Int J Clin Exp Med 2020;13(6):4202-4210
www.ijcem.com /ISSN:1940-5901/IJCEM0108864

Original Article

Adefovir dipivoxil combined with lamivudine in the treatment of hepatitis B cirrhosis

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Received February 7, 2020; Accepted March 3, 2020; Epub June 15, 2020; Published June 30, 2020

Abstract: Objective: To compare the differences between lamivudine alone and adefovir dipivoxil combined with lamivudine in the treatment of hepatitis B cirrhosis in therapeutic effect. Hepatitis B virus (HBV)-DNA negative conversion rate, hepatitis Be antigen (HBeAg) negative conversion rate, liver function changes, quality of life score, and incidence of adverse reactions were investigated. Methods: A total of 70 patients with hepatitis B cirrhosis were selected as subjects. The patients were divided into an observation group and a control group, with 35 patients in each group. All patients were given routine treatment. During one year of treatment, the patients in the control group were treated with lamivudine alone, while those in the observation group were treated with adefovir dipivoxil combined with lamivudine. Results: After one year of treatment, compared with control group, the total effective rate of the observation group was significantly higher (91.4% vs 71.4%; P<0.05). After one year of treatment, compared with control group, the HBV DNA negative conversion rate (77.1% vs 54.3%) and HBeAg negative conversion rate (57.1% vs 31.4%) of the observation group were significantly higher (P<0.05), but both indexes were not significantly different between two groups at the time point of 3 months and 6 months after treatment (P>0.05). Compared with control group, liver function indexes including alanine transaminase, aspartate transaminase and total bilirubin levels were significantly improved in the observation group , and the quality of life score was significantly higher (P<0.05). The incidence of adverse reactions in the observation group was higher than that in the control group, without significant difference (P>0.05). Conclusion: Compared with lamivudine alone, adefovir dipivoxil combined with lamivudine has significant advantages in treating patients with hepatitis B cirrhosis, including better therapeutic effect, increased HBV-DNA negative conversion rate and HBeAg negative conversion rate, better improvement in liver function, higher quality of life and adverse reactions.

Keywords: Lamivudine, adefovir dipivoxil, hepatitis B cirrhosis, therapeutic effect

Introduction

Hepatitis B cirrhosis is a chronic infectious disease commonly found in clinic. It is mainly caused by hepatitis B virus (HBV) infection, with a high mortality rate, and seriously affects the quality of life (QOL) of patients and threatens their physical and mental health [1, 2]. It has been reported that the incidence of complications such as upper gastrointestinal hemorrhage, liver cancer and liver failure are significantly increased when hepatitis B cirrhosis develops to decompensation stage, and the 5-year survival rate is about 14% [3]. Therefore, it is particularly important to choose safe and effective treatment options for patients with hepatitis B cirrhosis [4].

The principle of treatment for hepatitis B cirrhosis is to maximize the long-term inhibition or elimination of HBV in the body. At present, nucleoside analogues are the first-line antiviral drugs in patients with hepatitis B cirrhosis. The antiviral mechanism of nucleoside analogs is to inhibit the activity of HBV reverse transcriptase [5, 6]. Lamivudine, as a nucleoside analogue, is widely used in clinic; it can inhibit the replication of HBV to improve the symptoms, but it cannot kill the virus. Therefore, patients need to take lamivudine for a long time to control the symptoms. A study has shown that using lamivudine usually results in HBV mutation, and drug resistance or rebound after withdrawal may occur [7]. In order to improve the antiviral efficacy, more and more studies have attached importance to the combined application of lamivudine and other antiviral drugs in recent years [8]. Instead of lamivudine alone, drug combination can significantly reduce the risk of drug resistance of patients to lamivudine, and

significantly improve the treatment effects [9]. Therefore, it is of great value to find a method of drug combination with clear curative effects and less recurrence.

