transplantation; hepatitis B; lamivudine; hepatitis B immunoglobulins; entecavir

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Introduction

After more than ten years of development, liver transplantation in children in China has made significant progress and become a routine operation. Unlike in adult liver transplantation, biliary atresia is the main indication of pediatric liver transplantation (1), and living donor liver transplantation is the main method of pediatric liver transplantation in China (2,3). Hepatitis B virus (HBV) is

usually negative in children before operation. However, as China is a big country, the number of HBV carriers is high, so it is often found in preoperative evaluation that the donor liver is positive for HBcAg. As such, if the treatment is not appropriate, the risk of the onset of new hepatitis B increases after operation (4). Therefore, it is important to study the prevention and treatment of new hepatitis B after living donor liver transplantation in children.

Nucleoside analogues are highly effective antiviral drugs, however, the present application of current nucleoside analogues in children is not enough and treatment of hepatitis B in children lacks a mature program. In this study, the case data of a group of children with new hepatitis B after liver transplantation were retrospectively analyzed in order to explore the prevention and treatment of new hepatitis B in children after liver transplantation with livers positive for HBcAg and to examine the treatment of new hepatitis B. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/tp-20-485>).

Methods

General data

The general clinical data of 22 children undergoing living donor liver transplantation between January 2013 and December 2015 were collected. These children were categorized into two groups: one group of children stopped using lamivudine one year after their operation (group 1, n=7), while the other did not (group 2, n=15).

Inclusion criteria: (I) infants and young children under one year old; (II) children negative for HBsAg before operation; (III) living donor liver transplantation, the donor liver came from their father or mother, the donor liver was positive for HBcAg, negative for HBsAg, and negative for HBV DNA; (IV) 400 IU of hepatitis B immunoglobulins was used to prevent new hepatitis B after liver transplantation; (V) in the early stage after liver transplantation, 25 mg of lamivudine was given daily combined with intermittent intramuscular injection of hepatitis B immunoglobulin.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Tianjin First Center Hospital (2016N084KY) and informed consent was taken from all the patients.

Methods

During liver transplantation, basiliximab and glucocorticoid were used for immune system induction. After the operation, a routine immunosuppressive regimen was adopted (anti-rejection therapy with glucocorticoid and tacrolimus; glucocorticoids were usually stopped three months after operation).

Prevention and treatment plan of hepatitis B: All patients were treated with 25 mg of lamivudine daily combined with intermittent injections of hepatitis B immunoglobulins for antiviral therapy; a hepatitis B vaccine was administered one year after liver transplantation. For children with newly diagnosed hepatitis B, the drug was administered according to the age and weight of the child. Children over two years old and weighing >30 kg were treated with 0.5 mg of entecavir once a day for antiviral therapy. In this study, six newly diagnosed hepatitis B children were over two years old and weighed more than 30 kg, which was in accordance with the medication indications; another child developed hepatitis B at the age of 20 months and, taking into account the child's condition, 0.5 mg of entecavir once a day was additionally given.

Statistical analysis

SPSS 21.0 software was used for statistical analysis. Count data were evaluated using Fisher's exact probability test. Normally distributed measurement data were expressed as mean \pm standard deviation ($\bar{x} \pm SD$) and evaluated using a *t*-test. $P < 0.05$ was considered statistically significant.

Results

The effect of lamivudine combined with hepatitis B immunoglobulins in the prevention of new onset hepatitis B in children

Group 1 consisted of seven children who stopped taking lamivudine 12–24 months after operation (this was a failure to follow medical advice). These children were injected intermittently with hepatitis B immunoglobulins for antiviral therapy, but six of them developed hepatitis B 17–50 months after liver transplantation. There were no new cases of hepatitis B in group 2, which consisted of 15 children who continued to take lamivudine. The difference between the two groups was statistically significant ($P < 0.05$) (see *Table 1*).

