의학석사 학위논문

Long-term clinical outcomes of hepatitis B naïve recipients from core antibody-positive donors in pediatric liver transplantation

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이 정 무

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Abstract

Long-term clinical outcomes of hepatitis B naïve recipients from core antibody-positive donors in pediatric living donor liver transplantation

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Introduction: In the hepatitis B endemic area, using hepatitis B core antibody-positive (Anti-HBc antibody positive) grafts may expand the donor pool in liver transplantation. The aim of this study is to investigate the clinical outcomes of hepatitis B surface antibody-negative (HBsAb-) recipients from Anti-HBc antibody positive in pediatric living donor liver transplantation

Method: Between January 1999 and December 2010, 35 patients underwent pediatric living donor liver transplantation at Seoul National University Hospital. Hepatitis B immunoglobulin (HBIG) was given to all patients postoperatively.

Results: The mean median follow-up period was 157.4 (125.0-183.9) months, and de novo hepatitis B occurred in 9 cases (25.7%). Of these, six of them showed

abnormal findings on liver function test, confirmed as hepatitis after biopsy, but improved after antiviral treatment. Vaccination and preoperative antibody titers did not show a significant relationship with the de novo HBV recurrence rate. However, in the patients who have low anti-HBs titer (<200mIU/dL) in the postoperative periods or high the concentration of immunosuppressant (>8 ng/dL), de novo hepatitis B virus infection occurred more significant.

Conclusion: In conclusion, Anti-HBc antibody positive grafts can be safely used in pediatric living donor liver transplantation with appropriate antiviral prophylaxis.

Keywords: Hepatitis B, Hepatitis B core antibody, Liver transplantation, Pediatric liver transplantation

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Abbreviation

ECD Extended criteria donors

HBV Hepatitis B virus

HBIG Hepatitis B immunoglobulin

HBV-LC Hepatitis B related liver cirrhosis

SD Standard deviation

AST Aspartate aminotransferase

ALT Alanine aminotransferase

LT Liver transplantation

FK FK506

PELD Pediatric end-stage liver disease

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1. Introduction

As the indications for living liver transplantation expand, the number of people who need simple transplants registered on the waiting list is also increasing. However, due to the relative lack of adequate donor graft numbers, mortality rates on the liver transplant waiting list are increasing. This organ shortage problem is always an important issue in liver transplantation [1-4]. The shortage of organs has resulted in higher utilization of extended criteria donors (ECDs) including old age, hepatitis B surface antigen (HBsAg) positive, and fatty liver. The use of negative donors with a positive antibody against hepatitis B core antigen (anti-HBc antibody positive) is also an example of an ECD graft [2, 5-11]. There is a potential risk for anti-HBc antibody positive donors to have occult hepatitis B virus (HBV) infection, defined as the presence of liver or serum HBV DNA without serological evidence of chronic hepatitis B infection (HBsAg negative). There is a risk of transmitting HBV infection when these grafts are transplanted to HBsAg negative recipients (de novo HBV infection). The recent guideline recommends that antiviral agents should be used for preventing de novo HBV infection in this situation [12].

Nonetheless, anti-HBc antibody positive donors represent an important source of organs in HBV endemic areas, including countries in the Asia-Pacific region. In particular, in Korea, where the hepatitis B endemic area, Anti-HBc antibody positive donor grafts, and Hepatitis B immunoglobulin (HBIG) injections are used

to prevent hepatitis B infection, and taking antiviral drugs have sufficient preventive effects, thus showing good results without major problems. However, there is still controversy over the use of HBIG and vaccination regarding the use of Anti-HBc antibody-donated grafts in children such as biliary atresia or in patients who do not have hepatitis B.

