ORIGINAL ARTICLE

Comparing Effect of Double Dose of Hepatitis B Vaccine Verses Conventional Dose in Patients with Chronic Liver Disease

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ABSTRACT

Objective: To compare the effectiveness of double dose hepatitis B vaccine in patients with chronic liver disease versus conventional-dose

Study design: Randomized control trial

Place and Duration: Six months after the approval of synopsis i.e 15th March 2017 to 14th September 2017, Department of General Medicine, FFH, Rawalpindi

Methodology: A total of one hundred and sixteen (n=116) diagnosed cases of chronic liver disease of either gender between age 30 to 70 years were enrolled and were divided into two groups one received a double dose (2 ml, 40 µg) and the other received a conventional dose (1 ml, 20 µg). Quantitative anti-HBs was measured at three months in both groups.

Mean with standard deviation calculated for quantitative variables like age, anti-HBs level one month after 3rd dose and frequency and percentages in case of categorical variables like gender and effectiveness. Chi-square test was used to determine the significant difference in both groups regarding the effectiveness of vaccination. A p-value ≤0.05 was taken significantly.

Results: In patients who received double dose seroprotection (anit HBs >10 IU/ml) was achieved in 93.1% (n=54/58) patients, while the percentage was 77.6% (n=45/58) in patients who received a conventional dose (P<0.05).

Conclusions: Seroprotection (anit HBs >10 IU/ml) at three months was significantly better in patients who received the double dose of vaccine. Vaccine effectiveness was significantly better in younger age group.

Keywords: Chronic liver disease, HBsAg, Anti HBs.

Introduction

HBV infection continues to be a common cause of acute hepatitis. Hepatitis C virus (HCV) is a causative agent of chronic liver disease, cirrhosis, and hepatocellular carcinoma.[1] In Pakistan, more than ten million people are living with HCV. HCV is a common cause of chronic liver disease leading to cirrhosis and increases morbidity and mortality. Although there is no vaccine available for HCV, an effective vaccination is available for HBV. [1,2,3, 4]

Vaccine effectiveness (seroconversion with a hepatitis B surface antibody titer >10 IU/mL) in this setting is often blunted, with poor response rates to standard HBV vaccination in virally infected individuals when compared with the healthy subjects.[4] This phenomenon also occurs to other vaccines in adults, such as pneumococcal and influenza vaccine, in other immunocompromised hosts who are really at risk for opportunistic infections, such as individuals with hemodialysis, transplant, and

malignancy.[5] A vaccine against HBV is recommended as the primary means to prevent HBV super-infection in HCV infected individuals. In a trial effectiveness of double dose was 100% in patients with any kind of chronic liver disease while in patients with conventional dose was 87.5%.[6]

The rationale of the current study is that there is the difference in the rate of seroconversion with different dose of vaccine. As no local study is available and acute on chronic hepatitis has higher mortality, the current study may reduce mortality and morbidity in patients with the compensated chronic liver disease. The gathered data will help in better management of patients with HBV super-infection with HCV. This will eventually enable the physicians to implement more stringent monitoring to prevent the HBV super-infection in patients with HCV.

Methodology

A total of 116 patients with chronic liver disease, coming to the outpatient department were included in the study after informed consent. A randomized control trial study was conducted in Department of General Medicine, Fauji Foundation Hospital, Rawalpindi. The duration of the study was Six months after the approval of synopsis i.e. 15th March 2017 to 14th September 2017. Non -probability consecutive sampling was taken as sampling technique. The included patients randomized into two equal groups by using random number table. 58 selected patients were given double dose (2 ml 40μg) intramuscularly in the deltoid muscle at three different times at 0, 1 and 2 months and 58 patients were administered conventional dose (1 ml, 20 μg) similarly, included patients followed for three months and quantitative anti-HBs was measured. The response was labeled according to the operational definition of effectiveness. All variables of interests like age, sex and outcome variable (effectiveness) recorded on a structured questionnaire.

Effectiveness was labeled effectiveness if quantitative anti-HBs antibodies>10IU/ml are detected by ELISA, one month after the last dose of hepatitis B vaccine. The chronic liver disease was defined as end-stage liver disease that is characterized by disruption of normal liver parenchyma by bands of fibrosis and regenerative nodules on ultrasound. Chronic liver disease refers to the disease of liver lasting over six months and includes a wide range of liver pathologies which include inflammation (chronic hepatitis), liver cirrhosis and hepatocellular carcinoma. The conventional dose in three dosing schedule of 20 μg (1ml*) standard* hepatitis vaccine given intramuscularly in deltoid at 0, 1 and 2 months while double dose was 40μg (2ml) vaccine on the same schedule. Patients with both gender and age 30 – 70 years which were diagnosed cases of chronic liver disease were included in the study. HBsAg positive patients determined by a laboratory test, individuals already immunized against HBV (determined by history) and patient taking steroids and immunosuppressant drugs (determined by history) was taken as inclusion criteria of the study.

