

Original Research Article

Effect of tenofovir disoproxil and telbivudine on the growth and development of infants by blocking mother-to-child transmission of hepatitis B virus

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Sent for review: 20 May 2022

Revised accepted: 30 August 2022

Abstract

Purpose: To investigate the effect of tenofovir disoproxil and telbivudine on the growth and development of infants after blocking mother-to-child transmission (MTCT) of hepatitis B virus (HBV).

Methods: Seventy pregnant women with chronic hepatitis B (CHB) were recruited and allocated to tenofovir disoproxil group (n = 35) and telbivudine group (n = 35) using random number table method. Tenofovir disoproxil group was given 300 mg tenofovir disoproxil orally four times daily, while telbivudine group was given telbivudine 600 mg orally four times daily.

Results: After treatment, both groups showed no significant differences in serum HBV-DNA and ALT levels before delivery and 3 months after delivery (p > 0.05). Both groups showed no remarkable differences in the incidence of hypohydramnios, cholestasis, hypothyroidism, anemia, prolonged labor, fetal distress, and placental adhesions (p > 0.05). Both groups showed no significant differences in the rates of premature rupture of membranes, preterm birth, vaginal delivery, and cesarean section (p > 0.05). Both groups showed no significant differences in neonatal sex, gestational age at birth, weight, length, and Apgar scores (p > 0.05). The differences in the positive rates of HBVsAg, HBsAb, and HBeAg at birth and at 12 months were not statistically noticeable (p > 0.05).

Conclusion: Tenofovir disoproxil and telbivudine reduce HBV-DNA levels, effectively blocks MTCT, and have a similar safety profile for infants. Further investigations to confirm their safety as drugs for antiviral therapy in CHB pregnant women at 24 weeks of gestation is required.

Keywords: Tenofovir disoproxil, Telbivudine, Blocking hepatitis B virus, Mother-to-child transmission, Infants, Growth and development

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Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Chronic hepatitis B (CHB) is a common infectious disease which affects approximately 420 million people worldwide [1]. Approximately

11.2 – 12.5 % of pregnant women in China were hepatitis B surface antigen (HBsAg) positive in preconception screening [2]. Hepatitis B virus (HBV) causes infant infection through mother-to-child transmission (MTCT), and infants born to

HBV-infected pregnant women have a 60 % likelihood of contracting the infection [3,4]. Antiviral therapies in pregnant women with hepatitis B are beneficial in blocking MTCT of HBV. Tenofovir disoproxil, a new antiviral drug, and telbivudine, a synthetic chemically modified nucleoside, are used frequently as antiviral therapies during pregnancy [5,6].

Antiviral therapy with Class B drugs including tenofovir disoproxil and telbivudine are recommended for pregnant women with hepatitis B [7]. Although tenofovir disoproxil and telbivudine have been studied frequently for pregnant women with hepatitis B, the comparison of effectiveness of their application in pregnant women have not been adequately explored [8-10]. In addition, tenofovir disoproxil and telbivudine are rarely reported on long-term growth and neuropsychological development in infants.

This study is conducted to determine the short-term efficacy, safety, growth and development of infants at 12 months after delivery, and to analyze the application value of tenofovir disoproxil and telbivudine in clinical practice by treating pregnant women with hepatitis B at 24 weeks of gestation using tenofovir disoproxil and telbivudine.

METHODS

General data

Following ethical approval and in line with procedures involving human subjects [11], 70 pregnant women with CHB treated in the Hangzhou Xixi Hospital, Hangzhou, between January 2018 and January 2019, and with a gestational week of more than 24 weeks were recruited for this study. The pregnant women were allocated to tenofovir disoproxil group (n = 35) and telbivudine group (n = 35) using random number table method.

Inclusion criteria

Patients who met the following conditions were included: patients who met the diagnostic criteria of the Guidelines for the Management of Chronic Hepatitis B [12], patients aged 20 – 35 years, patients with gestational week > 24 weeks and < 28 weeks, and refused to terminate the pregnancy, HBV-DNA > 2 × 10⁵ copies/mL and 40 U/L ≤ alanine aminotransferase (ALT) ≤ 160 U/L, and patients who were first pregnancies and single live birth.