Hepatitis B related liver cirrhosis (HBV-LC) occupies most of the indication of adult liver transplantation in Korea. On the other hand, indications of pediatric liver transplantation are not usually for the diseases not related to HBV, such as biliary atresia or metabolic disease. In addition, compared to the average age of adult liver transplant patients in their 50s to 60s, children have a longer period of follow-up after liver transplantation and the possibility of reactivation of HBV should be observed for a longer time.[13, 14]

Even in many countries that are performing liver transplantation, including Korea, long term outcome results of liver transplantation using anti-HBc antibody graft in pediatric liver transplantation have not been reported. In addition, due to the development of new antiviral agents, there are currently reports on the usefulness of prophylaxis using nucleotide analogs, but in the past, it was difficult to use oral antiviral agents because of lamivudine resistance problems and insurance coverage issues. Instead, in Korea, a prophylaxis protocol using hepatitis B immunoglobulin (HBIG) was established and has been used in many centers. However, there was a lack of the standard of appropriate anti-HBs titer differs according to the transplant

surgeon in each center, and there was a disadvantage that HBIG should be regularly administered to maintain enough titer. Seoul National University Hospital (SNUH) has been using de novo HBV prophylaxis protocol without continuous injections through HBV vaccination at the point of stopping steroids while maintaining prophylaxis through HBIG administration for a short period. Several centers have reported the effect of active immunization for preventing de novo hepatitis B infection in the liver transplant using HBc antibody positive graft. However, the optimal titer and monitoring protocol of these centers are not standardized [15, 16]. In this study, we described the long-term outcome of pediatric liver transplantation using Anti-HBc antibody positive graft with de novo HBV prophylaxis combined with active immunization.

2. Materials and Methods

This study was conducted according to the current declaration of Helsinki, and the protocol was approved by the Institutional Ethics Committee at Seoul National University Hospital in Korea. From January 1999 to December 2010, 40 patients under the age of 18 who had undergone liver transplantation at Seoul National University Hospital were analyzed retrospectively. Of these, 35 patients were finally analyzed, excluding 4 patients who died within 1 year after liver transplantation and 1 patient who was followed up at another hospital. All surgical patients received HBIG at 100 IU/kg during the intermolecular period and at the same dose for 3 days after surgery, and HBsAb was measured for one year followed by an outpatient follow-up. At the 6 months after liver transplantation, oral steroids were discontinued, HBV vaccination was performed, and HBsAb was measured regularly. (Figure 1)

The recipients were admitted to the intensive care unit routinely for 4 days after transplantation. The recipients were administered tacrolimus and steroid as dual immunosuppressants. The steroid tapered off over 6 months after transplantation. Patients were evaluated once daily for 7 days and twice weekly during the hospital stay by post-transplant liver Doppler sonography. Aspirin was administered to prevent vascular thrombosis in patients. If there was no immediate postoperative complication, the recipient discharged 2 weeks after transplantation.

De novo HBV infection was defined as detection of HBV virus in the blood test of a polymerase chain reaction during the follow-up period, or hepatitis B infection confirmed by biopsy results in the case with liver function test abnormality. The patients with de novo HBV infection were treated with Nucleotide analog.

Statistical analysis

Results were expressed as means and standard deviations (SD) or as numbers and percentages. Continuous variables were compared using Student's t-tests, and categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Patient and graft survival rates were calculated using the Kaplan–Meier method and compared using the log-rank test. Potential univariate predictors of survival were analyzed by Cox regression analysis. P-values below 0.05 were considered statistically significant. All statistical analyses were performed using SPSS software (version 23; SPSS Inc., Chicago, IL, USA)

3. Results

3.1. Baseline characteristics

The average age of 35 patients was 51.5±40.5 months old, and 20 was Male and 15 women. The average body weight was 18.2±15.1 kg and the mean PELD score was 12.1±9.1. The most common diagnosis before transplantation was biliary atresia (n= 23, 65.7%). Deceased liver transplantation was performed in 2 patients and living liver transplantation in 33 patients. There were 18 fathers, 11 mothers, and 3 other family members, and 3 non-related donors.

The median follow-up period was 157.4 (125.0-183.9) months, and de novo HBV occurred in a total of 9 (25.7%) of 35 patients. Of these, 6 (66.6%) patients received antiviral agent treatment for liver function test abnormality or biopsy findings. There was no de novo HBV related graft loss or patient's death.

