Analysis of Changes in Plasma Tissue Factor and Serology in Treating Hemolytic Disease of the Newborn by Intravenous Gamma Globulin

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Abstract
Objective to study the changes in plasma tissue factor and serology in treating hemolytic disease of the newborn by intravenous gamma globulin. Methods 60 young children with hemolytic hyperbilirubinemia who visited our hospital from July, 2014 to July, 2015 were selected and randomized into observation group and control group. Conventional treatment and gamma globulin were adopted in control group and observation group respectively. Serum bilirubin levels, antibody titer, plasma levels of tissue factor, adverse reactions and therapeutic effect of young children in the two groups were observed. Results after treatment, the serum bilirubin level in observation group was 180.56±91.02 μmol/L, which was lower than the 263.04±90.12 μmol/L in control group. The difference was statistically significant (P<0.05). The difference in serum antibody titers between the two groups was not significant and it had no statistical significance (P>0.05). The TF level in observation group was 60.52±13.29 ng/L, which was lower than the 82.01±10.82 ng/L in control group. The difference was statistically significant (P<0.05). The incidence rate of adverse reactions in observation group was 10.00% (3/30), which was lower than the 33.33% (10/30) in control group. The difference was statistically significant (P<0.05). The total efficacy rate in observation group was 96.66% (29/30), which was higher than the 70.00% (21/30) in control group. The difference was statistically significant (P<0.05). Conclusion Intravenous gamma globulin has a significant efficacy in treating hemolytic disease of the newborn and it can lower plasma tissue factor and serum bilirubin to normal levels.

Keywords: Gamma globulin, Hemolytic disease of the newborn, Plasma tissue factor, Serology.

Introduction

Hemolytic disease of the newborn is an iso-immune hemolytic anemia that develops in a fetus whose blood group is incompatible with the mother and red blood cell are destructed because antibodies produced by the mother pass through the placenta, affecting the health of children.

The disease mostly occurs in the fetal and neonatal period and easily results in hyperbilirubinemia. If the disease is not promptly treated at early stage, it can evolve into bilirubin encephalopathy which leads to hands and feet movement slowly, hearing loss, mental deterioration and even lead to death in children [1]. Studies showed that gamma globulin was an immunoglobulin which can strength children's immunity and resistance to achieve effective anti-bacterial and anti-virus capabilities [2]. Since the neonatal immune function is not perfect and weak resistant, gamma globulin which increase the body's immune system has been used for pediatric clinical treatment in recent years and achieved good therapeutic effect. To improve the condition of children, the paper studies the changes in plasma tissue factor and serology in treating hemolytic disease of the newborn by intravenous gamma globulin. As the following this study is reported.

Material and Methods

General information: 60 young children with hemolytic hyperbilirubinemia who visited our hospital from July, 2014 to July, 2015 were selected in the study. Inclusion criteria [3]: (1) Diagnosed as hemolytic disease of the newborn, (2) Gestational age of 37 -42 weeks, (3) No other lesions. Exclusion criteria: (1) Disseminated intravascular hemolysis, (2) Gamma globulin allergy. All the patients were randomized into observation group and control group with 30 in each group according to a random number table. In observation group, there were 19 males and 11 females whose average weight was (3331.10±40.12) g and average days old was (5.18±1.21) days; in control group, there were 16 males and 14 females whose average weight was (3340.02±39.06) g and average days old was (5.88±1.32) days. All patients signed the informed consent. There was no statistically difference in general information between the two groups (P>0.05) and comparative analysis can be conducted.

Method: All the patients were randomized into observation group and control group according to a random number table. Young children in control group received conventional treatment including phototherapy, liver enzyme inducers and infusion. Young children in observation group received intravenous injection of gamma globulin (specification: 50mL/vial ; manufacturer: Shanghai Institute of Biological Products; batch number: 20140510) 800~1000mg/kg in one time on the basis of treatment in control group.

Observational parameters: Serum bilirubin levels, antibody titer, plasma levels of tissue factor, adverse reactions and therapeutic effect of young children in the two groups were observed. Serum bilirubin levels were

determined by Toshiba 7170A Automatic Biochemical Analyzer. TF were measured by Enzyme Linked Immunosorbent Assay. Antibody titers were tested by ELISA.

Efficacy evaluation criteria: Four grade criteria of complete response, partial response, no response and deterioration were adopted by observing the efficacy of patients in two groups according to the relevant literature. Complete response: decrease of serum bilirubin and plasma tissue factor to normal levels; partial response: significant decrease in serum bilirubin level and plasma level of tissue factor; no response: no change of serum bilirubin level and plasma level of tissue factor; deterioration: increase in serum bilirubin level and plasma level of tissue factor.

Statistical analysis: All the data were analyzed using software package SPSS 11.0. Quantitative data were expressed as average±standard deviation ($\bar{x}$ ±s). Groups were compared using analysis of variance and intergroup comparison was performed using t-test. Count data were expressed as the number of cases and percentage (%) and intragroup comparison were performed using chi-square test. The difference was regarded as statistically significant when P<0.05.

Results

Comparison of serum bilirubin levels between the two groups after treatment. The serum bilirubin level in observation group was lower than that in control group after treatment. The difference was statistically significant (P<0.05). See table 1.

Comparison of serologic test results between the two groups after treatment. The difference in serum antibody titers between the two groups was not significant and it had no statistical significance (P>0.05). See table 2.

Comparison of plasma level of tissue factor between the two groups after treatment. The plasma level of tissue factor in observation group was lower than that in control group after treatment. The difference was statistically significant (P<0.05). See table 3.

Comparison of adverse reaction between the two groups after treatment. The incidence rate of adverse reactions in observation group was lower than that in control group. The difference was statistically significant (P<0.05). See table 4.

