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Changing Anti-HBs Levels after Hepatitis B Vaccination in Medical University Students : Results of a 2-Year Follow-up

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SUMMARY

Background and Aim : The duration of protection afforded by Hepatitis B (HB) vaccination is unknown. We aimed to investigate the antibody persistence and protection from hepatitis B virus infection in medical university students.

Methods : The subjects were the students of both medical and nursing students who had enrolled at Dokkyo Medical University in April, 2012. We evaluated the HB vaccination results in 194 students (medical : 100, nursing : 94) who allowed us to observe during a 2-year follow-up. We measured antibody to HB surface antigen (anti-HBs) after completing one series of HB vaccinations, at 1 year and at 2 years.

Results : The anti-HBs positive (protective level ≥ 10 mIU/mL) rates of the students were shown after completing one series of HB vaccinations, at 1 year and at 2 years respectively. As follows : medical students : 97.9% \rightarrow 80.6% \rightarrow 63.3%, nursing students : 98.0% \rightarrow 84.8% \rightarrow 76.1%, and total students : 97.9% \rightarrow 82.6% \rightarrow 69.5%. The titers of the sustained anti-HBs positive students were significantly higher than the titers of the changed negative students of both medical and nursing students after completing HB vaccinations for 2 years ($P < 0.001$, respectively).

Conclusions : Approximately 30% of the students became anti-HBs seronegative during 2 years of follow-up. We should consider if it is necessary to administer additional vaccination for them to boost up thereafter.

Key Words : hepatitis B virus : HBV, hepatitis B vaccine, anti-HBs, anti-HBs seronegative status, medical university students

INTRODUCTION

For the significant purpose of vaccination for hepatitis B virus (HBV) in adults, it is an importance of prophylaxis against hospital infections and occupation-

al infections¹⁾. Currently, the prevalence of acute hepatitis B through horizontal transmission tends to be increasing. Especially, it is necessary to implement the prophylaxis against acute hepatitis by genotype A which is regarded as causing a high rate of inducing chronic hepatitis B^{2~4)}. In addition, it needs to prevent the poor prognosis of severe hepatitis B (so-called *de novo hepatitis B*) by immunosuppression and chemotherapy due to the condition that recognized existing HBV infection^{5,6)}. Moreover, it has a possibility to

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Table 1 Summary of studied medical university students

	Medical students	Nursing students	Overall
Number of subjects	100	94	194
Male/Female (% Male)	59/41 (59.0)	7/87 (7.4)	66/128 (34.0)
Mean age	19.4 ± 1.6	18.1 ± 0.2	18.7 ± 1.3

mean ± SD

cause acute hepatitis B due to post-transfusion⁷⁾. From these reasons, HB vaccination will be more significant and universal vaccination should be undertaken by all Japanese people in the future^{7,8)}.

In this study, we evaluated the results for HB vaccination in both the medical students and the nursing students at Dokkyo Medical University. Especially, we focused on observing the transition of anti-HBs titers from completing one series of vaccinations up to 2 years later in order to assess the usefulness of HB vaccination.

SUBJECTS AND METHODS

The subjects were the students of both medical and nursing students who had enrolled at Dokkyo Medical University in April, 2012. Before starting one series of the vaccinations, the students were the negative status of both HB surface antigen (HBsAg) and anti-HBs. For a series of vaccinations, the students took 3 times of HB vaccinations that applied an initial vaccine shot, the second one a month later, and the third one at 5 months. After completing one series of vaccinations, the students were observed for 2 years.

We used precipitated recombinant HB vaccine Bimugen[®] (The Chemo-Sero-Therapeutic Research Institute, Kumamoto) that derived from yeast. The administration route was a 10 µg/0.5 mL subcutaneous injection for 3 times in one series. Then, we evaluated that rate of anti-HBs became positive. We confirmed the results of anti-HBs at 4 months period, at 1 year and at 2 years by applying chemiluminescent immunoassay (CLIA). Anti-HBs was considered positive if the titer was ≥10 mIU/mL.

Statistical analyses were performed using Microsoft Excel[®] or IBM SPSS[®] statistical software. The results were expressed as mean ± standard deviation (SD) or mean ± standard error of the mean (SEM). Differences between two independent samples were examined by

calculating Mann-Whitney U test. A P value of <0.05 was considered significant.

RESULTS

1. Subjects profiles (Table 1)

The students were observed for 2 years after one series of HB vaccinations that consisted of the medical students : 100 (male : 59/female : 41) and the mean age was 19.4 ± 1.6, and the nursing students : 94 (male : 7/female : 87) and the mean age was 18.1 ± 0.2.

