Original Article

Efficacy of a two-dose hepatitis B vaccination with a novel immunostimulatory sequence adjuvant (Heplisav-B) on patients with chronic liver disease: a retrospective study

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Background: Patients with chronic liver disease (CLD) are more likely to have severe morbidity and mortality due to superimposed acute or chronic hepatitis B virus (HBV) infection and should receive routine vaccination against the virus. Heplisav-B is a two-dose, inactivated, yeast-derived vaccine that uses a novel immunostimulatory adjuvant. Our primary objective was to determine the efficacy of hepatitis B vaccination with Heplisav-B in patients with CLD.

Methods: This retrospective cohort analysis included patients ≥18 years old with CLD who received Heplisav-B from January 2018 to January 2021. All patients had anti-HBs <10 IU/L prior to vaccination and received two doses of Heplisav-B. Post-vaccination anti-HBs of ≥10 IU/L was considered successful vaccination. Basic demographic information, laboratory markers, and medical history were collected from the electronic health record.

Results: A total of 120 patients were included in analysis. The average age of patients was 59 years, 37% were female, and the most common etiology of liver disease was nonalcoholic fatty liver disease. Median days from 2nd vaccination to post-vaccination HBsAb levels was 121 days. 81/120 (67.5%) of patients had evidence of active immunity after receipt of Heplisav-B. On multivariable analysis, age >50 was associated with reduced odds of successful vaccination (OR =0.19, 95% CI: 0.03–0.76).

Conclusions: In patients with CLD, Heplisav-B's overall efficacy (67.5%) is greater than reports of Engerix-B (33–45%), and thus is an effective hepatitis B vaccine in this patient population, particularly in cirrhotic patients. Further studies regarding this vaccine are needed in patients with CLD and after liver transplantation.

Keywords: Hepatitis B; liver cirrhosis; Heplisav-B; Engerix-B; CpG1018

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Introduction

Viral hepatitis B infection is a major cause of both acute and chronic liver disease (CLD) worldwide, and if untreated, can lead to cirrhosis, hepatocellular carcinoma and death. Despite being a vaccine preventable disease, hepatitis B virus (HBV) infection resulted in 887,000 deaths worldwide in 2015 and is thought to have a global prevalence of around 3.7% (1,2). In those who have pre-existing CLD from other causes, studies have demonstrated that a superimposed hepatitis B infection is associated with a more severe hepatic injury, piecemeal necrosis, fibrosis, cirrhosis, fulminant hepatitis, hepatic failure and higher fatality rates (3-5). In

light of this complex picture, The Advisory Committee on Immunization Practices (ACIP) recommended HBV vaccination for all persons with CLD as an updated recommendation in 2006 (6).

Heplisav-B is a two-dose HBV vaccine approved for use by the Food and Drug Administration in 2017 for persons 18 years and older (7). It uses a novel yeast-derived recombinant Hepatitis B surface antigen (HBsAg) combined with a cytidine-phosphate-guanosine oligodeoxynucleotide (CpG-ODN) motif which binds to Toll-like receptor 9 and stimulates an immune response (8). In healthy populations, a strong body of evidence has found Heplisav-B to be more effective than a presently available vaccine, Engerix-B, a recombinant vaccine that utilizes an aluminum-based adjuvant. A study of four randomized control trials showed 90–100% seroprotective anti-HBs levels for Heplisav-B as opposed to 70.5–90.2% for Engerix-B (9-11). However, patients with CLD were not included in these trials and there is a paucity of evidence in the literature studying Heplisav-B in this patient population. Thus, our primary objective was to observe the efficacy of Hepatitis B vaccination with Heplisav-B in patients with CLD. We present the following article in accordance with the STROBE reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-22-12/rc).