Adefovir dipivoxil, as a new antiviral drug, and it also belongs to nucleoside drugs. It can not only inhibit reverse transcriptase, but also reduce the activity of DNA polymerase. A study has shown that adefovir dipivoxil has a low drug resistance rate and a good effect in the process of anti-HBV [10]. Thus, lamivudine and adefovir dipivoxil have their own advantages in anti-HBV, but the effects of lamivudine and adefovir dipivoxil in combination on anti-HBV may be different, and no unified conclusion has been formed. In one study, the therapeutic effect was used as the monitoring index to compare the difference between lamivudine and adefovir dipivoxil combined therapy and other anti-HBV drugs such as entecavil [11]. What's more, the effects of lamivudine and adefovir dipivoxil combined on liver function indexes and HBV negative conversion rate in patients with hepatitis B cirrhosis were analyzed before and after treatment [12]. At present, there are few reports on comparing the effect of lamivudine combined with adefovir dipivoxil and lamivudine alone on hepatitis B cirrhosis. In this context, this study selected 70 patients with hepatitis B cirrhosis, and used liver function, therapeutic effect, QOL, adverse reactions, HBV DNA negative conversion rate and hepatitis Be antigen (HBeAg) negative conversion rate as monitoring indexes to explore the anti-HBV effect of lamivudine combined with adefovir dipivoxil. The results of this study will provide experimental basis and theoretical basis for the treatment of hepatitis B cirrhosis.

Materials and methods

Patients

A total of 75 patients with hepatitis B cirrhosis admitted to Hainan General Hospital from January 2016 to December 2017 were selected in this research. Inclusion criteria: (1) Patients over 18 years old who met the diagnostic criteria for hepatitis B cirrhosis [13]; (2) Patients who received anti-HBV treatment for the first time for one year; (3) Patients whose HBeAg and HBV DNA were positively expressed according to laboratory examination results before treatment; (4) Patients who voluntarily participated and actively cooperated with the implementation of this study. Exclusion criteria: (1) Patients with dysfunction of heart, kidney, lung and other important organs; (2) Patients combined with malignant tumor diseases such as liver cancer; (3) Patients combined with other types of hepatitis such as autoimmune hepatitis; (4) Patients with cirrhosis due to other causes; (5) Patients who used antiviral drugs before; (6) Patients with mental illness; (7) Patients who were allergic to drugs such as lamivudine or adefovir dipivoxil. According to the inclusion criteria and exclusion criteria, patients were divided into an observation group and a control group. Patients in the control group were treated with lamivudine alone, while patients in the observation group were treated with adefovir dipivoxil combined with lamivudine. This study was approved by the Ethics Committee of Hainan General Hospital, and all the enrolled patients and their families signed the informed consent.

Treatment methods

All patients received symptomatic treatment, including liver protection, jaundice reduction, maintenance of internal environment stability, and nutritional support. In terms of anti-HBV, patients in the control group only took lamivudine (GlaxoSmithKline Pharmaceutical Co., Ltd.) at a dose of 100 mg once a day; patients in the observation group were treated with adefovir dipivoxil (GlaxoSmithKline Pharmaceutical Co., Ltd.) and lamivudine. The dose of lamivudine was the same as that of control group. The dose of adefovir dipivoxil was 10 mg once a day. The treatments both lasted for 1 year. During the treatment period, if the patients had side effects of drugs, could not recover after symptomatic treatment, such that affected the continuation of this study, they were withdrawn from this study.

Outcome measures

Main observation indexes: The main observation indexes in this study included therapeutic effect and HBV DNA negative conversion rate.

The therapeutic effects of the two groups were compared. After one year of treatment, the evaluation criteria for the therapeutic effect of the patients were shown in **Table 1** [14]. The total effective rate of treatment of each group

Table 1. Evaluation criteria of therapeutic effect in patients with hepatitis B cirrhosis

Therapeutic effect	Evaluation criteria
Ineffective	There was no improvement in clinical symptoms and liver function indexes, or the decrease of liver function index was less than 50% of the index before treatment.
Effective	The clinical symptoms were relieved significantly, and the decrease of liver function index was more than 50% of the index before treatment.
Markedly effective	The clinical symptoms basically disappeared and the liver function returned to normal.