2. Transition of anti-HBs positive rate (Figure 1)

The anti-HBs positive students (rate) were shown after completing one series of HB vaccinations, at 1 year and at 2 years respectively. As follows : medical students ; 98/100 (98.0%) → 79/98 (80.6%) → 62/98 (63.3%), nursing students ; 92/94 (97.9%) → 78/92 (84.8%) → 70/92 (76.1%), total students ; 190/194 (97.9%) → 157/190 (82.6%) → 132/190 (69.5%). The total students whose anti-HBs status turned out anti-HBs positive after one series of HB vaccinations, then changed to negative during a 2-year follow-up were 30.5% .

3. Transition of anti-HBs titers after one series of HB vaccinations, at 1 year and at 2-year (Figure 2)

The anti-HBs titers were shown in both the medical and nursing students at Figure 2.

4. The comparison between the sustained anti-HBs positive students and the changed negative students during a 2-year follow-up (Figure 3)

Regarding the students whose anti-HBs turned out positive after one series of HB vaccinations, we compared the students into 2 groups that the sustained

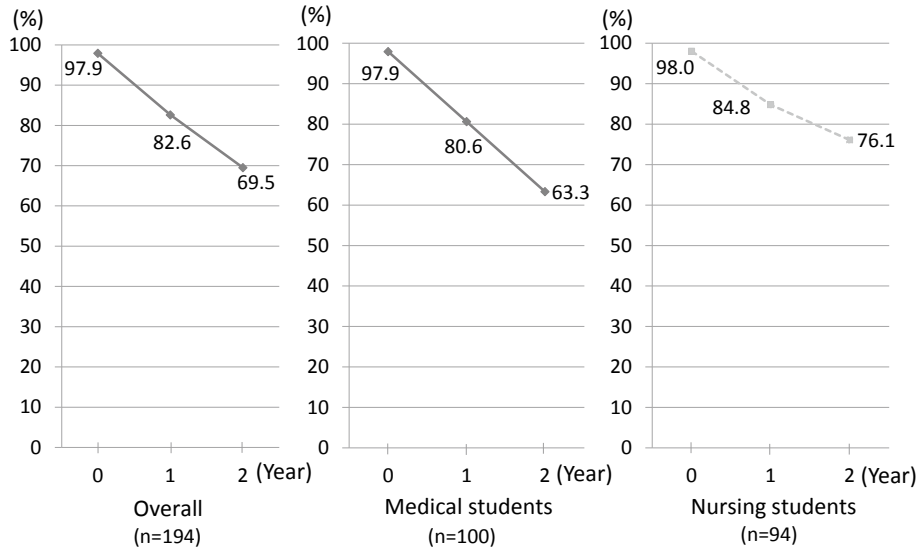


Figure 1 Transition of anti-HBs positive rate

The rate of anti-HBs positive decreased to 69.5% after 2 years of HB vaccinations in both the medical and nursing students.

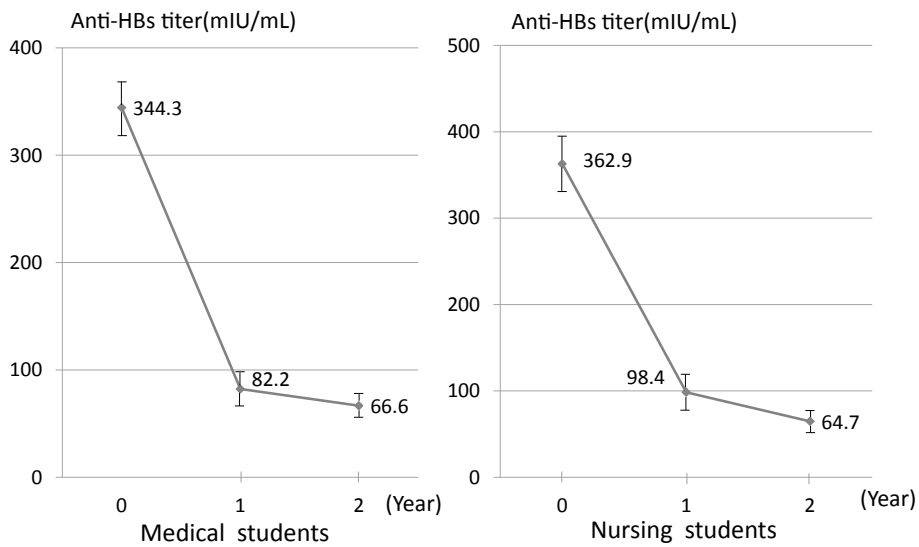


Figure 2 Transition of anti-HBs titers after one series of HB vaccinations, 1 year and 2 years

The anti-HBs titers were shown in both the medical and nursing students. Cut off value of anti-HBs titer : 10 mIU/mL. Data expressed as mean ± SEM.

anti-HBs positive students and the changed negative students during a 2-year follow-up. The anti-HBs titers of the sustained positive students were significantly higher than the changed negative students in both medical and nursing students during 2 years of follow-up ($P < 0.001$, respectively).

