INTRODUCTION

Hepatitis C is a common disease in Pakistan. It is a progressive disease over the number of years and tends to progress to cirrhosis and its complications.\(^1\) Patients with hepatitis C are vulnerable to develop other viral infections like hepatitis A and B and in the due course, in these patients with superadded viral infection, can result in serious complications and may become fatal.\(^2,3\)

Therefore, it is important to adequately protect persons with chronic HCV infections by immunization against hepatitis B and A. However, recent studies have shown that hepatitis B immunization in such patients is suboptimal.\(^4\) It is recommended that hepatitis B (HBV) vaccine should be administered early in the course of chronic HCV infection to protect them from super added viral infection because response may be lower as patients develop cirrhosis.\(^3\)

In Pakistan, the situation is much more alarming. A study from Lahore reported that only 20% doctors advised their patients about hepatitis B vaccination and even lesser numbers (15%) actually asked their hepatitis C patients about hepatitis B vaccination.\(^5\)

Several trials have been reported in which the hepatitis C patients have been vaccinated against hepatitis B.\(^6-10\)

However, the antibody response in these patients has been suboptimal in many studies.\(^6,9\) Since patients with hepatitis C are immunocompromised and have associated comorbidities, their response to hepatitis B vaccination and antibody titer to sero-protective levels is not achieved with standard dosage of vaccine.\(^7,9-11\)

Various formulations of hepatitis B vaccination have been developed and marked. Heberbiovac HB, a yeast derived recombinant vaccine is of Cuban origin and has been claimed to have more immunogenic activity than other formulations.\(^12-14\) Previous studies have shown that it has given better response to antibody level in normal healthy adults and neonates.\(^12,13\) Since HCV patients do not respond with antibody productions to the standard doses of hepatitis B vaccination, Heberbiovac-HB was considered to be a good candidate to assess its efficacy in antibodies production in these patients.

Therefore, the aim of this study was to assess the development of anti-HBs in patients with HCV and compare the same with normal healthy subjects.

METHODOLOGY

The study was carried out at the Department of Gastroenterology, Shifa International Hospital, Islamabad, Pakistan, from January 2009 to June 2012. An informed consent was taken from all study participants. During this period, 46 patients of HCV (HCV group) and 45 normal healthy subjects visiting the clinic were enrolled for the study. Patients aged 18-60 years, without clinical, biochemical or radiological evidence of cirrhosis, hepatocellular carcinoma, renal failure or any immuno-

ABSTRACT

Objective: To assess the effects of hepatitis B vaccination on the antibody titer in patients with chronic hepatitis C and to compare it with response in normal healthy subjects.

Study Design: Interventional study.

Place and Duration of Study: Shifa International Hospital, Islamabad, Pakistan, from January 2007 to January 2012.

Methodology: Hepatitis vaccination (Heberbiovac-HB 20) was given intramuscularly to the patients of chronic hepatitis C (HCV group) and normal healthy subjects (control group) at 0, 1 and 6 months intervals. Anti-HBs titer was determined after second and third injection to assess the antibody response.

Results: There were 46 patients in the HCV group and 45 patients in the control group. Mean age was 40.9 ± 9.8 years in the HCV group and 33.18 ± 8.35 years in the control group. Weight was 67.04 ± 13.5 kg in the HCV group and 71.78 ± 14.63 kg in the control group. Height was 162.45 ± 9.06 cm in the HCV group and 167.03 ± 7.83 cm in the control group. Anti-HBs antibody levels after the second injection were 253.89 ± 76.76 mlU/mL in the HCV group and 245.81 ± 72.65 mlU/mL in the control group (p=0.172). After third injection, the antibody levels were slightly higher in both groups.

Conclusion: In patients with chronic hepatitis C and normal healthy subjects, Heberbiovac HB in standard dosage gave sero-protective levels in both groups and antibody titers were not significantly different in control and HCV group.

Key Words: Hepatitis B. Hepatitis C. Hepatitis B vaccination. Hepatitis B antibody titer.
compromised illness were included in the study. Patients with auto-immune hepatitis or other liver disease were excluded from the study. All patients had baseline CBC, liver function tests, albumin, prothrombin time, chemistry, abdominal ultrasound and serology including anti-HBs.

All were administered Heberbiovac-HB 20 intramuscularly at 0, 1 and 6 months interval.

Antibody (anti-HBs) titers were determined after one month of second and after one month of third injection. Antibody titer of < 10 was considered non-responder, titer 10 - 100 was considered hyporesponder and seroconversion and titers > 100 were considered sero-protection. Side effects of vaccine were monitored during these periods.

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 16. Fisher’s exact test was used to assess categorical variables and student t-test for continuous variables.

RESULTS

There were 46 patients in HCV group and 45 in control group. The mean age was 40.93 ± 9.83 years in the HCV group and 33.18 ± 8.34 years in the control group. Height was 167.83 ± 7.06 cm in HCV group and 167.03 ± 7.83 cm in control group. Weight was 67.04 ± 13.15 kg in HCV group and 71.78 ± 14.63 kg in the control group. Antibody (anti-HBs) titers were 253.89 ± 76.76 mIU/mL in the HCV group and 245.81 ± 72.65 mIU/mL in the control group (Table I). After third injection, the antibody titers were 255.58 ± 72.35 mIU/mL and 247.34 ± 69.64 mIU/mL respectively. None of the recipient of vaccine suffered any significant side effect except mild fever in few patients.

Table I: Anti-HBs response and titers in HCV and control groups (n=91).

