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CELLULAR IMMUNITY INDICATORS IN NEWBORNS WITH HEMOLYTIC DISEASE UNDERGOING HIGH-TECH FETAL SURGERY

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Summary

One of the most serious complications of pregnancy in women is fetal and neonatal hemolytic disease, which develops as a result of the breakdown of red blood cells in the fetus under the influence of maternal anti-Rhesus antibodies.

The aim of the study: *Was to evaluate cellular immunity factors such as CD3+ basic T-lymphocytes, CD4+ T-helper cells, CD8+ T-suppressors, CD16+ T-killers, CD20+ B-lymphocytes and immunoregulatory index, in the cord blood of newborns with hemolytic disease caused by Rhesus conflict in pregnant women and who were treated in the antenatal period by intrauterine, intravascular hemotransfusion to the fetus.*

Materials and methods: *The studies were conducted at Republican perinatal center for the year 2024. A total of 50 newborns participated in the study and were divided into 3 groups. The 1st main group of 20 newborns with hemolytic disease who underwent «intrauterine, intravascular fetal hemotransfusion» surgery in the prenatal period, the 2nd comparison group of 20 newborns with hemolytic disease who did not undergo fetal surgery in the prenatal period, and the 3rd control group of 10 healthy newborns. All immunological studies were conducted at the Institute of Immunology of the Academy of Sciences of the Republic of Uzbekistan.*

Conclusions. *Intrauterine intravascular hemotransfusion to the fetus not only improves hematological parameters of fetal blood, but also improves the indicators of cellular immunity, in particular, contributes to the increase in the number of T lymphocytes, which favorably affects T-cell immunity and prevents the formation of immunodeficiency state at birth.*

Keywords: *Rh-immunization; Hemolytic Disease of the Newborn (HDN); CD3+; CD4+; CD8+; CD16+; CD20+; T-Lymphocytes; Immunoregulatory Index (IRI); B-lymphocytes; Intrauterine Intravascular Blood Transfusion (IIBT).*

Introduction

Republican perinatal center (RPC) is a facility where pregnant women with Rh immunization are concentrated for high-tech fetal surgeries, who have complicated obstetric-perinatal history (pregnancy losses, perinatal losses, disabled children). But at the same time in RPC perinatal mortality rates have a positive dynamics of change over the last 3 years. For example, if in 2021 the perinatal mortality rate was 18.4‰, in 2022 18.9‰ and in 2023 17.5‰. The percentage of Haemolytic Disease of the Newborn (HDN) in the neonatal mortality rate for RPCs is constantly decreasing, i.e. 6.4% (4) in 2021, 6.5% (5) in 2022 and 0% (0) in 2023. This situation is explained by the fact that in recent years fetal surgery has been widely introduced and successfully performed in RPC, which undoubtedly affects neonatal outcomes [1, 2]. To date, intrauterine, often repeated, intravascular hemotransfusion to the fetus during the antenatal period is considered the only reasonable therapy for fetal hemolytic disease [3, 4, 5]. According to some authors, the development of adverse pregnancy outcomes is often associated with gestational age and the timing of the first intrauterine intravascular blood transfusion (IIBT). Also, in terms of analysis of peak blood flow velocity in the middle cerebral artery (PBFV MCA), the development of adverse perinatal outcomes has been noted in pregnant women with PBFV MCA values of >1.5 MoM [6, 7]. IIBT is a progressive method of treatment of hemolytic diseases of the fetus, and many authors of modern obstetrics give due attention to this method of therapy, but at the same time they point out that blood transfusions, often multiple transfusions, which increase the level of hemoglobin, do not remove toxic bilirubin from the fetal body. Antibodies circulating in the newborn's body destroy its own and transfused donor red blood cells for one month after birth [8, 9]. Due to this fact, all newborns after birth are diagnosed with HDN and require replacement blood transfusion (RBT) [10]. Authors have studied some indicators of adaptive cellular immunity in newborns with hemolytic disease who received intrauterine, intravascular blood transfusion to the fetus in the prenatal period [11]. There are data in the literature that against the background of chronic hypoxia of severe degree due to severe hemolytic anemia in the cellular immunity link in the fetus there are serious changes in the form of stress-induced mobilization of CD34+ from hematopoietic organs to the peripheral blood, increase in natural killer cells, decrease in CD8+, CD4+ cells [12, 13, 14]. Based on the above data, we decided to study the indicators of innate cellular immunity in newborns with hemolytic disease.