3.2. Clinical outcomes of preoperative HBsAb negative patients (Anti-HBsAb less than 20 mIU/mL)(Figure2)

Of the 35 patients, 22 (62.9%) patients were less than 20 mIU/mL, and 13 (37.1%) patients were more than 20 mIU/mL in the preoperative evaluation. Of these, 6 patients developed de novo hepatitis B in the group with HbsAb less than 20 mIU/mL, and 5 patients received treatment. The other 3 patients improved without treatment. Figure 3 shows biopsy results immunohistochemistry stain of the patient with de novo hepatitis B virus infection. Minimal lobular activity and mild

portoperiportal activity with septal fibrosis were shown and HBcAg and HBsAg were strongly positive, but overall degrees of hepatitis was not severe. Antiviral treatment, laboratory findings of these patients recovered well.

3.3. Clinical outcomes of the recipients who underwent active Immunization (Figure 4)

23 (65.7%) patients had active immunization after transplantation. Of these, 6 patients developed de novo hepatitis B. 2 patients who had normal liver function have no treatment and 2 patients with elevation of aspartate aminotransferase (AST) and ALT(Alanine Aminotransferase) has been treated with an antiviral agent. The other 2 patients had stable liver function even after diagnosed with de novo HBV, but in the long term follow up, they underwent antiviral treatment due to AST and ALT elevation. After antiviral treatment, laboratory findings of these patients recovered well. (Table 3.)

3.4. Comparison of Non-de novo HBV group with De novo HBV group

We describe the comparison between the group with de novo HBV and the group without de novo HBV in Table 1. There were no significant differences in serological markers, including age, sex, weight, diagnosis, PELD score, and HBsAb titer, between the de novo hepatitis B group and the non-de novo group. In the group with HBsAb titer lower than 200 mIU/mL, the incidence of de novo

hepatitis B was significantly higher than in the group with higher HBsAb titer (290.1 ± 201.3 vs 100.1 ± 103.3, P<0.001)

3.5. Correlation of Anti-HBs titer with de novo HBV infection

All recipients received HBIG for 3 days after liver transplantation, and their anti-HBsAb was measured regularly. There were no cases of vaccination for active immunization and some received regular HBIG administration. In patients with anti-HBsAb less than 200 mIU/mL, 43.0% of patients had de novo hepatitis B, and only 14.3% were observed in patients with 200 mIU/mL or more. Thirteen patients (37.1%) in the group with HBsAb above 200 mIU/mL developed de novo hepatitis B in 3 patients, and 1 patient received treatment. A total of 6 patients (25.7%) who received treatment were patients with abnormalities in liver function tests or biopsies. (Figure 5)

3.6. Correlation of mean tacrolimus level with de novo HBV infection

The incidence of de novo hepatitis B was significantly higher in the group where the average blood concentration of tacrolimus was maintained above 8 ng/dL. In the group where the concentration of tacrolimus was maintained above 8 ng/dL, 66.7% of patients developed de novo hepatitis B, and in the group less than 8 ng/dL, only 21.2% occurred. (Figure 6)

4. Discussion

A concern when using a hepatitis B core antibody-positive graft in a patient with a negative hepatitis B core antibody is the occurrence of de novo hepatitis B. According to existing studies, there is a report that de novo hepatitis B can be prevented when appropriate preventive treatment is given by the administration of globulin alone such as HBIG[5, 14, 16]. In the case of Korea, which is an endemic area of hepatitis B, the number of core antibody-positive people is higher than that of other countries, and many patients who need live liver transplantation are on the waiting list. The proportion of pediatric patients with hepatitis B or core antibody-negative through hepatitis B vaccination is relatively high. However, since their donors were mostly parents and older adults, a large number of pediatric patients would not be able to benefit from liver transplantation if the positive core antibody graft was excluded from the donor condition. There have been no reports on the performance of core antibody-positive grafts in children, and although the recent EASL guidelines provided guidelines for adults, there were no recommendations for pediatric patients.

Similar to maintaining antibody titers in hepatitis B patients, maintaining titers above 200 mIU/mL in pediatric patients using core antibody-positive grafts suggests that it is helpful to prevent de novo hepatitis B infection. In addition, just as the possibility of opportunistic infections such as bacterial and fungal infections increases after transplantation[17, 18], hepatitis B can also occur again from

excessive immunosuppression[5, 19-21]. Excessive immunosuppression affects to transcription activity of HBV DNA. This is the same principle as preventing hepatitis B patients from receiving hematopoietic stem cell transplantation by taking antiviral drugs prophylactically. Maintaining antibody titers and preventing excessive immunosuppression is probably the best way to reduce the de novo hepatitis B. De novo rate was significantly higher in HBsAb less than 200 mIU/mL groups (P=0.021) and higher in mean FK level more than 8 ng/mL groups (P=0.003). There was no de novo related graft loss and all treatment required de novo patients are managed well. Thus there have been many attempts to minimize the risk for transmission of HBV to HBsAg-negative recipients using immunoprophylaxis regimens such as HBIG, lamivudine, and vaccination.