The effect of hepatitis B immunoglobulins alone for antiviral therapy

In group 1, six of the seven children developed new hepatitis B. The general clinical data before operation are shown in *Table 2*. These six children were all male, the median age was 8 [3–11] months old, the primary disease was

Table 1 Risk factors of new hepatitis B after living donor liver transplantation in infants and young children

Clinical data	Stopped using lamivudine one year after their operation (n=7)	Not stopped using lamivudine one year after their operation (n=15)	P
New hepatitis B (Y/N)	6/1	0/15	<0.05
Gender (male/female)	6/1	11/4	0.60
Age (months)	7.00±3.00	7.17±2.37	0.90
Kasai operation (Y/N)	2/5	6/9	0.65
Indications for liver transplant			0.40*
Gastrointestinal bleeding	1	0	
Intractable cholangitis	1	3	
Severe liver dysfunction	5	12	
PELD score	17.29±3.73	17.58±3.37	0.86
HbsAb (+/-)	4/3	9/6	1.00
HbcAb (+/-)	3/4	7/8	1.00
WBC (*10 ⁹ /L)	16.62±6.56	13.83±5.23	0.32
RBC (*10 ¹² /L)	3.87±0.25	3.77±0.29	0.47
PLT (*10 ⁹ /L)	268.14±134.74	328.25±90.73	0.26
Hb (g/L)	149.14±107.83	170.00±91.10	0.69
ALT (IU/L)	160.83±110.61	120.92±111.31	0.46
AST (IU/L)	333±197.63	351.67±184.46	0.84

Note: * indicates Fisher's exact probability.

congenital biliary atresia, and the pediatric end-stage liver disease (PELD) score was 17.17±4.07. Before operation, all 6 children tested negative for HBsAg and 3 tested positive for HbcAg. Their HBV DNA levels were <50 IU/mL. After discontinuation of lamivudine, the children were still injected intermittently with hepatitis B immunoglobulins to maintain the titer of hepatitis B immunoglobulins >100 IU/L; however, six of them were detected to be HBsAg (+) with HBV DNA >50 IU/mL at 24.33±13.95 months after operation (see Table 3, FK506 concentration was measured when hepatitis B virus infection is found).

The effect of antiviral therapy with entecavir alone after liver transplantation in children

Of the 22 children, six were found to have new hepatitis B after operation, of which only one had abnormal liver function (ALT 539.5 IU/L, AST 160.8 IU/L, and ALP 279.0 IU/L). Of these six children, five were given 0.5 mg/d

of entecavir for anti-HBV therapy, after which their HBV DNA decreased to normal levels (<50 IU/mL). In four of these children, HBsAg turned negative, but in one it did not. Another child was treated with lamivudine for anti-HBV therapy after the new onset of hepatitis B, resulting in their HBV DNA decreasing to a normal level (<50 IU/mL), but their HBsAg did not turn negative. All 6 children had normal liver function (see Table 4).

Discussion

Liver transplantation is the best way to treat neonatal congenital biliary atresia. However, due to the shortage of donors, living donor liver transplantation can be the most time-efficient way to complete the operation. China is a big country with a higher number of hepatitis B carriers: the prevalence of HBsAg in China is about 5%, and it has approximately 70 million cases of chronic hepatitis B infection (5). As such, when a donor undergoes the

Table 2 Preoperative data of 6 children who were newly diagnosed with hepatitis B before living donor liver transplantation

N	1	2	3	4	5	6
Gender (male/female)	Male	Male	Male	Male	Male	Male
Age (months)	11	3	5	8	9	9
Congenital biliary atresia	Y	Y	Y	Y	Y	Y
Blood type	A	A	B	O	A	B
Kasai operation (Y/N)	Y	N	N	Y	N	N
PELD score	22	11	14	20	19	17
HbsAb (+/-)	-	+	+	+	+	-
HbsAg (+/-)	-	-	-	-	-	-
HbcAb (+/-)	+	-	+	-	+	-
HbeAg (+/-)	-	-	-	-	-	-
HbeAb (+/-)	-	-	-	-	-	-
HBV DNA (IU/mL)	<50	<50	<50	<50	<50	<50
WBC (*10 ⁹ /L)	8.79	13.7	20.71	29.06	16.66	13.77
RBC (*10 ¹² /L)	3.58	3.93	4.16	4.12	3.61	4.02
PLT (*10 ⁹ /L)	192	396	109	491	279	248
Hb (g/L)	113	109	393	122	99	109
ALT (IU/L)	326.5	73.2	194.9	246.1	48.5	35.8
AST (IU/L)	234.6	156.5	301.3	605.8	131.2	293.3