<table>
<thead>
<tr>
<th>Antibody response (mIU / mL)</th>
<th>HCV Group</th>
<th>Control Group</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>(n=46)</td>
<td>(n=45)</td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>4 (9%)</td>
<td>2 (4%)</td>
<td>0.6768</td>
</tr>
<tr>
<td>10 - 100</td>
<td>1 (2%)</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt; 100</td>
<td>41 (89%)</td>
<td>43 (96%)</td>
<td>0.435</td>
</tr>
<tr>
<td>Antibody titers mIU / mL</td>
<td>253.89 ± 76.76</td>
<td>245.81 ± 72.65</td>
<td>0.172</td>
</tr>
</tbody>
</table>

*p-value less than 0.05 is considered significant using Fisher’s exact method.

DISCUSSION

Hepatitis B is a major health problem in Pakistan. For its prevention, hepatitis B vaccine was introduced many years ago and has given about 95% sero-protective levels after three injections in healthy adults. It has been shown to be highly effective in preventing hepatitis B. However, 5 - 10% of healthy individuals fail to develop sero-protective levels of anti-HBs and are considered to be non-responders.15 A study from Karachi which was done on healthy subjects showed that one month after the 3rd dose of a hepatitis B vaccine, 98.7% developed sero-protective levels of antibody with geometric mean titer of 488.83 mIU/L.16 The vaccine used in that study was Heprovac B, a recombinant vaccine, which is considered to have good immunogenicity. Heberbiovac-HB vaccine was used in this study because in previous studies, it was claimed to have high immunogenicity. A study from Iran showed that mean anti-HBs titers in 68 children were 482.1 mIU/mL at 6 months after the third dose of primary vaccination and 153 mIU/mL 5 years later.12 A similar study reported a 94.3% and 100% response in 141 children with the mean age of 1.9 years to booster dose of same vaccine after first and second booster dose in non-responders and hypo-responders.13 Moreover, all the children showed immunologic memory to booster dose.12

In this study, the response in control group was 96%, which is similar to that in normal Pakistani subjects.16 The anti-HBs response of HCV group was 89%, which although lower than control group, was not statistically significant (p=0.435) from the controls. In another study regarding HBV vaccine effect in hepatitis C patients, non-response was observed in 31% patients and low response (anti-HBs 10 - 99 mIU/mL) in 19% of patients, however, higher doses resulted in seroprotective antibody levels.11 Compared to these figures, the present results are much better. The mechanism for poor response in non-responders is not clear, but impairment in both humoral and cellular-mediated immune response has been implicated.11,17 A previous study which used two doses of same vaccine in 20 µg strength showed 96.3% response in healthy subjects.14 Similar results were found in this study after two injections but went on to third dose due to the fear that adequate antibody titers may not develop after two doses in HCV patients.

Several studies have reported various means to ensure antibody production in patients who do not develop seroprotective levels of anti-HBs after standard regimen. Double dose of combined hepatitis A and hepatitis B vaccine (TWINRIX)™ was administered at 0, 1, and 6 months in non-responders and 95% developed seroprotective antibody levels after third dose.15 An incremental effect of hepatitis A vaccine combined with hepatitis B vaccine also resulted in satisfactory antibody levels in non-responders.3,15 Intradermal administration of 10 microgram hepatitis B vaccine weekly for 8 weeks resulted in 79% seroconversion as compared to 40% response in hemodialysis patients.16 Repeated high dose (80 microgram) vaccine was also able to give seroprotective antibody level in non-responders.19 High dose short interval (40 microgram every month for 3 months) resulted in seroprotective response in 79% patients.7,10
Several investigators have used adjuvant therapies to enhance production of antibodies to seroprotective levels. Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) was used in 150 microgram dose first and then 20 microgram vaccine was given. It was compared with 40 microgram vaccine alone. GM-CSF was not considered better, as seroprotective rate of 64% was seen in GM-CSF group and 75% in high dose vaccine. A meta-analysis reported use of levamisole 100 mg daily 6 days before and 6 days after each vaccine dose and concluded a significant benefit of levamisole as an adjunct to hepatitis B vaccination in patients with renal failure.

There is still controversy about response of HCV patients to hepatitis B vaccine. Some authors believe that antibody response in HCV patients is suboptimal. HBV vaccine response was generally poor in those with cirrhosis and HCV genotype 1 hepatitis C patients. It has been recommended that HBV vaccine should be administered early in the course of chronic HCV infection as antibody response may be lower in patients who already have developed cirrhosis. Determination of post-immunization antibody level, especially in patients with cirrhosis or genotype 1, will allow HBV vaccine boosters, if needed. While recommendation for vaccination seem quite clear, still there is lack of knowledge and efforts on vaccination of HCV patients to hepatitis B vaccination. Some authors believe that antibody response in HCV patients is suboptimal.

In these patients, adequate antibody response indicated excellent immunogenicity of the vaccine used, as shown in several previous studies. The antibody level was high after the second dose and did not increase much in third dose indicating that two injections may be sufficient in these patients with this vaccination schedule. Limitations of the study included small sample size and single center study. Allergy panels were not performed to evaluate the response to normal antigens. Higher number of patients in different parts of the country may be helpful to validate the results of this study.

CONCLUSION

The hepatitis B vaccine used in the study resulted in sero-protective levels of antibody titer in chronic hepatitis C patients after two doses of injection. The response in HCV patients was same as in control subjects. It is possible that two doses of this highly immunogenic vaccine may be sufficient in these patients. However, it may be advisable to check the antibody levels after two doses to ensure that adequate sero-protective levels of antibody have developed.

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REFERENCES


