Annals of Clinical Microbiology and Antimicrobials

Research

Open Access

Comparison of the accelerated and classic vaccination schedules against Hepatitis B: three-week Hepatitis B vaccination schedule provides immediate and protective immunity

Nese Saltoğlu*[1], A Seza Inal[1], Yesim Tasova[1] and Ozlem Kandemir[2]

Address: [1]Department of Clinical Bacteriology and Infectious Diseases, Çukurova University Medical Faculty, Turkey and [2]Department of Clinical Bacteriology and Infectious Diseases, Mersin University Medical Faculty, Adana, Turkey

Email: Nese Saltoğlu* - nsalt@mail.cu.edu.tr; A Seza Inal - asinal@mail.cu.edu.tr; Yesim Tasova - tasova@cu.edu.tr; Ozlem Kandemir - kandemirege@hotmail.com

* Corresponding author

Published: 17 November 2003

Annals of Clinical Microbiology and Antimicrobials 2003, **2**:10

Received: 14 April 2003
Accepted: 17 November 2003

This article is available from: http://www.ann-clinmicrob.com/content/2/1/10

Abstract

Background: Hepatitis B virus infection although preventable by vaccination remains an important health issue throughout the world due to its morbidity, mortality and economical losses. Early seroprotection is desirable for people at high risk of exposure. The aim of this study was to determine whether three-week hepatitis B vaccination (on days 0, 10 and 21) provide seroprotection or not.

Methods: The 120 subjects enrolled into the study were divided into two groups and vaccinated by the classic (months 0, 1, and 2) or the accelerated (days 0, 10, and 21) schedules and antibody response determined on days 30, 60, and 90 and, if below 10 mIU/ml^{-1}, again on day 180. For each individual in the classic group (B) three subjects were enrolled in the accelerated group (A). Recombinant hepatitis B vaccine (Gen-Hevac B, Pasteur) was given as 20 micrograms intramuscular injections via the deltoid muscle. A booster dose on day 365 was administered for each group. Family members of hepatitis B carriers and volunteer health personnel were enrolled into group A. To the B group only volunteers who wanted vaccination against hepatitis B were included.

Results: After three doses of vaccine, Anti-HBs titers reached protective levels in both groups. The number of vaccinees with seroprotective levels of Anti-HBs (≥10 mIU/ml^{-1}) on day 30 was 53 (58.9%) in group A and 9 (30.0%) in group B ($p < 0.05$). On day 60, there was no difference between group A and B, with response rates of 84.4% (n = 76) and 80.0% (n = 24) respectively ($p > 0.05$). On day 90 there was no difference between group B and group A; with 26 (86.7%) and 79 (87.7%) responders respectively. In both groups those with Anti-HBs levels <10 mIU/ml^{-1} attained protective levels by day 180.

Conclusion: In this study, the three-week vaccination provided protective antibody titers within a shorter time compared to the classic schedule. Therefore, in order to provide rapid antibody production against hepatitis B virus, the accelerated vaccination schedule seems to be a good preference.

Background

Hepatitis B virus infection is a common viral disease, which constitutes a serious health issue throughout the world due to its morbidity, mortality and economical losses. It is estimated that there are 400–500 million chronically infected people on this globe [1]. In endemic areas hepatitis B is an important cause of mortality and is the main cause of hepatocellular carcinoma and cirrhosis, which are preventable by vaccination against hepatitis B. Effective treatment for chronic hepatitis B has not been established yet.

Vaccination against hepatitis B prevents not only the morbidity and mortality due to acute viral disease, but also chronic hepatitis B and its ultimately fatal complications [2]. Currently two different immunization schedules have been recommended for the recombinant vaccine: Repeat doses at months 1 and 6 or 1, 2 and 12 after the first dose [3]. By immunization seroprotection rate has been determined as 95–99% [4].

In such instances as living with a hepatitis B positive person or being a health care worker, it is desirable to acquire protection as quickly as possible. This study was designed to compare the effectiveness for early and late antibody response to the hepatitis B vaccine administered on days 10, 21 and 365 after the first dose versus the classic four-dose vaccination schedule.