Exclusion criteria

Patients who fell under the following criteria were excluded: Patients with complications such as upper gastrointestinal bleeding, hepatic encephalopathy, severe hepatitis and malignant tumors, patients with long-term administration of immunosuppressants and glucocorticoids, patients with HBV combined with other active infections, patients with a history of threatened abortion or previous abortion, patients with family history of genetic disorders, patients with spouses that have CHB, fetal malformation confirmed by ultrasound, presence of pregnancy-related comorbidities, patients who were allergic to tenofovir disoproxil and telbivudine, and patients with no history of hepatitis B antiviral treatment before treatment.

Treatments

The tenofovir disoproxil group received 6 hourly (four times daily) 300 mg dose tenofovir disoproxil orally (GlaxoSmithKline Ltd, H20153090) until delivery, while the telbivudine group received 6 hourly (four times daily) 600 mg dose of telbivudine orally (Beijing Novartis Pharmaceutical Co. Ltd, H20070028) until delivery. Within 12 h of delivery, the neonates received intramuscular injections of 100 IU/mL of hepatitis B immunoglobulin (Jiangxi Boya Biopharmaceutical Co. Ltd, S20053108) and 10 µg of recombinant yeast hepatitis B vaccine (Shenzhen Kangtai Biological Products Co. Ltd, S20110026, 0.5 mL) with 3-dose series at birth, 1, and 6 months. The newborn babies were followed up for 12 months after birth.

Evaluation of parameters/indicators

The serum HBV-DNA and ALT levels were observed before and after treatment in both groups; peripheral venous blood (3 mL) was collected before treatment, before delivery, and 3 months after delivery, and HBV-DNA levels were measured using real-time fluorescence quantitative PCR (Roche Pharmaceuticals, Switzerland). The ALT levels were measured by kinetic methods using an Abbott Aeroset Biochemistry Analyzer.

The following records were kept:

- Adverse reactions, including renal insufficiency and rhabdomyolysis.
- Pregnancy-related complications, including hypohydramnios, cholestasis, hypothyroidism, anemia, prolonged labor, pediatric distress, and placental adhesions.
- Pregnancy outcomes of both groups, including premature rupture of membranes,

preterm labor, spontaneous natural delivery, and cesarean section.

- Neonatal condition, including sex, gestational age at birth, weight, length, and Apgar score.
- Positivity rates of HBVsAg, HBsAb, and HBeAg in infants and toddlers.

The physical growth and developmental quotient (DQ) of infants and toddlers at 12 months were calculated using equation 1. Physical growth included body mass, height, head circumference, and DQ included adaptability, gross motor ability, fine motor ability, language ability, and social ability.

$$DQ = \frac{\text{Developmental age}}{\text{Actual age}} \times 100 \dots\dots\dots (1)$$

Scores ≥ 85 indicates normal development.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) 25.0 was adopted to analyze the data. Measurement data were described by mean \pm standard deviation (SD) and analyzed using the *t*-test. Enumeration data were analyzed using χ^2 test. *P* < 0.05 was considered to be statistical significance.

RESULTS

Baseline data of patients

Both groups exhibited no significant differences in age, disease duration, gestational age, HBV-DNA, and ALT (*p* > 0.05, Table 1).

Table 1: Comparison of baseline data (mean \pm SD, n = 35)

| Characteristic | Tenofovir disoproxil | Telbivudine | T | P-value |
|---------------------------------------|----------------------|--------------------|-------|---------|
| Age (years) | 26.33 \pm 2.05 | 25.94 \pm 2.10 | 0.786 | 0.435 |
| Duration of disease (years) | 5.34 \pm 0.97 | 5.63 \pm 0.91 | 1.290 | 0.201 |
| Gestational weeks (weeks) | 25.45 \pm 1.36 | 25.93 \pm 1.55 | 1.377 | 0.173 |
| HBV-DNA (log ₁₀ copies/mL) | 7.85 \pm 0.31 | 7.82 \pm 0.33 | 0.392 | 0.696 |
| ALT (U/L) | 139.25 \pm 12.67 | 138.91 \pm 13.05 | 0.111 | 0.912 |

