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A Study of Anti-HBs Titers Following Pentavalent Immunization (DTwP-HBV-Hib) in Term Normal Weight vs Low Birth weight Infants

Pediatrics

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ABSTRACT

Objective: To compare anti-HBs titers between term low birth weight (1800-2499 g) infants and normal birthweight infants, 6 weeks after last dose of primary immunization with pentavalent vaccine, and to study adverse events following immunization (AEFI) with pentavalent vaccine.

Participants: 265 low birthweight (1800-2499 g) and 265 normal birthweight (2500-4000 g) infants. Monovalent Hepatitis B vaccine was administered within 24 hours of birth followed by three primary doses of pentavalent vaccine at 6, 10 and 14 weeks. Anti-HBs titers were estimated after 6 weeks of third dose of pentavalent vaccine. Adverse events following immunization (AEFI) month were observed for a month after each dose of pentavalent vaccine.

Main Outcome Measures: Anti HBs antibody titers after 6 weeks of primary immunization, and AEFI.

Result: 443 (83.5%) infants (225 low birthweight and 218 normal birthweight infants) completed the follow-up. Seroprotection against hepatitis B virus was achieved in both groups after pentavalent vaccine administration. Anti HBs GMTs in low birthweight infants (194.8 mIU/mL) and normal birthweight infants (204.2 mIU/mL) were comparable (P = 0.17). No serious adverse events were observed in either group.

Conclusion: Three primary doses of pentavalent vaccine administered along with zero dose of Hepatitis B vaccine at birth provide good seroprotection. The vaccine appears to be safe in both low birth weight and normal birthweight infants born at term.

KEYWORDS

Combination Vaccines, Hepatitis B Vaccine, Immunogenicity, Low Birthweight Infants.

BACKGROUND

Universal immunization against hepatitis B in infancy starting at birth has resulted in marked reduction in HBV related chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. An anti-HBs concentration of >10 mIU/mL measured 1–3 months after administration of the last dose of the primary vaccination is considered a reliable marker of protection against HBV infection. However, the antibody response to hepatitis B vaccine has been shown to depend on the schedule of vaccination, birth weight, gestation, chronological age, gender, genetic factors, co-morbidities and the immune status of the vaccinee. Preterm infants weighing <2000g at birth may not mount an adequate response to hepatitis B vaccine. The World Health Organization (WHO) recommends that the birth dose of hepatitis B vaccine to such preterm infants should not be counted and an additional dose of hepatitis B vaccine should be given to them. Term low birth weight (LBW) infants weighing 1800 to 2499 g; with several of them being small for gestational age, may lie in the grey zone of the immunity where they may be vulnerable despite being born chronologically mature. Immunogenicity of monovalent hepatitis B vaccine in term low birth weight babies has been found to be satisfactory. However, there is inadequate data on the immunogenic response of hepatitis B vaccine after immunization with pentavalent vaccine (DTwP-HBV-Hib) among term LBW infants when 'zero' dose of monovalent hepatitis B vaccine is also administered at birth. This study compared anti HBs titres after 6 weeks of primary immunization with pentavalent vaccine between term infants weighing 1800- 2499 g at birth and normal birth weight infants. Infants in both groups were also observed for adverse events following pentavalent vaccine administration.

MATERIAL AND METHODS

This study was conducted in the Departments of Pediatrics, Pathology and Microbiology at Indira Gandhi Institute of Medical Sciences (IGIMS), Patna, Bihar over a period of 9 months (August 2019-May 2020).

Clinically healthy eligible neonates born consecutively at term gestation were allocated in LBW (1800 to 2499 g) and normal birthweight (2500 to 4000g) groups within 24 hours of birth till desired sample size was reached. Infants born to hepatitis B positive mothers, neonates suffering from sepsis, birth asphyxia, meconium aspiration syndrome, gross congenital anomalies, requiring exchange transfusion and whose families were planning to leave the area before the period of completion of study were excluded.

Sample size was calculated based on the study by Sharma, *et al*. Wherein indigenous pentavalent vaccine produced anti HBs geometric mean titers (GMT) of 616.7 mIU/mL in healthy term infants. Expecting a difference of 15% in anti-HBs titers between LBW and normal birthweight babies, at 80% power and 5% level of significance, 476 infants were required, equally divided between LBW and normal birthweight groups. Considering an estimated attrition rate of 10%, we planned to recruit 265 infants in each group (total 530 infants).

Pentavalent vaccine consisting of Diphtheria, Tetanus, Pertussis, Hepatitis B, and Haemophilus influenzae type B Conjugate vaccine adsorbed (Serum Institute of India Ltd, Pune) was used. Each dose of 0.5 mL contained Diphtheria Toxoid 25 Lf (30 IU), Tetanus Toxoid 2.5 Lf (40 IU), *B. pertussis* (whole cell) 16 OU (4.0 IU), HBsAg (rDNA) 10 mcg and Purified capsular HiB Polysaccharide (PRP) conjugated to Tetanus Toxoid (carrier protein) 10 mcg.

