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Original Research Article

Efficacy of Hepatitis B Immunoglobulin and Hepatitis B Vaccine in Prevention of Perinatal Transmission of Hepatitis B

Jyoti Ranjan Behera[1], Manas Ranjan Mallick[2], Sanjaya Kumar Jena[3], Rashmi Ranjan Barik[4], Debashisha Roy[5], Anil Kumar Mohanty[6]

[1,3,4]Assistant Professor, Department of Pediatrics, MKCG Medical College and Hospital Berhampur Ganjam Odisha, India - 760004

[2]Associate Professor, Department of Pediatrics, MKCG Medical College and Hospital Berhampur Ganjam Odisha, India - 760004

[5]Associate Professor, Department of General Surgery, SCB Medical College and Hospital Cuttack Odisha, India - 753007

[6]Professor & HOD, Department of Pediatrics, SCB Medical College and Hospital Cuttack Odisha, India - 753007

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Corresponding author: Dr. Rashmi Ranjan Barik

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Abstract:

Introduction: Hepatitis B is a major global health problem and is a most serious type of viral hepatitis, which puts the people at high risk of death from cirrhosis of the liver and liver cancer. Approximately 30% of the world's population, or about 2 billion persons, have serological evidence of either current or past infection with hepatitis B virus. Most people in China and India become infected with HBV during childhood. India has intermediate endemicity of Hepatitis B, with Hepatitis B surface antigen (HBsAg) prevalence between 2% and 7% among populations studied. It has been estimated that, in India of the 25 million infants born every year, over one million run the lifetime risk of developing chronic HBV infection. Every year over 100,000 Indians die due to illnesses related to HBV infection.

Objectives: To evaluate the efficacy of HBIG and HBV vaccine in infants born to HBsAg/HBeAg positive mothers by testing for Anti-HBsAg Anibody titres, 2 months after completing immunization. To find what percentage of infants are HBsAg positive even after completing the vaccination.

Methodology: Hospital based prospective cohort study of sample size 77 babies born from HBsAg/HBeAg positive mothers. Infants were given 0.5ml Hepatitis B Immunoglobulin and 10 µg recombinant DNA Hepatitis B vaccination at birth followed by 2nd and 3rd dose of Hepatitis B vaccination at 6 weeks and 6 months of life respectively. At the age of 8 months of life tested for HBsAg and Anti-HBs antibody. Depending on the antibody titres, infants will be classified as either responders (≥10miu/ml) or non-responders (<10 miu/ml). Data were processed using SPSS software version 20.0.

Results: In LBW infants comprises 45.4% of total study subjects. Maximum babies (79.22%) were delivered by LSCS method.27.2% infants were delivered from mothers having positive for HBeAg and HBsAg.3.89% of study subjects were found to be non-responders at the end of primary hepatitis B vaccine immunization. At the end of primary immunization, all the infants were found to be negative for HBsAg. All vaccine non-responders were delivered through vaginal route($p<0.0001$) which is clinically significant. Out of total three non-responders all of them were LBW babies($p<0.0001$) which is clinically significant. There is no correlation between sex of the infants and maternal HBeAg status.

Conclusion: This study indicate that hepatitis B vaccine in association with HBIG administered at birth provides immediate and long term protection against HB virus infection in infants born to hepatitis B carrier mothers. Birth weight of infants has co-relation with vaccine response, with low vaccine response in LBW subjects as compared to normal birth weight infants. Mode of delivery also contributed to vaccine response as babies born through vaginal route had low response to vaccine as compared to babies born through LSCS.

Keywords: Hepatitis B, Perinatal transmission, Hepatitis Vaccine.

Introduction

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus. It is a major global health problem and the most serious type of viral hepatitis. It can cause chronic liver disease and puts people at high risk of death from cirrhosis of the liver and liver cancer.

Approximately 30% of the world's population, or about 2 billion persons, have serological evidence of either current or past infection with hepatitis B virus [1]. Of these, an estimated 350 million have chronic HBV infection and at least one million chronically infected persons die each year of chronic liver disease, including cirrhosis and liver cancer.

Hepatitis B is endemic in China and other parts of Asia including India. Most people in this region become infected with HBV during childhood. In these regions, 8% to 10% of the adult populations are chronically infected. Liver cancer caused by HBV is among the first three causes of death from cancer in men, and a major cause of cancer in women. High rates of chronic infections are also found in the Amazon and the southern parts of eastern and central Europe. In the Middle East and Indian sub-continent, an estimated 2% to 5% of the general population is chronically infected. Less than 1% of the population in Western Europe and North American is chronically infected.

