Hepatitis B vaccine: Immunogenicity in an extremely low-birthweight infant

Yamana, Keiji
Iwatani, Sota
Fujioka, Kazumichi
Iijima, Kazumoto
Morioka, Ichiro

(Citation)
Pediatrics International,60(5):489-490

(Issue Date)
2018-05-28

(Resource Type)
journal article

(Version)
Accepted Manuscript

Clinical Notes

Immunogenicity of hepatitis B vaccines in an extremely low birth weight infant

Running title: Immunogenicity of hepatitis B vaccine

Keiji Yamana, MD, Sota Iwatani, MD, PhD, Kazumichi Fujioka, MD, PhD, Kazumoto Iijima, MD, PhD, Ichiro Morioka, MD, PhD

Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe 6500017, Japan

*Corresponding author:
Ichiro Morioka, MD, PhD
Department of Pediatrics, Kobe University Graduate School of Medicine
7-5-1, Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan
Phone: +81-78-382-6090, Fax: +81-78-382-6099, E-mail: ichim@med.kobe-u.ac.jp

Number of text page: 4
Number of words: 698
Number of reference page: 1
Number of figures: 1

Key words: extremely low birth weight infant, hepatitis B virus, hepatitis B vaccine, immunogenicity, mother-to-child infection

From 2013, infants born from mothers carrying serum hepatitis B (HB) surface antigen (HBsAg) receive a HB immunoglobulin at birth and HB vaccines at birth, and at 1 and 6 months of age in Japan (prevention protocol for mother-to-child HB virus infection).[1] Due to immature immune responses to HB vaccine, the American Academy of Pediatrics[2] and Japan Pediatric Society[3] recommends that infants with <2000 g birth weight are given an additional dose of HB vaccination at 2 months of age. However, no case report on extremely low birth weight (ELBW) infants has shown the trajectory of immunogenic responses in this prevention protocol including an additional dose at 2 months of age.

Case

The case who was born from a 29-year-old Chinese mother (gravida 0, para 0) with HBsAg is reported with informed consent. At 20 weeks of gestational age, serum HBsAg, HB envelope antigen, HB virus core related antigen, and HB virus-DNA were positive (67878 IU/mL, 1531.9 sample relative light units/cut off, >7.0 Log U/ml, and 9.7 Log copies/ml, respectively). Both serum HB surface antibody (HBsAb) and HB envelope antibody were negative. The HB virus genotype was type C. A male newborn weighing 918 g was born at 25 weeks and 4 days of gestational age via cesarean section due to fetal distress.

He was admitted to our neonatal intensive care unit due to extremely low birth weight. Along with respiratory and circulatory treatments, intravenous immunoglobulin (IVIG, 500 mg/10 mL, Venoglobulin IH™, Japan Blood Products Organization, Tokyo) was administered soon after birth because of hypo-immune globulinemia (serum total IgG level: 280 mg/dL). At 11 hours after birth, a total of 200 U/mL of HB immune globulin (Dried HB globulin "NICHIYAKU" ™, Nihon Pharmaceutical, Tokyo) was injected intramuscularly in the right and left femoral

muscles (100 U/0.5 mL in each side), and HB vaccine (0.25 ml, Bimmugen™, Kaketsuken, Kumamoto) was injected subcutaneously at the left side of the upper arm. No side effects, such as redness, swelling, or induration were observed. Then, HB vaccines were again administered at 1 and 2 months of age. He grew up with breast milk feeding and discharged at 4 months of age. The fourth HB vaccine was injected at 6 months of age.

Figure 1 shows the trajectory of HBsAb titers in this case. The HBsAb titer reached a peak at 1 month of age, and decreased to the lowest level at 4 months of age, but the HBsAb level was more than 10 mIU/ml. Then, the HBsAb titer gradually increased, and after the fourth HB vaccine, it finally increased over 100 mIU/ml at 12 months of age. Serum HBsAg was negative at 12 months of age.

Discussion

We reported HBsAb titers in an ELBW infant who received 4 doses of HB vaccine. Our case clearly showed that our prevention protocol for mother-to-child HB virus infection with an additional dose at 2 months of age (0, 1, 2, and 6 months of age) achieved sufficient seropositivity of HBsAb at 12 months of age. The infant had a HBsAb titer of 47 mIU/mL at the time of discharge even with an additional vaccine at 2 months of age. Because ELBW infants are usually discharged from hospital at 3-4 months of age, and then, they are in close contact with their mother who are HB virus carriers, it is important for the ELBW infant to have a sufficient HBsAb titer at that time.

