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Efficacy and safety of telbivudine treatment for the prevention of HBV perinatal transmission

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Abstract

To observe the efficacy of telbivudine in chronic hepatitis B (CHB) women with high viral load during pregnancy and the long-term effects on intelligence, growth, and development of the newborns.

A total of 87 patients were included. Forty-two patients received telbivudine orally 600 mg per day and treatment initiated from 12 weeks after gestation until the 12th postpartum week. Forty-five patients were untreated according to principle of informed consent. All infants received injection of hepatitis B immune globulin (HBIG; 200 IU) and were vaccinated with recombinant HBV vaccine. Wechsler preschool intelligence scale was used to assess mental and neuropsychological developments of these children till they were 6 years old. Data including serum HBV DNA viral load, Apgar score, and scores of Wechsler preschool intelligence scale were analyzed and compared.

Levels of both serum HBV DNA and ALT in patients who received telbivudine were significantly decreased at the 12th week after delivery, compared with baseline levels ($P < .01$). No significant changes were observed in patients not receiving telbivudine ($P > .05$). Serum HBV DNA and ALT levels at the 12th week after delivery in the telbivudine group were significantly lower than those of patients without telbivudine ($P < .01$). The serum HBsAg-positive rate in neonates 7 months of age was 0%, which was significantly lower than that in control group (11.11%) ($P < .05$). No statistical differences were observed between the 2 groups regarding maternal cesarean section rate, adverse pregnancy rate, postpartum bleeding rate, neonatal body mass, Apgar score, neonatal malformation incidence, or intelligence development of newborn.

Telbivudine is effective to reduce the viral load in CHB mothers with high viral load and could lower the perinatal transmission rate. Both mental and physical development in neonates with exposure to telbivudine during perinatal period were similar to those without telbivudine exposure.

Abbreviations: ADV = adefovir, CHB = chronic hepatitis B, CI = confidence interval, ETV = entecavir, HBsAg = hepatitis B surface antigen, HBV DNA = hepatitis B virus deoxyribonucleic acid, LAM = lamivudine, PCR = polymerase chain reaction, SD = standard deviation, TDF = tenofovir disoproxil.

Keywords: Hepatitis B virus, long-term efficacy and safety, mother-neonatal transmission, pregnancy, telbivudine

1. Introduction

Chronic hepatitis B virus (CHB) infection remains to be a global health problem.[1–5] Vertical transmission of Hepatitis B Virus (HBV) from mothers to their infants at birth or during prenatal period is a major contributor to HBV epidemics.[6,7] The combination of both hepatitis B immunoglobulin (HBIg) and HBV vaccine in newborn was the conventional prevention for HBV perinatal transmission.[8,9] However, prevention rate still needs improvement, especially in CHB mothers with high viral load (such as serum HBV DNA $> 10^{6-7}$ IU/mL). Thus, perinatal application of nucleos(t)ide analogues was recommended in CHB mothers with high HBV DNA concentrations to reduce the transmission rate, besides HBIg and HBV vaccination.[5]

The previous study showed that telbivudine (LdT) was effective to reduce serum HBV DNA in highly viremic pregnant women.[10] Initiation of LdT during the third trimester of pregnancy to block mother-to-infant transmission of HBV was recommended according to previous trials.[11,12] However, the safety profile of long-term LdT duration in pregnant women with high viral load and potential effects on mental and physical development of newborns remains to be explored. The aim of our study was mainly to evaluate the efficacy and safety profile of

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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telbivudine in pregnant women with high HBV load and the long-term effects on both mental and physical development of their newborns.

2. Methods

2.1. Study population and study design

HBV-infected pregnant women between 20 and 35 years old were enrolled from January 2009 to February 2012 at the Chengyang People's Hospital of Qingdao. Telbivudine was administrated from 12 weeks after gestation to the 12th postpartum week. All patients had HBV DNA levels great than 10^7 IU/mL. Coinfection with hepatitis C virus, hepatitis D virus, hepatitis A virus, hepatitis E virus, human immunodeficiency virus, concurrently being confirmed with other liver diseases (drug-induced hepatitis, nonalcoholic steatohepatitis, autoimmune hepatitis, ntrahepatic cholestasis of pregnancy, etc.) or having signs of fetal dysplasia were excluded. Informed consents were received from all the patients before enrollment.

