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Hepatitis B vaccination in preterm infants: three-year follow-up

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Summary

Background: *An optimal vaccination schedule for VLBW infants is still under debate. The aim of the study was to analyze factors influencing the efficacy of hepatitis B vaccination in VLBW infants.*

Material and Methods: *211 newborns of HBsAg negative mothers (mean birth weight 1234±24g and mean gestational age 29.2±0.18 weeks) were observed. The patients who were vaccinated before their transfer to the tertiary NICU (mean age: 1 day, range: 0–9) were enrolled into the group A (early vaccination, N=100), the others into the group B (delayed vaccination, N=111). In the group B vaccination was postponed on average until the 53rd day of life (range: 11–179 day). According to the schedule of vaccination two subgroups of infants were identified - receiving 3 doses (at the age of 0, 1 and 6 months, n=81) or 4 doses of vaccines (at the age of 0, 1, 2 and 12 months, n=105). After 2, 12 and 36 months from the beginning of vaccination the serum level of antiHBs was measured.*

Results: *A positive response (⩾10mIU/ml) was found after 2 months in 42 (51%) and 60 (69%) newborns (p<0.01); after 12 months in 46 (82%) and 62 (91%) newborns, and after 3 years in 25 (76%) and 37 (84%) newborns in the group A and the group B respectively. More infants from the group A received an additional, unscheduled dose of vaccine (11% vs. 2.7%, p=0.02). Per protocol analysis after 36 months from the beginning of vaccination reveled the significantly lower number of responders in the group of early vaccinated babies (64% vs. 88%, p=0.04). There was a statistically significant lower response in newborns vaccinated before the 32nd week of post conceptual age (after 2 months: 49 vs. 68%; p<0.01, after 12 months: 80 vs. 92%, and after 3 years: 74 vs. 85%). It was also found that the prevalence of Gram-negative sepsis was higher in the group B newborns that showed no response to the vaccination. The number of responders after 36 months did not differ significantly between the groups of infants receiving 3 or 4 doses of primary vaccination (75 vs. 86%). During the follow-up no case of hepatitis B was observed.*

Conclusions: *Newborns' response to hepatitis B vaccination depends on post-conceptual age. The authors suggest that the vaccination of newborns born before the 28th week of gestational age should be delayed until the 2nd month of life. There is no evidence that a 4-dose schedule is more effective than a 3-dose schedule in preterm infant.*

Key words: hepatitis B vaccine • prematurity • antibodies • immunogenicity

BACKGROUND

Hepatitis B is still one of the major health problems in the world. It is estimated that 300 million people worldwide carry HBs antigen, and yearly 2–3 millions of people die due to hepatitis B. Poland belongs to the countries of a middle risk of infection. The carrier rate in Poland has been reported to be 1.6% [1]. Many studies have shown that hepatitis B vaccination prevents both vertical and horizontal transmissions. Therefore, obligatory vaccination against hepatitis B was initiated in Poland in 1996. The Polish Neonatal Society advises hepatitis B vaccination just after birth in all infants, regardless of birth weight or gestational age, but an optimal vaccination schedule for very low birth weight infants is still under debate [2]. The aim of the study was the analysis of factors influencing the efficacy of hepatitis B vaccination in very low birth weight infants.

MATERIAL AND METHODS

Subjects

Over the period of 8 years (June 1995 – June 2003) 211 newborns were recruited to the study. Inclusion criteria were as follows: (a) birth weight ⩽2000 g, (b) gestational age <37 weeks, (c) age on admission <10 days, (d) negative maternal HBs antigen. Infants who had received anti-HBs immunoglobulin were excluded.

Table 1. Baseline characteristic of studied infants.

	Early hepatitis B vaccination (N=100)	Delayed hepatitis B vaccination (N=111)	p
Birth weight (g) (x±SEM)	1334±35	1141±31	<0.01*
Gestational age (wks.) (x±SEM)	30±0,25	28.6±0,2	<0.01*
Apgar score after 5 min. (Median; range)	6 {2–10}	6 {1–10}	n.s.**
Female	50 (50%)	57 (51%)	n.s.***
Weight at the first vaccine dose (g)(x±SEM)	1371±37	1632±39	<0.01*
Postconceptual age at the first vaccine dose (wks.) (x±SEM)	30±0.4	37.7±0.68	<0.01*
The need of mechanical ventilation	61 (61%)	71 (64%)	n.s.***

n.s. – non significant; * t-student test;
** Mann-Whitney U-test; *** Fischer's exact test

Table 2. Comparison of effectiveness of vaccination between the groups of early and delayed hepatitis B vaccination.