A sample size of approximately 116 (58 patients in each group) was calculated by using WHO sample size calculator with level of significance: 5%, power of test: 80%, anticipated population proportion 100% 6 and 87.5% 6. Data entered and analyzed using SPSS version 17.0. Mean with standard deviation calculated for quantitative variables like age, anti HBs level one month after 3rd dose and frequency and percentages in case of categorical variables like gender and effectiveness. Chi square test was used to determine the significant difference in both groups regarding the effectiveness of vaccination. A p-value $\leq$0.05 was taken significantly. Data was stratified for age and gender. Post-stratification Chi-square test was applied with p-value $\leq$0.05 was considered significant.

Results

A total of one hundred and sixteen (n=116) diagnosed cases of chronic liver disease of either gender between age 30 to 70 years were enrolled in the study. All the patients divided into two groups one received a double dose (2 ml, 40 μg) and the other received conventional dose (1 ml, 20 μg). Quantitative anti-HBs was measured at three months in both groups. Mean age (year) of male patients in both the groups was 58.9$\pm$8.5 and 56.8$\pm$9.2 respectively whereas mean age (years) of female patients among both the groups was 57.1$\pm$7.6 and 56.3$\pm$8.8 respectively as shown in Table. I. Distribution of gender was presented in Table. II. There were 33 (56.9%) and 35 (60.3%) male patients among both groups whereas 25 (43.1%) and 23 (39.7%) female patients in both the

groups respectively. In patients who received double dose seroprotection (anit HBs >10 IU/ml) was achieved in 93.1% (n=54/58) patients, while the percentage was 77.6% (n=45/58) in patients who received conventional dose which statistically significant (p-value 0.018).

Table I: Demographic Profile of the study Population (age distribution)

		Age (years) Mean±SD
Double Dose	Male	58.9±8.5
	Female	57.1±7.6
	Total	58.1±8.1
Conventional Dose	Male	56.8±9.2
	Female	56.3±8.8
	Total	56.7±8.9

Table II: Effectiveness & Mean Anti HBs in both study groups after at three months after immunization

		Double dose	Conventional dose	Total
Gender	male	33 (56.9%)	35 (60.3%)	68 (58.6%)
	female	25 (43.1%)	23 (39.7%)	48 (41.4%)
Mean Anti HBs (IU/ml) (03 months after immunization)		210.4±59.4	71.3±42.2	
		Double dose	**Conventional dose**	**p-value***
Effectiveness	present	54 (93.1%)	45 (77.6%)	0.018
	absent	04 (6.9%)	13 (22.4%)	

P≤0.05 was taken as level of significant

Discussion

With the improvement in hepatitis B prevention and control, more attention is currently being devoted to adult hepatitis B immunization. A US report in 2007 showed that the highest proportion of new hepatitis B infections occurs in the 25- to 44-year-old age group.[7] Vaccination for high-risk adults was started in the USA in 1998,[8] and adult hepatitis B vaccination was introduced to community primary health care and rehabilitation clinics in 2006.[9] The standard schedule for hepatitis B vaccine was 0, 1 and 6 months, and it was widely used all over the world. Due to the large time span of immunization, some people cannot complete the full vaccinations.[10] In a study by Kollar et al.[11] it reported that only about 50% of the people can complete the 3-dose vaccination plan. The 0–1–6 months schedule is easy to carry out in children. As the mobility in adults is higher than children, it has been hypothesized that shortening the time interval between vaccinations may improve the compliance of adults.[12] There were a lot of flexibility immunization schedules in other countries, such as accelerated series 0/1/2-month and 0/7/21-day et al. Chen SY et al.[13] study compared the two different schedules 0–1–3 months and 0–1–6 months, the result showed that the anti-HBs seroprotection rates were both high in the 2 schedules. Xu F et al.[14] study showed the same result. Belloni et al.[15] study compared the two schedules and found that the antibody levels showed no significant difference one year after the full vaccinations. Therefore, we carried out 0–1–2 months schedule as it was simple and reportedly effective. The main aim of the present study was to compare the effectiveness of double dose hepatitis B vaccine in patients with chronic liver disease versus conventional dose. A total of one hundred and sixteen (n=116) diagnosed cases of chronic liver disease of either gender between age 30 to 70 years were enrolled and were divided into two groups one received a double dose (2 ml, 40 μg) and the other received a conventional dose (1 ml, 20 μg). Quantitative anti-HBs was measured at three months in both groups. Our results showed that in patients who received double dose seroprotection (anti HBs >10 IU/ml) was achieved in 93.1% (n=54/58) patients, while the percentage was 77.6% (n=45/58) in patients who received a conventional dose ($P<0.05$). Effectiveness was significantly better in younger age group (30-50 years $P<0.05$). No significant difference was observed when results were stratified with respect to gender ($P>0.05$).

