Original Research Article

A study of anti-HBS titers following pentavalent immunization (DTWP-HBV-HIB) in term normal weight vs low birthweight infants

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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 birth weight (1800-2499g) and 265 normal birth weight (2500-4000g) infants. Monovalent Hepatitis B vaccine was admin is tered 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 eachdose of pentavalent vaccine. Main outcome measures: Anti HB santi body titers after 6 weeks of primary immunization, and AEFI. **Result:** 443(83.5%) infants (225 lowbirthweightand218normal 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 birth weight infants (194.8mIU/mL) and normal birth weight in fants (204.2mIU/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 zerodose of Hepatitis Bv accineat birth provide good sero protection. The vaccine appears to be safe in both low birth weight and normal birth weight in fants born atterm.
Key Word: Combination vaccines, Hepatitis B vaccine, Immunogenicity, Low birthweight infants.

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INTRODUCTION

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 measured1–3monthsafteradministrationofthelastdose 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 vaccine. 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 gestationalage, may lie in the greyzone of the immunity where they may be vulnerable despite being born chronologically mature. Immunogenicity of monovalent hepatitis B vaccine in term low birthweight babies has been found to be satisfactory. However, there is inadequate data on the

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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 pentavalentvaccinebetweenterminfantsweighing1800-2499gatbirthandnormalbirthweightinfants.Infantsin both groups were also observed for adverse events following pentavalentvaccine administration.

MATERIAL AND METHODS

This study was conducted in the Departments of Pediatrics, Pathology and Microbiology at Darbhanga Medical College and Hospital, Laheriasarai, Bihar overaperiod of 17 months (December2015-April 2017) after approval from the Ethical Committee of the institute and written informed consent from the parents. Clinically healthy eligible neonates born consecutively at term gestation were allocated in LBW (1800to2499g) and normal birth weight (2500 to 4000g) groups within 24 hours of birth till desired sample size was reached. Infants born to hepatitis B positive mothers, neonate ssuffering from sepsis, birth asphyxia, meconium aspiration syndrome, gross congenital anomalies, requiring exchange transfusion and whose families were planning to leave the are a 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 birth weight babies, at 80%powerand5%levelof 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 Haemophilusinfluenzae 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 HiBPolysaccharide(PRP)conjugated to TetanusT oxoid (carrierprotein)10mcg. We collected 2 mL of cord blood in plain sterile vial from placentalend and stored at–20ºCafterseparationof 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 administeredintheanterolateralaspectofthighwithin24 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. In fants were called at 6 weeks (+2 weeks), 10weeks (+2 weeks) and 14 weeks (+2 weeks), and 0.5 mL pentavalentvaccine(DTwP-HBV-Hib)was administered by in tramuscular injection in to the anterolateralaspect of thigh by trained staff nurses. Trivalent OPV was also administered simultaneously. All in fants 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-HB stiters were estimated using enzyme linked immunosorbentassay (ELISA) based kits (DIA.PRO, Diagnostic Bioprobes Sr l, Italy). The calibrators and samples were tested as per the protocol provided with the kit. Validation check was carriedoutonthecontrols. *Statistical analysis*: The GMTs were calculated by taking the antilog of them ean of the log arithmictrans formation of the titers. Anti body 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-squaretest.

TheanalysiswascarriedoutusingSPSS20.0software.

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 of443 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. Maximumanti-HBstitersattainedwere280mIU/mLand 282 mIU/mL, respectively in LBW and normal birth weight groups. Mean (SD)anti-HBstiterswere206.76mIU/mL and 214 (55.46) mIU/mL, respectively for LBW and normal birth weight infants (*P*=0.17).Anti-HBs GMTs were194.76mIU/mLand204.2mIU/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 pentavalentvaccine. Common adverseevents were fever, tenderness and induration. All the adverse events resolved with symptomatic management. These adverse events decreased with subsequent doses of immunization.