Among those who relapsed, no occurrence of severe graft damage, cirrhosis, or hepatocellular carcinoma that required retransplantation were found. However, these recipients must follow up until their 50s, the predominant age of hepatocellular carcinoma. Considering that antiviral agents with high potency have a low recurrence rate, high therapeutic effect, and good long-term results even if recurrence has occurred, taking oral antiviral agents in all patients as in the current guidelines is cost, drug resistance. In pediatric patients with low compliance, it will be a problem to be reconsidered.

Recently, the trend of hepatitis B prevention after liver transplantation has changed. In the past, the focus was on the minimization of resistance and the

therapeutic effect, so it has changed from HBIG or Lamivudine monotherapy to combination therapy. However, periodic infusion of IV drugs requires continuous outpatient visits and is not as good as monotherapy in terms of cost. Since then, with the advent of 3rd generation antiviral agents, entecavir and tenofovir, as the efficacy of nucleotide analog monotherapy increases, excellent results of monotherapy in combination therapy have been reported now for patient convenience and cost reduction.

In Korea, the oral antiviral agent is now covered by insurance for liver transplantation using Anti-HBc antibody positive graft. However, in the case of pediatric patients, there are many cases of poor compliance who do not take even immunosuppressants during adolescence periods, so taking a life-long antiviral agent may not be applied as an effective preventive method. In addition, as the life expectancy is long, the economic burden of drugs that must be taken for a whole lifetime may be a barrier to treatment in other countries.

In this sense, active immunization can be a good alternative to avoid oral antiviral agents or intermittent injection of HBIG for high response patients with good antibody formation and maintenance of 200 mIU/ml or more. In this study, the vaccine alone did not prevent de novo HBV, but in the group that maintained the titer well after the vaccine, only 13.7% of the cases that occurred without a special oral antiviral agent showed acceptable results.

In a recent paper on active immunization, it has been reported that the incidence of de novo HBV was low in the group whose anti-HBs titer was maintained through vaccination. The high response group is firstly selected through vaccination, then in the group with poor antibody formation, an antiviral agent that can be applied or if the titer is maintained through intermittent HBIG administration. It is expected that the de novo HBV prophylaxis tailored protocol in pediatric patients can be established.

In conclusion, prophylaxis after liver transplantation using Anti-HBc antibody positive graft is essential to prevent de novo HBV occurrence. It may be helpful to maintain the proper titer of anti-HBs and prevent excessive immunosuppression regularly. If we select a good response group through vaccination and apply an appropriate immunosuppressant protocol, we can prevent the economic and medical side effects arising from taking life-long antiviral agents.

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Table 1. Perioperative findings of the recipient who underwent pediatric LT using Anti-HBc antibody positive graft

		N=35
Age, mean ± SD, month		51.5±40.5
Sex, male: female		20:15
Bodyweight, mean ± SD, kg		18.2 ± 15.1
Diagnosis		
	Biliary atresia	23 (65.7%)
	Others	12(34.3%)
Relation, n (%)		
	Father	18 (51.4%)
	Mother	11(31.4%)
	Other family	3 (8.6%)
	Unrelated	3 (8.6%)
PELD score		12.1 ± 9.1
Serological markers	Preoperative Anti-HBs (mIU/L)	164.6 ± 107.2
	Preoperative Anti-HBs ≥ 20, n (%)	13 (33.3%)
	Preoperative Anti-HBe, n (%)	1 (0.0%)
Follow up period after LT, mean ± SD, months		151.8 ± 21.6
Vaccination, n (%)		23 (65.7%)
Mean FK level (LT to event), mean ± SD, ng/mL		6.73 ± 1.2
Mean Anti-HBs titer (LT to event), mean ± SD, mIU/mL		241.4±143.2