Table 2. Comparison of general information

Group	Observation group (n=35)	Control group (n=35)	t/χ^2	P
Male/female (n)	22/13	20/15	0.238	0.626
Age (year)	47.1 ± 3.8	45.8 ± 3.3	1.528	0.131
Course of disease (year)	5.9 ± 0.7	6.2 ± 0.9	1.557	0.124
Albumin (g/L)	28.7 ± 3.1	28.4 ± 2.9	0.418	0.677
Prothrombin activity (%)	45.7 ± 6.8	45.3 ± 5.9	0.263	0.794
Hypertension (n)	6	8	0.357	0.550
Diabetes (n)	5	4	0.128	0.721
Child-Pugh classification			0.596	0.742
A	22	21		
B	10	9		
C	3	5		

was calculated as: total effective rate of treatment = (1 - number of ineffective cases/total number of cases) * 100%.

The serum HBV DNA negative conversion rate was compared between the two groups. At 3 months, 6 months and 1 year after treatment, according to the operation steps in the instructions of HBV DNA fluorescence quantitative PCR kit (Thermo Fisher Company, USA), the HBV DNA level of each group was detected by ABI 7500 fluorescence quantitative PCR instrument (purchased from American Applied Biosystems Company), and finally the HBV DNA negative conversion rate of each group was calculated. HBV DNA negative conversion rate = HBV DNA negative conversion cases/total cases * 100%.

The serum HBeAg negative conversion rate was compared between the two groups. At 3 months, 6 months and 1 year after treatment, HBeAg level in each group was measured by the fully automated AXSYM SYSTEM immunoanalyzer (purchased from Abbott Company, USA) according to the procedures in the enzyme immunoassay kit (Abbott Company, USA). HBeAg levels greater than 1.0 s/co were considered positive. Finally, the HBeAg negative conversion rate of each group was calculated. HBeAg negative conversion rate = HBeAg negative conversion cases/total cases * 100%.

Secondary observation indexes

The secondary observation indexes of this study included liver function and QOL score.

The difference of liver function indexes between the two groups were compared before treatment and one year after treatment. Venus blood, 3-5 mL was extracted from elbow vein in the morning under fasting conditions and liver function indexes (alanine transaminase (ALT), aspartate transaminase (AST) and total bilirubin (TbiL)) were detected by the fully-automatic biochemical analyzer (purchased from Beckman Kurt Co., Ltd., USA).

QOL scores were compared between the two groups before treatment and 3 months, 6 months and 1 year after treatment [15]. The QOL of patients was evaluated by the simple scale of QOL measurement. This scale is formulated by the World Health Organization, and the items assessed mainly include psychological state, physiological state, environmental field and social relationship field. In a total score of 100, the lower the score is, the worse the QOL is, and vice versa.

Statistical analysis

SPSS 22.0 software was used to analyze the experimental data. The measurement data were expressed as mean ± standard deviation, and the enumeration data were expressed as percentage (%). Comparison between the two groups was performed by independent sample t-test. Paired t-test was used for comparison before and after treatment. Comparison between different time points in the same group was conducted by ANOVA of repeated measurement, and the post test was conducted by Bonferroni method. Chi-square test is used for comparison between two groups. There was a significant difference at $P<0.05$.

Results

Comparison of general information

There was no significant difference between the observation group and control group in basic data such as gender, age, Child-Pugh classification, and course of disease ($P>0.05$), and there was comparability between the two groups (**Table 2**). During the follow-up period, 1

