Prevention of Vertical Transmission of Hepatitis B Virus A Randomized Clinical Trial and A Cost - Effectiveness Analysis

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Abstract : *A randomized clinical trial and economic analysis was conducted to assess the cost-effectiveness of combined and active immunization for prevention of vertical transmission of hepatitis B virus in high risk newborns (mothers with + HBsAg and + HBeAg). Eighty newborns whose mothers had positive HBsAg and HBeAg were randomized into either combined or only active immunization. These newborns were followed up for 1 year for HBsAg and HBeAg using ELISA technique. The rates of protection of vertical transmission of HBV by combined and active immunization alone were 91.9 and 84.2 per cent respectively. There was no statistically significant difference between the 2 regimens. The cost for prevention of one case of vertival transmission of HBV was 714 baht for vaccine alone and 1847 baht for combined immunization. Combined immunization should be as cost-effective as active immunization only if the cost of HBIG is less than 57 baht or the effectiveness of the vaccine alone regimen is less than 30 per cent.*

Although combined immunization offers the most effective measure for prevention of vertical transmission of HBV. Immunization by vaccine alone is much more cost-effective and should be used for mass immunization. (Thai J Obstet Gynaecol 1989;1:123-7.)

Keywords : vertical transmission, hepatitis B virus, randomized clinical trial, cost-effectiveness analysis

Hapatitis B virus (HBV) infection is endemic in Southeast Asia and tropical Africa[1]. Chronic carriers of HBsAg are at high risk of chronic persistent hepatitis, chronic active hepatitis and primary hepatocellular carcinoma[2-4]. In countries where HBV is endemic, transmission from carrier mothers to their infants has

been estimated to be the cause of about 20 to 40 per cent of all chronic HBV carriers[5]. Such transmission might account for as many as 50 million chronic HBV carriers throughout the world. In addition, chronic HBV carriers serve as a continuing source of infection for others. Thus, prevention of the vertical transmission of HBV should be one of the top priorities in the control and prevention of HBV infection and its associated sequeles.

The most important factor determining whether or not a mother will infect her child is the presence or absence of hepatitis B e-antigen (HBeAg)[6, 7]. HBsAg carrier mothers who were also HBeAg positive infected more than 90 per cent of their infants and most of these infants also became chronic carriers[7]. So, infants born to mothers with positive both HBsAg and HBeAg are at the highest risk of becoming HBsAg carriers.

Hepatitis B immunoglobulin (HBIG) alone or in combination with hepatitis B vaccine has been shown to be effective in the interruption of vertical transmission of hepatitis B virus[8-13]. Passive-active immunization by HBIG and hepatitis B vaccine seems to be the most effective method but it represents a tremendous increase in cost. Four doses of hepatitis B vaccine alone at birth, one month, two months and six months has been shown in a randomized clinical trial to be effective in prevention of HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg. The degree of protection of vaccine alone was not significantly less than those who received HBIG plus vaccine[11]. This might be explained by the small number of subjects in each study group. In Thailand the carrier rates of HBsAg have been reported to be 8 to 10 per cent[14, 15]. If hepatitis B vaccine alone can prevent vertical transmission of HBsAg as effectively as passive-active immunization by HBIG and hepatitis B vaccine, it should be the most cost-efective method. We, therefore, conducted a randomized clinical trial to assess the effectiveness of three doses of hepatitis B vaccine compared to hepatitis B vaccine in combination with HBIG in prevention of vertical transmission of HBV. A cost-effectiveness analysis was carried out using the data from the randomized clinical trial.

Materials and Methods

Starting from January 2, 1985, all pregnant women who attended the antenatal clinic, Srinagarind Hospital, Khon Kaen University were screened for HBsAg in their sera, using the reverse passive hemagglutination (RPHA) technique. Sera from HBsAg pregnant women carriers were further tested for HBeAg, also by RPHA technique. These pregnant women with positive HBsAg and HBeAg were invited for an interview by the principal investigator. The risk of vertical transmission of HBV and the design of the study were explained to them. Special well-baby care was provided for their infants by the pediatricians. Written informed consent was obtained from each mother. Infants born

to these mothers were randomized into the vaccine and vaccine in combination with HBIG groups, (40 for each group). Infants in the vaccine group received 3 doses of hepatitis B vaccine (H-B VAX® containing 10 mcg per 0.5 ml) within 24 hours after birth, at 1 and 6 months of age. Infants in the combination group received 1 ml of HBIG (Hyperhep® containing 200 IU of anti-HBs per ml) within 24 hours after birth and 3 doses of vaccine at the corresponding time with the vaccine group. The vaccine was given intramuscularly in the anterolateral thigh. HBIG was injected separately in the other thigh. Infants of both groups were screened for HBsAg at birth, 1 month, two months, four months and six months by RPHA technique using two capillary tubes of blood and at one year of age by ELISA technique, Fig. 1. One week prior to the appointment date, memoranda was mailed to remind each mother. If the mothers and their infants did not show up on the appointment date, a second memorandum was sent to ask them to come the following week. If they did not show up at the next appointment schedule, the research assistant visited them, collected the infant's sera and made an appointment for the next visit if the mothers wanted to continue participating in the study.

