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Effect of intravenous immunoglobulin for neonates with severe enteroviral infections with emphasis on the timing of administration

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ABSTRACT

Background: The benefits of intravenous immunoglobulin (IVIG) therapy for severe neonatal enterovirus infections are still controversial.
Object: To evaluate whether timing of IVIG administration might affect clinical outcomes of neonates with severe enteroviral infections.
Study designs: We retrospectively analyzed 67 neonates with culture-confirmed severe enteroviral infection, defined as hepatitis with coagulopathy and thrombocytopenia. Clinical features, outcomes and the usage of IVIG therapy were collected and analyzed. IVIG administered within 3 days of illness onset was classified as early IVIG therapy.
Results: Of the 67 cases, 38 (57%) were male, 27 (40%) were premature, 57 (85%) had disease onset within 7 days of life and all but 2 cases were caused by coxsackievirus B group. Ten infants (15%) had clinically evident myocarditis. 41 infants (61%) received IVIG therapy and 29 were early IVIG therapy. Fifteen infants (22%) eventually died, without IVIG therapy for 7 infants. The deceased had a significantly higher peak serum aspartate aminotransferase (AST) level than the survivors (3539 vs. 866 IU/L, $p < 0.01$). The timing of IVIG therapy was highly correlated with the timing of peak AST level in patients with early IVIG therapy. Multiple logistic regression analysis showed that a higher nadir hemoglobin level (adjusted odds ratio 2.8, 95% confidence interval: 1.4–5.4), no concurrent myocarditis (42.6 [3.4–5289]) and early IVIG therapy (14.7 [1.3–163]) were independently associated with a favorable prognosis.
Conclusions: In defined severe neonatal enterovirus infections, serum AST level correlated with the disease severity. Early IVIG therapy, if needed, may be beneficial for survival.

1. Background

Manifestations of neonatal enterovirus infections range from inapparent infection to severe illness and even death. Factors affecting the severity of neonatal enterovirus infections include virus serotype, mode of transmission, and presence of passively acquired, serotype-specific maternal antibodies [1–3]. Severe neonatal enteroviral infections are commonly associated with coxsackievirus group B or echovirus, occur within the first two weeks of life and the mortality rate is higher than 30% [1,4,5]. Hepatitis with coagulopathy and concurrent myocarditis are the two hallmarks of severe neonatal enteroviral infections [4–6]. Currently, treatment of neonatal enterovirus infections is primarily supportive; possible beneficial effects of intravenous immunoglobulin (IVIG) or the antiviral agent, pleconaril, have been suggested but are inconclusive [7–13].

In the debate of therapeutic effect of IVIG therapy, the timing of IVIG therapy was rarely addressed. Kimura et al. ever indicated that

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initiating IVIG therapy within 3 days of severe neonatal coxsackievirus B3 (CVB3) infections may be beneficial to survival, but this issue has rarely been addressed since then [14]. This study retrospectively analyzed the clinical features, treatment, and prognosis of 67 neonates with severe enteroviral infection, with emphasis on the association between the timing of IVIG therapy and the clinical outcome.

2. Objective

To evaluate whether timing of IVIG administration might affect clinical outcomes of neonates with severe enteroviral infections

3. Study designs

3.1. The patients

The databases of the virology laboratory of Chang Gung Memorial Hospital (CGMH) were retrieved for eligible patients. From 1990 to 2005, a total of 272 neonates with enteroviral infections were identified and a total of 51 cases (19%) fulfilling the criteria of severe enteroviral infections were included. Of these 51 patients, 36 patients occurred before 1999 and had been reported previously [2]. In Taiwan the reporting system for severe enterovirus infections, including neonatal cases, was constructed since 2002. In 2005, a total of 26 neonates with severe infections, including 10 from CGMH, were reported to the Centers for Disease Control (CDC) of Taiwan; the 16 additional cases from other hospitals (14 treated in tertiary care centers) were also included in this study. Relevant clinical information including demographics, clinical symptoms and signs, detailed laboratory data and the usage and the timing of IVIG therapy, were collected.

The virus isolation and identification were performed in the virologic laboratory of CGMH using a standard method described previously [2].