HBsAb titer ≥10 mIU/mL is generally used as a seroprotection level.[4,5] Although all infants with ≥2000 g birth weight who received 3 doses of HB vaccine at 0, 1, and 6 months of age in our hospital had a sufficient HBsAb level (median [range]: 210 [21–898] mIU/ml, n=12), a previous study has reported that ELBW infants who

75 received 3 doses of HB vaccinations at birth and at 1-3 and 6-8 months of age had
76 only 52% seropositive rate.[4] A previous study has reported that 98.4% of preterm
77 infants vaccinated using another 4-dose HB vaccine protocol (0, 1, 2, and 12 months
78 of age) had a protective level.[5] A four doses of HB vaccine may be needed to obtain
79 sufficient seropositive rate in ELBW infants as recommended by the Japan Pediatric
80 Society.
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Acknowledgments

This study was supported by grants from the Ministry of Health, Labor, and Welfare of Japan (Number: H25-Kanen-Ippan-011) and Scientific research (B) of JSPS KAKENHI (Number: 17H04341).

Disclosure

All authors have none to declare for this work. Outside the submitted work, I.M. have received grants from Japan Blood Product Organization, Daiichi Sankyo Co., Ltd., MSD Co., Ltd., AbbVie LLC, Taisho Toyama Pharmaceutical Co., Ltd., and Air Water Inc.; lecture fees from MSD Co., Ltd., Pfizer Japan, Inc., Novo Nordisk Pharma Ltd., Shionogi Co., Ltd., AbbVie LLC, Japan Vaccine Co., Ltd., Asahikasei Medical Co., Ltd., and Atom Medical Corp.; manuscript fees from Atom Medical Corp., Sanofi K.K., Asahikasei Medical Co., Ltd., and Japan Blood Product Organization,; and honoraria from Sanofi K.K. K. I. has received grants from Novartis Pharma K.K., Japan Blood Product Organization, Pfizer Japan, Inc., Kyowa Hakko Kirin Co., Ltd., AbbVie LLC, JCR Pharmaceuticals Co., Ltd., Daiichi Sankyo, Co., Ltd., Genzyme Japan K.K., Teijin Pharma Ltd., Miyarisan Pharmaceutical Co., Ltd., CSL Behring, Novo Nordisk Pharma Ltd., Air Water Inc., and Astellas Pharma Inc., Lecture fees from Pfizer Japan, Inc., Asahi Kasei Pharma Corp., Kowa Pharmaceutical Co., Ltd., MSD Co., Ltd., Alexion Pharmaceuticals, AstraZeneca K.K., Meiji Seika Pharma Co., Ltd., Novartis Pharma K.K., Zenyaku Kogyo Co., Ltd., Daiichi Sankyo, Co., Ltd., Springer Japan, Medical Review Co. Ltd., Chugai Pharmaceutical Co., Ltd., Boehringer Ingelheim, and Nikkei Radio Broadcasting Corporation, manuscript fees from Chugai Pharmaceutical Co., Ltd., and consulting fees from Zenyaku Kogyo Co., Ltd., Astellas Pharma Inc., Ono Pharmaceutical Co.,

Ltd. and Takeda Pharmaceutical Co., Ltd.

Authors' Contributions

All authors contributed to the intellectual content of this manuscript and approved the final manuscript as submitted. K.Y. and I.M. drafted the initial manuscript. K.Y. and S.I. collected the clinical data. K.Y., I.M. and K.F. interpreted the data. K.I. revised the article critically for important intellectual content.

Figure legends

Figure 1. Trajectory of serum HBsAb titers

* Effects of the IVIG on HBsAb titer: the patient received 500 mg/10 mL of Venoglobulin IH™, which has approximately 100 mIU/mL of HBsAb titer. Assuming that his circulating blood volume is 72 mL (80 mL/kg body weight) and the bioavailability of IVIG is 100%, IVIG treatment might have increased HBsAb titer by 14 mIU/mL. However, as the half-life of immunoglobulin is 27 days†, the effect is limited.

** Effects of the HB immune globulin on HBsAb titer: the titer at 4 months of age (47 mIU/mL) can be explained only by the HB immune globulin at birth because the half-life of HB immune globulin is 23 days†.

† These data are from the medical package insert of Venoglobulin IH™ or Dried HB globulin "NICHIYAKU"™.

HB, hepatitis B; HBsAb, HB surface antibody; IVIG, intravenous immunoglobulin.

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