LT, Liver transplantation; SD, Standard deviation; FK, FK506

Table 2. Comparison of Non-de novo HBV group with De novo HBV group

		Non de novo (N=26)	De novo (N=9)	P-value
Age, mean ± SD, month		53.1 ± 50.2	46.0± 32.4	0.088
Sex, male: female		14:12	6:3	0.700
Bodyweight, mean ± SD, kg		17.9 ± 13.9	19.6 ± 20.0	0.675
Diagnosis				0.656
	Biliary atresia	17 (65.4)	6 (66.7)	
	Others	9 (34.6)	3 (33.3)	
Relation, n (%)				0.325
	Father	12 (46.2%)	6 (66.7%)	NS
	Mother	9 (34.6%)	2 (22.2%)	NS
	Other family	2 (7.7%)	1 (11.1%)	NS
	Unrelated	3 (11.5%)	0(0.0%)	NS
PELD score		11.4 ± 9.8	14.3 ± 9.3	0.439
Serological markers	Preoperative Anti-HBs (mIU/L)	189.6± 296.6	92.5 ± 67.9	0.130
	Preoperative Anti-HBs ≥ 20, n (%)	10 (38.5%)	3 (33.3%)	1.000
	Preoperative Anti-HBe, n (%)	1 (3.8%)	0 (0.0%)	1.000
Follow up period after LT, mean ± SD, months		138.2 ± 60.1	157.3 ± 40.8	0.384
Vaccination, n (%)		17 (65.4%)	6 (66.7%)	1.000
Mean FK level (LT to event), mean ± SD, ng/mL		6.5 ± 1.2	7.4 ± 1.4	0.055
Mean Anti-HBs titer (LT to event), mean ± SD, mIU/mL		290.1±201.3	100.1±103.3	0.001

LT, Liver transplantation; SD, Standard deviation; PELD, Pediatric end-stage liver disease;

FK, FK506

Table 3. Clinical characteristics of De novo HBV group

	Gender	Age at LT	Primary diagnosis	Vaccination	Recurrence treatment	AST	ALT	Biopsy	LT-to recurrence (month)	Age at recurrence
1	F	1	Biliary atresia	N	N	N	N	Y	39.8	4
2	F	1	Biliary atresia	Y	Y	Elevated	Elevated	Y	143.6	13
3	F	1	Biliary atresia	Y	N	N	N	N	121.7	11
4	M	1	Biliary atresia	Y	Y	Elevated	Elevated	Y	23.9	3
5	F	2	Biliary atresia	N	Y	Elevated	Elevated	Y	15.9	4
6	M	2	Biliary atresia	Y	Y	Elevated	Elevated	Y	35.9	5
7	F	2	Wilson's disease	N	Y	Elevated	Elevated	N	12.2	3
8	F	6	Allagille syndrome	Y	N	N	N	Y	131.6	17
9	M	14	Fulminant hepatic failure	Y	Y	Elevated	Elevated	Y	23.9	16

HBV, Hepatitis B virus; LT, Liver transplantation; SD, AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; M, Male; F, Female; Y, Yes; N, No

Figure Legends

Figure 1. De novo HBV prophylaxis protocol in the patients who underwent LT using an anti-HBc antibody positive graft. The first HBIG was infused in the anhepatic phase intraoperative periods. We used intravenous HBIG until postoperative 3 days. Then, check the anti-HBs titer and perform additional HBIG infusion when it is less than 20 mIU/m. When steroids are discontinued 6 months to 1 year after surgery, HBV vaccination is usually performed over 3 times for active immunization.