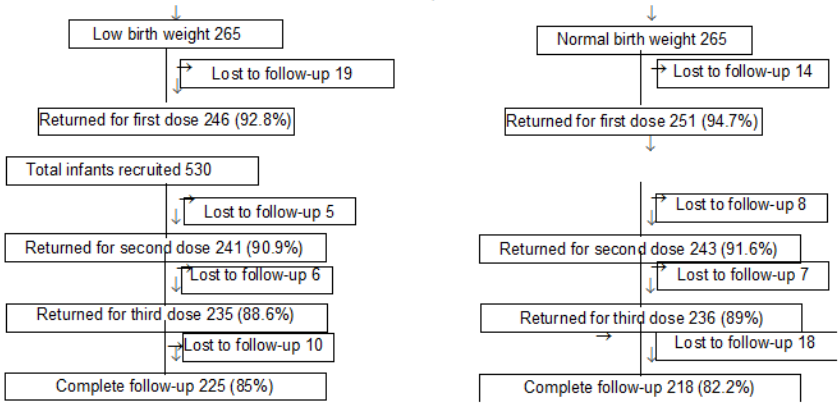

Figure 1: Distribution of participants in the study.

Table 1: Baseline Parameters Of Enrolled Infants Atbirth

Parameters	Lowbirth Weightgroup (n=225)	Normalbirth Weightgroup (n=218)
Gestationalage(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(1.4)
CordbloodAntiHBstiters#$	0.0(0.0-0.0)	0.0(0.0-0.0)

Table 2: Incidence of advents in infants Receiving pentavalent vaccine (N=443) Adverseevent after 1sdtose pvalue after 2nd dose pvalue after 3rd dose pvalue

	LBW (n=225)	NBW (n=218)	LBW (n=225)	NBW (n=218)	LBW (n=225)	NBW (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)	4 (1.8)	6 (2.8)	0 (0)	0 (0)	0	0	
Induration#							
Any	72 (32)	73(33.5)0.6	42 (19.1)	43 (19.7)	0.919(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)	0.350(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)	0.85(2.2)	5 (2.3)	1.0
Diarrhea	12 (5.3)	9(4.13) 0.6	5 (2.2)	7 (3.2)	0.50(0)	0 (0)	

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 infant sir respective of their birth weight, attained sero protective titres (anti-HBs >10 U/mL). Baseline anti-HBs titers observed in the cord blood samples were negligible, and after four dose sofhepatitis B vaccine, given as monovalent Hepatitis B vaccine at birth followed by three primary doses of pentavalent vaccine, all infants achieved sero protective 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 to lerability of thev accine. A good(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 sero protection rates ranging from 97% to 100%. Studies evaluating different brands of pentavalent (DT w P-HBV- Hib) vaccine reported comparable anti HBs GMT in all infants. Our study reiterates that pent avalentvaccineis highly immunogenicininfants immunized with monovalent the patitis Bvaccineat birth. Al though, all in fants inour study achieved seroprotective titers, thean ti HBsGMTs 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 seroprotectivetitre (>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 in fants. These results correlate well with our results where term LBW infants attained good immune response and reiterate the fact that pentavalent vaccine is as immunogenicas these parately 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 schedulewhen pentavalent vaccine was used as compared to separately administered DPT and Hepatitis B vaccine. The vaccine was also safeandtolerablein 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 seroprotectiveanti HBs GMT in LBW and normal birth weight in fants and that the immunization with pentavalent vaccine appears to be safe.