Subjects and Methods

This study was carried out during a one-year study period in the Clinical Bacteriology and Infectious Disease Department of the Medical Faculty of Çukurova University. One hundred and forty five subjects who were negative for HBsAg, Anti-HBs, Anti-HBc tests were enrolled. Twenty five subjects were excluded because they were lost to follow-up. The remaining 120 subjects, who were healthy volunteers and had no history of vaccination for hepatitis B, were included.

Individuals with a known immune deficiency condition (eg: HIV positivity), diabetes mellitus, chronic renal failure, pregnancy, age above 60 years, children under age 2 years, and those with histories of occupational exposure were excluded from the study. In group A family members of hepatitis B carriers and health personnel agreeing to join the study were included while in B group healthy individuals without any history of exposure who reported for vaccination against hepatitis B were included.

After approval, participants were assigned to either a three-week schedule (on days 10 and 21 after the first dose) as group A or the standard schedule (on month 1 and 2, after the first dose) as group B. For each individual in the standard Group B, three subjects were enrolled into group A. The recombinant hepatitis B vaccine (Gen-Hevac B, Pasteur) was given as 20 μg intramuscular injections via the deltoid muscle. The booster dose on day 365 was planned for each group. The local ethics committee approval was obtained for the study.

Anti-HBs levels were detected in serum samples of subjects obtained on days 30, 60 and 90 after the first vaccination. Subjects whose antibody titers failed to reach the seroprotective level on day 90 were retested on day 180. HBsAg, Anti-HBc and Anti-HBs levels were determined by EIA (Abbott, AuxSYMSys).

The geometric average of the Anti-HBs levels in both groups, on days 30, 60 and 90 after the first vaccination were determined. The protective level of Anti-HBs was defined as titers ≥10 mIU/ml. The results were evaluated using the Fisher's exact test and geometric mean titers were compared using the Wilcoxon test. Results are given with a 95% confidence level.

Results

Group A consisted of 90 subjects, 50 (55.6%) female and 40 (44.4%) male, with an average age of 25.91 ± 11.92 years. There were 30 subjects in group B, 16 (53.3%) female and 14 (46.7%) male, with an average age of 22.53 ± 9.30 years. There was no significant statistical difference in age or sex between the two groups ($p > 0.05$).

Of all subjects, health care workers accounted for 23.3% of group A and 40% of group B ($p < 0.05$).

After three doses of vaccine, the Anti-HBs titers reached protective levels in both groups. The rate of vaccinees who had seroprotective levels of Anti-HBs (≥10 mIU/ml) on day 30 was 53 (58.9%) in group A and 9 (30.0%) in group B ($p < 0.05$). On day 60, there was no significant difference between group A and B, with rates of response at 84.4% (n = 76) and 80.0% (n = 24) respectively ($p > 0.05$). On day 90 there was no difference between group B and group A; 86.7% (n = 26) vs 87.7% (n = 79) (Table 1). Serum samples taken on day 180 indicated that protective antibody titers were attained in subjects of both groups, who had titers <10 mIU/ml^{-1} on day 90. With the booster dose (on day 365), Anti-HBs levels were over 100 mIU/ml in 60 and >1000 mIU/ml in only 12 subjects (6 from each group). In both groups there was no statistically significant difference in the antibody titers between males and females ($p > 0.05$).

The geometric average was estimated as 33.3, 72.4, 81.6 for group A, and 12.2, 55.8, 118.8 for group B on days 30, 60 and 90, respectively.

Table 1: Comparison of the AntiHBs responses after accelerated (A) and traditional (B) hepatitis B vaccination.

	Day 30			Day 60			Day 90			Day 180		
	Group A	Group B	p	Group A	Group B	p	Group A	Group B	p	Group A	Group B	p
AntiHBs < 10 mlUml-1 (%)	41.1	70.0	0.05	15.6	20.0	NS	12.3	13.3	NS	-	-	
AntiHBs ≥ 10 mIU ml^{-1} (%)	58.9	30.0	0.05	84.4	80.0	NS	87.7	86.7	NS	100	100	NS
AntiHBs GMT (CL)	33.3	12.2		72.4	55.8		81.6	118.8				

GMT: Geometric mean titer CI: 95% confidence interval NS: Not significant

Comparison of the Anti-HBs responses after the classic and accelerated hepatitis B vaccinations are shown in table 1.