	Early hepatitis B vaccination (N=100)	Delayed hepatitis B vaccination (N=111)	p (Fischer's exact test)
Responding to vaccine after 2 months of vaccination (n/%)	42/82 (51%)	60/87 (69%)	0.01
Responding to vaccine after 12 months of vaccination (n/%)	46/56 (82%)	62/68 (91%)	0.1
Responding to vaccine after 36 months of vaccination (n/%)	25/33 (76%)	37/44 (84%)	0.1
Additional dose(s) of vaccine	11 (11%)	3 (2.7%)	0.02
Responding to vaccine after 36 months of vaccination – per protocol analysis (n/%)	14/22 (64%)	37/42 (88%)	0.04

Intervention

The patients who were vaccinated before their transfer to the tertiary NICU were enrolled into the group of early vaccination (group A), others into the group of delayed vaccination (group B). The newborns included into the group A received the next vaccination according to two schedules: from June 1995 through December 1998 four doses of vaccine (at the age of 0, 1, 2 and 12 months) and from January 1999 through June 2003 three doses of vaccine (at the age of 0, 1 and 6 months). In the group B vaccination was postponed (on average until the 53rd day of life, range: 11–179 day). Serum HbsAg and liver enzymes were evaluated before the first dose of vaccine. The newborns included into the group B received vaccines according to two schedules: (a) at the 0, 1, 2, 12 month (from June 1995 through December 1998) or (b) at the age of 0, 1, 6 months (from January 1999 through June 2003). A recombinant hepatitis B vaccine was used in all infants (Engerix B, GlaxoSmithKline Biologicals, Belgium, 10 mg per dose or Euvax B, Aventis Pasteur, 10 mg per dose). After 2 months (after 2 doses), 12 months (after 3 doses) and 36 months from the beginning of vaccination the serum level of antiHBs was measured. Blood samples were allowed to clot and antiHBs antibody titers were determined using commercial radioimmunoassay kits (Abbott Laboratories). A positive response to vaccination was defined as an antiHBs level ⩾10 mIU/ml.

Statistical analysis

Categorical variables were statistically analyzed using a chi-square test or a Fischer exact test. Continuous variables were analyzed using a t-student test or a Mann-Whitney U-test. Statistica for Windows statistical software version 6.0PL (StatSoft, Inc.2001) was used for the analyses, and $p<0.05$ was considered statistically significant.

RESULTS

Basic characteristic of the studied infants is presented in Table 1. The mean birth weight (±SEM) of studied infants equaled to 1234±24 g and the mean gestational age (±SEM) equaled to 29.2±0.18 weeks. 74 (35%) newborns weighed less than 1000 g, and the birth weight of 89 (42%) newborns was between 1001–1500 g.

One hundred newborns were enrolled into the group of early vaccination (group A) and 111 into the group of delayed vaccination (group B). According to the schedule of vaccination two subgroups of infants were identified – receiving 3 doses (n=81) or 4 doses of vaccines (n=105). Twenty-five newborns had individual schedules.

The mean follow-up time equaled to 5.3 years (range: 1.1–6.7 years). At the end of the study 149 infants were more than 3 years old, and 62 were 1–3 years old. In all newborns at least one antiHBs level was measured. One hundred sixty-nine patients (80%) had the antiHBs level measured after 2 months since the beginning of vaccination, 124 (59%) after 12 months and 77/149 (52%) after 3 years.

A positive response (⩾10 mIU/ml) was found after 2 months in 42 (51%) and 60 (69%) infants ($p<0.01$); after 12 months in 46 (82%) and 62 (91%) children, and after 3 years in 25 (76%) and 37 (84%) children in the group A and the group B respectively (Table 2.). More infants from the group A received an additional, unscheduled dose of vaccine (11% *vs.* 2.7%, $p=0.02$). Per protocol

Table 3. Effectiveness of vaccination according to postconceptual age.