Immunologic methods of research: Studies of immune status of newborns in umbilical cord blood were conducted on the 1st day of life in the Laboratory of Basic Immunology at the Institute of Human Immunology and Genomics, Academy of Sciences of the Republic of Uzbekistan. Determination of cellular immunity included CD3+, CD4+, CD8+, CD20+, CD16+/56+ and was carried out using monoclonal antibodies of the company BD (USA) by flow cytofluorimetry (BD Accury C6). The immunoregulatory index (IRI), which is the ratio of the number of CD4+ T helper cells to the number of CD8+ T lymphocytes, was calculated manually. The normal IRI in healthy children and adults is greater than one.

Statistical processing of the results was carried out using methods of parametric and nonparametric analysis.

Accumulation, correction, systematization of the initial information and visualization of the obtained results were carried out in Microsoft Office Excel 2018 spreadsheets. Statistical analysis was performed using the program IBM SPSS Statistics v.26 (developer – IBM Corporation). When comparing means in normally distributed populations of quantitative data, Student's t-criterion was calculated. The obtained values of Student's t-criterion were evaluated by comparing them with critical values. Differences in the indicators were considered statistically significant at the level of significance $p<0.05$.

Results and Discussion: We aimed to perform immunologic studies and to justify the efficacy of fetal intrauterine intravascular hemotransfusion by assessing cellular immunity in newborns who underwent fetal surgery. Therefore, immunological studies of cellular immunity were performed in cord blood of newborns with HDN who underwent intrauterine hemotransfusion and those who did not undergo fetal hemotransfusion. The results are summarized in Table-1 below.

Analysis of the results showed that the number of CD3+ T lymphocytes in the comparison group was significantly reduced by 2.2 times compared to the control group, and in the main group the number of CD3+ T lymphocytes was not significantly different and the reduction was only 1.2 times. This indicates that after intrauterine hemotransfusion there is an improvement in the indicators of cellular immunity, in particular, an increase in the number of T lymphocytes, which favorably affects T-cell immunity and prevents the formation of immunodeficiency state at birth. The number of helper/inducer T lymphocytes CD4+ in the comparison group was also significantly reduced in comparison with the control values in 2.2 times, and in the main group of helper T lymphocytes CD4+ the reliable difference was not observed and the reduction was only 1.2 times.

Indicators of T-cytotoxic lymphocytes CD8+ in the comparison group were significantly increased by 1.4 times in comparison with the control group, and in the main group the number of CD8+ cells was not significantly different and the increase was only 1.1 times. The immunoregulatory index was significantly reduced in the comparison group by 2.7 times in relation to the data of the control group, and in the main group this index was reduced only 1.3 times in relation to the control and there was no significant difference.

Table-1

Main cell parameters of newborn birth immunity (umbilical cord blood), (M±m, %)

Parameters	Main group (n-20)	Comparison group (n-20)	Control group (n-10)
CD3+, %	47,88±1,96	28,66±1,51 *	62,44±5,31
CD4+, %	39,24±2,38	21,55±1,78 *	47,53±5,52
CD8+, %	20,46±1,22	25,82±1,66 *	18,60±3,36
CD4+/CD8+, (IRI)	1,67±0,18	0,85±0,06 *	2,32±0,24
CD20+, %	12,34±1,75	19,42±1,56	17,56±1,64
CD16+/CD56+, %	9,55±1,45	14,66±2,42 *	8,35±1,24

*Note: * – reliability of differences with the control group p<0.05*

The results of the study of CD20+ B lymphocytes in the group of newborns with traditional management was insignificantly increased and no significant difference was observed. The same unreliable difference was found with CD20+ B lymphocytes in the main group in relation to the values of the control group.