Hepatitis B is a major health problem in India. Based on the prevalence of Hepatitis B carrier state in the general population, countries are classified as having high (8% or more), intermediate (2-7%), or low (less than 2%).India has intermediate endemicity of Hepatitis B, with Hepatitis B surface antigen (HBsAg) prevalence between 2% and 7% among populations studied [2] . The prevalence does not vary significantly by region in the country. The number of HBsAg carriers in India has been estimated to be over 40 million (4 crores). It has been estimated that, in India of the 25 million infants born every year, over one million run the lifetime risk of developing chronic HBV infection. Every year over 100,000 Indians die due to illnesses related to HBV infection.

Aims and Objectives of Study

1. To evaluate the efficacy of HBIG and HBV vaccine in infants born to HBsAg/HBeAg positive mothers by testing for Anti-HBsAg Anibody titres, 2 months after completing immunization.
2. To find what percentage of infants are HBsAg positive even after completing the vaccination.

Materials and Methods

Study design: Hospital based prospective cohort study was conducted in SNCU, New born ward and OPD of S.C.B.MCH and SVPPGIP during the period Feb.2013 to Oct, 2014. There were 93 enrolled cohort out of which in 77 subjects, the study was performed as 16 subjects were lost to follow up

Inclusion criteria:

Infants born to HBsAg/HBeAg carrier mothers who have received HBIG and HBV vaccination (0, 6week, 6 month)

Exclusion criteria:

- Those who have not completed 3 doses of HBV vaccination
- Those who have lost for follow up.

Methodology:

The study was conducted by registering all affected HBsAg/HBeAg positive mothers in their last trimester of pregnancy who deliver at SCB Medical College, Cuttack. Their names, detailed address including phone number were recorded in a prescribed format. Their infants were given 0.5ml Hepatitis B Immunoglobulin and 10 µg recombinant DNA Hepatitis B vaccination at birth followed by 2^{nd} and 3^{rd} dose of Hepatitis B vaccination at 6weeks and 6months of life respectively. At the age of 8 months of life, 3 ml of venous blood was drawn from the infants who have completed their vaccination.(Antibody titre reaches peak approximately about 1 to 3 months after completing the full course of vaccination).

Serum was separated and transported to laboratory where it was stored at-80^0C till analysis. Serum samples collected were tested for HBsAg and Anti-HBs antibody titre measured by enzyme linked immuno sorbent assays. Seroprotection for anti-HBs was defined as an anti-HBs level of ≥10miu/ml. Infants two months after the end of primary vaccination (i.e. 8 months of age) tested positive for HBsAg will be excluded from the study. The remaining infants will then be tested for AntiHBsAg antibody titres.

Depending on the antibody titres, infants will be classified as either responders(≥10miu/ml) or non-responders (<10 miu/ml).Those infants who are non-responders were given one more booster dose of 10 µg Hepatitis B vaccination at 8 months of life and retested again after 2 months. Testing for HBsAg and Anti-HBs antibody titres was done at department of microbiology, SCB Medical College.

Statistics: The data were processed using SPSS software version 20.0. The dependency of seroprotective rate on the host factors was assessed by using x^2 test. The mean level of anti-HBs was expressed as GMT (geometric mean titre).

Observation

Table1: Birth weight distribution (n=77)

Weight in gram	cases	%
≤1499	1	1.3
1500-2499	35	45.45
≥2500	41	53.24

In this study normal birth weight babies were 53.24%, LBW comprises of 45.45% and rest 1.3% constitute ELBW.

Table 2: Mode of delivery distribution (n=77)

Mode	Cases	%
NVD	14	18.18
ASST.VD	2	2.59
LSCS	61	79.22

Majority of the cases (79.22) were delivered by LSCS followed by NVD (18.18). Only 2.89% babies were delivered by Asst.VD.

Table 3: Maternal antigenic status in study group (n=77)

Antigenic status	Cases	%
HBsAg + HBeAg	21	27.27
HBsAg	56	72.72

In this study mothers having HBsAg positive were choosen (n=77). Out of this 27.27% mothers were positive for both HBsAg and HBeAg.

Table 4: Sex distribution (n=77)

Sex	Cases	%
Male	45	58.44
Female	32	41.55

Maximum numbers (58.44%) of cases were male babies and rest (41.5%) was female.

Table 5: Response to vaccination (n=77)

Anti HBSAg titre	Cases	%
Responders(≥10 miu/ml)	74	96.1
Non-responders(<10 miu/ml)	3	3.89

Out of total enrolled cohort, infants having anti- HBs titre of <10 miu/ml (non-responders) constitute 3.89% and majority (96.1%) were having titre of ≥10 miu/ml (responders).