Table 2: Comparison of serum HBV-DNA and ALT levels (mean \pm SD, n = 35)

| Group | Serum HBV-DNA (log ₁₀ copies/mL) | | | ALT (U/L) | | |
|----------------------|---|-----------------|-------------------------|------------------|------------------|-------------------------|
| | Before treatment | Before delivery | 3 months after delivery | Before treatment | Before delivery | 3 months after delivery |
| Tenofovir disoproxil | 3.72 \pm 0.37 | 4.13 \pm 0.15 | 4.63 \pm 0.57 | 50.92 \pm 5.17 | 88.33 \pm 7.02 | 66.92 \pm 3.13 |
| Telbivudine | 3.76 \pm 0.39 | 4.06 \pm 0.17 | 4.55 \pm 0.52 | 51.15 \pm 5.65 | 87.76 \pm 7.11 | 67.23 \pm 3.39 |
| T | 0.440 | 1.827 | 0.613 | 0.178 | 0.338 | 0.398 |
| P-value | 0.661 | 0.072 | 0.542 | 0.860 | 0.737 | 0.692 |

Serum HBV-DNA and ALT levels

Compared with the levels before treatment, there were no noticeable differences in serum HBV-DNA and ALT levels before delivery and 3 months after delivery (*p* > 0.05, Table 2).

Adverse reactions

No adverse reactions such as renal insufficiency, rhabdomyolysis, malaise, respiratory tract infection, pain and abdominal discomfort were observed in both groups during treatment. Both groups showed no statistically significant difference in the incidence of headache, nausea, and vomiting, (*p* > 0.05, Table 3).

Pregnancy comorbidities

Both groups exhibited no significant differences in the incidence of hypohydramnios, cholestasis, hypothyroidism, anemia, prolonged labor, fetal distress, and placental adhesions (*p* > 0.05; Table 4).

Pregnancy outcomes

No noticeable differences were observed in the rate of premature rupture of membranes, preterm labor, spontaneous natural delivery, and cesarean section in both groups (*p* > 0.05), and no miscarriage, stillbirth, or malformation occurred in either group. These data are presented in Table 5.

Table 3: Comparison of the incidence of adverse reactions (n = 35)

| Group | Headache | Nausea | Vomiting |
|----------------------|-----------|------------|------------|
| Tenofovir disoproxil | 7 (20.00) | 10 (28.57) | 9 (25.71) |
| Telbivudine | 9 (25.71) | 14 (40.00) | 12 (34.29) |
| χ^2 | 0.324 | 1.015 | 0.612 |
| P-value | 0.569 | 0.314 | 0.434 |

Table 4: Comparison of pregnancy comorbidities (n = 35)

| Group | Hypoamniotic fluid | Cholestasis | Hypothyroidism | Anemia | prolonged labor | Fetal distress | Placental adhesions |
|----------------------|--------------------|-------------|----------------|----------|-----------------|----------------|---------------------|
| Tenofovir disoproxil | 2 (5.71) | 1 (2.86) | 2 (5.71) | 3 (8.57) | 2 (5.71) | 1 (2.86) | 1 (2.86) |
| Telbivudine | 3 (8.57) | 1 (2.86) | 2 (5.71) | 1 (2.86) | 1 (2.86) | 2 (5.71) | 2 (5.71) |
| χ^2 | 0.215 | 0.000 | 0.000 | 1.061 | 0.348 | 0.348 | 0.348 |
| P-value | 0.642 | 1.000 | 1.000 | 0.303 | 0.555 | 0.555 | 0.555 |

Table 5: Comparison of pregnancy outcomes (n = 35)

| Group | Premature rupture of membranes | Premature birth | Natural birth | Cesarean section |
|----------------------|--------------------------------|-----------------|---------------|------------------|
| Tenofovir disoproxil | 3 (8.57) | 1 (2.86) | 23 (65.71) | 12 (34.29) |
| Telbivudine | 4 (11.43) | 1 (2.86) | 21 (60.00) | 14 (40.00) |
| χ^2 | 0.159 | 0.000 | 0.245 | 0.245 |
| P-value | 0.690 | 1.000 | 0.621 | 0.621 |

Table 6: Comparison of HBVsAg, HBsAb, and HBeAg positivity rates (n = 35)

| Group | At birth | | | 12 months | | |
|----------------------|----------|----------|----------|-----------|-------------|----------|
| | HBVsAg | HBsAb | HBeAg | HBVsAg | HBsAb | HBeAg |
| Tenofovir disoproxil | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 35 (100.00) | 0 (0.00) |
| Telbivudine | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 35 (100.00) | 0 (0.00) |
| χ^2 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| P-value | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |

