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ORIGINAL ARTICLE

Efficacy of Antiviral Therapy in HBsAg-Positive Pregnant Women to Reduce Mother-to-Infant Transmission of Hepatitis B Virus

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Abstract

Background and Objectives Hepatitis B is a major health concern in Asia. Chronic hepatitis B virus (HBV) infection may cause hepatic cirrhosis and liver cancer. HBV is transmitted horizontally through blood and blood products and vertically from mother to infant. Perinatal infection is the main route of transmission in regions with high prevalence of hepatitis B surface antigen (HbsAg) carriage, and perinatal transmission leads to high rates of chronic infection. Therefore, it is important to prevent mother-to-child transmission (MTCT) of HBV1. The present study aims at comparing the use of antivirals (lamivudine vs tenofovir) in reducing MTCT.

Materials and Methods A total of 60 HbsAg-positive pregnant women were enrolled in the prospective study to test the efficacy of antiviral (lamivudine vs tenofovir—category B drug) to reduce mother-to-child transmission and monitor hepatitis B viral status in infant. HbsAg-positive pregnant women aged 18–43 years at gestational age between 28 and 32 weeks were followed up. They were tested for HBsAg, liver function test and HBeAg. In whom HbeAg was positive, HBV viral load was tested. Sixty patients with high viral load (>6 log copies/ml) were recruited in the study. Alternate patients were randomized into two groups. Group A comprised 31 subjects treated

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with lamivudine 100 mg daily starting from 28 to 32 weeks of gestation (third trimester) and continued to 1 month after delivery. Group B comprised 29 pregnant women who were treated with tenofovir 300 mg daily from 28 to 32 weeks of gestation and continued to 1 month post-partum. The newborn babies were given HBIG within 24 h after delivery and HBV vaccines at 0, 1 and 6 months. HBsAg infectivity was tested in the infant at 1 year after birth.

Results Antivirals, lamivudine/tenofovir treatment in HBV carrier mothers from 28 weeks of gestation along with active and passive immunization of new born may interrupt MTCT of HBV efficiently. Tenofovir, category B drug, is more effective in preventing transmission of HBV infection to infants ($p = 0.004$).

Keywords MTCT · HBV · Viral load · Lamivudine · Tenofovir

Introduction

Maternal screening and active and passive immunoprophylaxis have reduced the perinatal transmission of hepatitis B virus (HBV) dramatically. Without immunoprophylaxis, chronic HBV infection occurs in up to 90% of children by age of 6–18 months if the mother is positive for both hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg). However in spite of standard active and passive immunoprophylaxis, there is a failure rate of 10–15%, and these neonates develop hepatitis infection due to intrauterine infection transmission. Therefore, the American Association for the study of Liver Diseases (AASLD) recommends that all pregnant women should be screened for HbsAg during the I trimester, even if previously vaccinated or tested [1]. If patient is HbeAg positive, HBV DNA levels need to be estimated. Wang et al. used 6 log copies/ml as cut-off, and if HBV DNA levels were ≤6 log copies/ml, the failure rate of prevention of MTCT was 1.9%, and if levels were ≥6 log copies/ml, the failure rare was as high as 23.4% [1]. Antiviral therapy during the third trimester of pregnancy in high-risk women with chronic HBV infection reduces viral load in the mother and may decrease the risk of perinatal transmission [2].

Methodology

This prospective study was conducted at Institute of Maternal and Child Health, Government Medical College Kozhikode, Kerala, from January 2015 to July 2016. Ethical clearance for the study was taken from the institutional ethics committee. Informed consent was taken from the patients for including them in the study to test the efficacy of antiviral (lamivudine vs tenofovir—category B drug) to reduce mother-to-infant transmission and monitor hepatitis B viral status in infant.

HbsAg-positive pregnant women aged 18–43 years at gestational age between 28 and 32 weeks were followed up. They were tested for HBsAg, liver function test and HBeAg. In whom HbeAg was positive, HBV viral load was tested. Sixty patients with high viral load (>6 log copies/ml) were recruited in the study. Alternate patients were randomized into two groups.

Group A comprised 31 subjects treated with lamivudine 100 mg daily starting from 28 to 32 weeks of gestation (third trimester) and continued to 1 month after delivery.

Group B comprised 29 pregnant women who were treated with tenofovir 300 mg daily from 28 to 32 weeks of gestation and continued to 1 month post-partum.

The newborn babies were given HBIG within 24 h after delivery and HBV vaccines at 0, 1 and 6 months. HBsAg infectivity was tested in the infant at 1 year after birth.

Statistical Analysis

Data were entered into Microsoft Excel and analysed using open-source R statistical software package version 3.0.2. Data were summarized as mean and percentage. Unpaired *t* test was used to test the difference between the two groups. Paired data were analysed using paired t test. Chi-square test was used to analyse the difference in proportion, and *p* value was calculated. The primary outcome was considered significant if *p* value was <0.05.

Results

A total of 60 women were enrolled in the study with 31 patients in Group A, receiving lamivudine 100 mg daily and 29 patients in Group B receiving 300 mg daily tenofovir from 28 to 32 weeks till one month post-partum.