We collected 2 mL of cord blood in plain sterile vial from placental end and stored at –20ºC after separation of serum. Breastfeeding was initiated within 1 hr after normal delivery; and within 2 hrs in babies delivered through caesarean section. Monovalent recombinant Hepatitis B vaccine (dose 0.5 mL, 10 mcg purified HBsAg), manufactured by Biological E Ltd, India, was administered in the anterolateral aspect of thigh within 24 hours of birth, by a trained staff nurse. BCG and OPV zero dose were also administered at the same time. Birth weight, length and head circumference were recorded at birth by standard methods.

Infants were called at 6 weeks (+2 weeks), 10 weeks (+2 weeks) and 14 weeks (+2 weeks), and 0.5 mL pentavalent vaccine (DTwP-HBV-Hib) was administered by intramuscular injection into the anterolateral aspect of thigh by trained staff nurses. Trivalent OPV was also administered simultaneously. All infants were monitored for 1 hour following immunization for development of any adverse event. Mother/guardian was given a proforma to record the adverse events at home, and was advised to contact telephonically or return back on occurrence of any serious adverse event. The proforma for adverse

events was checked at each follow-up visit and minor adverse events such as fever and local tenderness were managed symptomatically. Weight, length and head circumference were recorded at each visit by standard methods. Mothers were counselled to bring the infants 6 weeks after the third dose of pentavalent vaccine and 2 mL venous sample was collected in plain vial; serum was stored at –20ºC.

Serum samples were thawed and anti-HBs titers were estimated using enzyme linked immunosorbent assay (ELISA) based kits (DIA.PRO, Diagnostic Bioprobes Srl, Italy). The calibrators and samples were tested as per the protocol provided with the kit. Validation check was carried out on the controls.

Statistical Analysis:

The GMTs were calculated by taking the antilog of the mean of the logarithmic transformation of the titers. Antibody titers between the two groups were compared using unpaired student t-test. Proportion of infants developing adverse events following immunization (AEFI) was assessed using chi-square test. The analysis was carried out using SPSS 20.0 software.

RESULTS

A total of 93.1% (443) infants completed follow-up (LBW 94.5%; normal birth weight 91.6%) (*Fig*. 1). *Table* I depicts the baseline characteristics of participants in both groups.

The median (IQR) cord blood anti HBs levels of 443 infants was 0 (0,0). Minimum level of anti HBs titers observed after 6 weeks of primary immunization with pentavalent vaccine was 40 mIU/mL in both the groups. Maximum anti-HBs titers attained were 280 mIU/mL and 282 mIU/mL, respectively in LBW and normal birth weight groups. Mean (SD) anti-HBs titers were 206.76 mIU/mL and 214 (55.46) mIU/mL, respectively for LBW and normal birthweight infants (*P*=0.17). Anti-HBs GMTs were 194.76 mIU/mL and 204.2 mIU/mL in LBW and normal birthweight infants, respectively and the difference was not significant (*P*=0.17).

Table II shows the adverse events observed in 443 infants of the two groups who completed three doses of pentavalent vaccine. Common adverse events were fever, tenderness and induration. All the adverse events resolved with symptomatic management. These adverse events decreased with subsequent doses of immunization.

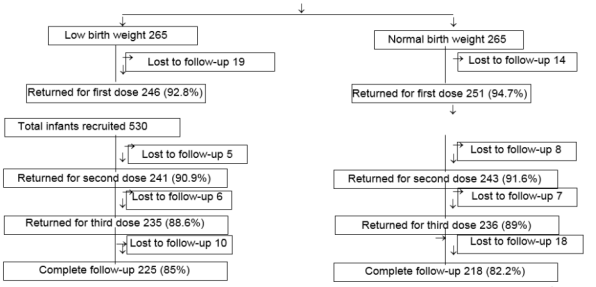

Fig. 1 Distribution Of Participants In The Study.

Table I Baseline Parameters Of Enrolled Infants At Birth

Parameters	Low Birth Weight Group (n=225)	Normal Birth Weight Group (n=118)
Gestational age (wk)*	37.8 (0.7)	39.4 (1.4)
Birthweight (g)*	2119 (187.9)	2781.6 (269)
Length (cm)*	47.5 (0.9)	49.7 (1.4)
Head circumference (cm)*	32.5 (0.8)	33.9 (0.6)
Cord blood Anti HBs titers#$	0.0 (0.0-0.0)	0.0 (0.0-0.0)

***Values expressed as mean (SD) #Values expressed as median (IQR);$in mIU/mL.**

Table II Incidence Of Adverse Events In Infants Receiving Pentavalent Vaccine (n=443)