Methods

We conducted a retrospective observational cohort study among patients with a diagnosis code of CLD (alcohol-related liver disease, non-alcoholic fatty liver disease, etc.) not related to chronic hepatitis B and a record of Heplisav-B administration. Patients included in the study were seen at the Mayo Clinic in Florida, Arizona, or Rochester from January 2018 to January 2021. All patients under 18 years of age were excluded from the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of Mayo Clinic (No. 20-001290) and informed consent was not required from patients given that all data in this study were extracted from the electronic health record and there was no direct patient contact.

Data extracted from electronic medical records included patient demographics, laboratory values, etiology of liver disease (including non-alcoholic fatty liver disease, alcohol-related, hepatitis C virus, autoimmune, primary sclerosing/biliary cholangitis, cardiac, vascular, and idiopathic) diagnosis of cirrhosis, calculated MELD-Na scores at time of vaccination, use of immunosuppressive medications, medical comorbidities (including chronic kidney disease, diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, hypertension, hypothyroidism, HIV infection, and malignancy), and body mass index.

All patients who received vaccination had absence of immunity to HBV (defined as anti-HBs levels <10 IU/L) prior to vaccination. However, documentation of past HBV vaccination to a vaccine other than Heplisav-B was not readily available in the medical record. All patients received two standard doses of Heplisav-B at least one month apart from each other. Post-vaccination anti-HBs levels were measured at least one month after the date of the last vaccination dose. Post-vaccination anti-HBs level of ≥10 IU/L was considered successful vaccination and active immunity.

Exclusion criteria included patients with a history of liver transplantation, age <18 years, and patients who received an HBV vaccine from a different manufacturer in between pre- and post-vaccination testing.

Statistical analysis

Continuous variables were summarized with the sample mean and standard deviation. Categorical variables were summarized with number and percentage of patients. For comparing categorical variables, we used Fisher's exact test. For comparing continuous variables, we used Student's *t*-test (normally distributed data) or Wilcoxon's rank sum test. A multivariate logistic regression model was used to identify predictors for treatment response; we included variables that were statistically significant or borderline significant between the two groups (responders versus non-responders). Odds ratios, confidence internal and P values were reported. All tests were two-sided with alpha level set at 0.05 for statistical significance. Receiver operating characteristic (ROC) curve was used to determine a cut-off age that best predicts response to Heplisav-B. Statistical analyses were performed using BlueSky Statistics®, Version 7.20.

Results

One hundred and twenty patients were included in analysis. The average age of patients was 58±11.1 years and 39% were female. Regarding ethnicity, 82% were Caucasian, 7% were Hispanic or Latino, 3% were African American, 5% were unreported, and 2% were Asian. Cirrhosis was present in 104/120 (86.7%) of the patients, and the average

Table 1 Etiology of chronic liver disease

Etiology	All (n=120)
Non-alcoholic fatty liver disease	56 (47%)
Alcohol-related	23 (19%)
Hepatitis C	12 (10%)
Autoimmune	5 (4%)
Primary sclerosing cholangitis	8 (7%)
Primary biliary cholangitis	4 (3%)
Cardiac	3 (3%)
Vascular	1 (1%)
Idiopathic	3 (3%)
Other*	5 (4%)

* includes alpha-1-antitrypsin deficiency, granulomatous hepatitis, sarcoidosis, and familial intrahepatic cholestasis type 3 (MDR-3 deficiency).

MELD score was 14.2±5.9. The most common etiology of liver disease was non-alcoholic fatty liver disease, followed by alcohol-associated liver disease and chronic hepatitis C infection (*Table 1*).

Regarding the primary outcome, 81/120 (67.5%) of patients had evidence of active immunity after vaccination with Heplisav-B (HBsAb ≥10 IU/L). Of these patients, 47/120 (39.2%) had post-vaccination HBsAb levels of ≥100 IU/L. In those with a positive response, average anti-HBs levels were 329±382 IU/L. The time period from the final vaccination dose to post-vaccination HBsAb levels ranged from 30–352 days, with a median of 135 days. The median time between doses was 35 days with a range from 24–217 days. No significant difference was seen in the time period between doses or between the final dose and antibody testing when compared in responders and non-responders.

