Plasmapheresis in Rhesus Incompatible Pregnancy and Hemolytic Disease of Fetus and Newborn

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Abstract

Despite anti-D immune prophylaxis introduction into clinical practice RhD-alloimmunization still presents a problem nowadays. The purpose of this study was to determine the effectiveness of plasmapheresis and blood exchange-transfusion to diminish unconjugated bilirubin and free hemoglobin in newborns. The second purpose was to study plasmapheresis ability to prevent hemolytic disease of the fetus and newborn (HDFN) during pregnancy.

Subsequent clinical and laboratory studies confirm plasmapheresis to be more effective and safe than blood exchange-transfusion to treat HDFN and plasmapheresis performed in pregnant women was rather effective to prevent HDFN.

Keywords: Rhesus Incompatibility; Hemolytic Disease; Unconjugated Bilirubin; Fetus; Newborn; Replacement Blood Transfusion; Plasmapheresis

Introduction

Currently, according to WHO findings for 184 countries, 18% of those born alive in over than 32 weeks term have a risk of hyperbilirubinemia and 24% of them are even at risk of the fetus and newborn death [1]. In the United States, the incidence of HDFN was 10.6 per 10,000 births [2]. The frequency of HDFN in the Russian Federation ranges from 0.1 to 2.5% [3]. In European countries, there is one case of HDN for 200-300 childbirth. The development of the hemolytic disease of newborns (HDN) in children born by women with Rh-sensitization reaches 63%. In 7% of women, high Rh-sensitization leads to complicated pregnancy, intrauterine and perinatal pathology. Thus, intrauterine growth retardation of Stage II or Stage III is detected in 8.4% of cases. However, if there is a group of pregnant women with this pathology present in the settings of specialized units the number of children with signs of intrauterine hypotrophy increases up to 15-20%. The most immunogenic among all red blood cell antigens of the Rh system is D-antigen, which is 95% of cases is the cause of severe HDFN. The intensity of the red blood cells destruction process is evaluated by the magnitude of the antibodies titer to antigens of the red blood cells, i.e., the higher the titer, the more intense is the red blood cells hemolysis. But clinically, this pattern is not always revealed. In practice, a clear correlation between the titer of antibodies and the severity of the disease is observed only during the first pregnancy. Rh-antibodies related to class G globulins are of primary importance in the development of HDFN. There are 4 subclasses of IgG – IgG1, IgG2, IgG3, and IgG4. They are actively transferred to the fetus and increase the level of maternal antibodies in the fetus bloodstream. IgG1 and IgG3 are mainly of clinical importance, the titer magnitude of which identifies the risk of erythrocytes hemolysis [4]. Anti-D immunization is carried out to prevent HDFN, but it is not always timely and successful [5]. Severe forms of hyperbilirubinemia in newborns considering the level of unconjugated bilirubin (UB) above 310-340 µmol/l (in premature infants 170 µmol/l) at risk of nuclear jaundice developing can be eliminated only with by replacement blood transfusion (RB) [3]. During pregnancy, when severe fetal anemia is detected, intrauterine intravascular erythrocyte transfusion is used, but this

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often (up to 7.5%) leads to a number of complications, including the fetus or newborn death [6-10]. One of the modern methods to treat HDFN is plasmapheresis (PA) during pregnancy. PA appears to be effective in the treatment of neonates with hyperbilirubinemia resulted from HDFN [11-15]. These tactics are found in the American Association of Apheresis (ASFA) Guidelines, which emphasizes the need to perform plasmapheresis courses in Rh conflict from the earliest stages of pregnancy (7-12 weeks) and to resort to intrauterine blood transfusion only in cases of insufficient effectiveness [16].

The aim of this study was to study the effect of PA and RBT in hemolytic disease of newborns (HDN) on the dynamics of UB and free hemoglobin (FH), as well as to perform a comparative evaluation of newborns considering their clinical and laboratory findings following PA and RBT and of newborns following PA in their mothers, having Rh-sensitization during pregnancy associated with a high Rh-antibodies titer.

