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Single Hepatitis B Booster Dose in High-risk Children with Suboptimal Surface Antigen Antibody Responses After 3-dose Primary Vaccine Series

This was a descriptive study of 30 children born to HBsAG positive mothers between June 2009 and December 2013. All children had anti-HBs response ≤100 IU/L after 3 doses of hepatitis B vaccine primary series. A single booster dose led to hepatitis B surface antibody titers ≥100 IU/L in (85%) of children.

Keywords: *Immunization, Prevention, Seroprotection.*

Approximately 10% of infants are non-responders or have suboptimal vaccine response with hepatitis B surface antibody (anti-HBs) titers ≤100 IU/L three months post-3 dose hepatitis B vaccine series [1-4]. Controversy remains over the need for booster dose in suboptimal responders with antibody levels 10-100 IU/L. None of the international guidelines address this, especially in high-risk infants born to hepatitis B chronic carrier mothers [1,5]. The study aimed to describe the change in anti-HBs titers in infants born to hepatitis B carrier mothers and anti-HBs titer of ≤100 IU/L after the 3 dose primary series; and to determine if for infants with anti-HBs titer of 10-100 IU/L, a single booster of 10 µg hepatitis B vaccine will increase the anti-HBs titers to >100 IU/L.

This was a descriptive study of children born between June 2009 to December 2013, to hepatitis B surface antigen (HBsAg) - positive mothers, at a tertiary university hospital in Singapore, with anti-HBs response ≤100 IU/L after completing 3 doses of hepatitis B 10 µg vaccine given at birth, and age of 1 month and 6 months. Vaccine response was defined based on anti-HBs level done 3 months after completion of the third vaccine dose *viz*. non-responder (anti-HBs <10 IU/L) or suboptimal responder (anti-HBs ≥10 IU/L but ≤100 IU/L). Occult HBV infection was defined as the presence of hepatitis B infection with undetectable hepatitis B surface antigen (HBsAg) [6].

Demographic data and details of maternal HBV infection were collected for all children. Baseline anti-HBs levels were checked for children who were suboptimal responders before administration of the fourth booster dose [intramuscular 10 µg monovalent hepatitis B (Engerix B, GSK, Wavre, Belgium)]. Eight weeks post-booster, HBsAg, HBV DNA, hepatitis B core antibody (anti-HBc) and anti-HBs titres were measured. Children who were non-responders received a repeat three dose vaccine series and were excluded from follow-up. Children whose mothers had hepatitis C virus or HIV infection, or children born before 37 weeks gestation, had a birthweight less than 2.5 kg, or known primary immuno-deficiency, were excluded. Informed consent was obtained from their parents and assent from those older than 6 years. Study was approved by the National Healthcare Group Domain Specific Review Board.

Data were analyzed with SPSS version 25.0. Comparisons were done using Mann Whitney test, and significance was taken as $P<0.05$.

Thirty-nine children (3 non-responders and 36 suboptimal responders) were eligible for the study; 30 (13 females) were recruited (3 non-responders and 27 suboptimal responders). Mean (SD) age at time of recruitment was 63 (31.5) months. Majority were Chinese (80%). Mean (SD) birth weight was 3.22 (0.26) kg. Twenty-four were breastfed until 9 months, 6 were born *via* Caesarean section.

Five (16.7%) mothers were HBeAg positive with HBV DNA viral load of >200,000 IU/mL in their third trimester prior to starting tenofovir. Two (6.7%) received tenofovir during the last trimester. There was incomplete data for 9 children; 4 (13.3%) declined booster vaccination and 5 (16.7%) declined blood tests post-booster for personal reasons. Hence, 21 children had both pre and post-booster serological results for analysis. No children had detectable HBV DNA or reactive anti-HBc.

Median (IQR) anti-HBs titers 3 months after completion of the primary vaccine series was suboptimal at 52 (22-77) IU/L. Median (IQR) anti-HBs titers just prior to booster vaccine further dropped to 7 (2-11) IU/L (P<0.05); 3 (10%) children had values <10 IU/L. Mean (SD) time from completion of three-dose vaccine series to booster vaccine was 62.6 (31.1) months. Median (IQR) anti-HBs titer rose significantly to 606 (134-1000) (P<0.05)) IU/L post-booster vaccine. Eighteen children (85.7%) demonstrated good anti-HBs response (>100 IU/L) after the booster dose. Three children (14.3%) continued to have suboptimal response post-booster vaccine (***Fig.* 1**).

Our study demonstrated that 85.7% of children with suboptimal immune response post-primary series achieved anti-HBs >100 IU/L after a single booster dose, supporting the 2018 ACIP guidelines that a single booster is sufficient instead of three repeat doses [5].

We also demonstrated that anti-HBs titers in infants born to hepatitis B carrier mothers, and who had suboptimal antibody titer three months after completing the three-dose primary series, declined further over the next four years. Occult HBV infection was not detected in this population as a cause of suboptimal response. Our small series contributes to supporting evidence for a single booster, which is cheaper and logistically easier, instead of repeating the three dose series. A single booster may also increase adherence to vaccinations and conserve public health resources involved in vaccine administration.

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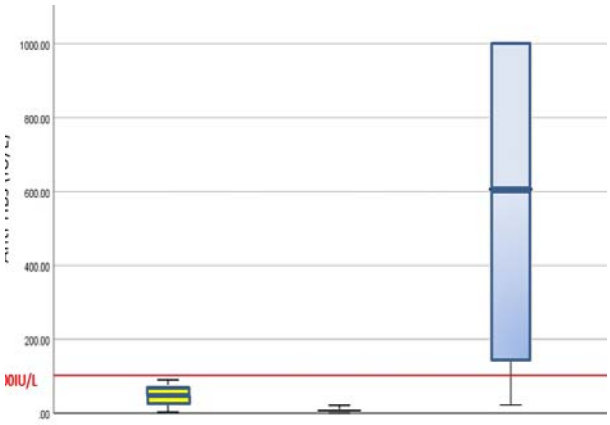

FIG. 1 *Box plot of anti-HBs versus time points.*

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