Table 2 shows univariable analysis of several characteristics compared between patients who responded to vaccination (n=81) and those who did not respond (n=39). There was a statistically significant difference (P=0.01) between non responders' age (61.7 years) and responders' age (57.2 years). A higher average BMI and proportion of male and cirrhotic patients was also seen in non-responders, but this difference did not reach statistical significance. There was no major difference seen in MELD scores between both groups. Interestingly, there was a lower proportion of patients on immunosuppressive medications within the non-responder group, but this difference was not statistically significant (P=0.32). Regarding medical comorbidities, a higher proportion of patients with diabetes mellitus and chronic kidney disease (including patients on dialysis) was seen in non-responders but did not reach statistical significance.

Multivariable analysis on response to vaccination is shown in *Table 3*. Patients over age 50 had significantly reduced odds (OR =0.19, 95% CI: 0.03–0.76) of successful vaccination. Patients with diabetes mellitus and cirrhosis also had reduced odds of successful vaccination, but these did not reach statistical significance. Female patients had increased odds of successful vaccination, but this also failed to reach statistical significance.

Discussion

Prior studies have shown that in patients who have pre-existing CLD from other causes, acute infection with hepatitis B increases the risk for a more severe liver disease (3-5). For instance, Hepatitis B infection in patients with nonalcoholic fatty liver disease is associated with advanced fibrosis, cirrhosis and possibly hepatocellular carcinoma (12,13). Furthermore, in patients with cirrhosis awaiting transplantation, HBV vaccination is recommended as post-transplantation *de novo* HBV has been reported in 1–3.5% of patients (14). Despite these risks, recent data shows that HBV vaccination in adults with CLD in the United States are suboptimal. In 2018, only 35.7% of patients with CLD reported receiving at least 1 dose of HBV vaccine, compared to 30.2% of adults without CLD, suggesting there are missed opportunities to vaccinate those with CLD (15).

However, successful vaccination can be challenging as patients with CLD are known to have blunted responses to HBV vaccination. For instance, a study in patients with chronic hepatitis C virus (HCV) infection reported a 55% seroconversion rate using three standard doses (20 µg) of a recombinant vaccine (Engerix-B) over a 6-month period (16). There is some variability in the literature on the response rates to Engerix in this population as another study of patients with chronic HCV a response rate of 79% (17). Cirrhosis can cause several alterations in immune function including impairment in T-cell dependent function that can affect response to vaccinations (18). Considering this blunted response, early vaccination has been emphasized, especially in hepatitis C patients, as liver disease progression leads to worse immunological response (5). In transplant candidates, the reported response rates to standard recombinant vaccine are as low as 20–40% (19). Using accelerated schedules (i.e., 2 months) and double dosing of recombinant vaccine (40 µg) has shown an

Table 2 Characteristics of responders and non-responders to vaccination

Variables	Responders (N=81)	Non-responders (N=39)	P value
Age (years), mean ± SD	57.2±12.0	61.7±8.2	0.0174
Female, n (%)	34 (42.0)	13 (33.3)	0.42
Cirrhosis, n (%)	67 (82.7)	37 (94.9)	0.086
MELD score, mean ± SD	13.5±5.6	14±6.6	0.35
On immunosuppressive medication, n (%)	18 (22.2)	5 (12.8)	0.322
BMI (kg/m^2), mean ± SD	30.6±6.8	32.5±6.8	0.17
DM, n (%)	30 (37.0)	22 (56.4)	0.05
On insulin, n (%)	22 (27.2)	13 (33.3)	0.37
COPD, n (%)	6 (7.4)	4 (10.3)	0.72
CKD, n (%)	18 (22.2)	12 (30.8)	0.54
Hemodialysis, n (%)	3 (3.7)	3 (7.7)	0.66
CAD, n (%)	10 (12.3)	3 (7.7)	0.54
Hypertension, n (%)	27 (33.3)	14 (35.9)	0.84
Hypothyroidism, n (%)	15 (18.5)	4 (10.3)	0.295
HIV, n (%)	3 (3.7)	0	0.55
Malignancy, n (%)	6 (7.4)	7 (17.9)	0.12

SD, standard deviation; MELD, Model for End-Stage Liver Disease; BMI, body mass index; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CAD, coronary artery disease; HIV, human immunodeficiency virus.