Results

The prevalence of HBsAg among pregnant women who attended the antenatal clinic at Srinagarind Hospital was

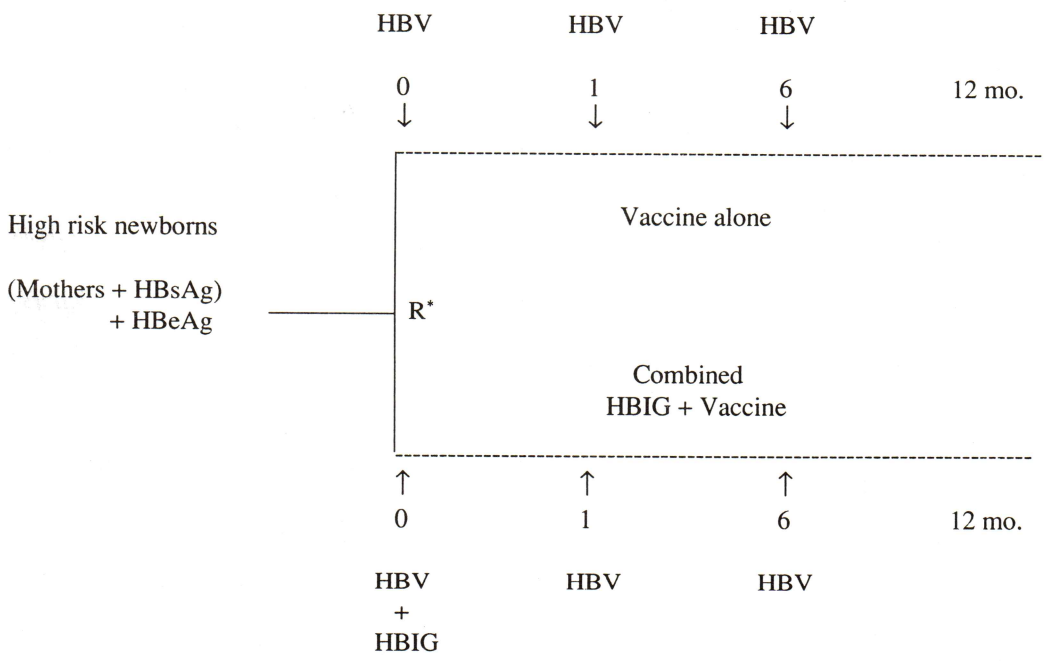

Fig. 1 Immunization schedule of both regimens
R* = Randomization

6 per cent. About one-third of these women also had positive HBeAg. Thirty-eight of forty infants in the vaccine alone group completed the one-year follow up schedule, while 37 of 40 infants in the combined group completed the same one year follow up schedule. The effectiveness of vaccine alone and combined vaccine and HBIG in preventing the vertical transmission of hepatitis B virus was 84.2 and 91.9 per cent respectively. The difference was not statistically significant (p=0.25, Fisher's Exact Test), Table 1. The cost for protection of one case of vertical transmission of HBV by vaccine alone regimen was 714 baht, while that of combined regimen was 1847 baht (US$ 1=25 baht), Table 2. The marginal cost, i.e. the cost for obtaining better prevention by adding HBIG to vaccine alone regimen was 13750 baht per one addition case prevention, Table 3.

Table 1 Effectiveness of immunization regimens

Regimen	Effectiveness* (95% CI)
Vaccine alone	32/38 = 84% (73-96)
Combined HBIG and Vaccine	34/37 = 92% (91-101)

P =0.25, Fisher's Exact Test
* Effectiveness = Negative HBsAg at 12th month

Table 2 Cost-effectiveness of immunization regimen

Analysis	Vaccine alone regimen	Combined regimen
Cost per case*	600	1700
Effectiveness	84 %	92 %
Cost per one case protection	714 (600 -0.84)	1847 (1700 - 0.92)

* 1 dose of vaccine = 200 baht
1 dose of HBIG = 1100 baht

Table 3 Marginal cost

Cost of combined immunization per 100 cases	=	170000 B
Cost of vaccine alone immunization per 100 cases	=	60000 B
Additional cost for combined immunization per 100 cases	=	110000 B
Number of cases prevented by combined regimen (Effectiveness 92%)	=	92
Number of cases prevented by vaccine alone regimen (Effectiveness = 84%)	=	84
- number of addition cases prevented	=	8
- additional cost for one addition case prevented (Marginal cost)	=	110000-8 13750 B

Discussion

This study confirmed the findings that the combined HBIG and vaccine regimen is the most effective regimen in preventing vertical transmission of hepatitis B virus. Hepatitis B vaccine alone regimen is also very effective. Although the combined regimen is more effective, the difference was not statistically significant. This study had an 80 per cent power in detecting 30 per cent difference given α-ereor = 0.05, β-error = 0.2 [14]. By economic analysis, the vaccine alone is much more cost-effective and should be recommended for mass immunization. Sensitivity analysis revealed that combined immunization would be as cost-effective as vaccine alone only if the cost of HBIG is less than 57 baht per

dose or the effectiveness of the vaccine alone regimen is less than 30 per cent which is very unlikely.

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