Our results are quite similar to already published data on the subject. In a similar study Li J, Yao J et al evaluated the one-month immune response to two different doses (10 and 20 μg) of recombinant hepatitis B vaccine in adults aged 20-46 years. The participants were divided into 2 groups: group I received 3 doses of 10 μg hepatitis B vaccine at 0, 1 and 3 months, and group II received 3

doses of 20 μg at the same time points. The anti-HBs levels were measured one month after the third vaccination. Their results showed that the anti-HBs seroprotection rates (anti-HBs ≥ 10 mIU/mL) after the third vaccination were 88.05% and 94.06% in group I and group II respectively. Better responses were observed in young adults. [16]

Several other studies have used double doses i.e 10 μg and 20 μg, of hepatitis B vaccine. In a study by Kulkarni et al.[17] a group of adults aged 19–57 years received three 20-μg doses of recombined hepatitis B vaccine at 0, 1 and 6 months. Their results showed that one month after the third vaccination, the seroprotection rate was 96%. In another study by Joshi et al.,[18] 120 healthy adults received 20 μg Engerix-B and Shanvac-B at 0, 1 and 2 months, which provided seroprotection rates of 91.4% and 96.4% respectively. Another study by Xu F et al [19]. used two different dosages 10 μg and 20 μg in a 0–1–3 months schedule, which obtained seroprotection rate of 98.36% and 97.86% respectively and had no significant difference. In the present study, 20 μg and 10 μg of the hepatitis B vaccine were administered at 0, 1 and 2 months; the seroprotection rates one month after the third dose were 93.1% and 77.6% respectively. The difference in seroprotection rates between the two groups was significant; thus, these 2 doses, 10 μg and 20 μg, are effective in healthy adults. In addition, the mean anti HBs reported in our study are lower compared to other studies that used the 0/1/6-month schedule; this is probably because the interval between the last 2 doses of the primary series is different between the studies.[20,21] when the vaccine was administered as an accelerated series at 0, 1 and 2 months, the seroprotection rate at the third month was 96.4% and the mean anti-HBS was 60.2 mIU/mL, as shown in an earlier study that used 20 μg Engerix B vaccine.[22]

The duration of immunity after hepatitis B vaccine vaccination is not known, but generally, it is considered that the higher the antibody titers after vaccination, the longer the protection will last.[23],[24] An anti-HBs level greater than 10 mIU/ml is considered to provide protection against hepatitis B infection, and an anti-HBs level exceeding 100 mIU/ml is considered to indicate long-term immunity.[25] Qian W et al.[26]reported seroprotection provided by 10 μg or 20 μg doses of hepatitis B vaccine persists for 23 years in more than half of vaccinated individuals. In the present study, the mean values after administration of the 40 μg dose was higher than those after the 20 μg dose. This result was similar to those of previous studies. it is, therefore suggested, based on these findings, 40 μg may be the appropriate dose that provides longer protection.

In this study, younger adults showed a better response. In agreement with this finding, increasing age was shown to be an important factor that affects immunogenicity, as evidenced by the decline in the seroprotection rate and mean antiHBs values in the higher age groups.It is similar to that reported in earlier studies: Ren JJ et al.[27] reported seroprotection rates of 92% and 80% in the 16–34 years and 35–49 years groups respectively. Another study[28] found seroprotection rates of only 60% at the age of 40 years and more. These findings indicate that good immunity in people who are vaccinated at a younger age.

There were few limitations in the present study. Firstly, due to the short observation time; we could not assess the long-term effects of the vaccination. Additionally, we did not collect the data of body mass index (BMI) which may affect the immunity effect. Finally, the present study has a limited number of subjects to draw conclusions on the recommended dosage and it should be tested on a larger number of subjects before recommending it for adult routine vaccination.

Conclusion

The study concluded that seroprotection (anit HBs >10 IU/ml) at three months was significantly better in patients who received the double dose of vaccine. Vaccine effectiveness was significantly better in younger age group.

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