Table 3 Postoperative data of 6 children who were newly diagnosed with hepatitis B before living donor liver transplantation

N	1	2	3	4	5	6
After operation						
HbsAb (+/-)	+	+	+	+	+	+
HbsAg (+/-)	-	-	-	-	-	-
HbcAb (+/-)	+	-	+	-	-	-
HbeAg (+/-)	-	-	-	-	-	-
HbeAb (+/-)	+	-	-	-	-	-
New hepatitis B after operation						
New onset time (months)	26	50	22	24	13	11
FK506 (ng/mL)	3.0	1.9	2.4	3.0	4.3	5.2

preoperative examination, they are often found to be HBcAb positive, HBsAg negative, and to have HBV DNA <50 IU/mL. One study revealed that donated livers that are positive for HBcAb do not affect the long-term prognosis of patients, but preventive measures should be taken (6).

A study in Spain also revealed that there is no significant difference in survival rate between positive HBcAb and negative HBcAb donors (68% vs. 76%, P>0.05) (7). Positive HBcAb indicates that HBV has been or is being infected and that HBV DNA replication exists in the body; the

Table 4 Clinical data of new cases of hepatitis B infection before and after treatment

N	1	2	3	4	5	6
Before treatment						
Liver function	Normal	Abnormal	Normal	Normal	Normal	Normal
HbsAb (+/-)	-	-	-	-	-	-
HbsAg (+/-)	+	+	+	+	+	+
HbcAb (+/-)	+	+	+	+	+	+
HbeAg (+/-)	-	-	+	+	-	-
HbeAb (+/-)	+	+	-	-	+	+
HBV DNA (IU/mL)	4*10 ²	8*10 ³	2.1*10 ³	3*10 ²	7.9*10 ⁶	6.5*10 ⁵
ALT (IU/L)	326.5	73.2	194.9	246.1	48.5	35.8
AST (IU/L)	234.6	156.5	301.3	605.8	131.2	293.3
TBIL (μmol/L)	230	167	332	435	76	35
DBIL (μmol/L)	196	151	278	376	50	24
Therapeutic regimen	Entecavir	Entecavir	Entecavir	Entecavir	Entecavir	Lamivudine
After treatment						
Liver function	Normal	Normal	Normal	Normal	Normal	Normal
HbsAb (+/-)	+	-	+	-	+	-
HbsAg (+/-)	-	+	-	-	-	+
HbcAb (+/-)	+	+	+	+	+	+
HbeAg (+/-)	-	-	-	-	-	-
HbeAb (+/-)	+	+	+	+	+	+
HBV DNA (IU/mL)	<50 IU/mL	<50 IU/mL	<50 IU/mL	<50 IU/mL	<50 IU/mL	<50 IU/mL
ALT (IU/L)	32.3	40.1	19.9	24.1	539.5	35.8
AST (IU/L)	25.6	34.4	30.3	60.8	160.8	29.3
TBIL (μmol/L)	20	16	23	19	26	26
DBIL (μmol/L)	16	10	16	12	22	20

incidence of hepatitis B after operation therefore increases after a positive HBcAb liver is used as the donor liver, and effective preventive measures should be taken to prevent new hepatitis B after operation (8).