There was no significant difference with respect to age and parity between the two groups (Table 1). Age was ranged between 19 and >30 years and parity from 1 to >3.

Table 2 shows that 73% of partners were HbsAg positive and 26% were HbsAg negative. Fifty percentage of patients were diagnosed as HbsAg positive in their first pregnancy, 43% in their second pregnancy and 6% in their third pregnancy. Fifty of patients delivered vaginally, and 50% underwent caesarean section for various foetal or maternal indications. Liver function test was normal in 66% of patients, and slight abnormality was seen in liver enzymes in 33% of patients but did not need active interventions.

Table 1 Demography

Number		%
Age group (years) $n = 60$		
<19	3	5
20–30	49	81
>30	8	13
Parity		
Para 1	19	31
Para 2	19	31
Para 3 and above	22	36

Antiviral therapy was initiated before 30 weeks of gestation in 36% of patients, between 31 and 34 weeks in 53% and beyond 34 weeks in 10% of patients in both the groups. 66.7% had no side effects of either drug but 33.3% had minor side effects like nausea or occasional headache, which was insignificant in both the groups.

Mean maternal viral load was 6.3 log copies in Group A patients and 6.54 log copies in Group B patients. Antiviral therapy was initiated at mean 31.9 weeks of gestation in Group 1 and 28 weeks in Group B patients. Those mothers who received treatment with antiviral for <5–6 weeks had

Table 2 Comparison between HbsAg Positive and HbsAg Negative cases

Husband HbsAg status			
Positive		44	73
Negative		16	26
Diagnosis of HBV infection			
First pregnancy		30	50
Second pregnancy		26	43
Third pregnancy		4	06
Mode of delivery			
Vaginal		30	50
C-section		30	50
Liver function test			
Normal		40	66
Abnormal		20	33
Initiation of antiviral therapy (weeks)			
<30		22	36
31–34		32	53
>34		6	10
Side effects of antiviral therapy			
Nil		40	66.7
Minor		20	33.3
Mean maternal HBV copies versus drug			
Group A (lamivudine)		2.4×10^6	
Group B (tenofovir)		3.5×10^6	
Initiation of treatment versus drug (mean)			
Group A (lamivudine)		31.9 weeks	$p = 0.95$
Group B (tenofovir)		28 weeks	
Duration of treatment versus baby status			
<5–6 weeks		Positive	$p = 0.0001$
>9 weeks		Negative	
	Positive (%)	Negative (%)	p
Mean duration of treatment and baby status			
<30 weeks	0	100	0.001
31–34 weeks	28.1	71.9	
>34 weeks	83.3	6.7	
Mode of delivery and baby status			
Normal labour	13.3	86.7	0.067
Caesarean section	10	90	

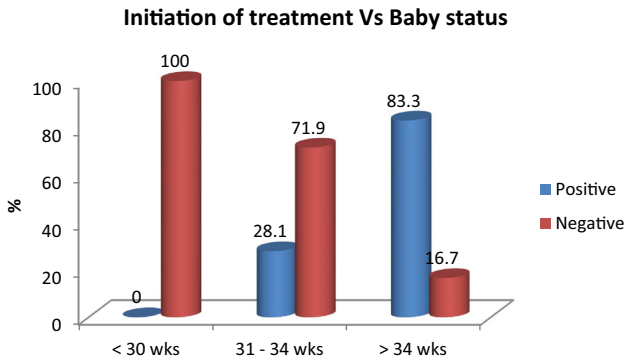

Fig. 1 Initiation of treatment Vs Baby status

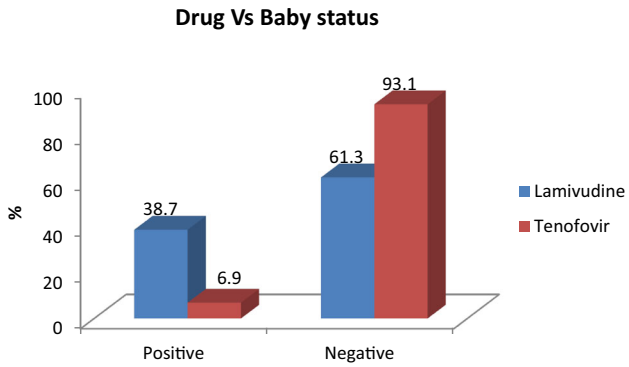

Fig. 2 Drug Vs Baby status

Table 3 Comparative analysis between Lamivudine and Tenofovir

Side effects	Group A Lamivudine	Group B Tenofovir	*p*
Nil	64.5%	69%	0.715
Minor	35.5%	31%	
HBV DNA load	6.3 log copies	6.54 log copies	0.11
Duration of treatment	8.1 weeks	8.14 weeks	NS
Baby status			
HbsAg positive	38.7%	6.9%	0.004

HbsAg-positive babies than those mothers who had antiviral for >9 weeks ($p = 0.0001$), mothers with antiviral started before 30 weeks had nil infectivity to their babies while those who were started on antiviral between 31 and 34 weeks of gestation had 28.1% babies infected and those who started beyond 34 weeks had 85.3% infectivity (Fig. 1), which is statistically significant ($p = 0.001$).

