Selected Summaries

Immunization for Hepatocellular Carcinoma

[Chang MH, Chen C], Lai MS, Hsu HM, Wu Tc, Kong MS, et al. Universal Hepatitis B Vaccination in Taiwan and the Incidence of hepatocellular Carcinoma in Children. N Eng } Med 1997; 336:1855-1859].

Taiwan which has a population of 21 million, launched its mass hepatitis B vaccination programme in July 1984. Initially given to neonates born to HBs Ag positive mothers, it was extended to all neonates from July 1986. Till 1992, plasma derived vaccine was used following 0,1,2, 12 months schedule and from November 1992, recombinant vaccine was used following 0,1,6 months schedule. Those who missed the scheduled vaccination were encouraged to get vaccinated on a fee for service basis. The overall vaccine coverage rate was 84-94%.

The ultimate goal of hepatitis B vaccination programme was to reduce the virus related mortality particularly from hepatocellular carcinoma (HCC). In Taiwan close to 100% of children with HCC are HBs Ag positive as opposed to 70-80% of adults with HCC. Overall decrease in HCC as a result of the vaccination programme may not be seen for 40 years or longer in Taiwan since the incidence of HCC peaks in the sixth decade of life. The early evidence of the impact of the vaccination programme could be the reduction in the incidence of childhood HCC. With this objective in mind, the authors (who are part of Taiwan Childhood Hepatoma Study Group) collected data on incidence of childhood HCC and mortality from 1981 to 1994. To exclude children with hepatoblastoma, only children 6 years old and above were studied.

The average incidence of HCC in 6-14 years old children was 0.70 per 1,00,000 children in 1981-1986. It declined to 0.57 for the period from 1986 to 1990. When the cohort who had been vaccinated reached 6 years of age, *i.e.,* from 1990, the incidence of HCC was 0.36 for the period 1990-1994. The age adjusted relative risk of HCC after as compared with before 1990 (i.e., after and before the effect of vaccination started) was 0.33 ($p < 0.001$). More specifically there were 82 instances of HCC (0.52 per 1,00,000) in birth cohort 1974-1984 as compared to only 3 instances of HCC (0.13 per 1,00,000) in the after programme birth cohort 1984-1986, ($p < 0.001$). Of the 3 cases of HCC in the vaccinated cohort, 2 were born to HBsAg carrier mothers and became seropositive despite vaccine and immunoglobulin administration. The third child despite being HBsAg negative, had HBV genome detected in the liver tissue by polymerase chain reaction assays. The age adjusted relative risk of death due to HCC after as compared to before July 1990 was 0.51 ($p < 0.001$). Neither the overall incidence of childhood cancers nor the incidence of brain tumors in children showed similar decrease during the study period, thereby ruling out the decrease in HCC as a secular trend.

Comments

HCC is one of the 10 most common cancers in the world and it bears a consistent and specific causal association with hepatitis B virus with an attributable risk of about

80%(l). Thus hepatitis B virus is second only to tobacco among the known human carcinogens. The key event in oncogenesis is believed to be the integration of HBV genome into the host hepatocyte DNA and this could be prevented only by eliminating the HBV carrier state by an active immunization programme. Previously it was shown that in Taiwan, a hyperendemic zone of HBV, with universal immunization of infants, the HBV carrier state in 6 year old children was reduced from 10% in the period 1981 to 1986 to about 0.8-0.9% in the period 1990-1994(2). This study demonstrates that the reduction in carriage rate is associated with a concomitant reduction in HCC. Thus the present study, for the first time, provides the direct evidence of the effectiveness of hepatitis B vaccination in reducing the incidence of HCC and firmly establishes the causal role of HBV in hepatocellular carcinoma. Quite rightly, this Taiwanese study has been hailed as 'a milestone in the annals of preventive medicine'!(3).