REFERENCES

1. Ali SS, Chandrashekar SR, Singh M, Bansal RK, Sharma DR, Arora D. A multicenter, prospective, open-label, non-comparative study to evaluate the immunogenicity and tolerance of a new, fully liquid pentavalent vaccine (DT wP-Hep B-Hib vaccine). Hum Vaccin.2007;3:116-20.
2. Arora NK, Ganguly S, Agadi SN, Irshad M, Kohli R, Deo M, *et al.* Hepatitis B immunization in low birthweight infants: do they need an additional dose? ActaPaediatr. 2002; 91: 995-1001.
3. Bhave S, Bhise S, Chavan SC, Naik SS, Pusapati RVLN, Bavdekar A, *et al.* Hepatitis Bv accinationinpremature and low birth weight (LBW) babies. Indian Pediatr. 2002; 39: 625-31.
4. Chatrath R, Saili A, Jain M, Dutta AK. Immune status of fullltermsmall-for-gestationalageneonates in India. JTrop Pediatr.1997;43:345-8.
5. Chatterjee S, Rego SJ, D'Souza F, Bhatia BD, Collard A, Datta SK, *et al.* The immunogenicity and safety of a reduced PRP-content DTP w-HBV/Hib vaccine when administered according to the accelerated EPI schedule. BMC Infect Dis. 2010;10: 298.
6. Gatchalian S, Reyes M, Bernal N, LefevreI, Dav id M, Han HH, *etal.* Anew DTPw-HBV/Hibvaccineisimmunogenic and safe when administered according to the EPI (Expanded Programme for Immunization) schedule and following hepatitis B vaccination at birth. Hum Vaccin. 2005; 1: 198-203.
7. Gentile A, Umido V, Czerniuk P, Nacul J, SeigelchiferM, Hilbert AK, *et al.* Immunogenicity and reactogenicity of a combined fully liquid DTP w-Hep B-Hibpentavalent vaccine in healthy infants: Noclinicallyrelevantimpact of a birth dose of hepatitis B vaccine. Int J Infect Dis. 2011; 15: 24-9.
8. Gomber S, Sharma R, Ramachandran VG, Talwar V, Singh B. Immunogenicity of hepatitis Bv accine in corporated in to the expanded program of immunization schedule. Indian Pediatr.2000;37:411-3
9. Hollinger FB. Factors influencing the immune response to hepatitis B vaccine, booster dose guidelines, and vaccine protocol recommendations. Am J Med.1989; 87: 36S-40S.
10. Jack AD, Hall AJ, Maine N, Mendy M, Whittle HC.What level of hepatitis B antibody is protective? J Infect Dis. 1999; 179: 489-92.
11. Lubchenco LO, Hansman C, Boyd E. Intrauterine growth

in length and head circumference as estimated from live births at gestational ages from 26 to 42 weeks. Pediatrics. 1966; 37: 403-8.
12. Raqib R, Alam DS, Sarker P, AhmadSM, Ara G, Yunus M, *et al*. Low birth weight is associated with altered immune function in rural Bangladeshi children: a birth cohort study. Am J ClinNutr.2007;85:845-52.
13. Sadoh AE, Nwaneri DU, Ogboghodo BC, Sadoh WE. Effect of introduction of pentavalent vaccine as replacement for Diphtheria-Tetanus-Pertussis and Hepatitis B vaccines on vaccination uptake in a health facilityinNigeria.Vaccine.2016;34:2722-8.
14. Sharma H, Yadav S, LalwaniS, Gupta V, Kapre S, Jadhav S, *et al*. AphaseIIIrandomized, controlled study to assess the immunogen icity and to lerability of DTPw-HBV-Hib, a liquid pentavalent vaccine in Indian infants. Vaccine. 2011; 29: 2359-64.
15. SharmaH,Yadav S, Lalwani S, Kapre S, Jadhav S, Parekh S, *et al*. Antibody persistence of two pentavalent DTw P-HB-Hibvaccines to the age of 15-18 months, and response to the booster dose of quadrivalent DTwP-Hib vaccine.Vaccine.2013;31:444-7.
16. Sharma HJ, Yadav S, Lalwani SK, Kapre SV, Jadhav SS, Chakravarty A, *et al*. Immunogenicity and safety of an indigenously manufactured reconstituted pentavalent (DTwP-HBV+Hib) vaccine in comparison with a foreign competitor following primary and booster immunization in Indian children. Hum Vaccin.2011;7:451-7.
17. Singh M, Manerikar S, Malaviya AN, Premawathi, Gopalan R, Kumar R. Immune status of low birth weight babies. Indian Pediatr.1978;15:563-7.
18. World Health Organization. Hepatitis B vaccines: WHO positionpaper. Wkly EpidemiolRec.2009;84:405-20.

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