Table 6: Anti-HBs antibody titre (n=77)

Titre in miu/ml	Cases	%
<10	3	3.89
10-99	21	27.27
≥100	53	68.83

Of the total 74 responders group 27.27% infants were having borderline antibody titre (10-99 miu/ml) and 68.83% infants had adequate antibody titre of ≥100 miu/ml. Minimum GMT was 2.8 miu/ml and highest GMT was 610.7 miu/ml. The mean GMT was 156.9 miu/ml.

Table 7: HBsAg status in infants after primary immunization (n=77)

Status	Cases	%
Positive	0	0
Negative	77	100

Two months after completion of primary immunization all the infants were found to be negative for HBsAg.

Table 8: Vaccination response in relation to Mode of delivery (n=77)

	Normal VD	Assisted VD	LSCS	Total
Responder(≥10 miu/ml)	12	1	61	74
Non-responders (<10 miu/ml)	2	1	0	3
	14	2	61	77

P<0.0001. In this study all non-responders (n=3) were delivered by vaginal route (p<0.0001).Out of total non-responders 66.6 % (n=2) were delivered through normal vaginal route and 33.3% (n=1) through assisted.

Table 9: Vaccination response in relation to birth weight (n=77)

	≤1499	1500- 2499	≥ 2500	Total
Responder	0	33	41	74
Non-responder	1	2	0	3
	1	35	41	77

P: 0.0001. All the three non-responders were LBW infants (p<0.0001).In this study one (33.33% of non-responders) infant having ELBW was non-responders. Rest two (66.6%) infants were in 1500 gm and 2499 gm birth weight.

Table10: Vaccination response in relation to maternal HBe Antigen status (n=77)

	HBe Ag positive	HBe Ag negative	Total
Responder	19	55	74
Non-responder	2	1	3
	21	56	77

P: 0.1181, OR: 0.17, C.I:0.01480-2.016. In this study 66.6% (n=2) of total non-responders were delivered from mothers having both HBsAg and HBeAg positive and rest 33.3% (n=1) was delivered from mother having only HBsAg positive (p=0.1181).

Table 11: Vaccination response in relation to sex of the baby (n=77)

	Male	Female	Total
Responder	43	31	74
Non-responder	2	1	3
	45	32	77

P: 0.7681, OR: 0.69, C.I:0.0601-7.998. In this study 2.22% (n=2) of male infants and 3.1% (n=1) of female infants were non-responders (p=0.7681, OR=0.69, 95% C.I. =0.06-7.99).

Table 12: Chi-square test of factors influencing anti-HBs titres after primary immunization (N=21)

	Total	Anti-HBs titre(10-99 miu/ml)	RR(95%CI)
		n %	
1.Sex of infant			
Male	43	10 23	0.65(O.28-0.87)
Female	31	11 35	
2.LBW			
Yes	33	13 39	1.9(1.01-2.89)
No	41	8 20	
3.Mother HBeAg-positive			
Yes	19	9 47	2.1(1.11-3.018)
No	55	12 22	

Out of 21 infants having borderline anti HBsAg titre (10-99 miu/ml), LBW infants were 1.9 times and infants born to HBeAg positive mothers were 2.1 times more vulnerable to fall in this group. Sex has no relation to vaccine response.

Table 13: Sero protection rate in non-responders after HB vaccine booster dose (n=3)

	Cases	%
Low responders(anti HBs 10 -99miu/ml	2	66.66
Responders(≥100 miu/ml)	1	33.33

In this study after giving one booster dose, 66.66% of non-responders become low responders and 33.3% becomes responders.

Discussion

Hepatitis B is a potentially life-threatening liver infection caused by hepatitis B virus. Infants born to HBsAg positive mother has 5-15% transmission rate and it can be as high as 90% if mother is also HBeAg or HBV DNA positive.

The present work was conducted in SNCU and new born ward of S.C.B. M.C.H and SVPPGIP, Cuttack from February 2013 to October 2014.The observation were made and illustrated with tables as follows.

Subjects were categorised as responders (anti-HBsAg titre ≥10 miu/ml) and non-responders (anti HBsAg titre <10 miu/ml).

Table 1, showed out of total enrolled cohort (n=77), VLBW (wt≤1499 gm) comprises 1.3%, LBW (wt1500-2499gm) comprises 45.45%.Normal birth weight constitute the rest(53.2%).

Table 2,showed proportion of mode of delivery in study subjects and out of 77 study subjects, infants born through NVD comprises 18.18%,through assisted VD comprises of 2.5% and rest were delivered by LSCS constitute 79.22%.

