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Prophylaxis of intravenous immunoglobulin and acyclovir in perinatal varicella

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Abstract Maternal chickenpox around the time of delivery can cause severe and even fatal illness in the newborn but an effectively preventive method has not yet been established. We proposed that a combination of intravenous immunoglobulin (IVIG) and acyclovir (ACV) intravenously could effectively prevent perinatal varicella. A group of 24 newborn infants whose mother had developed a varicella rash within 14 days before and after delivery were studied. Some 15 infants whose mothers’ rash appeared within 7 days before and 5 days after delivery were categorised as an at-risk group and received IVIG prophylaxis (500 mg/kg) administered soon after birth or post-natal contact either alone or with intravenous acyclovir (5 mg/kg every 8 h) for a total of 5 days starting from 7 days after the onset of maternal rash. Of four infants receiving IVIG alone, two developed clinical varicella. None of ten infants receiving both IVIG and ACV contracted varicella. One infant receiving ACV alone had no varicella vesicles either. Of nine infants in the not at-risk group four had undetectable varicella-zoster virus antibody on admission and developed clinical varicella subsequently.

Conclusion The combination of intravenous immunoglobulin given soon after birth and prophylactic acyclovir intravenously administered 7 days after the onset of maternal rash can effectively prevent perinatal varicella.

Key words Acyclovir · Intravenous immunoglobulin · Perinatal varicella

Abbreviations ACV acyclovir · IVIG intravenous immunoglobulin · VZIG varicella-zoster immune globulin · VZV varicella-zoster virus · VZVG varicella-zoster virus antibody IgG · ZIG zoster immune globulin

Introduction

Maternal chickenpox around the time of delivery can cause severe and even fatal illness in the newborn. The severity of the baby’s illness is determined by the timing of the mother’s illness in relation to delivery [6]. The risk is reported to be greatest when the mother’s rash appeared within 4 days before and up to 2 days after delivery [6, 14]. The administration of varicella-zoster immune globulin (VZIG) or zoster immune globulin (ZIG) to these high risk infants is recommended to prevent or reduce the severity of the illness [6, 14]. Neonatal infections may still occur in about 50% of the infants receiving ZIG prophylaxis and some of these infections may still be severe or fatal [3, 10, 11, 13, 15]. Therefore, some investigators [8, 9, 19], based on clinical

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experience, suggest that a combination of VZIG (or ZIG) and acyclovir (ACV) may be helpful for babies at risk of neonatal varicella. However, cases of neonatal varicella still occur.

Recently, we and others [2, 12, 20] demonstrated that after household or intimate contact with varicella cases, prophylactic oral ACV given to the susceptible siblings or playmates at the beginning of secondary viraemia (9 days after contact) in the late incubation period may prevent the attack of varicella. Hence we propose that prophylactic intravenous ACV given to the neonates at risk for severe varicella, starting from 7 days after maternal varicella, may prevent neonatal varicella. However, to keep the study infants from being at the risk of developing severe varicella, we also administered prophylactic intravenous immune globulin (IVIG) to each at-risk infant soon after birth in this study.

Patients and methods

Between September 1996 and July 1998, 24 newborn infants whose mothers had varicella rash within 14 days before and after delivery were included in this study. Some 15 babies whose mother’s rash appeared within 7 days before and 5 days after delivery were categorised as being at risk and the remaining nine formed the not-at-risk group. All but one of the infants in the at-risk group received prophylaxis of a single dose of 500 mg/kg of IVIG, administered soon after birth or notification of maternal varicella, either alone or with the addition of intravenous ACV (5 mg/kg every 8 h) for a total of 5 days, commencing 7 days after the onset of maternal rash. The infants in the not at-risk group received nothing for prophylaxis. All the infants were observed and examined by physicians. The skin lesions were classified as mild (<50 vesicles), moderate (50–100 vesicles) severe (>100 vesicles) according to the number of skin lesions.

Varicella-zoster virus antibody IgG (VZV IgG) was measured by enzyme-linked immunoassay method (HUMAN, Germany) in all infants on admission and, in 11 infants, at 3 months of age or later. Fifteen blood samples obtained on admission were also used for the detection of VZV DNA by nested polymerase chain reaction [18].

Results

Of the 24 infants, 13 were male and 11 female. Except for two premature infants, all infants were term babies. Fifteen infants were in the at-risk group and nine in the not-at-risk group. The clinical manifestations in relation to maternal varicella in these infants are shown in Table 1. Except for three infants whose mothers’ rash appeared 7 days before delivery, all the other infants in the at-risk group had no VZV IgG on admission. Of the 15 infants in the at-risk group, 4 infants received IVIG alone as prophylactic medication and two of them developed clinical varicella. Of the ten infants receiving both IVIG and ACV as prophylaxis, none developed clinical varicella. One infant, admitted beyond 4 days of life, received ACV alone as prophylaxis and had no varicella vesicles subsequently. The detailed results of prophylactic medications for these at-risk infants are shown in Table 2.

Among seven infants whose mothers’ rash appeared more than 7 days before delivery, VZV IgG was not detected in two infants. VZV DNA was detected only in one infant but both infants subsequently developed clinical varicella. Two infants whose mothers developed varicella more than 5 days after delivery both subsequently developed clinical varicella.

Discussion

In neonates with varicella, previous investigators have found a relatively high case fatality rate (30%) in defined-risk neonates, whose mothers had varicella within 4 days before and 2 days after delivery [6, 14]. Lack of VZV IgG at birth was demonstrated in these infants [4]. These observations have led to the current recommendation that VZIG (or ZIG) should be given to these defined-risk neonates [6, 14]. Hånggren et al. [10] gave ZIG to 41 such neonates but 21 (51%) infants became infected and two cases were severe. Miller et al. [15] reported 281 neonates with perinatal varicella treated with VZIG. Of these infants, 60% were infected and 16 of 19 infants with severe varicella were in the defined-risk group. No babies died in either studies (Table 3). However, death from varicella following VZIG treatment has been documented [11, 13]. A combination of VZIG and ACV (simultaneous administration) was therefore suggested by some investigators [8, 9, 19] but

<table>
<thead>
<tr>
<th>Varicella symptoms in neonates</th>
<th>Timing of appearance of maternal rash</th>
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<tr>
<td></td>
<td>&gt;7 days before delivery (n = 7)</td>
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<tr>
<td>VZV IgG (+) on admission</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4</td>
</tr>
<tr>
<td>Subclinical</td>
<td>1/4</td>
</tr>
<tr>
<td>Clinical</td>
<td>2</td>
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<tr>
<td>Mild</td>
<td>2</td>
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<tr>
<td>Moderate</td>
<td>0</td>
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<td>Severe</td>
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</table>

*a 15 infants received IVIG and/or ACV prophylaxis

*b No ACV