5. The student had anti-HBs positive after one series of HB vaccinations and anti-HBs titer decreased < 10 mIU/mL at 1 year. Then, the anti-HBs titer showed a natural boost-up at 2 years. (Figure 4)

As for a case of male medical student, his anti-HBs titer showed positive (159.4 mIU/mL) after complet-

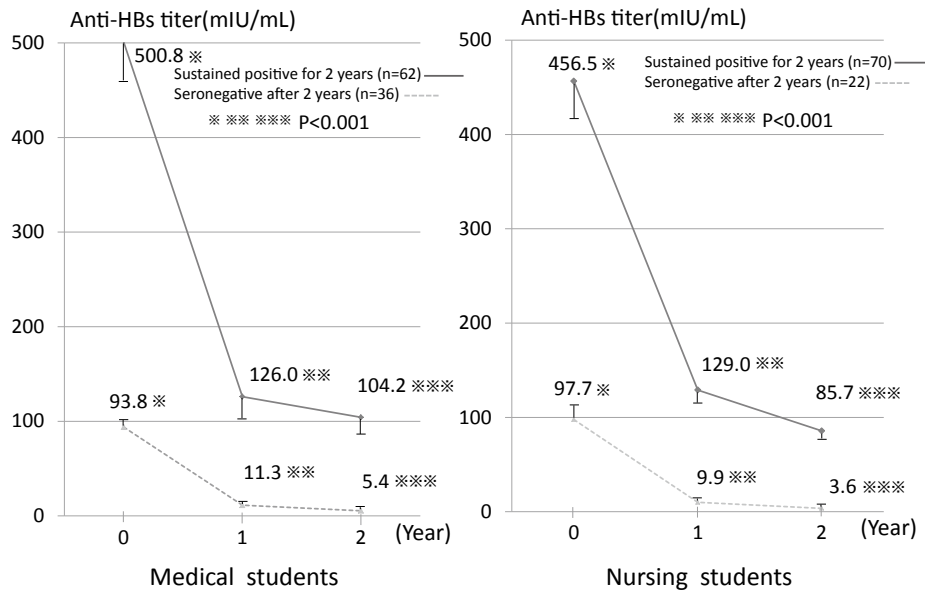


Figure 3 The comparison between the sustained anti-HBs positive students and the changed anti-HBs negative students

The titers of the sustained anti-HBs positive students were significantly higher than the titers of the changed anti-HBs negative students in both the medical and nursing students ($P < 0.001$, respectively).

Cut off value of anti-HBs titer : 10 mIU/mL. Data expressed as mean \pm SEM.

Differences at $P < 0.05$ were considered significant. *, **, *** $P < 0.001$.

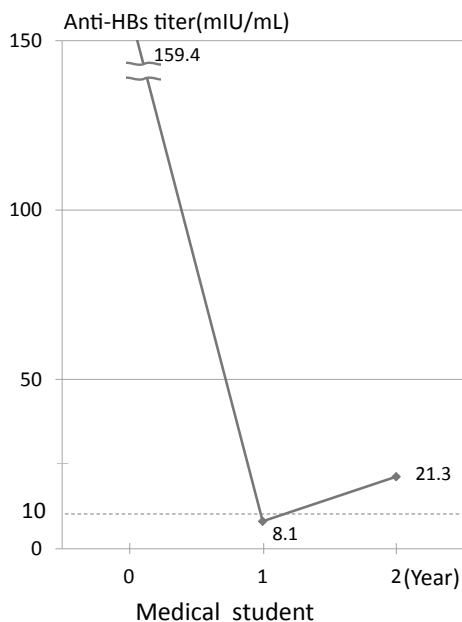


Figure 4 A case of male medical student turned out positive as 159.4 mIU/mL after one series of HB vaccinations. One year later, the anti-HBs titer changed to negative as 8.1 mIU/mL. At 2 years, the anti-HBs titer naturally turned out positive again as 21.3 mIU/mL. Cut off value of anti-HBs titer : 10 mIU/mL.

ing one series of vaccinations, and it turned out negative (8.1 mIU/mL) at 1 year. His anti-HBs titer was increased to positive again (21.3 mIU/mL) as a natural course observation at 2 years.

DISCUSSION

HB vaccination is significantly important to prevent vertical HBV infections that transmitted from HBV carrier mothers to their newborn infants^{9~12}. Further, it is possible to cause some horizontal transmission in daily life such as father-to-child transmission or group infections in nursery schools¹³. In a case of HBV infection in adulthood, the 30~50% of patients is likely to develop acute hepatitis after 6 weeks to 6 months incubation period. Among those patients, a little less than 1% of acute hepatitis is likely to develop into fulminant hepatitis and a considerable number of patients could be fatal a outcome^{7,8}. The infection risk rates are 30% in HBV, 1.8% in hepatitis C virus (HCV) and 0.3% in human immunodeficiency virus (HIV). The risk of HBV infection rate is significantly high¹⁴.