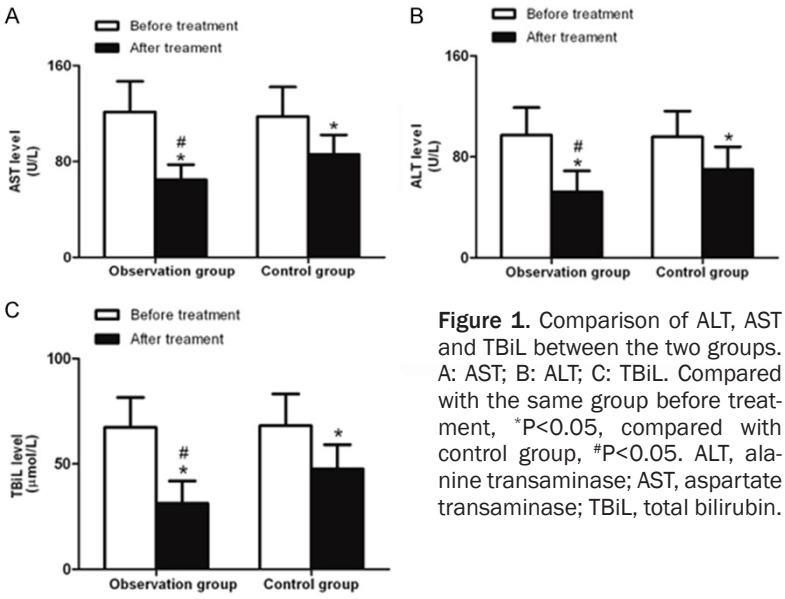

Figure 1. Comparison of ALT, AST and TBiL between the two groups. A: AST; B: ALT; C: TBiL. Compared with the same group before treatment, *P<0.05, compared with control group, #P<0.05. ALT, alanine transaminase; AST, aspartate transaminase; TBiL, total bilirubin.

Table 3. Therapeutic effect of hepatitis B cirrhosis in two groups

Group	Ineffective	Effective	Markedly effective	Total effective rate (%)
Observation group (n=35)	3	21	11	91.4
Control group (n=35)	10	16	9	71.4
χ^2		4.645		4.629
P		0.098		0.031

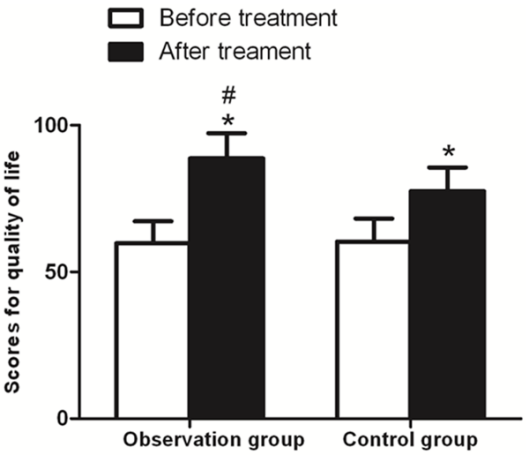

Figure 2. Comparison of QOL scores at one year after treatment between the two groups. Compared with the same group before treatment, *P<0.05, compared with control group, #P<0.05. QOL: quality of life.

patient in the control group was lost to follow-up and 2 patients withdrew from the study for the following reasons: 1 patient died and 1 patient developed liver cancer. In observation group, 1 patient was lost to follow-up and 1 patient withdrew from the study due to cardiac insufficiency. Finally, 70 patients were enrolled in this study, including 35 in the observation group and 35 in the control group.

Comparison of liver function indexes

Before treatment, there were no significant differences in the levels of ALT (97.2 ± 21.8 U/L vs 95.8 ± 20.4 U/L), AST (121.4 ± 25.5 U/L vs 117.5 ± 24.7 U/L) and TBiL (67.3 ± 14.2 μmol/L vs 68.1 ± 15.1 μmol/L) between the observation group and control group (P>0.05). After one year of treatment, the levels of ALT, AST and TBiL in the observation group and control group were significantly lower than those before treatment (all P< 0.05). After one year of treatment, compared with control group, patients in the observation group had significantly lower levels of ALT (52.3 ± 16.6 U/L vs 70.1 ± 17.8 U/L), AST (64.8 ± 12.6 U/L vs 85.9 ± 16.3 U/L) and TBiL (31.2 ± 10.7 μmol/L vs 47.6 ± 11.5 μmol/L), with significant differences (all P<0.05). See **Figure 1**.

Comparison of therapeutic effect

After one year of treatment, there were 11 markedly effective cases, 21 effective cases and 3 ineffective cases in the observation group; with the total effective rate of treatment being 91.4%. In comparison, the markedly effective, effective and ineffective cases in the control group were 9, 16 and 10, respectively, accounting for a total effective rate of 71.4%. There was a significant difference in the total effective rate between the two groups (χ^2=4.629, P=0.031). See **Table 3**.