In total, 13.3% of infants delivered vaginally were HbsAg positive compared to 10% who delivered by caesarean section although not statistically significant ($p = 0.067$). Table 3 shows a comparative analysis of the two drugs. Only minor side effect in the form of nausea was seen with the usage of lamivudine and tenofovir in 33.5 and 31%, respectively ($p = 0.715$). There was no significant difference between the pre-treatment HBV viral load between the two groups ($p = 0.11$). There was no significant difference in the duration of antiviral treatment in the two groups, 8.1 weeks in Group A versus 8.14 weeks in Group B.

However, the difference in HbsAg status of babies at 1 year of age was statistically significant ($p = 0.004$), with 38.7% of babies having infection with maternal lamivudine (Group A) use and 6.9% with mothers on tenofovir (Group B) as shown in Fig. 2.

Discussion

According to various studies, there is a linear co-relation between vertical transmission and maternal $\log_{10}$ viral load [3, 4], although mother-to-child transmission is less likely when HBV DNA levels are less than 5.3 log copies at the time of delivery. In our study, the mean level of HBV DNA at which antiviral was started was 6.3 and 6.54 log copies, respectively, in Group A (Lamivudine) and Group B (Tenofovir). Due to financial constraints in government set-up, we could do only a single estimation of HBV DNA in our patients. However, the infection transmission to the newborn was seen in 38.7% in Group A (Lamivudine) and 6.9% in Group B (Tenofovir), in spite of receiving immunoglobulin and active immunization at birth. The analysis also revealed that although the drugs were given for equal duration in both groups, the Group B receiving tenofovir was more effective in reducing maternal-to child transmission [3]. The analysis also shows that if the antiviral was started as early as 28 weeks there was no perinatal transmission of hepatitis infection, but if the treatment was started beyond 34 weeks the viral transmission was as high as 83.3% [5].

With regard to MTCT of HBV during delivery, it is still controversial whether the mode of delivery (vaginal vs caesarean section) affects the vertical transmission rate of HBV [4]. The most likely route for intrapartum HBV transmission could be transplacental leakage of HBV-positive maternal blood during uterine contractions during delivery. With high viral load, an elective caesarean section before the onset of labour may reduce the risk of intrapartum transmission of HBV infection. Therefore, HBV DNA ≥8 log copies/ml in the antepartum period may be an important factor when considering for caesarean section. Women with HBV DNA >11 log copies should be definitely considered for caesarean section [5]. In our analysis, 13.3% of patients with normal delivery had infants positive with HbsAg and 10% of those who underwent caesarean section ($p = 0.067$). However, the

indication of caesarean section in these patients was mainly due to maternal or foetal indication and HBV DNA load was not the deciding factor.

Conclusions

Antiviral treatment in HBV carrier mothers from 28 weeks of gestation effectively reduces MTCT, as indicated by infant screening of HbsAg. Both lamivudine and tenofovir are safe for HBV carrier mothers in late pregnancy and tenofovir has an upper edge in prevention of HBV transmission to infant than lamivudine in addition to immunoglobulins and hepatitis vaccination.

However, high-quality, well-designed, double-blind, randomized controlled and large size clinical trials should be performed for more convincing results.

Compliance with Ethical Standards

Conflict of interest Dr. Jyoti Ramesh Chandran and Dr. Sajala Vimal Raj declare that they have no conflict of interest.

Human and Animal Rights Dr. Jyoti Ramesh Chandran and Dr. Sajala Vimal Raj declare that no human research participants were involved in composing this article. Dr. Jyoti Ramesh Chandran and Dr. Sajala Vimal Raj declare that no animals were involved in the study.

Ethical Standards All the procedures followed in the study were in accordance with the ethical standards of the institution; ethical committee of the institution had critically evaluated the study and its methodology and given the approval before the study was started.

Informed Consent Informed written consent was obtained from every patient to enrol them in the study.

References

1. Terrault NA, Bzowej NH, Chang K-M, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63(1):261–83.
2. Zhang Z, Chen C, Li Z, et al. Individualized management of pregnant women with high hepatitis B virus DNA levels. WJG 20th anniversary special issue (9): hepatitis B virus. World J Gastroenterol. 2014;20(34):12056–61.
3. Papadakis MA, Elefsiniotis IS, Vlahos G, et al. Intrauterine-transplacental transmission of hepatitis B virus (HBV) from hepatitis B e antigen negative (precore mutant, G1896A) chronic HBV infected mothers to their infants. Preliminary results of a prospective study. J Clin Virol. 2007;38(2):181–3 **Epub 2006 Dec 4**.
4. Wiseman E, Fraser MA, Holden S, et al. Perinatal transmission of hepatitis B virus: an Australian experience. Med J Aust. 2009;190:489–92.
5. Calvin Q, Pan MD, Zhongping Duan MD, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. N Engl J Med. 2016;374:2324–33.