Comparative Immune Responses of Two Commercial Hepatitis B Vaccines

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One hundred healthy hepatitis B virus (HBV) seronegative persons were enrolled in a single blind randomized study to compare antibody and clinical responses to yeast recombinant S antigen vaccine (YSHBV) (Hepavax-gene, 1 ml: 20 μgr = one dose) and Chinese hamster ovary cells (CHO) recombinant Pre S2 + S vaccine (CS2SHBV) (Genhevac B, 0.5 ml: 20 μgr = one dose). 50 participant (group I) received 20 μgr of YSHBV by intramuscular (IM) injection at 0^{th},1^{st} and 6^{th} months (mo). 50 participants (group II) received 20 μgr of CS2SHBV by IM injection at 0^{th}, 1^{st} and 2^{nd} mo. Serological and biochemical responses were measured at 0^{th}, 1^{st}, 2^{nd}, 3^{rd}, 6^{th} and 7^{th} months in both groups. The proportion of vaccines with minor local complaints (mainly local pain, myalgia) and proportion developing antibody to surface antigen (anti-HBs) were similar for both vaccine groups (p >0.05), but anti-HBs titers were generally higher among recipients of CS2SHBV. Anti-HBs developed in 92% and 96%, in group I and II by 7^{th} month, respectively. These data imply that YSHBV vaccine is as well tolerated and immunogenic as CS2SHBV vaccine. However, further studies are necessary to compare the duration of immunity after vaccination for two vaccines. [Journal of Turgut Özal Medical Center 1996;3(3):169-172]

***Key Words**: Hepatitis B, vaccination, anti-HBs titers*

Ticari iki hepatit B aşısının immun cevabının karşılaştırılması

Randomize, tek kör planlanan bu çalışmada hepatit B için seronegatif olan sağlıklı 100 kişi test edildi. Yeast recombinant S antijen aşısı (YSHBV) (Hepavax-gene, 1 ml: 20μgr = 1 doz), Chinese hamster ovary (CHO) recombinant Pre S2+ S aşısı (CS2SHBV) (Genhevac B, 0.5 ml: 20 μgr = 1 doz) ile antikor ve klinik cevap yönünden karşılaştırıldı. 50 kişiye (group I) 20 μgr YSHBV aşısı 0, 1, ve 6. aylarda IM yapıldı. Diğer 50 kişiye (grup II) 20 μgr CS2SHBV aşısı 0, 1, ve 2. aylarda IM yapıldı. Gruplarda serolojik ve biyokimyasal ölçümler 0, 1, 2, 3, 6, ve 7. aylarda yapıldı. Her iki grupta aşıya bağlı minör komplikasyonlar (esas olarak kol ağrısı ve miyalji) ve yüzey antijenine karşı gelişen antikor (Anti-HBs) sonuçları benzer bulundu (p> 0.05). Fakat Anti-HBs titreleri genellikle CS2SHBV aşısı alanlarda daha yüksek bulundu. Anti-HBs oranı 7. ayda I. ve II. grupta sırasıyla % 92 ve % 96 olarak bulundu. Bu sonuçlara göre YSHBV aşısı S2SHBV aşısı gibi tolere edilebilir ve onun gibi immun cevap geliştirir. Bununla birlikte bu iki aşının immunitesinin uzun zaman periyotlarında karşılaştırılmasını yapan başka çalışmalar gerekir. [Turgut Özal Tıp Merkezi Dergisi 1996;3(3):169-172]

***Anahtar Kelimeler**: Hepatit B, aşılama, anti-HBs titreleri*

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The prevention of infection and disease caused by hepatitis B virus (HBV) depends on the production of adequate levels of antibodies directed against the antigenic regions of the HBV envelope proteins. These proteins are pre-S1, pre-S2 and S (1,2).

For several years , there have been three types vaccines licensed for prevention of hepatitis B viral infection. First generation was purified from the plasma of individuals chronically infected HBV and it contains pre S + S antigens (Heptavax-B) (1981). Second generation was developed from the yeast by recombinant DNA techniques and it contains only S antigens (Hepavax-gene, Engerix B, Recombivax HB). Third generation was developed from Chinese hamster ovary cell (CHO) culture by rDNA techniques and it contains Pre S2 + S (Genhevac B) (1989) (1-5).

In recent years it is reported that third generation HBV vaccines are more immunonogenic than conventional HBV vaccines (6,7).

In this study, we describe results of a randomized, blinded trial for comparing the immunogenicity and tolerability of an investigational; yeast recombinant HBV vaccine containing S antigen with a CHO recombinant HBV vaccine containing pre S2 + S antigen.

MATERIAL AND METHODS

One hundred (100) healthy participants, aged 20 to 45 years (mean 28.50 ± 5.80) (60 males, 40 females) were recruited from Malatya area and Turgut Özal Medical Center workers. All subjects were in good health by history, physical examination, and had negative tests for all serological markers of hepatitis B virus (ELISA, Organon) (HBsAg, anti-HBc, anti-HBs) and had a normal ALT level 1 week prior to the first vaccine injection.