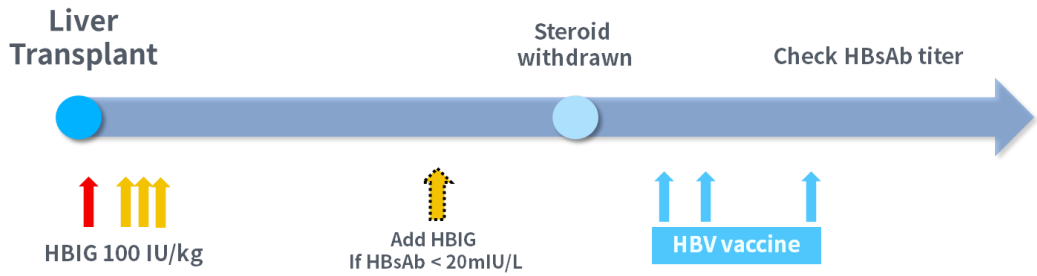

Figure 2. Clinical outcomes of preoperative HBsAb negative patients (Anti-HBsAb less than 20 mIU/mL). Thirteen patients (37.1%) in the group with HBsAb above 200 mIU/mL developed de novo hepatitis B in 3 patients, and 1 patient received treatment. A total of 6 patients (25.7%) who received treatment were patients with abnormalities in liver function tests or biopsies.

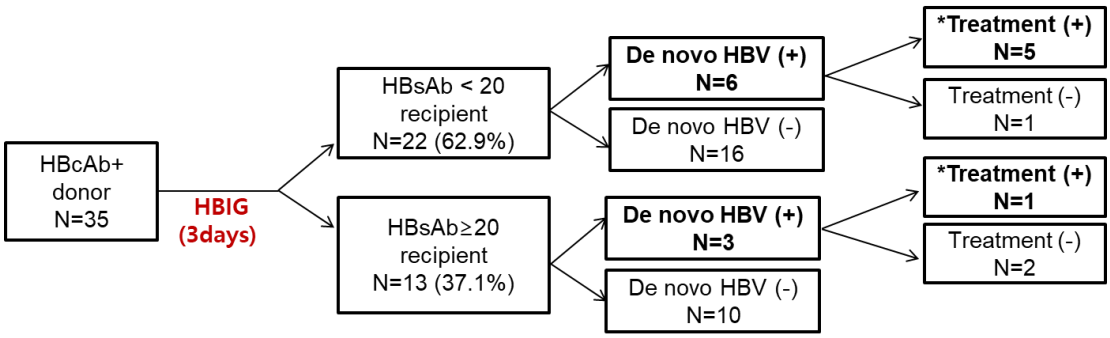

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Figure 3. Pathologic findings of the patients with de novo hepatitis B infection after LT using an anti-HBc antibody positive graft. Immunohistochemistry results show a strong positive of HBcAg(A) and HBsAg(B). Mild portal inflammation was demonstrated at the biopsy due to liver function test abnormality(C, D). There was mild inflammation before treatment of antiviral agent, but after the treatment of antiviral agent, the inflammation was decreased (E. F)