Postconceptual age	⩽28 weeks	29–32 weeks	32–36 weeks	>36 weeks
Responding to vaccine after 2 months of vaccination (n/%)*	9 (40%)	23 (52%)	38 (69%)	32 (67%)
Responding to vaccine after 12 months of vaccination (n/%)*	13 (72%)	29 (86%)	36 (90%)	30 (94%)
Responding to vaccine after 36 months of vaccination (n/%)	7 (70%)	16 (76%)	19 (86%)	20 (83%)

* $p<0.05$ for chi-square Pearson test

Table 4. Risk factors influencing efficacy of vaccination in the group of infants with delayed vaccination.

	Responders (N=60)	Non-responders (N=27)	p
Birth weight (g) (x±SEM)	1181±44	1140±55	n.s.*
Gestational age (wks.) (x±SEM)	28.9±0.25	28.6±0.23	n.s.*
Apgar score after 5 min. (Median; range)	6 {1–10}	6 {1–10}	n.s.**
Female	32 (52%)	8 (30%)	0.06***
Weight at the first vaccine dose (g)(x±SEM)	1605±50	1786±79	n.s.*
Postconceptual age at the first vaccine dose (wks.) (x±SEM)	38.1±1.1	37.8±1.0	n.s.*
Gain weight to the date of first vaccination (g/wk) (x±SEM)	56±6.3	63±7.0	n.s.*
The need of mechanical ventilation	36 (59%)	16 (59%)	n.s.***
Blood products administration during 7 days after any vaccination (n/%)	43 (73%)	20 (77%)	n.s.***
Gram-negative sepsis (n/%)	4 (6%)	5 (19%)	0.1***

n.s. – non significant; * t-student test;

** Mann-Whitney U-test; *** Fischer's exact test

analysis after 36 months from the beginning of vaccination reveled a significantly lower number of responders in the group of early vaccinated babies (64% *vs.* 88%, p=0.04). There was a statistically significant lower response between children vaccinated before the 28th week of post conceptual age and these vaccinated between the 28–32nd week of post conceptual age (Table 3.).

The number of responders after 36 months after the beginning of vaccination did not differ significantly between the groups of children receiving 3 or 4 doses of vaccination (75 *vs.* 86%). During the follow-up no case of hepatitis B was observed.

Additionally, risk factors influencing efficacy of vaccination in the group of infants with delayed vaccination were analyzed. The prevalence of Gram-negative sepsis was higher in the group B children who showed no response to the vaccination. Birth weight, weight at vaccination, post conceptual age, and weight gain before vaccination did not differ between the groups of responders and non-responders (Table 4.).

Discussion

In the studied group a positive response to hepatitis B vaccination after 2 months was noted in 60% children and after 12 months in 87% children. In the published studies success rate of hepatitis B vaccination was reported as 25–66% and 52–95% respectively [3–9]. Observed differences between the studies depend on the studied population and vaccination policies used.

In the studied population the response of early vaccinated babies was significantly lower compared to late vaccinated babies. Losonsky et al. studied 148 preterm infants vaccinated just after birth [5]. After 2 doses of vaccine a positive response was observed only in 25% cases. Authors observed a significantly lower response of ELBW babies (only 11%). After 3 doses 52% of babies who weighed less than 1000 g responded, 68% of these who weighed between 1000–1500 g, and 84% of the babies who weighed >1500 g. Almost all (26/27) non-responders had birth weight <1700 g.

A comparison of the efficacy of early vaccination between full-term and preterm newborns was presented by Freitas de Motta et al. [10]. Three months after the 3rd dose the seroconversion rate in preterm infants was significantly lower than in full term infants (77% *vs.* 98%). The authors conclude that the administration of hepatitis B vaccine shortly after birth in preterm infants with the weight <1800 g may be inadequate.

In our population, we found a significant correlation between maturity of the baby and its response rate. A positive response in newborns vaccinated before the 32nd week of post conceptual age after 2 months of beginning of vaccination occurred only in 49% cases, after 12 months in 80%cases and after 3 years in 74% cases. Similar observations were published by Sood et al. [11]. A good response (antiHBs level >100 mIU/ml) after 2 doses of vaccine was observed in 95% babies with birth weight >2500 g, 60% infants weighing 1800–2499 g, and only 10% newborns weighing less than 1800 g. After 3 doses the response rates were 100%, 90% and 45%, respectively.