Discussion

Immunization of susceptible persons against hepatitis B is necessary to prevent not only acute disease but also the carrier and chronic states of hepatitis B infection. The initial immune response to hepatitis B vaccines following the basic immunization series is an important determinant of the duration of immunity. Clinical trials have demonstrated the safety and efficacy of the hepatitis B vaccine [3,4].

Increasing the dose of vaccine, administering the inoculation intramuscularly and giving the vaccine more frequently can enhance the immune response. Although dose and intervals of hepatitis B vaccine is standardized, the schedule chosen for administering the vaccine also influences the antibody response [3]. Different accelerated schedules for hepatitis vaccination B has been used in neonates, immune competent adults or special hosts such as liver transplant candidates or alcoholic patients. Several studies have demonstrated that the accelerated schedule provides not only sufficient but also rapidly rising antibody levels for hepatitis B protection [5-17].

Immunization studies with normal hosts showed good response by the accelerated schedule. Orsolini and Goldfarb reported more rapid and comparatively high seroprotection rates with the conventional schedule in neonates [5,6]. Wahl noticed significantly higher protective antibody levels against Hepatitis B two weeks after the second dose of vaccine in the short interval vaccination and that all the vaccinees of this short interval vaccination schedule had seroconverted within two months. In addition Wahl noticed a more rapid achievement of the protective antibody levels. These findings led to the suggestion that the accelerated schedule could provide protective antibody levels earlier enough for especially those individuals at a high risk for HBV exposure [7]. Wilkinson et al investigated antibody levels among medical students and individuals at high risk and found that levels above 100 mIU/L were effective in the accelerated vaccination schedule [8]. In a five-year study, Belloni et al reported that there is no difference in antibody levels between the traditional and accelerated schedules at the end of the vaccination [9].

A few articles have been reported on patients with underlying immunological disorders who failed to produce protective antibody levels. In four different studies performed on alcoholic patients, hemophiliacs and liver transplant candidates, protective antibody levels could not be attained by the accelerated vaccination schedule probably due to the low responsiveness to immunization in these special hosts [10-13].

In the present study, on day 30, seroprotection of the vaccinees was 58.9% in group A and 30.0% in group B. Marchou et al and Kaya et al. have stated similar rates for both schedules [14,15]. In two different studies, Harries and Wahl reported seroprotection rates of 40% and 48% respectively, one month afterwards in an accelerated immunization schedule. Results of these studies indicate that the accelerated vaccination schedule could provide early protective immunity [7,16].

In our study, the Anti-HBs levels on day 60 in both groups were similar. The antibody titers provided by the classic schedule were similar to those by the three-week schedule on day 90 with no statistically significant differences between the two groups

Marchou et al reported similar results on two schedules in two different studies. In the two studies, one on chimpanzees by Ivarson et al and the other on humans by Wahl, the six-week schedule was found to be successful in post-exposure prophylaxis [7,17].

On day 90 eleven cases in group A and four cases in group B were found to have anti-HBs titers <10 IU. No case with levels below the protective level was found in both groups on day 180. Marchou et al has reported early and persistent protective immunity through accelerated schedule.

Besides they suggested application of the booster dose both schedules [14,18].

The geometric mean of antibody titers varied depending on the group selected for analysis. For example, all subjects or only responders at specifically designated anti-HBs levels. In this study, all subjects were investigated for the geometric mean titer.

In conclusion, in our study, the three-week vaccination provided protective antibody titers within a shorter time compared to the classic schedule. On follow-up, antibody titers were similar in both groups. It may be suggested that the accelerated dose vaccination protocol could be used for persons under high risk, such as family members of a hepatitis B virus carrier or health care workers or those wishing to travel to regions with high hepatitis B prevalence.

NS designed and coordination in the study, written the manuscript, ASİ participated in carried out and written manuscript, YT participated in coordination, OK participated in carried out.

Acknowledgments

The authors thank to Dr Gulsah Seydaoglu (Çukurova University, Medical Faculty, Department of Biostatistics) for statistical help with the study.