Comparison of therapeutic effect between the two groups after treatment. The total response rate in observation group was higher than that in control group. The difference was statistically significant (P<0.05). See table 5.

Table 1
Comparison of serum bilirubin levels between the two groups after treatment ($\bar{x}$ ±s, μmol/L)

Group	Case	Serum bilirubin levels		t value	P value
		Before treatment	After treatment		
Observation group	30	352.10±101.13	180.56±91.02	6.9056	0.0000
Control group	30	369.18±100.20	263.04±90.12	4.3138	0.0001
t value		0.6571	3.5270		
P value		0.5137	0.0008		

Table 2
Comparison of serologic test results between the two groups after treatment ($\bar{x}$ ±s, %)

Group	Case	1:16	1:32	1:64	1:128
Observation group	30	20（66.66）	5（16.66）	3（10.00）	2（6.66）
Control group	30	17（56.66）	6（20.00）	4（1.33）	3（10.00）
t value		0.8154			
P value		0.4148			

Table 3
Comparison of plasma level of tissue factor between the two groups after treatment ($\bar{\chi}$ ±s, ng/L)

Group	Case	TF		t value	P value
		Before treatment	After treatment		
Observation group	30	101.12±20.23	60.52±13.29	9.1872	0.0000
Control group	30	118.72±15.42	82.01±10.82	10.6739	0.0000
t value		3.7898	6.8683		
P value		0.0004	0.0000		

Table 4
Comparison of adverse reaction between the two groups after treatment [n (%)]

Group	Case	Fever	Allergy	Shock	Total incidence rate
Observation group	30	2（6.66）	1（3.33）	0（0.00）	3（10.00）
Control group	30	5（16.66）	3（10.00）	2（6.66）	10（33.33）
X^2value		1.4555	1.0714	2.0690	4.8118
P value		0.2276	0.3006	0.1503	0.0283

Table 5
Comparison of therapeutic effect between the two groups after treatment [n (%)]

Group	Case	Complete response	Partial response	No response	Deterioration	Total response rate
Observation group	30	20（66.66）	9（30.00）	1（3.33）	0（0.00）	29（96.66）
Control group	30	14（46.66）	7（23.33）	5（16.66）	2（6.66）	21（70.00）
U/X^2value		1.7480				7.6800
P value		0.0805				0.0056

Discussion

Hemolytic disease of the newborn develops in a fetus when RBCs from the fetus enter the circulation of the mother and stimulate production of IgG antibody in the mother, then maternal antibodies cross the placenta and react with the corresponding antigens on the fetal RBCs to break down and destroy the cells [5]. The clinical symptoms include shortness of breath, rapid heartbeat, slow movement of hands and feet, hearing loss, mental deterioration, and even lead to death [6]. Studies showed that ABO blood group incompatibility was the most common cause which accounted for 85% or more and next was Rh incompatibility which took about 15%.TF is a transmembrane glycoprotein which does not express alone. In the case of hemolytic disease, TF is activated with inflammatory factors such as tumor necrosis factor to promote the expression of monocytes and vascular endothelial cells in an indirect or direct way which lead to TF levels increasing and occurrence of disseminated intravascular coagulation. [7]

In serology, maternal serum IgG antibody titer of 1:64 is a threshold. If it is equal to or greater than 64, there is a greater chance of children with hemolytic disease. Some studies show that children with hemolytic disease are related maternal IgG [8]. Bilirubin includes total bilirubin, direct bilirubin and indirect bilirubin. Total bilirubin is the sum of direct bilirubin and indirect bilirubin sum [9]. An increasing level of bilirubin easily leads to neonatal jaundice and high bilirubin encephalopathy in a severe case which may cause death in children. Early treatment of hemolytic disease of the newborn can improve the condition and immune function in children to improve the quality of life of children [10]. Traditional conventional clinical treatment cannot achieve the desired effect and studies have shown that gamma globulin, as a passive immunotherapy, can transfer the immunoglobulin to children, improve the immune status of children rapidly to a protective state and also plays a role in fight of bacterial and viral infections. [11]

Humoral immunity of new-born are mainly derived from the placenta transmission. It will gradually decompose with the maternal IgG levels after birth. At the time their own synthesis ability is low which is easy to cause a variety of physical ailments. Gamma globulin is capable of adjusting cellular immune function in children and activates immune cells to improve immune function in children [12]. It can also lower the serum bilirubin level and TF level to improve the condition and prognosis of children [13, 14]. 95% and above of gamma globulin are immunoglobulin which will rapidly increase children IgG levels after entering the body, reduce the destroy of red blood cells and supply high levels of neutralizing antibodies to prevent hemolytic process and reduce bilirubin level which can effectively improve the condition and the quality of life of children. [15]

Experiments in this study also indicated that the gamma globulin can effectively improve the condition and immune function in children. In the study, for children who received gamma globulin, their serum bilirubin level and TF level were significant lower than those treated by traditional method and their serum antibody titer was also better than that treated by traditional method. The incidence rate of adverse reactions in group treated with gamma globulin was 10.00% (3/30) and it was 33.33% (10/30) in group using traditional method. The total efficacy rate in group treated with gamma globulin was 96.66% (29/30) and it was 70.00% (21/30) in group using traditional method. The difference between two groups was statistically significant. Therefore, we also believe that gamma globulin is an effective treatment for hemolytic disease of the newborn which can lower bilirubin and TF to normal levels to improve the condition and quality of life of children.

Through the study, the author concludes that enough patience should be given and doses of drug should be paid attention in the treatment of hemolytic disease of the newborn to avoid discomfort in children while observing the treatment of children.

In summary, intravenous gamma globulin has a significant efficacy in the treatment of neonatal hemolytic disease which can lower plasma tissue factor and serum bilirubin to normal levels, worth clinical promotion.

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