Adverse Event	After 1st dose		P value	After 2nd dose		P value	After 3rd dose		P value
	LBW	*NBW*		*LBW*	*NBW*		*LBW*	*NBW*	
	(n=225)	*(n=218)*		*(n=225)*	*(n=218)*		*(n=225)*	*(n=218)*	
Tenderness *Redness*#	73 (32.4)	62(28.4)	0.4	55 (24.4)	49 (22.5)	0.6	37 (16.4)	34 (15.6)	0.8
Any	54 (24)	44 (20.2)	0.5	24 (10.7)	28 (12.8)	0.2	12 (5.3)	19 (8.7)	0.1
Mild (<5 mm)	10 (4.4)	7 (3.2)		8 (3.6)	4 (1.8)		0 (0)	0 (0)	
Moderate (5-20 mm)	40 (17.8)	31 (14.2)		16 (7.1)	24 (11)		12 (5.3)	19 (8.7)	
Severe (>20mm) *Induration*#	4 (1.8)	6 (2.8)		0 (0)	0 (0)		0	0	
Any	72 (32)	73 (33.5)	0.6	42 (19.1)	43 (19.7)	0.9	19 (8.4)	20 (9.1)	0.4
Mild (<5 mm)	12 (5.4)	10 (4.6)		0 (0)	0 (0)		0	0	
Moderate (5-20 mm)	57 (25.3)	56 (25.7)		43 (19.1)	43 (19.7)		19 (8.4)	20 (9.1)	
Severe (>20 mm)	3 (1.3)	7 (3.2)		0 (0)	0 (0)		0	0	
Fever									
Any	103(45.8)	105(48.1)	0.6	105 (46.7)	98 (44.9)	0.3	50(22.2)	48 (22)	0.7
100.1-101ºF	43 (19.1)	49 (22.5)		50 (22.2)	41 (18.8)		31 (13.8)	26 (12)	
101.1-102ºF	40 (17.8)	42 (19.2)		50 (22.2)	46 (21.1)		19 (8.4)	22 (10)	
>102ºF	20 (8.9)	14 (6.4)		5 (2.2)	11 (5)		0 (0)	0 (0)	
Vomiting	16 (7)	13 (5.6)	0.7	9 (4)	10 (4.2)	0.8	5 (2.2)	5 (2.3)	1.0
Diarrhea	12 (5.3)	9 (4.13)	0.6	5 (2.2)	7 (3.2)	0.5	0 (0)	0 (0)	

Values expressed as n (%); No child had persistent cry, seizures or anaphylaxis, excessive sleepiness or restlessness; #Assessed at 1 hr. after vaccination.

DISCUSSION

We evaluated the immunogenicity of the hepatitis B vaccine component of pentavalent vaccine in term low birthweight and normal birthweight babies. In this study we found that all infants irrespective of their birthweight, attained seroprotective titres (anti-HBs >10 U/mL). Baseline anti-HBs titers observed in the cord blood samples were negligible, and after four doses of hepatitis B vaccine, given as monovalent Hepatitis B vaccine at birth followed by three primary doses of pentavalent vaccine, all infants achieved seroprotective levels of anti HBs titers and Anti HBs GMTs were comparable in LBW and normal birth weight infants delivered at term gestation.

The assumed difference of 15% in the anti HBs titres between LBW and normal birth weight infants was arbitrary and this could have affected the actual sample size. The other limitation of the study was that the number of infants studied might not address safety and tolerability of the vaccine. Agood (93%) follow-up of the infants at 6 weeks after immunization is the strength of the study.

Earlier studies have shown concerns that LBW infants have low levels of T and B lymphocytes and lower vaccine specific IgG responses as compared to normal birth weight babies. Studies evaluating the immunogenicity of hepatitis B component of pentavalent vaccine in term infants enrolled at 6 weeks of age have concluded the vaccine to be immunogenic with seroprotection rates ranging from 97% to 100%. Studies evaluating different brands of pentavalent (DTwP-HBV- Hib) vaccine reported comparable anti HBs GMT in all infants. Our study reiterates that pentavalent vaccine is highly immunogenic in infants immunized with monovalent hepatitis B vaccine at birth. Although, all infants in our study achieved seroprotective titers, the anti HBs GMTs observed in our trial were lower than those reported in the above studies in both normal birth weight and LBW infants. Different pharmacological preparations and physical properties of the vaccine; characteristics of ELISA testing kits and ethnicity may be the possible reasons for different immunogenicity and levels of GMTs. However, this difference does not seem to be clinically significant because anti HBs seroprotective titre (>10 mIU/mL) is attained in all children.

There are studies documenting the good immunogenicity of monovalent hepatitis B vaccine in both low birth weight and normal birth weight infants. These results correlate well with our results where term LBW infants attained good immune response and reiterate the fact that pentavalent vaccine is as immunogenic as the separately administered monovalent vaccine. A retrospective cohort study in Nigeria analyzing the immunization records from June 2011 to May 2013 revealed the significant improvement in uptake of vaccines and completion of the schedule when pentavalent vaccine was used as compared to separately administered DPT and Hepatitis B vaccine. The vaccine was also safe and tolerable in these studies.

CONCLUSION

We conclude that three primary doses of pentavalent vaccine administered along with zero dose of Hepatitis B vaccine at birth achieved comparable seroprotective anti HBs GMT in LBW and normal birth weight infants and that the immunization with pentavalent vaccine appears to be safe.

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