References

1. Moradpur D, Wands JR: **Understanding hepatitis B virus infection.** *N Engl J Med* 1995, **332:**1092-1093.
2. Szmuness W, Stevens CE, Harley EJ, Zang EA, Oleszko WR, William DC, Sadowski R, Morrison JM, Kellner A: **Hepatitis B vaccine.** *N Engl J Med* 1980, **303:**833-41.
3. Hollinger FB: **Factors influencing the immune response to hepatitis vaccine, booster dose guidelines, and vaccine protocol recommendations.** *Am J Med* 1989, **87(S3A):**36S-40S.
4. Lemon SM, Thomas DL: **Vaccines to prevent viral hepatitis.** *N Engl J Med* 1997, **332:**196-204.
5. Orsolini P, Belloni C, Klersy C, Campisi D, Chirico G, Togni C, Maccarini U, Polatti F, Martinetti M, Salvaneschi L *et al.*: **Anti-HBV neonatal immunization with recombinant vaccine. Part I. Critical appraisal for a long-lived antibody course.** *Vaccine* 1995, **13(6):**551-4.
6. Goldfarb J, Baley J, Medendorp SV, Seto D, Garcia H, Toy P, Watson B, Gooch MW 3, Krause D: **Comparative study of the immunogenicity and safety of two dosing schedules of Engerix-B hepatitis B vaccine in neonates.** *Pediatr Infect Dis J* 1994, **13(1):**18-22.
7. Wahl M, Hermodsson S, Iwarson S: **Hepatitis B vaccination with short dose intervals – a possible alternative for post-exposure prophylaxis?** *Infection* 1988, **16(4):**229-32.
8. Wilkinson SE, Morath M, Bennett DL, Burgess MA, Isaacs D: **Accelerated schedule of hepatitis B vaccination in high-risk youth.** *J Paediatr Child Health* 1996, **32(1):**60-2.
9. Belloni C, Pistorio A, Tinelli C, Komakec J, Chirico G, Rovelli D, Gulminetti R, Commolli G, Orsolini P, Rondini G: **Early immunisation with hepatitis B vaccine: a five-year study.** *Vaccine* 2000, **18:**1307-1311.
10. Rosman AS, Basu P, Galvin K, Lieber CS: **Efficacy of a high and accelerated dose of hepatitis B vaccine in alcoholic patients: a randomized clinical trial.** *Am J Med* 1997, **103(3):**217-22.
11. Santagostino E, Mannucci PM, Gringeri A, Rumi MG, Rafanelli D, Rocino A, Schiavoni M, Chistolini A, Di Bona E, Muleo G: **Accelerated schedule of hepatitis B vaccination in patients with hemophilia.** *J Med Virol* 1993, **41(2):**95-8.
12. Kallinowski B, Benz C, Buchholz L, Stremmel W: **Accelerated schedule of hepatitis B vaccination in liver transplant candidates.** *Transplant Proc* 1998, **30(3):**797-9.
13. Engler SH, Sauer PW, Golling M, Klar EA, enz C, Stremmel W, Kallinowski B: **Immunogenicity of two accelerated hepatitis B vaccination protocols in liver transplant candidates.** *Eur J Gastroenterol Hepatol* 2001, **13(4):**363-7.
14. Marchou B, Picot N, Chavanet P, Auvergnat JC, Armengaud M, Devilliers P, Cerisier JE, Marie FN, Excler JL: **Three-week hepatitis B vaccination provides protective immunity.** *Vaccine* 1993, **11:**1383-5.
15. Kaya A, Erol S, Taşyaran MA, Aktaş O, Y Imaz Ş: **Early antibody response of 3-weeks hepatitis B vaccination schedule.** *J of Turkish Med* 1997, **2:**1-4.
16. Harries AD, Clark M, Beeching NJ, Lavelle J, Mutton KJ: **Early anti-HBs antibody response to accelerated and to conventional hepatitis B vaccination regimens in healthy persons.** *J Infect* 1991, **23(3):**251-4.
17. Iwarson S, Wahl M, Ruttimann E, Snoy P, Seto B, Geretty RJ: **Successful postexposure vaccination against hepatitis B in chimpanzees.** *J Med Virol* 1988, **25(4):**433-9.
18. Marchou B, Excler JL, Bourderioux C, Salaun J, Picot N, Yvonnet B, Cerisier JE, Salamon H, Auvergnat JC: **A 3-week hepatitis B vaccination schedule provides rapid and persistent protective immunity: A multicenter, randomized trial comparing accelerated and classic vaccination schedules.** *Clin Infect Dis* 1995, **172:**258-60.