The 3 cases of HCC in the vaccinated population is a matter of concern. Documentation of vaccine response by measurement of anti HBsAg titers in infants born to HBsAg carrier mothers and in case of non responders, giving booster doses as recommended by American Academy of Pediatrics may bring down significantly the occurrence of break-through cases(4). Since recombinant vaccines were used only from November 1992, the cohorts who received them will reach age six only in 1998. The present study therefore presents the efficacy of plasma derived vaccine only. It will be interesting to find out if the recombinant vaccines achieve better protection.

Coming to the Indian scenario there are an estimated 36 million HBV carriers or 4% of the population(5). Though the Government has been considering the possibility of including HBV vaccine in UIP ever since it was launched in 1985, funds constraint has been a major deterrent. About 500 crores are needed for immunizing 25 million children born in India every year which is about one fourth of the Health Department's 'budget allocation for the year 1997-98(6).

WHO has recommended the adoption of universal hepatitis B immunization for infants, adolescents or both by the end of this year and given the fact that universal hepatitis B vaccination programme is now in place in 85 countries including third world countries like Gambia(7), let us hope that Hepatitis B vaccine will be included in India's UIP during the ninth five year plan!

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Blood Transfusion and Retionopathy of Prematurity

[Hesse L, Eberal W, Schlaud M, *Poets CF. Blood transfusion, iron load and retinopathy of prematurity. Eur] Pediatr 1997; 56: 465-470].*

This study was a prospective observational cohort study in a level III Neonatal Intensive Care Unit to study the relationship between blood transfusion, iron overload and retinopathy of prematurity (ROP). During a 24 month period, data on volume of blood transfused during the first 6 weeks of life and on incidence of ROP were collected in all surviving very low birth weight infants (n=114; median birth weight 1130 g). ROP developed in 49 infants (43%); 23 of these (20% of the total population) had threshold disease and received cryotherapy. Association between these data and value for serum iron, transferrin and ferritin measured at weekly intervals were analyzed in a nested case control design by logistic regression.

Infants who developed ROP had significantly lower gestational age at birth and birth weights, received additional inspired oxygen and mechanical ventilation for longer periods of time and had more blood transfused. After adjustment for gestational age of birth, duration of oxygen therapy (FiO_2 > 0.3) and duration of mechanical ventilation, the relative risk for developing ROP was 6.4 (95% CI 1.2-33.4) for infants who had received 16-45 ml/kg and 12.3 (1.6-92.5) for those who had received more than 45 ml/kg of blood (reference 0-15 ml/kg). In contrast there was no independent relationship between ROP and any of the parameters on iron metabolism analyzed. This study confirmed the role of blood transfusion as an independent risk factor for ROP. This relationship does not appear to be mediated by increased iron load.

Comments

With increased survival of very low birth weight infants, the incidence of ROP is increasing. The need to identify potential modifiable risk factors for this disease thus becomes more and more pressing. Blood transfusion is one such risk factor which has been implicated in earlier studies(l,2). But data on iron metabolism and correlation with actual volume of blood transfused had not been previously determined. Also association has not been shown to be independent of other confounding factors in some previous studies(2). Since most risk factors of ROP are closely related to prematurity, they are found to be highly interdependent. This makes it difficult to define the specific role of any individual factor in the pathogenosis of ROP. Multivariate regression analysis used in this study provides a helpful tool in this situation which has been used earlier also in two studies(l,3).

The present study clearly suggests that repeated blood transfusions increase the

risk of ROP. However, because of the observational nature of this study it cannot be concluded that a more restrictive transfusion policy will reduce the incidence of ROP particularly as there is evidence that low level of tissue oxygenation which would be expected if VLBW infants are transfused less frequently may also be a risk factor for ROP(4). Only a randomized control trial can answer this clinically important question.

Recent data have highlighted the risks associated with transfusion, transmission of infection(5) sensitization of variety of blood component antigens(6) and even graft versus host disease(7). It is, therefore, important to consider its risks versus benefits before administering blood transfusions in various neonatal situations.

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