Comparison of QOL scores

Before treatment, there was no significant difference in QOL score (59.8 ± 7.5 vs 60.4 ± 7.8) between the observation group and control

Table 4. Comparison of QOL scores before and after treatment

Group	Before treatment	At 3 months after treatment	At 6 months after treatment	At 1 year after treatment	F	P
Observation group	59.8 ± 7.5	67.2 ± 6.8*	75.4 ± 7.1*	88.7 ± 8.6*	94.610	<0.001
Control group	60.4 ± 7.8	65.9 ± 6.3#	72.6 ± 6.9#	77.5 ± 8.1#	76.753	<0.001
P	0.744	0.410	0.099	0.018		

Note: Compared with observation group before treatment, *P<0.05; compared with control group before treatment, #P<0.05. QOL, quality of life.

Table 5. Comparison of adverse reactions

Group	Abdominal distension and diarrhea	Nausea and vomiting	Dizziness and headache	Thrombocytopenia	Abnormal urine protein	Total adverse reaction rate
Observation group (n=35)	1	2	1	1	2	20.0% (7/35)
Control group (n=35)	1	1	0	1	1	11.4% (4/35)
χ^2	0.000	0.348	1.014	0.000	0.348	0.971
P	>0.999	0.555	0.314	>0.999	0.555	0.325

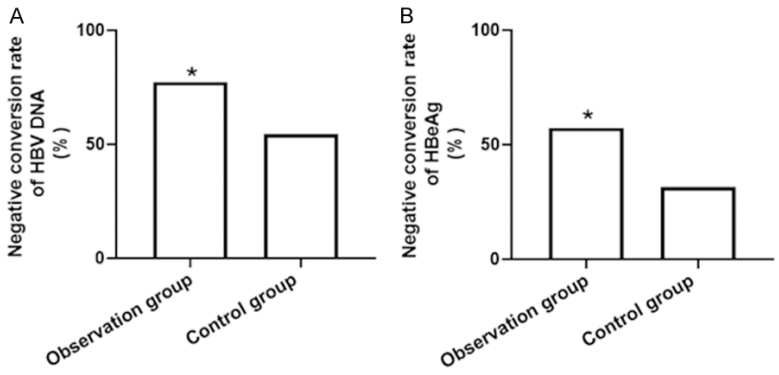

Figure 3. Comparison of HBV DNA negative conversion rate and HBeAg negative conversion rate between the two groups at one year after treatment. A: HBV DNA negative conversion rate; B: HBeAg negative conversion rate. Compared with control group, *P<0.05. HBV, hepatitis B virus; HBeAg, hepatitis Be antigen.

group (P=0.744). After treatment, the QOL scores of patients in both groups were significantly increased compared with those before treatment (all P<0.05). Compared with control group, the QOL score of the observation group was significantly higher (88.7 ± 8.6 vs 77.5 ± 8.1) after one year of treatment (P<0.05), but it was not different between the two groups before treatment, 3 months after treatment or 6 months after treatment (all P>0.05). See **Figure 2** and **Table 4**.

Comparison of incidence of adverse reactions

During one year of treatment, the incidence of adverse reactions was 20.0% (7/35) in the observation group and 11.4% (4/35) in the control group. There was no significant difference in the incidence of adverse reactions between the two groups (P=0.325). Good recovery was achieved after clinical symptomatic treatment. See **Table 5**.

Comparison of HBV DNA negative conversion rate and HBeAg negative conversion rate

After one year of treatment, there were 27 cases of HBV DNA negative conversion in the observation group with a rate of 77.1%; while 19 patients in the control group made the HBV DNA negative conversion rate of 54.3%. There was a significant difference in HBV DNA negative conversion rate between the two groups (P<0.05). After one year of treatment, the HBeAg negative conversion rate in the observation group was significantly higher than that in the control group (57.1% vs 31.4%; P<0.05). See **Figure 3** and **Table 6**.

