Titer of anti-HBs antibodies following a booster vaccination among medical students

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Abstract. Infection by hepatitis B virus (HBV) is a universal health problem in the world including Indonesia. It is predicted there are more than 2 billion peoples exposed to the virus with 1.5 million new cases diagnosed yearly worldwide. According to a recent data in Indonesia, it is estimated that twenty eight million people have been infected to Hepatitis B and C, in which 14 million of those are potential or capable to develop a hepatocellular carcinoma after 30 years. Peoples at a higher risk of contracting HBV infection are the health workers as well as the medical student accidentally, through minor skin cuts or needle punctures. Vaccination to HBV is the best strategy to prevent the HBV infection. This research aimed to determine the level of anti-HBs in the medical student, before and after the Hepatitis B vaccination. This research was conducted comparatively on 48 medical students prior to their duty in the teaching hospital. It was discovered in the research that there is a significant difference in terms of anti-HBs level prior and after the vaccination on both male and female subjects with value p < 0.05. In conclusion, there was a protective effect of HBV vaccine among medical student at The University of Warmadewa.

1. Introduction
Hepatitis B virus infection is a major public health problem in the world. Hepatitis B virus has caused worldwide infections with roughly 240 million people becoming its victims, in which some of them have been reported to have proceeded to chronic Hepatitis B, whereas Hepatitis C has infected around 170 million people. Around 1.5 million people in the world die due to complication of chronic Hepatitis B virus each year such as cirrhosis, liver failure or hepatocellular carcinoma [1].

Hepatocellular carcinoma (HCC) is one of the most malignant tumours and has a high mortality rate [2,3,4]. The strongest factor associated with HCC development in epidemiology is chronic hepatitis B infection. Chronic hepatitis B infection plays an important role in the progression of HCC.

Hepatitis B virus (HBV) is a member of hepadna viridae family. This virus is type-1 hepadnavirus, which is notably the first of its kind to have been identified. The HBV is a hepatotropic virus contains DNA with circular double rings consisting of 42-nm-4-gen 3200 nucleotide. The Antigen component existing in the core is Hepatitis B e antigen (HBeAg). This specific antigen indicates there is a virus replication occurring in the lymphocyte, spleen, kidney as well as liver in particular. The presence of HBeAg in the serum reveals the immune tolerance phase of the HBV infection. Study shows the presentation of HBeAg may promote HBV chronicity by functioning as an immune regulator protein [5]. This mechanism may be the main mechanism which responsible for the high chronic HBV infection
rate. Hepatitis B virus is not cytopathic, both liver damage and viral control, and therefore clinical outcome depend on the complex interplay between virus replication and host immune response [6].

HBV is very efficiently transmitted in setting of a percutaneous injury that involve an instrument coated with or containing HBV–infected blood. Healthcare worker, include medical student are a high risk group to exposure HBV infection [7]. Healthcare workers had a seroprevalence of HBV infection that was 5 to 10 times higher than the general population. There is a risk of 1%-6% of acquiring HBV from a needle stick injury when the source patient is only HBsAg positive. This risk however, increases to 22%-40% when the source patient is both HBsAg positive and HBeAg positive [8].

Vaccination is the most effective and riskless way to control and eradicate the infection caused by the Hepatitis B. Indonesia has routinely conducted the vaccination against the Hepatitis B as its immunity program development since 1992. The Vaccine of Hepatitis B, which is currently put into utilization, originates from the surface of Hepatitis B virus (surface antigen/HBsAg). It is formulated through the DNA recombinant technique, a process in which gen S of the Hepatitis B virus is utilized through insertion. The Vaccine of Hepatitis B contains protein HBsAg which is capable of inducing the immune response of the host cell from which the anti-Hbs is constructed. This particular antibody component is capable of inhibiting the Hepatitis B virus attachment from entering the host cell [9]. The antibody titre becomes protective against the antigen of Hepatitis B surface (anti-Hbs) following the vaccination with amount of ≥ 10 IU/L. This dosage proves capable of preventing the disease thus being classified and accepted to be the precise amount which is able protect against the Hepatitis B [10].

2. Material and methods

The research is experimental in which One Group Pre Test and Post Test Group Design was applied as its pattern. The research was conducted from August to December 2017 located at Universitas Warmadewa. The number of the student involved in the study was 48 of medical students of Universitas Warmadewa. The age of the sample was 19-22 years old with unreactive HBsAg. The sampling technique was simple random sampling. The level of HbsAg and anti-Hbs from the samples were examined prior to the vaccination and then followed by the re-examination for the anti-Hbs 3 months after the vaccination. Ethical clearance for the study was sought and obtained from the University of Udayana/Sanglah Hospital ethics and research committee. The data was analyzed using statistical package for social science (SPSS) version 17.0. Test of significance between proportions was assessed using Wilcoxon, and a p value of 0.05 or less was considered significant at a 95% confidence interval.