Material and Methods

A review of 70 newborns’ case histories taken from 1997 to 2017 was made if they had undergone PA and RBT treatment. All the newborns studied were divided into three groups: Group 1 included 37 newborns that had undergone plasmapheresis (PA) on the 2nd and 4th day of life. The indications for PA in these newborns were: 
- UB increase following RBT by more than 5-7 micromole/l per hour
- UB index exceeds 300 micromole/land tends to increase further despite conservative therapy.

These children underwent syringe membrane plasmapheresis according to the previously developed method [17] (Fig.1). Russian PFM-800 and Rosa plasma filters were used. The plasma filter system has a filling volume of 35ml (up to 10% of the circulating blood volume - CBV). Prior to blood sampling, the line was filled with fresh frozen plasma (FFP). During the PA session, up to 238.4±12.5 ml of auto plasma (up to 2 CPV) was removed with a simultaneous filling of the FFP (in the amount of about 110% of the removed one). In total, 2 PA sessions were held on the 2nd and 4th day after birth. Taking into account the low level of hemoglobin in HDN, in order to stabilize the newborn’s hemodynamics in 6 cases, erythrocyte transfusion was performed before PA started.

Group 2 included 16 newborns, whose mothers, having Rh-insensitivity in the presence of Rh-antibodies, had undergone a course of membrane PA (Hemophenix device) at 22-24 weeks of gestation in the mode from 3 to 5 sessions with 1-2 weeks interval.

In one session, the PA removed up to 784.6±25.5 ml of auto plasma. The filling was carried out with isotonic sodium chloride solution. The total volume of the plasma removed during the course of PA amounted up to 1-1.5 CPV. The multiplicity of PA procedures depended on the Rh-antibodies titer dynamics. The same membrane PFM-800 and Rosa plasma filters were used [18].

Group 3 (control) included 17 newborns, having undergone RBT only to treat HDN. Indications for RBT were:
- UB level in the umbilical cord blood after birth was over 50 nmolk/l;
- UB hourly growth in the 1st day of life was over 5.5 µmol/land if for 6 hours the UB level reached 170 µmol/l (from 30 µmol/l at birth).

The UB level tables worked out by the University of Kentucky International Center in newborns with different body weight in the first day of life were used for indications to RBT, which was carried out at the rate of 170-200 ml/kg body weight (up to 2.5 CBV) [19]. The RBT course consisted of two operations in 1-3 days of the life of children. In the first day of their life, the average hourly growth of UB was 12.6±1.6 micromole/l, so all of them had RBT.

The basis to study the detoxification methods effectiveness in HDN clinical and laboratory findings were applied. Clinical findings included assessment of neurological symptoms dynamics on the 1st, 3rd, and 5th days of life of children with HDN. Hemodynamics control was performed considering the heart rate, blood pressure, ECG, breathing frequency, SatO2 and body temperature of the newborn using a “Siemens” heart monitor. Laboratory diagnostics included the determination of unconjugated bilirubin (UB), which is the main marker of HDN, and free hemoglobin (FH) – an indicator of the erythrocytes cell membranes stability. FH was determined before and after PA and RBT operations. The CBV was calculated for all the newborns. A comparative analysis was made to decide whether the children of the 1st, 2nd and 3rd groups are to be transferred to the Department of Newborns Pathology and what the average stay of newborns in the intensive care unit is.

Results and Discussion

It was found that despite RBT implementation in newborns of the 1st and 3rd groups in the first day of life there was a significant increase in UB by the end of the 2-nd day (Table 1), which required PA procedures to be performed in these groups.

Table 1: UB dynamics after birth in newborns of the studied groups

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It was noted that in newborns of Group 2 whose mothers had been treated for Rh-sensitization during pregnancy with a course of membrane PA there were more stable UB findings by the end of the 2nd day and significantly lower (p<0.05) than in newborns of Group 1 and Group 3. This group of newborns also had a minimal hourly UB increase and did not need RBT. The study analysis showed a significant UB decrease (p<0.05) in Group 1 and, especially, in Group 2 of newborns whose mothers had undergone PA courses, compared with the control Group 3 (Table 2).