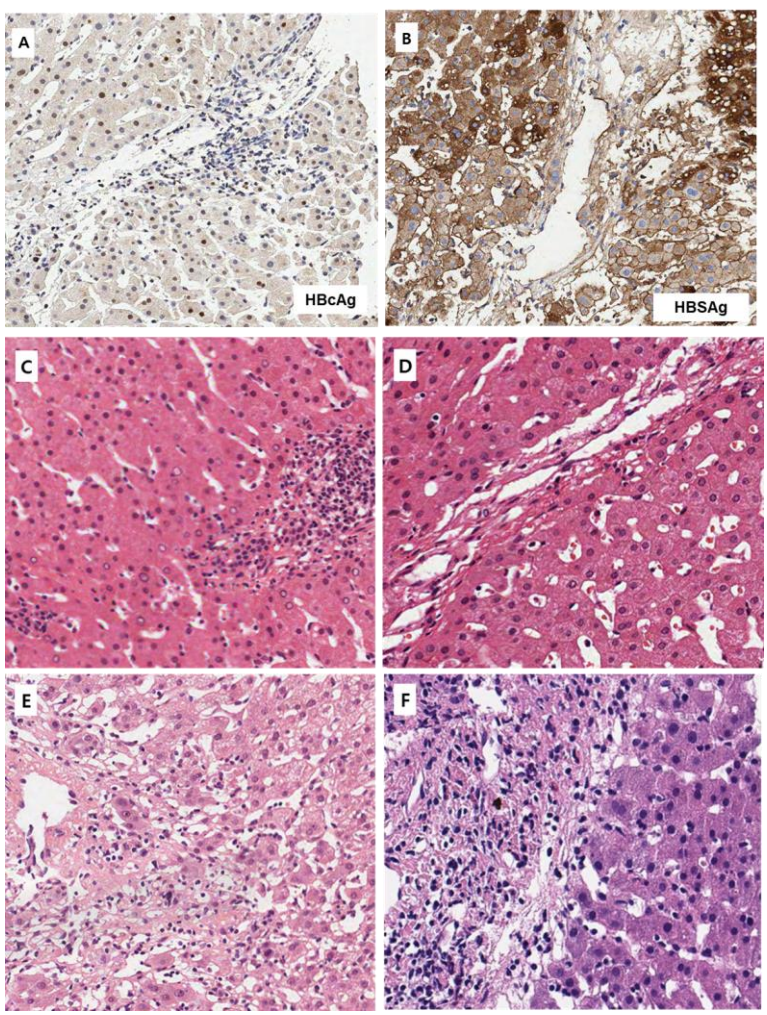


Figure 4. Clinical outcomes of preoperative HBsAb negative patients with active immunization

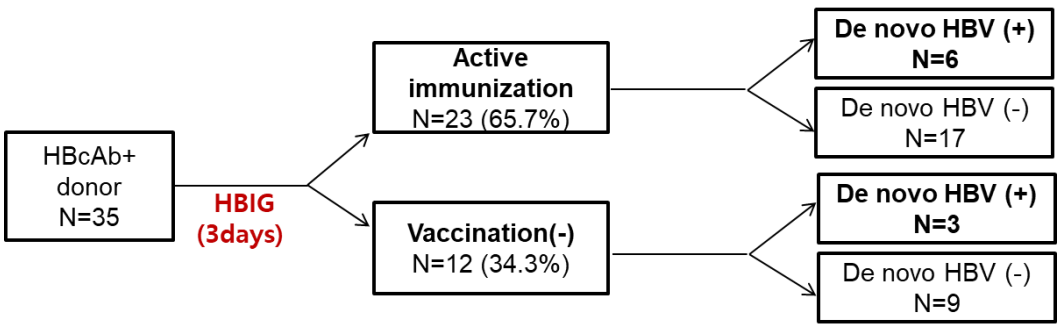


Figure 5. Correlation of Anti-HBs titer with de novo HBV infection. In patients with anti-HBsAb less than 200 mIU/mL, 43.0% of patients had de novo hepatitis B, and only 14.3% were observed in patients with 200 mIU/mL or more. (P=0.021)

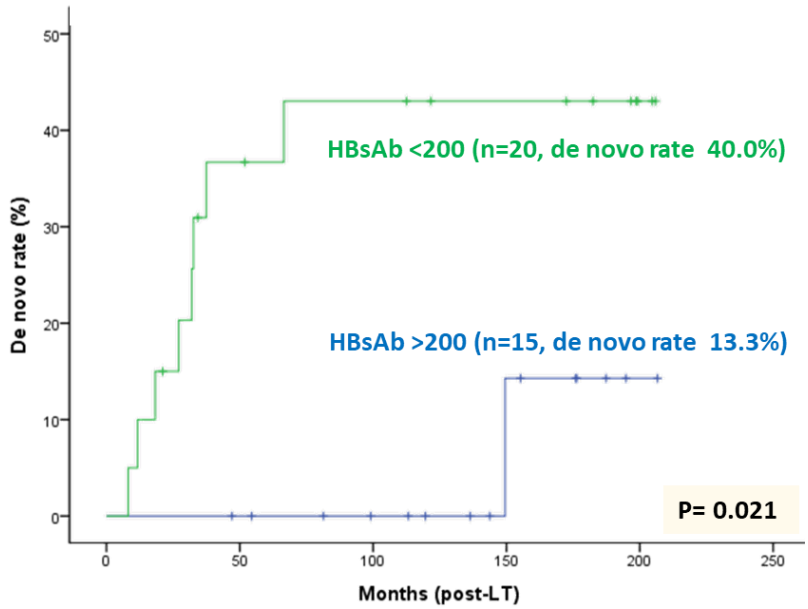
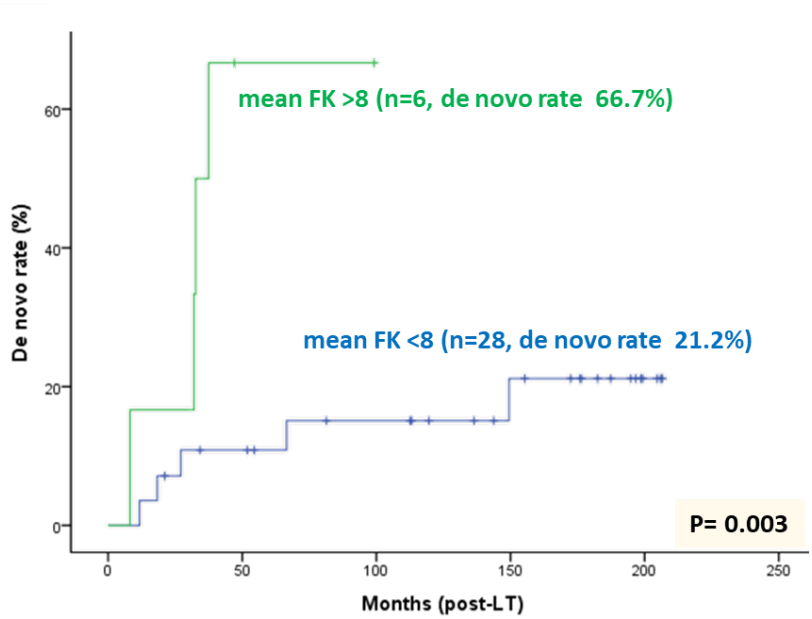