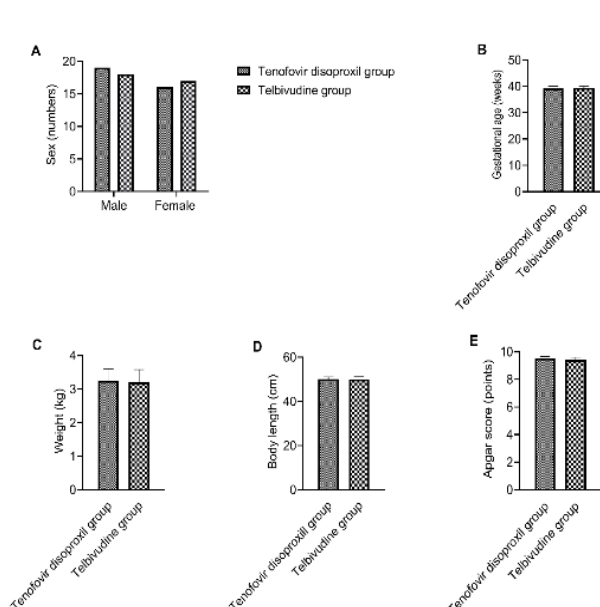


Figure 1: Comparison of neonatal condition. Results showed no statistically significant differences in sex (A), gestational age at birth (B), weight (C), length (D), and Apgar score (E) between the two groups of newborns

Neonatal condition

Both groups showed no significant difference in sex, gestational age at birth, weight, length, and Apgar score ($p > 0.05$; Figure 1).

Positivity rates HBVsAg, HBsAb, and HBeAg

No noticeable differences were found in positive rates of HBVsAg, HBsAb, and HBeAg between infants at birth and at 12 months ($p > 0.05$, Table 6).

Growth and development indicators at 12 months

Both groups showed no noticeable differences in weight, length, head circumference, adaptability, gross motor ability, fine motor ability, language ability, and social skills at 12 months ($p > 0.05$, Figure 2). The results suggest that the antiviral treatment of tenofovir disoproxil and telbivudine during pregnancy produce similar safety profiles in the long-term physical development and developmental quotient of infants.

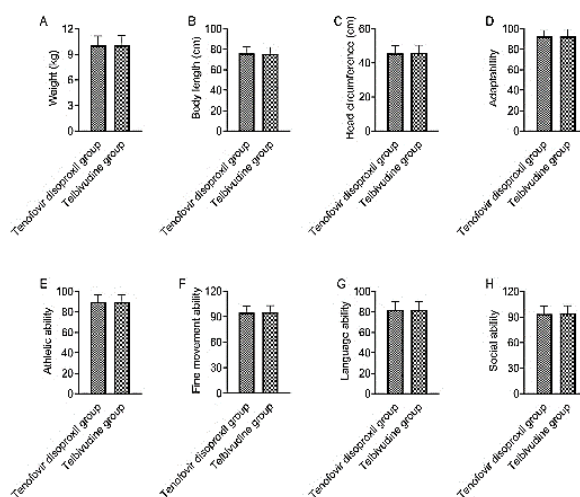


Figure 2: Comparison of growth and development indicators at 12 months of age. Results showed no noticeable differences in weight (A), length (B), head circumference (C), adaptability (D), gross motor skills (E), fine motor skills (F), language skills (G), and social skills (H) of infants and toddlers at 12 months of age, respectively

DISCUSSION

Mother to child transmission (MTCT) is one of the important ways of HBV infection, the risk of which exceeds 95 % in unvaccinated infants [13]. Once infected with HBV, infants develop chronic liver injury, which affects their growth and development [13].

The routine administration schedule for hepatitis B vaccine prevents infants and young children from being infected with HBV, with a failure rate of 5 - 15 %, which may be caused by intrauterine infection of the fetus [2,14]. Hence, attention needs to be paid to the antiviral treatment of women with hepatitis B during pregnancy to suppress viral replication and reduce the risk of intrauterine HBV infection.

Tenofvir disoproxil is a novel nucleotide reverse transcriptase inhibitor that suppresses viral replication primarily through the competitive binding of natural deoxyribose substrates, inhibition of viral polymerase, and insertion into a termination strand in DNA [15]. Telbivudine is a new levonucleoside anti-HBV drug whose active antiviral component is mainly -5,-triphosphate, which can compete with the -5,-triphosphate of HBV viral DNA, inhibit the DNA polymerase of HBV, and inhibit viral replication [16]. Tenofvir disoproxil and telbivudine can reduce HBV viral load in pregnant women with high viral loads [17]. This study found that tenofvir disoproxil exhibited effects similar to that of tibivudine in pregnant women with HBV infection at 24 weeks

of gestation. The HBV load in both groups showed no significant difference before delivery. This suggests that tenofvir disoproxil is as effective as telbivudine. Serum HBV-DNA and ALT levels were elevated in both groups 3 months after delivery when compared to those before delivery, which could be attributed to the fluctuations in postpartum immune status after delivery.