Table 3 Multivariate logistic regression of response to vaccination

Variables	Odds ratio	Confidence interval (2.5%, 97.5%)	P value
Age >50 years	0.1978	0.03, 0.76	0.0383
Gender (female)	1.3821	0.60, 3.29	0.45
Diabetes mellitus	0.5067	0.22, 1.14	0.10
Cirrhosis	0.3888	0.06, 1.64	0.25

increase antibody response rate for patients awaiting orthotopic liver transplant (OLT) to 44–67.5% (20,21).

Only one other published study has examined the efficacy of Heplisav-B in patients with CLD, in which they reported a 63% antibody response rate in 60 patients (22). The authors also reported a reduced response rate of 45% in patients with CLD who received Engerix-B vaccination. In our population of 120 patients, we report a similar seroconversion rate of 67.5% with Heplisav-B. Furthermore, it is important to note that 86.7% of our study population had cirrhosis, with a high average MELD score of 14.2. Thus, our population more closely represents a pre-transplant population and differs from the population studied primarily in Amjad *et al.*'s study which only contained 34% cirrhotic patients (22).

Patients above the age of 50 showed significantly reduced odds of successful vaccination and there was an overall higher average age in non-responders. These results are consistent with prior studies, including a meta-analysis of 24 studies with recombinant hepatitis B vaccination that showed an increased pooled relative risk of vaccine failure in older individuals (RR =1.76, P<0.001) (23,24). We also observed a higher proportion of patients with diabetes in non-responders, although this was only borderline statistically significant (P=0.05) likely related to our reduced sample size. There is a strong body of evidence to show that patients with diabetes have a reduced response to both Engerix-B and Heplisav-B (25,26).

Aside from increased efficacy, there are other advantages of vaccination with Heplisav-B. Prior studies have shown increased cost-effectiveness of Heplisav-B compared to Engerix-B in certain high-risk patient populations such as those with CKD, diabetes, inflammatory bowel disease, and healthcare workers (27,28). Heplisav-B may improve patient compliance of HBV vaccination due to its two-dose series over 1 month, as opposed to other vaccination series that use three doses over 6 months. The safety of Heplisav-B has not been evaluated specifically in patients with CLD, but has been reported to have a similar safety profile to Engerix-B (29).

The limitations of this study include its observational and retrospective nature. Although our sample size was limited, our study contains a larger sample size than any prior published study on Heplisav-B within this specific population. Due to the dearth of published literature regarding this vaccine within this population, we believe that our results provide relevant and important information that may help guide clinical practice in HBV vaccination. Additional studies should examine the efficacy of Heplisav-B in patients after liver transplantation as well as examine the use of double dosing regimens in patients with CLD. In summary, we demonstrate higher rates of seroprotection after vaccination with Heplisav-B in patients with CLD when compared to reports of Engerix in this population. We recommend Heplisav-B as the preferred vaccine in this cohort of patients.

In conclusion, we show that Heplisav-B's overall efficacy (67.5%) is greater than historical reports of Engerix-B (33–45%) in patients with CLD. Thus, Heplisav-B is an effective hepatitis B vaccine in this patient population. There is only one other previously published study regarding Heplisav-B in patients with CLD (22). This study has the largest sample size of patients who received Heplisav-B compared to any previously published study.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tgh.amegroups.com/article/view/10.21037/tgh-22-12/rc

Data Sharing Statement: Available at https://tgh.amegroups.com/article/view/10.21037/tgh-22-12/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tgh.amegroups.com/article/view/10.21037/tgh-22-12/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of Mayo Clinic (No. 20-001290) and informed consent was not required from patients given that all data in this study were extracted from the electronic health record and there was no direct patient contact.

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