Blondheim et al. presented results of the study comparing efficacy of early vaccination between preterm and

full term infants [3]. After 1–2 months after the 3rd dose of vaccine the seroconversion rate did not differ between the studied group (88.7 *vs.* 93.4%). The authors conclude that hepatitis B vaccination is effective in most preterm infants. However, the mean birth weight of preterm group was 1.53 kg. In 1998, Belloni et al. published the data of hepatitis B vaccine immunogenicity in the cohort of 2209 neonates, including 241 preterm babies [12]. All infants received vaccines at the age of 4 days and 1 and 6 months. There was no difference in the seroconversion rate between the group of preterm and full term babies 1 month after the 3rd dose of vaccine. In the citied study, however, the authors treat less immature babies than we do.

Information on long term immunogenicity in preterm infants is limited. Khalak et al. evaluated 16 preterm and 17 full term babies at the age of 3 years [13]. The ratio of a positive response was similar in both groups (75 *vs.* 71%). The results of a 3-year follow-up study, presented by Linder et al., compared two three-dose protocols: vaccination beginning within 24 hours and delayed until the weight of 2000 g was reached [14]. In the group of delayed vaccination, the percentage of infants who reached a positive antiHBs antibody level was significantly higher (92.5 *vs.* 52.4%). A report of a seven-year follow-up of vaccine response was published by Kirmani et al. [15]. They evaluated 16 extremely preterm babies (birth weight <1000 g, gestational age <29 weeks). The antibody titers were significantly lower compared to full term babies, but similar proportions of children had protective HbsAB titers.

In our study we found a similar seroconversion rate in children who received an early and delayed vaccination. However, in the group of early vaccination more infants received unscheduled doses of vaccines. Analyzing the group of patient who received only scheduled doses; the number of non-responders was significantly higher in the group of early vaccinated children compared to late vaccinated children.

Because of the lower efficacy of early vaccination, some authors studied usefulness of early vaccination schedules containing one more dose. In the study performed by Ballesteros et al. twenty-nine preterm babies (mean birth weight 1398 g) received doses of vaccines at birth and the age of 1, 5 and 9 months [6]. Arora et al present similar results [16]. In preterm infants who received the fourth dose the proportion of infants with protective antibody levels (12.2%) was significantly higher than the proportion reached with only three doses.

In the present study we used 2 schedules of vaccination. At the age of 36 months the efficacy of both schedules was similar.

Additionally, risk factors influencing the efficacy of vaccination in the group of infants with delayed vaccination were analyzed. Birth weight, weight at vaccination, post conceptual age, and weight gain before vaccination, required respiratory support, blood products transfusions and steroid treatment did not differ between the groups of responders and non-responders. Only the prevalence of Gram-negative sepsis was non-significantly higher in the group of the newborns with delayed vaccination who showed no response to the vaccination. Similar results were presented by Blondhaim et al. [3]. Losonsky et al. observed a correlation between the seroconversion rate and weight gain during the first 6 months of life and the authors suggest that babies with poor weight gain need the evaluation of antibody titer at the age of 1 year [5].

Since 1994 the American Academy of Pediatrics recommended delaying the start of hepatitis B immunization in low-risk premature infants weighing less than 2 kg at birth until they reach 2 kg or until 2 months of age. In 2003 this statement was reevaluated and at present the AAP recommends to reschedule the first dose of hepatitis B vaccine: 'Medically stable preterm infants with birth weight less than 2000 g should receive the first dose of hepatitis B vaccine as early as 30 days of chronological age regardless of gestational age or birth' [17].

The presented results and the review of available studies support such thesis. However, the implementation of the AAP guidelines in other countries should be considered carefully. The local risk of HBV infection should constitute the main factor influencing hepatitis B vaccination policy. Balancing the risk of infection (current epidemiological status of Poland) and the lack of efficacy of early vaccination in extremely immature babies of HBsAg negative mothers, the authors suggest that the vaccination of newborns born before the 28th week of gestational age should be delayed until the 2nd month of life. Moreover, in babies with an increased risk of non-responding to vaccination, such as a history of Gram negative sepsis and poor weight gain, the evaluation of antiHBs level after primary vaccination should be considered. In preterm babies before the 3rd dose of hepatitis B vaccination, after major surgical procedures if antiHBs level is not known, hepatitis B immunoglobulin (HBIG) should be administered.

CONCLUSIONS

In the studied population the response of early vaccinated babies was significantly lower compared to the late vaccinated babies. Newborns' response to hepatitis B vaccination depends on post conceptual age. The authors suggest that the vaccination of newborns born before the 28th week of gestational age should be delayed until the 2nd month of life. There is no evidence that a 4-dose schedule is more effective than a 3-dose schedule in preterm infants.

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