The decision of patients to receive LdT or not was dependent on their willingness after discussion with their physicians. LdT was administered as 600 mg per day orally. All infants received standard HBV vaccinations (within 12 h of birth, at Week 4, and at Week 24) and HBIg injection. Serum HBV DNA, HBeAg, HBsAg, HBsAb, ALT, aspartate aminotransferase were tested at the time of delivery, 1st and 7th postpartum months. The infants' respiratory rate, weight, length, breast feeding status, and intelligence quotient were evaluated at each visit during follow-up period. Wechsler preschool intelligence scale was implemented to assess intelligence development.

2.2. Laboratory tests

Serum HBV DNA levels were quantified with fluorescence polymerase chain reaction (PCR) (Shanghai Kehua Bio-engineering Co, Ltd, Shanghai, China),[13,14] serum markers of HBV infection including serum HBeAg, HBsAg, and HBsAb were determined using an enzyme-linked immunosorbent assay (Shanghai Kehua Bio-engineering Co Ltd). Laboratory examination of liver and kidney function was performed with an automated bioanalyzer.

2.3. Efficacy and safety assessment

Perinatal transmission was determined by both serum HBV DNA and HBsAg in the peripheral blood of infants at month 7, according to international guideline recommendations.

2.4. Statistical methods

Statistical analysis was performed with SPSS 19.0 software (SPSS, Inc, Chicago, IL). Results were expressed as mean ± SD. *F* test and Student test were used for the comparisons of continuous variables between groups, χ^2 test was used to analyze categorical variables among groups. Two-sided alpha risk was set at 0.05.

3. Results

3.1. Patient disposition and baseline characteristics

A total 87 mothers were enrolled: 42 in the LdT-treated group and 45 in the control group. Baseline demographics and clinical characteristics were comparable between the LdT-treated and the control groups, including Age, HBV DNA level, ALT levels (Table 1).

Table 1

Clinical characteristics of patients enrolled.

	LdT group	Control group	*P* value
Sample size	42	45	–
Age, y	25.2 ± 4.4	25.7 ± 4.0	.73
HBV DNA (log_{10} IU/mL)	7.88 ± 0.42	7.87 ± 0.54	.92
ALT, U/L	124.4 ± 53.2	124.1 ± 44.2	.97

ALT = alanine aminotransferase, HBV = hepatitis B virus, LdT = telbivudine.

3.2. Efficacy of telbivudine in mothers

At the time of delivery, the mean serum HBV DNA levels in the LdT-treated group were significantly lower than that in control group (Table 2). The mean serum HBV DNA levels of LdT-treated group dropped from 7.88 ± 0.42 to 3.78 ± 0.56 log_{10} copies/mL at the time of delivery, whereas mean serum HBV DNA levels of control group remained high. At the 12th postpartum week, the average serum HBV DNA levels in the LdT group were 3.10 ± 0.34 log_{10} copies/mL, much lower than that in control groups ($P < .001$).

3.3. Mother to child transmission

Forty-two infants in LdT groups and 45 infants in control group were born. Serum HBsAg status of all infants were detected at the 7th months after birth. The results showed that serum HBsAg-positive rate was 0% (0/42) in LdT group and 11.11% (5/45) in control group Table 3.

3.4. Safety of telbivudine in infants

No significant difference was observed between infants from 2 groups, with respect to weight, height, and Apgar scores (Table 4). Scores of Wechsler preschool intelligence scale test in infants till their 6-year old indicated that their intelligence developments were not affected by perinatal telbivudine exposure, compared with infants from control groups as shown in Table 5.

4. Discussion

Consistent with previous reports, our study showed that perinatal LdT application in pregnant women with high viral load was effective and safe to reduce the transmission rate. Comparison of safety profiles between infants from the 2 groups

Table 2

Dynamic HBV DNA change in the 2 groups.