Previous studies have focused on the prevention of new hepatitis B in adults, finding that the use of hepatitis B immunoglobulins combined with lamivudine is effective (9). Tanaka *et al.* revealed that low doses of hepatitis B immunoglobulins combined with lamivudine can effectively prevent hepatitis B recurrence after liver transplantation, with a 10-year recurrence rate of only 8.6% (10). Vasudevan *et al.* found that tenofovir fumarate combined with

lamivudine can also prevent the recurrence of hepatitis B after adult liver transplantation (11). However, there remains a lack of an effective and recognized plan for the postoperative prevention of hepatitis B in children.

The results of a previous study revealed that the incidence of new hepatitis B after living donor liver transplantation in children was closely related to positive donor HBcAg (12). The present study retrospectively analyzed the data of 22 children who were treated with hepatitis B immunoglobulins combined with lamivudine. In group 2 there was no new onset of hepatitis B, and no side effects occurred, thereby demonstrating the safety

and effectiveness of the treatment. In group 1, six of the seven children (85.71%) developed new hepatitis B at 24.33 ± 13.95 months after operation, revealing that the effect of hepatitis B immunoglobulins alone in the prevention of new hepatitis B is poor. This is consistent with the findings of a previous study (13).

In the present study, the routine detection of HBV undertaken in some children after operation found that only HBsAg was positive, but there was still a risk of new hepatitis B after operation. The main reason for this may be that there is covalently closed circular DNA (cccDNA) in the nucleus of the liver, and antiviral therapy cannot completely eliminate cccDNA. This highlights the necessity for antiviral drugs to be used continuously (14). The present study revealed that using a combination of lamivudine and hepatitis B immunoglobulins in the prevention of new hepatitis B after liver transplantation is effective and that the incidence of new hepatitis B was significantly higher after stopping lamivudine. The findings of Chen *et al.* suggested that the use of lamivudine alone is more effective in the prevention of new hepatitis B after liver transplantation but that combining it with hepatitis B immunoglobulins does not make it significantly more effective (15).

Of the six children who had new onset hepatitis B in group 1, five were given entecavir antiviral therapy after detection of the virus—only one child resumed the use of lamivudine. After treatment, the HBV DNA of all six children decreased to normal levels (<50 IU/mL). Of the five children who were given entecavir, the HBsAg of four of them turned negative, while in one it did not. This indicates that entecavir has a significant effect in the treatment of postoperative new hepatitis B in children. However, in the children treated with lamivudine, although the virus replication turned negative, HBsAg was still positive.

The treatment of chronic hepatitis B in children lacks effective treatment and preventative drugs. In 2016, a clinical trial of entecavir and a placebo in the treatment of chronic hepatitis B in children included 180 patients, 25% of whom were children aged 2–12 years. The results of the study revealed that entecavir was well tolerated in the treatment of chronic hepatitis B in children and that there were no adverse events or growth effects (16). At present, entecavir is approved by the U.S. Food and Drug Administration for the treatment of chronic hepatitis B in children aged 2–16 years. Its recommended application scheme states that it can be used for children aged two and

above and not weighing less than 10 kg (and that children above 30 kg should use an adult dose of 0.5 mg/d) (17,18). China's 2015 guidelines for chronic hepatitis B state that entecavir is safe and effective in the treatment of chronic hepatitis B in children (19–21). The main side effect of entecavir is kidney injury. In the present study, however, no renal injury was identified in the seven children treated with entecavir, which suggests that entecavir is safe and effective in the treatment of new hepatitis B after liver transplantation in children.

Currently, antiviral drugs approved for the treatment of chronic hepatitis B in children include interferon α , lamivudine, entecavir, adefovir dipivoxil, and tenofovir (22). However, there is no perfect treatment for new hepatitis B after liver transplantation in children. In this study, entecavir was used to treat new onset hepatitis B after liver transplant, in which it proved effective. However, due to the small number of cases analyzed in this study, and the fact that it was a retrospective study, its conclusions are limited. A prospective randomized controlled study with an expanded sample is needed.

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was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Tianjin First Center Hospital (2016N084KY) and informed consent was taken from all the patients.

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