Figure 6. Correlation of mean tacrolimus level with de novo HBV infection. The incidence of de novo hepatitis B was significantly higher in the group where the average blood concentration of tacrolimus was maintained above 8 ng/dL. In the group where the concentration of tacrolimus was maintained above 8 ng/dL, 66.7% of patients developed de novo hepatitis B, and in the group less than 8 ng/dL, only 21.2% occurred.



요약(국문초록)

서론: 간이식 공여자의 숫자가 많지 않아, 대기자 리스트 환자들의 사망률이 증가하고 있다. B 형 간염환자가 많은 한국을 비롯한 아시아 태평양 지역에서 부족한 공여자 수급을 위해 공여자의 범위를 늘리는 노력이 지속되고 있으며, B 형 간염 코어항체 양성 이식편을 사용하는 것 역시 이에 일환으로 볼 수 있다. 하지만 이식 이후 B 형 간염의 재발할 가능성이 있어 적절한 예방법이 꼭 필요하다. 본 연구에서는 B 형 간염 표면항체 음성인 소아 수혜자에서 코어항체 양성 이식편을 이용하여 간이식을 받았을 때의 장기 성적과, 예방법으로서의 백신의 역할에 대해 알아보고자 한다.

방법: 1999년 1월부터 2010년 12월까지, 서울대학교병원에서 B 형간염 코어양성 이식편을 이용한 소아 간이식 환자 35명의 임상기록을 후향적으로 분석하였다. 환자들은 정주용 헤파빅을 수술 중, 수술 후 3일간 주입 받았으며, 이후 스테로이드를 끊을 6개월에서 1년사이에 B 형 간염 백신 접종을 받았으며 이후 B 형간염의 발생여부를 추적관찰 하였다.

결과: 평균 중위 추적 기간은 157.4 (125.0-183.9) 개월이었으며, B 형 간염은 9례(25.7%)에서 발생하였다. 추적관찰 중 B 형간염의 발생으로 인한 사망이나, 이식편 손실은 발생하지 않았다. 이중 6명은 간기능 검사에서 이상소견을 보여, 조직검사 후 간염으로 확인되었으나 치료 후 호전되었다. 백신 접종여부 및 수술 전 항체역가는 발병률과 유의한 관계를 보이지는 않았지만, 항체 역가가 200mIU/dL 로 낮거나, 면역억제제의 농도가 8 ng/dL 다 높았던

환자에서 환자에서 새로운 B 형간염바이러스 감염이 더 유의하게 많이 나타났다.

Conclusion: 소아 간이식에서 코어항체 양성 이식편을 이용하여도 적절한 면역억제제의 투여와 B형간염바이러스 예방법을 이용하면 큰 합병증 없이 간이식환자의 장기생존을 기대할 수 있다.

주요어: B형 간염, 간이식, B형 간염 코어 항체, 소아 간이식

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