**Table 2: UB dynamics in newborns, having undergone the second session of PA and RBT and in newborns from mothers after a course of PA during pregnancy**

<table>
<thead>
<tr>
<th>Groups</th>
<th>3 days</th>
<th>4 days</th>
<th>5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PA</td>
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<td></td>
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</tr>
<tr>
<td>n = 37</td>
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<td></td>
<td></td>
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<tr>
<td>175.9±35.1</td>
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<tr>
<td>315.9±35.1*</td>
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<tr>
<td>350.1±13.4*</td>
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<tr>
<td>2. Newborns from mothers with PA during pregnancy</td>
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<tr>
<td>n = 16</td>
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<tr>
<td>170.1±11.5</td>
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<tr>
<td>290.1±12.9*</td>
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<td>224.4±10.1*</td>
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<td>3. RBT</td>
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<td>n = 17</td>
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<tr>
<td>173.5±33.5</td>
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</tr>
<tr>
<td>300.5±33.5*</td>
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<tr>
<td>390.3±10.2*</td>
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</tbody>
</table>

Note: * - p< 0.05 compared to RBT  
** - p< 0.05 compared to PA

It was noted that in newborns of Group 2 whose mothers had been treated for Rh-sensitization during pregnancy with a course of membrane PA there were more stable UB findings by the end of the 2nd day and significantly lower (p<0.05) than in newborns of Group 1 and Group 3. This group of newborns also had a minimal hourly UB increase and did not need RBT. The study analysis showed a significant UB decrease (p<0.05) in Group 1 and, especially, in Group 2 of newborns whose mothers had undergone PA courses, compared with the control Group 3 (Table 2).

The level of FH in newborns of the studied groups is presented in Table 3. Attention is drawn to the initially high VEG, which after PA sessions came to normal, but after RBT there was an even greater increase in it (in Group 2 FH was not investigated).

**Table 3: FH dynamics before and after PA and RBT procedures (g/l)**

<table>
<thead>
<tr>
<th>Groups</th>
<th>First operation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
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<td>After</td>
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<td>After</td>
<td>Before</td>
<td>After</td>
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<tr>
<td>1 gr. PA</td>
<td>2.3±0.2</td>
<td>1.3±0.1*</td>
<td>1.1±0.1</td>
<td>0.5±0.3*</td>
<td>2.5±0.2</td>
<td>3.5±0.3</td>
<td>2.2±0.3</td>
<td>3.6±0.3</td>
</tr>
<tr>
<td>n=37</td>
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<tr>
<td>3 gr. RBT</td>
<td>2.5±0.2</td>
<td>3.5±0.3</td>
<td>2.2±0.3</td>
<td>3.6±0.3</td>
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<tr>
<td>n=17</td>
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</tbody>
</table>

Note: * - p< 0.05 compared to RBT  
** - p< 0.05 compared to PA

In the hemolytic disease of the newborn, the method of syringe membrane plasmapheresis provided faster normalization of free hemoglobin and unconjugated bilirubin level in the blood. The developed syringe method of membrane plasmapheresis for newborns is the most simple and safe method to treat HDN. Replacement blood transfusion helps to remove defective red blood cells but does not sufficiently free the newborn body from autoantibodies, because they are distributed not only in the circulation but also in the interstitial space.

Prophylactic membrane plasmapheresis during pregnancy in the case of Rh-antibodies elevated levels can significantly reduce the level of unconjugated bilirubin in newborns at birth, without resorting to replacement blood transfusion and eliminates the need for an intraterine infusion of red blood cells into the umbilical cord vessels.

**References**


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Figure 1: Procedure of single-needle syringe embrance plasmapheresis in a newborn.