For the reasons described as follows, the HB vacci-

nation will be more significant in the future and it is considered that universal HB vaccination should be undertaken by all Japanese people eventually^{7,8)}.

Firstly, for the purpose of preventing hospital infections, HB vaccination should be significantly important for doctors and nurses who contact with patients directly and also for the janitorial workers who deal with laundry and cleaning that may directly contact with blood and body fluid of patients. HBV infections are likely to happen through needle-stick injuries, cut wounds with sharp tools used for patients, exposures of mucous membrane with blood and body fluid and exposures of wounded skin as small wounds or infections. Fulminant hepatitis can be infected unknowingly through small wounds that are not recognized, urine, sweat, saliva or tears from other people^{7,8)}.

Furthermore, it is important to prevent from developing acute hepatitis B through horizontal transmission among adults. Currently, it is proved that HBV genotype A is increasing that about 10% of acute hepatitis B in Japan would become chronic and/or protracted^{15,16)}. More than 90% of co-infection of HIV/HBV as STD (sexually transmitted disease) is caused by genotype A infection^{17,18)}. In addition, there is a report about the reactivated HBV with complications after cancer chemotherapy and immunosuppressive therapy. By introducing molecular target drugs, it was reported that an emergence of new *de novo hepatitis B* due to the reactivation from a case of HBsAg negative^{19~21)}. And the prevention of post-transfusion hepatitis B is also important^{7~8)}.

It is addressed how anti-HBs titer changes with time after one series of HB vaccinations^{22~24)}. For the minimum amount of anti-HBs titer in order to prevent HBV infection was defined as 10 mIU/mL in accordance with the reference preparation criteria by World Health Organization (WHO) and this study was applied with that criteria^{7,8)}. Regarding 97.9% of the total students who turned out anti-HBs seropositive after one series of vaccinations, we had observed the transition of the anti-HBs titers during a 2-year follow-up. Then 30.5% of the total students turned out the anti-HBs seronegative status. As the results of the observation, the titers of the sustained anti-HBs positive students were significantly higher compared with the titers of the changed anti-HBs negative stu-

dents in both medical and nursing students ($P < 0.001$, respectively). Consequently, it was proved that the anti-HBs titers were high after one series of vaccinations among the sustained anti-HBs positive students. As for a factor of the difference between the sustained positive students and the changed negative students, it could be involved in the variance of immune responsiveness²⁵⁾. The transition of anti-HBs was hypothetically considered that divided into 4 types: 1) sustained high anti-HBs, 2) decreased from high anti-HBs, 3) sustained low anti-HBs, and 4) decreased from low anti-HBs to negative. We continue to follow up the transition of anti-HBs titers at an annual physical examination once a year carefully.

Exceptionally, a student's anti-HBs turned out seropositive after HB vaccinations, and then his status became negative after one year. Finally, it changed to re-anti HBs positive after 2 years (Figure 4). In this case, there was a possibility that he was newly-infected. Also, it could be considered that the result was changeable at the respective tests if the anti-HBs titer was a relatively low concentration near the boundary of negative and positive^{7,8)}.

Regarding the evaluation for HB vaccination responses and the gender differences, generally speaking, the response of females is a favorable clinical response^{7,8)}. It was reported that females have better antibody productivity than males^{26,27)}. One of the reasons is that estradiol allows to enhance the immune responsiveness. Therefore, it is pointed out the possibility of the better immunological response because females have the higher estradiol consent in the serum²⁸⁾. In this study, we could not evaluate the differences by gender. The reason was considered that the number of subjects was not well-balanced between male and female besides the number subjects itself was not large for the study samples.

After one series of HB vaccinations, the result of non-responsive students who had not turned out seropositive was 2.1% (4/194). For the additional countermeasures against non-responsive students, we have tried to repeat 3 injections with regular amount of administration 1 year later, to apply the muscle injection or to change the kind of vaccines²⁹⁾. However, it is not clarified which countermeasure brings the most effective result to gain anti-HBs and this issue will be

a future study aim^{7,8)}.

In conclusion, approximately 30% of the students turned out anti-HBs seronegative after HB vaccinations during a 2-year follow-up. If cases of the anti-HBs become positive and then change to negative during the process, booster doses are not recommended for persons with normal immune status who have been fully vaccinated in accordance with the guidelines by Centers for Disease Control and Prevention (CDC) in the United States³⁰⁾. However, the students are placed in the environment with high risk of HBV infection. Therefore, it should require considering to determine if and when the booster immunization will be necessary.

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Conflicts of interest

The authors disclose no conflicts.

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