3. Results and discussion

Based on the experimental result of Wilcoxon, the significance is defined <0,001 (p < 0,05). From the data in table 1, therefore, it can be concluded that there is a noticeable difference in the anti-HBs level occurring between time before and after the Hepatitis B vaccination was given to the female samples.

|                      | n | Median (min-max) | p        |
|----------------------|---|-----------------|----------|
| Prior to vaccination | 29| 1,95            | <0,001   |
| After vaccination    | 29| 1000            |          |

Based on the experimental result of Wilcoxon, the significance is defined <0,001 (p < 0,05). From the data in table 2 which is similar to data of the female group, therefore, it can be concluded that there is a noticeable difference in the anti-HBs level occurring between the time before and after the Hepatitis B vaccination was given to the males samples.
Table 2. The average difference in anti-HBs level prior and after the vaccination on male group.

|               | n  | Median (min-max) | p    |
|---------------|----|------------------|------|
| Prior to vaccination | 19 | 2.03             | <0.001 |
| After vaccination       | 19 | 491.4            |      |

Table 3 reveals the Wilcoxon result on the significance at 0.01 (p>0.05). From the data above, therefore, there is no significant average difference in the anti-HBs level prior and after the vaccination implemented on both female and male groups.

Table 3. The comparison of average difference in anti-HBs prior and after the vaccination on male and female groups.

|      | n | P  |
|------|---|----|
| Female | 29 | 0.01 |
| Male   | 19 |     |

A noticeable average difference in the anti-HBs of the female group prior and after the vaccination was discovered upon this research with p<0.001. The 3-dosage Hepatitis B vaccination was implemented on the adults. The second dosage was implemented 4 weeks after the first one, and then followed by the third one 5 weeks later. During post-vaccination, HBsAg can temporarily become positive which is followed by the intensification performed by anti-HBs titer [11]. From the occurrence of this particular antibody, it is expected that it can contribute protection againsts the Hepatitis B infection. In a research conducted by Liguo et al (2014), it was discovered that the positive HBsAg underwent intensification in 20-39-year-old group with no prior vaccination. However, there is no intensification performed by HBsAg titer after the vaccination at adult state [12].

In the research conducted in China and Iraq, the female group having been vaccinated appears to have higher antibody response compared to that of the male group. Several researches revealed that there is a decrease of lymphocyte T in the male group rather than the female group [13,14]. The level of both IgM and IgG serum in the male group was also discovered to be higher than it is in female group. The difference in terms of immunity between the male and female is highly associated with sex hormones such as estrogen, progesterone, and testosterone which are different from each of them [15].

The level of HBs is used as a benchmark to measure the success rate of the Hepatitis vaccin in countering the risk of negative Hepatitis. The expected success rate following the vaccination is ≥10 mIU/mL, provided the level of anti-HBs shows intensification in the samples after the vaccination itself [16].

The research reveals that there is significant finding on the average level of anti-HBs prior and after the Hepatitis vaccination on the female group as shown in the table 2, from which therefore, it can be concluded that hepatitis vaccin has proved effective in giving protection to the male group.

This result corresponds to the research conducted by Fadlyan et al (2013) showing there is an average difference in the anti-HBs level is higher after the vaccination than it is before the implementation [16]. The anti-HBs titer significantly increases following the Hepatitis B vaccination. An occurrence of lymphocyte B memory appearing after the Hepatitis B vaccination indicates there is a circulation of cell B which produces in-vitro anti-HBs. Moreover, the anti-HBs in the serum may be accompanied by the quick increase of anti-HBs after a boost of dosage during an undetected situation [17].

The difference in the antibody level in the circulation during post-vaccination is influenced by the immune system of the individuals receiving the vaccine. The immune response is individual by nature, depending on both internal and external factors. One of the internal factors is sex [18].
The different immune response between males and females is also highly influenced by steroid hormone such as estrogen, progesterone, and testosterone which are individually different across respective sexes. It was discovered in this research that there is insignificant difference in the anti-HBs level prior and after the vaccination on the female group rather than the male group. The result of this result corresponds to the research conducted by Aswati et al (2013) which shows there is no difference in the anti-HBs level between males and females [17].

Most previous study have demonstrated that there is a sexual disparity in the development of HBV-related HCC. Female HBV carriers generally have lower viral load than male carriers, the risk of HBV-associated HCC is lower in female than in males. Some study suggested that HBV-associated HCC may be a hormone-responsive malignant tumor [19,20].

The protective effect of VHB vaccine in the current study is discordance with the finding of another study, whereas only one-fourth of the student have protective titer of antiHBs post vaccination. In addition, almost 75% of the medical student who has a booster VHB vaccine has antiHBs titer less than 10 mIU/mL in the previous study [21].

The high titre of antiHBs finding in this study may cause by the short period of the observation post vaccination (3 months after vaccination). In contrast with other study which found decreasing of antiHBs titre over time among the medical student and healthcare worker 5 through more than 10 years after VHB vaccination [22].

4. Conclusion
The study found a significant level of anti-HBs titre before and after vaccination among medical students of Universitas Warmadewa before their duty in the teaching hospital. This finding reveals the protective effect of anti-HBs vaccine to HBV infection and may implemented to the people at high risk to get this infection such as the medical students or the healthcare workers.

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