Table3, showed maternal antigenic status at the time of delivery and demonstrated that 27.2% of mothers (n=21) were positive for both HBsAg and HBeAg. Rest 72.7% were positive for only HBsAg which co-relate with other studies by Besley et al 1977[13] in which32%, Zhu et al 2010 in which 36.5%, in Elke et al 2009 [18] in which 29% of study subjects were positive for both HBsAg and HBeAg.

Table 4, showed out of total study subjects, 58.44% were male babies and rest were (41.5%) female which co-relate with study done by Han et al 2012[30] where male infants constitute 55.45% female infants constitute the rest(45%).

Table 5, showed out of 77 subjects, 3.89% (n=3) were non-responders (anti-HBsAg <10 miu/ml) and 96.1% (n=74) were responders (antiHBs≥10 miu/ml) [p<0.0001] which co-relate with studies done by Zhu et al 2010 [6] in which 5%, Mele at al 2001 [28] in which 3.3% and Hank et al 2010 [30] where they found 3.1% were non-responder.

Table 6, showed at the end of primary immunization, 3.89% were having anti HBsAg titre <10 miu/ml,68.83%(n=53) were having titre of ≥100 miu/ml and rest 27.27%(n=21) were in borderline with antibody titre in between 10-99 miu/ml. This study correlate with study done by Han K et al 2010 [30] in which non-responders were 3.1%,responders were 68%, low/borderline responders were 28.9% of study subjects.

In table 7,we have documented HBsAg status in infants after primary immunization and in this study all subjects were tested to be negative for HBsAg which correlate with studies done by Xu Zy et al 1985 [15] and Ding L et al 1993.

Beasley et al 1983 [13] observed 3% were carrier for HBsAg and in Elke et al 2009 [18] study, 4% of subjects and in Steven CE et al 1987(29) study, 4.8% of subjects were positive for HBsAg.

This study differ from later three studies might be due to low enrolled cohort.

Table 8, showed that out of total delivery by vaginal route 18.7% (n=3) were non-responders (p<0.0001), which is clinically significant. Study done by Pan C.Q. et al 2013 [21] observed vaccine failure in 1.4% cases delivered by ECS and 3.6% cases delivered by vaginal route.

Wang J et al 2002 [3] shows 10.5% cases delivered by ECS and 28% cases delivered by vaginal route show vaccine failure. In a study conducted by Yang J et al 2008 [36] observed no significant difference in vaccine response in relation to mode of delivery. This study differs from other study due to low study subjects.

In reference to table 9, all non-responders were LBW infants.8.33% (n=3) of LBW subjects were non-responders (p<0.0001), which is clinically significant. This study correlate with studies done by Freitas et al 2002 [37] and Han K et al 2012 [30] where seroprotection rate of LBW neonates was lower than normal weight neonates.

Table 10, shows there is no correlation between maternal HBeAg status and vaccine response. Out of 21 study subjects who were delivered from mothers were positive for both HBsAg and HBeAg, 9.5%(n=2) were non-responders (p<0.1181) .This study correlate with other studies done by Amani et al 1995, Han K et al 2012 and Lee C et al 2006 [3].

Table11 showed there is no correlation between sex of infants and vaccine response.

In this study 4.44% (n=2) of male infants and 3.1% (n=1) of female infants were non-responders (p=0.7681).Similar results were found in studies done by Ding et al 1993, Hollinger et al 1989 [7], Han K et al 2012 [30].

In table 12, another sub group made as low – responders (antiHBs titre 10-99 miu/ml), who had risk for HB infection/carrier. Sex of baby was not related to immunological response. LBW infants were 1.9 times more vunerable to fall in low-responders group as compared to normal weight neonates. Both the above results were consistent with Han K et al 2012 [30] study.

Infants born to HBeAg positive mothers were 2.1 times more low- responders than infants born to only HBsAg positive mothers, which is consistent with Deng et al 2000 [8] and Tian C et al 2007 studies. Table 13, showed that all non-responders (n=3) were converted to responder group (antiHBs titre≥10 miu/ml) after one booster dose of hepatitis B vaccine.

Out of this 66.6% (n=2) became low responders (anti HBs10-99 miu/ml) and 33.3% (n=1) become adequate responders (anti-HBs titre ≥100 miu/ml). In Han K et al 2012 [30] study after revaccination 14.7% become low responders and 85.3% became responders.

Conclusion

1. This study indicate that hepatitis B vaccine in association with HBIG administered at birth provides immediate and long term protection against HB virus infection in infants born to hepatitis B carrier mothers.
2. Birth weight of infants has co-relation with vaccine response,with low vaccine response in

LBW subjects as compared to normal birth weight infants.
3. Mode of delivery also contributed to vaccine response as babies born through vaginal route had low response to vaccine as compared to babies born through LSCS.

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