	LdT group	Control group	*P* value
Sample size	42	45	–
HBV DNA (log10 copies/mL)			
At baseline	7.88 ± 0.42	7.87 ± 0.54	.92
At delivery	3.78 ± 0.56	7.87 ± 0.39	<.001
At postnatal 3 mo	3.10 ± 0.34	7.76 ± 0.58	<.001

HBV = hepatitis B virus, LdT = telbivudine.

Table 3

Detection of HBV marker of infants in all groups at month 7.

	LdT group	Control group	*P* value
Sample size	42	45	–
HBsAg status			.026
Positive	0 (0%)	5 (11.11%)	
Negative	42 (100%)	40 (88.89%)	

ALT = alanine aminotransferase, HBV = hepatitis B virus, LdT = telbivudine.

indicated LdT had no impact on the newborns. Follow-up of infants' intelligence till they were 6 years old with Wechsler preschool intelligence scale indicated that perinatal LdT exposure did not affect their intelligent development, compared with infants from control group. As far as we know, this was the first study to evaluate impact of perinatal LdT exposure on intelligency of children.

Mother to child transmission (MTCT) remains an important way of HBV transmission. Prophylactic use of HBIg and HBV vaccination was recommended to reduce the risk of perinatal transmission. However, recent studies found that 8% to 30% vertical transmission occurs even with prophylactic measures, particularly in mothers with serum HBeAg positive.[15] Sustained high serum HBV DNA in pregnant women before delivery was associated with higher perinatal transmission incidence and failure of HBV immunization.[16] It was reported that the immunization failure ratio could reach 30% in pregnant patients whose HBV DNA was higher than 10^8 copies/mL.[17] Recent studies had shown that maternal serum viral load in the third trimester of gestation was correlated with HBV infection of their infants and MTCT could not be prevented completely by vaccination and HBIg. Perinatal nucleos(t)ide analogues were recommended by consensus and guidelines to improve MTCT prevention.

Previous advances showed that telbivudine had no effects on human nucleotides stability or DNA synthesis.[18] Recently 1 meta-analysis including 26 studies, involving 3622 pregnant CHB women, showed that LdT, LAM, or tenofovir was effective to reduce MTCT rate with no significant increased adverse maternal or fetal events.[19] Consistently, our study indicated that telbivudine treatment during pregnancy in women with high viral load could effectively block MTCT.[20,21] Moreover, our study showed that perinatal LdT exposure did not affect the intelligent development of infants.

This study had limitations. First, the sample size was relatively small and it was a single-center study. Further studies with larger sample need to confirm the potential effect on intelligent development and extended follow-up to observe the intelligent development of infants after 6 years old or comparison to infants whose mother were healthy would be included in our next study.

Table 4

Comparison of baseline conditions of 2 groups of newborns.

	LdT group	Control group	*P* value
Sample size	42	45	–
Age of birth, wk	39.1 ± 1.2	39.4 ± 1.0	.21
Weight, kg	3.2 ± 0.3	3.3 ± 0.3	.12
Height, cm	50.5 ± 1.0	50.8 ± 1.0	.17
Apgar scores	9.92 ± 0.25	9.94 ± 0.20	.68

LdT = telbivudine.

Table 5

Comparison of 2 groups of children in intellectual development.

	LdT group	Control group	*P* value
Sample size	42	45	–
Intellectual scores			.66
Excellent	3 (7.1%)	3 (6.7%)	
Intelligence	6 (14.3%)	3 (6.7%)	
Normal	32 (76.2%)	37 (82.2%)	
Abnormal	1 (2.4%)	2 (4.4%)	
Retardation	0 (0%)	0 (0%)	

ALT = alanine aminotransferase, HBV = hepatitis B virus, LdT = telbivudine.

In our study, the 2 groups are comparable in only a few variables. As most patients did not know the exact time of infection, neither their family history, disease duration was not included in our study.

5. Conclusion

Perinatal LdT treatment showed efficacy to reduce MTCT in pregnant women of high HBV DNA and did not affect infants' intelligent development.