Discussion

Lamivudine, a kind of nucleoside analogue, is a typical antiviral drug of deoxynucleotides and is widely used in clinic [16]. After lamivudine is activated by phosphorylation *in vivo*, it can

Table 6. Comparison of HBV DNA negative conversion rate and HBeAg negative conversion rate (n (%))

Group	HBV DNA negative conversion rate			HBeAg negative conversion rate		
	At 3 months after treatment	At 6 months after treatment	At 1 year after treatment	At 3 months after treatment	At 6 months after treatment	At 1 year after treatment
Observation group	12 (34.3)	18 (51.4)	27 (77.1)	6 (17.1)	9 (25.7)	20 (57.1)
Control group	10 (28.6)	15 (42.9)	19 (54.3)	5 (14.3)	7 (20.0)	11 (31.4)
χ^2	0.265	0.516	4.058	0.108	0.324	4.690
P	0.607	0.473	0.044	0.743	0.569	0.030

Note: HBV, hepatitis B virus; HBeAg, hepatitis Be antigen.

compete with dCTP so as to inhibit the replication of HBV and reduce the inflammatory response in the liver, thereby preventing the further deterioration of the disease and improve prognosis [17]. Lee et al. showed that the metabolites of lamivudine can also infiltrate into the DNA chain in the synthesis process of HBV to interfere with the replication of HBV; but the normal metabolism of deoxy nucleoside and the intracellular mitochondrial structure are rarely affected by this [18]. The results of this study showed that the total effective rate of lamivudine alone in the treatment of hepatitis B cirrhosis was 71.4%, and the HBV DNA negative conversion rate could reach 54.3%. Compared with before treatment, using lamivudine alone could significantly improve the liver function and QOL of patients, and the incidence of adverse drug reactions was low, which was basically consistent with the results reported by Jaffe et al. [19]. In addition, another study has reported that during the long-term antiviral therapy of lamivudine alone, drug withdrawal is likely to lead to recurrence and increase the risk of drug resistance [20].

In order to overcome the deficiency of lamivudine, adefovir dipivoxil combined with lamivudine was used in this study. At present, no statistical conclusion has been drawn on the effect of combined antiviral drugs in patients with hepatitis B cirrhosis. Adefovir dipivoxil, one of the acyclic analogs of 5'-monophosphate deoxyadenosine, is currently believed to have an antiviral mechanism different from lamivudine, as it can inhibit the replication of HBV DNA. Mainly, the drug is converted into adefovir diphosphate by phosphorylation in the body, and after adefovir diphosphate is integrated into the HBV DNA, the DNA chain length is terminated or the drug competes with dCTP to produce an antiviral effect. Compared with lamivudine, adefovir dipivoxil is reported to be cheaper, and have significant antiviral effects and low incidence of induced drug resistance [21]. Woo et al. reported that adefovir dipivoxil combined with lamivudine can reduce the risk of drug resistance induced by lamivudine in patients with decompensated hepatitis B cirrhosis, and the antiviral effect is more significant [22]. The combination of drugs not only improves the effect of clinical treatment, but also avoids the risk of drug resistance induced by monotherapy. The results of this study also showed that adefovir dipivoxil combined with lamivudine was more effective than lamivudine alone. Moreover, compared with control group, liver function indexes including AST, ALT and TBiL levels in the observation group were significantly decreased, with significant differences. The reason may be that the application of the drugs in combination can inhibit the replication of HBV, help to reduce the production of hepatitis cells, and transfer them to normal hepatocytes, thus improving the liver function of patients. In addition, compared with control group, the QOL score, HBV DNA negative conversion rate and HBeAg negative conversion rate of the patients in the observation group were significantly increased. The significant efficacy of combination therapy compared with lamivudine alone, is conducive to the improvement of patients' QOL, and this is similar to the results reported by Srivastava et al. and Yang et al. [23, 24]. In addition, in terms of drug safety, both groups of patients showed mild adverse drug reactions without significant difference, although the observation group showed slightly higher incidence than the control group, indicating that the adverse drug reactions of combined drugs were acceptable and relatively safe.

There were some limitations in this study including the small sample size, single-center study, lacking of long-term follow-up results, no classification comparison, and unclear relevant

mechanism. A multicenter controlled study with large sample size and long-term follow-up is needed for further confirmation in the future.

In conclusion, adefovir dipivoxil combined with lamivudine is more effective than lamivudine alone in antiviral treatment for patients with hepatitis B cirrhosis, with high HBV DNA negative conversion rate, significant improvement in liver function indexes, high QOL, and relative safety. The results of this study provide experimental basis for clinical treatment of hepatitis B cirrhosis.

Disclosure of conflict of interest

None.

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