The HBV infection, abnormal liver function, and improper drug usage affects the safety of pregnant women and fetal development. Hence, attention should be paid to the safety of tenofvir disoproxil and telbivudine during pregnancy [18,19]. This study showed no noticeable difference in hypohydramnios, cholestasis, hypothyroidism, anemia, prolonged labor, fetal distress, and placental adhesions in pregnant women treated with tenofvir disoproxil versus telbivudine, suggesting that both groups had no significant differences in pregnancy comorbidities during pregnancy. No significant differences were found in the premature rupture of membranes, preterm delivery, spontaneous natural delivery, and cesarean section between the two groups. Both groups experienced no miscarriage, stillbirth, or malformation, and showed no noticeable differences in the sex, gestational age at birth, weight, length, and Apgar score, indicating that tenofvir disoproxil showed the same safety profile as telbivudine during pregnancy.

It has been reported that tenofvir disoproxil and tenofvudine treatment can reduce the rate of MTCT (total odds ratio = 0.15) and increase HBV-DNA suppression, and there is no significant association with preterm/premature birth, congenital malformations, low birth weight, miscarriage, or fetal/infant death [10]. A study also found an association between tenofvir and mild gastrointestinal distress, which may negatively affect fetal bone growth, an outcome that might only be limited to late gestation [20]. However, these adverse reactions were not found in the present study. No significant differences were observed in HBVsAg, HBsAb, and HBeAg positivity rates at birth and at 12 months, wherein infants were 100 % HBsAb positive and negative for HBVsAg and HBeAg at 12 months of age, indicating that all infants developed immunity.

A study reported that mothers with > 200,000 or > 1,000,000 IU/mL of viral loads face a high risk of immunoprophylactic failure, and antiviral drugs were recommended during the third trimester of pregnancy, while tenofvir disoproxil and telbivudine were considered as the first-line

treatment by the Food and Drug Administration [21]. Both groups exhibited no noticeable differences in weight, length, head circumference, adaptive skills, gross motor skills, fine motor skills, language skills, and social skills at 12 months, suggesting that tenofovir disoproxil and telbivudine showed high safety during pregnancy. Tenofovir disoproxil has been reported to be superior to telbivudine in antiviral therapy for CHB pregnant women in a previous study [22].

It is believed that the most appropriate approach is to start tenofovir disoproxil in combination with immunoprophylaxis in the third trimester so as to interrupt MTCT. However, tenofovir disoproxil and telbivudine exhibited no differences in efficacy and safety. Further in-depth studies with larger sample sizes may be needed. It was also reported that renal impairment could be caused by long-term use of tenofovir disoproxil [23]. However, this study did not find these adverse reactions in mothers and infants, which could be due to the short duration of treatment and the short observation period.

CONCLUSION

Tenofovir disoproxil and telbivudine reduce HBV-DNA levels, effectively blocks MTCT, and have similar safety profiles. Both drugs are recommended for antiviral therapy in pregnant women with hepatitis B at 24 weeks of gestation. The study used a small sample size and did not observe the long-term physiological safety of the mother and infant, which needs to be further investigated in a larger sample study.

DECLARATIONS

Acknowledgements

This work was supported by the Hangzhou Social Development Scientific Research Active Design Project (grant no. 20172016A03); Zhejiang Provincial Medical and Health Research Project (grant no. 2018KY628) and Hangzhou Health Science and Technology Plan (General) Project (grant no. 201870354).

Funding

None provided.

Ethical approval

The research was carried out with the approval of the Ethics Committee of Hangzhou XiXi

Hospital (approval no. 2017-11). All patients or their families provided signed informed consent.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Chengjing Tao and Shourong Liu designed the study and performed the experiments, Jiannv Hu and Suying Zhang collected the data, Xiuli Bai, Chun Zhao and Zhongbao Zuo analyzed the data, Chengjing Tao and Shourong Liu prepared the manuscript. All authors read and approved the final manuscript.

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