Author contributions

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References

[1] Zheng Z, Liao W, Liu L, et al. Effect of nucleos(t)ide analogue on serum HBsAg level in chronic hepatitis B patients: a 3-years study. Biomed Pharmacother 2020;122:109698.
[2] Zheng C, Yan H, Zeng J, et al. Comparison of pegylated interferon monotherapy and de novo pegylated interferon plus tenofovir combination therapy in patients with chronic hepatitis B. Infect Drug Resist 2019;12:845–54.
[3] Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1–98.
[4] European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the LiverEASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370–98.
[5] Anaedobe CG, Fowotade A, Omoruyi CE, et al. Prevalence, socio-demographic features and risk factors of Hepatitis B virus infection among pregnant women in Southwestern Nigeria. Pan Afr Med J 2015;20:406.
[6] Goyal A, Murray JM. The impact of vaccination and antiviral therapy on hepatitis B and hepatitis D epidemiology. PLos One 2014;9:e110143.
[7] Yi W, Li MH, Xie Y, et al. Prospective cohort study on the efficacy and safety of telbivudine used throughout pregnancy in blocking mother-to-child transmission of hepatitis B virus. J Viral Hepat 2017;24(suppl 1): 49–56.

[8] Li J, Chang MS, Tran TT, et al. Management of chronic Hepatitis B in pregnancy. J Clin Gastroenterol 2017;51:789–95.
[9] Abara WE, Cha S, Malik T, et al. Prenatal screening for and prevalence of Hepatitis B surface antigen in pregnant women and prevention of transmission to infants born to infected mothers-Guam, 2014. J Pediatric Infect Dis Soc 2018;7:290–5.
[10] Lim SS, Liao HT, Tsai CY. Telbivudine associated mitochondrial myopathy. Liver Int 2018;38:1139.
[11] Zhang H, Pan CQ, Pang Q, et al. Telbivudine or lamivudine use in late pregnancy safely reduces perinatal transmission of hepatitis B virus in real-life practice. Hepatology 2014;60:468–76.
[12] Hu Y, Xu C, Xu B, et al. Safety and efficacy of telbivudine in late pregnancy to prevent mother-to-child transmission of hepatitis B virus: a multicenter prospective cohort study. J Viral Hepat 2018;25:429–37.
[13] Cai SH, Lv FF, Zhang YH, et al. Dynamic comparison between Daan real-time PCR and Cobas TaqMan for quantification of HBV DNA levels in patients with CHB. BMC Infect Dis 2014;14:85.
[14] Xue X, Cai S. Comment on "Assessment of Liver Stiffness in Pediatric Fontan Patients Using Transient Elastography". Can J Gastroenterol Hepatol 2016;2016:9343960.
[15] Han GR, Cao MK, Zhao W, et al. A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. J Hepatol 2011; 55:1215–21.
[16] Han GR, Jiang HX, Yue X, et al. Efficacy and safety of telbivudine treatment: an open-label, prospective study in pregnant women for the prevention of perinatal transmission of hepatitis B virus infection. J Viral Hepat 2015;22:754–62.
[17] Wu Q, Huang H, Sun X, et al. Telbivudine prevents vertical transmission of hepatitis B virus from women with high viral loads: a prospective long-term study. Clin Gastroenterol Hepatol 2015;13:1170–6.
[18] Tan Z, Yin Y, Zhou J, et al. Telbivudine treatment of hepatitis B virus-infected pregnant women at different gestational stages for the prevention of mother-to-child transmission: Outcomes of telbivudine treatment during pregnancy. Medicine (Baltimore) 2016;95:e4847.
[19] Brown RJ, McMahon BJ, Lok AS, et al. Antiviral therapy in chronic hepatitis B viral infection during pregnancy: a systematic review and meta-analysis. Hepatology 2016;63:319–33.
[20] Sun W, Zhao S, Ma L, et al. Telbivudine treatment started in early and middle pregnancy completely blocks HBV vertical transmission. BMC Gastroenterol 2017;17:51.
[21] Zhou C, Yu Y, Yang Q, et al. Motor development delay in offspring is associated with prenatal telbivudine exposure. Medicine (Baltimore) 2018;97:e0053.