Analysis of killer activity of immunity of newborns showed that the number of killer lymphocytes CD16+/56+ in the comparison group was significantly increased by 1.8 times, and in the main group the number of killer lymphocytes CD16+/56+ was increased only by 1.1 times, which is not a significant difference compared to the values of the control group.

Based on our results, it can be concluded that against the background of intrauterine and intravascular hemotransfusion to the fetus in the prenatal period, there is an improvement of cellular immunity factors in the newborn, as evidenced by our findings. It should be noted that we found a significant increase in the total number of T lymphocytes, T helpers/inducers and IRI, which are the main components of immunity and form a full cellular immune response of the organism regardless of age, moreover, prevent the formation of immunodeficiency.

Conclusions

1. The number of CD3+ T lymphocytes and CD4+ T helper cells was significantly reduced by 2.2 times in the comparison group compared to the control group. The immunoregulatory index (IRI) was also reduced by 2.7 times in the comparison group compared to the control group, and there was no significant difference in the main group.

2. The number of CD8+ cytotoxic lymphocytes and CD16+ killer lymphocytes were significantly increased by 1.4 times and 1.8 times, respectively, compared with the neonates in the control group.

3. CD20+ B lymphocyte counts in both groups of newborns in the main and comparison groups were not significantly different from those in the healthy newborn group.

4. Intrauterine, intravascular hemotransfusion to the fetus not only improves hematological parameters of fetal blood, but also improves the indicators of cellular immunity, in particular, contributes to the increase in the number of T lymphocytes, which favorably affects T-cell immunity and prevents the formation of immunodeficiency state at birth.

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ПОКАЗНИКИ КЛІТИННОГО ІМУНІТЕТУ У НОВОНАРОДЖЕНИХ З ГЕМОЛІТИЧНОЮ ХВОРОБОЮ ПРИ ПРОВЕДЕННІ ВИСОКОТЕХНОЛОГІЧНОЇ ФЕТАЛЬНОЇ ХІРУРГІЇ

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Резюме.

Одним із найбільш серйозних ускладнень вагітності у жінок є гемолітична хвороба плода та новонародженого, яка розвивається внаслідок розпаду еритроцитів у плода під впливом антирезусних антитіл матері.

Мета дослідження: оцінити такі фактори клітинного імунітету, як CD3+ основні Т-лімфоцити, CD4+ Т-хелпери, CD8+ Т-супресори, CD16+ Т-кілери, CD20+ В-лімфоцити та імунорегуляторний індекс, у пуповинній крові новонароджених з гемолітичною хворобою, спричиненою резус-конфліктом, у вагітних жінок та які проходили лікування в антенатальний період шляхом внутрішньоутробного, внутрішньосудинного переливання крові плоду.

Матеріали і методи. Дослідження проводились у Республіканському перинатальному центрі у 2024 році. У дослідженні взяли участь 50 новонароджених, які були розподілені на 3 групи. 1-ша основна група – 20 новонароджених із гемолітичною хворобою, яким у внутрішньоутробному періоді виконано оперативне втручання «внутрішньоутробна внутрішньосудинна гемотрансфузія плоду», 2-га група порівняння – 20 новонароджених із гемолітичною хворобою, яким у внутрішньоутробному періоді не проводились операції на плоді, 3-я контрольна група – 10 здорових новонароджених. Всі імунологічні дослідження проводилися в Інституті імунології Академії наук Республіки Узбекистан.

Висновки. Внутрішньоутробне внутрішньосудинне переливання крові плоду не тільки покращує гематологічні показники крові плода, але й покращує показники клітинного імунітету, зокрема сприяє збільшенню кількості Т-лімфоцитів, що сприятливо впливає на Т-клітинний імунітет і запобігає формуванню імунодефіцитного стану при народженні.

Ключові слова: резус-імунізація; гемолітична хвороба новонароджених; CD3+; CD4+; CD8+; CD16+; CD20+; Т-лімфоцити; імунорегуляторний індекс; В-лімфоцити; внутрішньоутробне внутрішньосудинне переливання крові.

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