Two vaccines were used: Hepavax-gene and Genhevac-B vaccines. Hepavax-gene comprises 20µgr HBV S protein. S protein is derived from fermentation cultures of a recombinant strain of the yeast (YSHBV). Genhevac-B comprises 20 µgr S protein and Pre S2 protein are derived from the CHO cell culture by recombinant DNA technology (CS2SHBV).

Participants who met the eligibility requirements were assigned sequential case numbers which were randomly allocated to either YSHBV or CS2SHBV. Sequential intramuscular (IM) injection of 1mL YSHBV vaccine (one dose) into a flaccid deltoid muscle was carried out at 0^{th}, 1^{st}, and 6^{th} months; and, 0.5 ml CS2SHBV (one dose) vaccine into deltoid muscle was carried out at 0^{th}, 1^{st}, and 2^{nd} months.

Participants were asked to record any injection site reaction or systemic complaint that might occur. This follow up period of blood samples for determination of HBV serological markers (HBsAg, anti-HBs, anti-HBc) and ALT level 0^{th}, 1^{st}, 2^{nd}, 3^{rd}, 6^{th}, and 7^{th} months after injection of vaccine. At these times all participants were questioned for concerning any in term illness, activity exposure or medications which might influence study parameters.

ELISA method were used for the determination of serological markers on previously frozen sera. Titers of anti-HBs were calculated in IU/L according to kit methods. An anti-HBs antibody titer of ≥ 10 IU/L in considered a 'protective level' (1,8-10).

The X^2 test was used for the statistical comparison of proportions of vaccines developing after vaccination.

RESULTS

All 100 participants completed the series of three vaccine injections. Their characteristics were shown in Table 1. Side effects were shown in Table 2.

Seroconversion rates of anti-HBs were shown in Table 3.

Anti-HBs titers at 7^{th} month were shown in Table 4.

Table 1. Demographic characteristics of participants

Characteristic	Group I	Group II
n	50	50
Age	20-45	20-45
Mean age	27.50 ± 4.48	29.60 ± 6.01
Males/Females	35/15	25/25
Hepatitis markers (-)	50	50
Normal ALT/AST level	50	50

Table 2. Side effects of vaccination

Side effect	Group I*	Group II*
General	--	--
Local		
• Edema	1 %2	2 %4
• Local pain	5 %10	6 %12
• Myalgia	1 %2	1 %2
• Other	2 %4	3 %6

*p > 0.05, between group I and II.

DISCUSSION

Many studies were done for hepatitis B prevention. It has become well known that hepatitis B is the most serious disease among viral hepatitis group disease, which is caused by the hepatitis B virus. Based on such research and knowledge , many kinds of developments were carried out in attending to prevent or treatment (1,3,11).

Studies have proved that the pre S2 region is significantly more immunogenic than the S region of HBsAg and contains a T-cell epitope capable of generating T-cell helper activity that may facilitate production of anti-HBs (5,6).

In this study, anti-HBs titers increased after each dose of two vaccines. And seroconversion rates of group I and II were 92% and 94% at 7th months, respectively. This difference was not statistically significant (p>0.05) (Table 3). Miskovsky *et al.* (1) found 95% and 96% for protective anti-HBs titers for YSHBV and CS2SHBV vaccines, respectively (p>0.05). Trepo *et al.* (3) found 80% and 87.8% for protective anti-HBs titers for similar vaccines (p<0.01). In others studies, Gizaris *et al.* (6) and Excler *et al.* (12) found 100% and 99.5% seroconversion of CS2SHBV vaccine, respectively.

We found the incidence of side effects as 2-12% in both groups. Symptoms were mild and transient and the most common symptom was local pain. These results were consisted with the others in literature (Table 2) (1,6).

Table 3. Seroconversion rates of two vaccines (anti-HBs)

		Vaccine		Seroconversion rate (%) after first injection (month)				
Group	n	type	mo	1	2	3	6	7 mo
I	50	YSHBV	(0, 1, 6)	34	62	62*	91	92
II	50	CS2SHBV	(0, 1, 2)	36	64	92**	94	94

*and ** rates are statistically significant (p< 0.05). p> 0.05, for the other rates.

Tablo 4. Anti-HBs titers at 7th months

		Anti-HBs titers IU/L					
		< 10		10 -50		51 to up	
Group	n	n	%	n	%	n	%
I*	50	4	8	20	40	26	52
II*	50	3	6	18	36	29	58

*p> 0.05 for anti-HBs titers.

As a conclusion, the results of this study indicate that YSHBV vaccine is as tolerable as and as immunogenic as CS2SHBV vaccine. However, duration of immunity should be investigated for a long time period for two vaccines.

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