3.2. Definitions

Severe neonatal enterovirus infection was defined as the presence of hepatitis and coagulopathy in a neonate (<1 month old) with culture-confirmed enterovirus infection. Hepatitis with coagulopathy was defined as presence of an serum aspartate aminotransferase (AST) level higher than 3 times the upper normal limit, thrombocytopenia (platelet count $<10^5/mm^3$), and prolonged prothrombin time/activated partial thromboplastin time [5]. Clinically evident myocarditis was defined as presence of tachyarrhythmia accompanied by decreased cardiac output (left ventricle ejection fraction <50% on an echocardiogram) or an elevation of serum level of cardiac fraction of creatine kinase or troponin-I without other alternative explanations for cardiac dysfunction. Meningitis was defined as presence of pleocytosis (white cell count >30/uL) or enterovirus in cerebrospinal fluid (CSF). Premature birth was defined as a gestation age of <37 weeks. Onset of disease was defined as the appearance of body temperature instability (fever or hypothermia), poor feeding, or poor activity noted by the caregivers. Early IVIG therapy was defined as IVIG administered to the patients within 3 days of illness onset; those received IVIG therapy beyond three days of illness onset were regarded as late IVIG therapy.

3.3. Statistics

The data were analyzed using SPSS Version 12.0. Data of each clinical feature and laboratory item was presented as a median (inter-quartile range) or frequency (%). A Mann–Whitney *U* test was applied to process continuous variables, and a chi-square or Fisher's exact test was applied to process categorical data. A Spearman's correlation coefficient (rho) was used to calculate the correlation between variables. Possible prognostic factors were screened using univariate analysis, and factors with a *p*-value of 0.2 or less were incorporated into stepwise multiple logistic regression to adjust for confounding factors simultaneously and to calculate the multivariate-adjusted odds ratio for risk factors. A p value < 0.05 was considered significant.

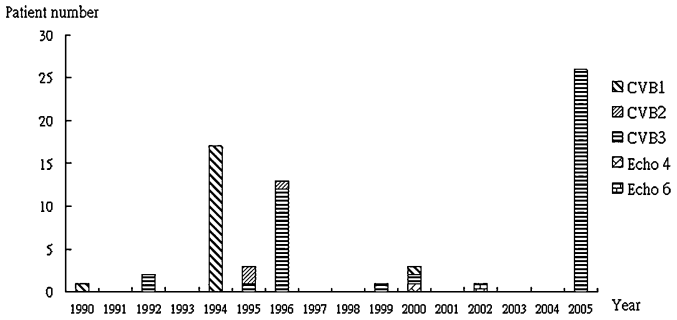

Fig. 1. Distribution of the calendar year of the 67 enrolled neonates. Most patients were enrolled in 1994, 1996, and 2005. CV: coxsackievirus; echo: echovirus.

4. Results

4.1. Epidemiological and clinical information

A total of 67 infants, mainly in 1994, 1996, and 2005, were included (Fig. 1). The major serotypes included coxsackievirus B1 (CVB1) (28%), and CVB3 (64%). All of the patients had EV identified from multiple sites and included throat swab in 56 patients, rectal swab in 53, CSF in 36, urine in 26, blood in 5, and ascites in 1. Five cases in 2005 also had CB3 detected in the blood by real-time polymerase chain reaction [15]. No significant association was observed between the serotype of enteroviruses and prognosis. Ten neonates (15%) had clinically evident myocarditis, and meningitis was noted in 93% of the 41 patients who received a lumbar puncture. A total of 15 (22%) died and included 3 caused by CVB1 infections, 1 by CVB2, 9 by CVB3, and one each by echovirus 4 and echovirus 6, respectively. The case fatality rate was not statistically different ($p = 0.58$) between the first 8-year period (9/36, 25%) and the second 8-year period (6/31, 19.4%). Of the deceased, the median hospital stay was 9 days (interquartile range, 7–21 days), five patients experienced a rapid clinical deterioration within 24 h of admission and seven patients did not receive IVIG therapy.

Of the 67 patients, 57 (85%) experienced symptom onset within 7 days of life, three experienced symptom onset from day 8 to day 14 of life, and seven from day 15 to one month of life. Body temperature instability, including fever and hypothermia, was the initial symptom for 60 (90%) patients. Of the remaining 7 patients without significant body temperature instability, poor activity, poor feeding, or jaundice were the initial presenting symptoms. 27 (40%) patients were born prematurely. Ecchymosis or petechiae were present in all patients within 1 or 2 days after symptom onset, and ascites was noted in 24 (36%) patients. Neonatal sepsis was suspected in all patients on admission. All patients received antibiotics and blood component transfusions, including red blood cells, platelets and fresh frozen plasma, during hospitalization. IVIG therapy was used in 41 (61%) patients. Maternal plasma transfusion was used in one survivor, who also received IVIG therapy. None of these patients received pleconaril therapy. Intramuscular hepatitis B immune globulin was used in one patient at birth and this patient also received IVIG within 3 days of illness. Extracorporeal mem-