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RESEARCH ARTICLE

CLINICAL EFFICACY OF INTRAVENOUS IMMUNOGLOBULINS IN NEWBORNS WITH RESPIRATORY DISTRESS SYNDROME COMPLICATED BY "VENTILATOR-ASSOCIATED" PNEUMONIA

[1]Kushnareva M.V. and [2]VetrovaE.V.

[1]Doctor of Biological Sciences, Professor, Chief Researcher at the Department of Neonatology and Pathology of Young Children, Veltischev Research and Clinical Institute for Pediatrics and Pediatric Surgery of the Pirogov Russian National Research Medical University of the Ministry of Health of the Russian Federation, Moscow, Russia; [2]Candidate of Medical Sciences, Doctor of the highest category, anesthesiologist, intensive care unit, neonatologist, pediatrician, Department of Intensive Care and Intensive Care for newborns, A.K. Yeramishantsev City Clinical Hospital, Moscow, Russia

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***Corresponding author:**
Kushnareva M.V.

ABSTRACT

Contexte: Introduction. The high incidence of "ventilator-associated" pneumonia (VAP) in premature infants and mortality from this disease necessitatethe need to optimize treatment and prevention. Objective. To conduct a comparative analysis of the clinical course of VAP in infants who received intravenous immunoglobulins (IVIg) from the 2nd day of life, in the acute period of pneumonia and in newborns who did not receive IVIg. **Material and methods:** We observed 112 premature infants with respiratory distress syndrome who were on mechanical ventilation. VAP developed in 98 infants. **Results:** It was found that the inclusion of IVIg into the treatment complex for infants with respiratory distress syndrome (RDS) on mechanical ventilation of the lungs (MVL) on the second day of life allows to significantly (by 2 times) reduce the risk of pneumonia, the duration and severity of the disease, including with the outcome in sepsis, mortality (by 2 times) and the frequency of bronchopulmonary dysplasia formation compared to newborns who received IVIg in the acute period of pneumonia and with infants who did not receive immunotherapy. The use of IVIg at the onset or in the acute period of VAP increased the effectiveness of therapy compared to the basic treatment complex. **Conclusion:** Early administration of IVIg (from the second day of life) in the complex treatment of RDS in infants at high risk of developing pneumonia is the most appropriate, as it reduces the incidence of this complication and increases the effectiveness of its treatment.

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INTRODUCTION

Pneumonia is one of the most common infectious and inflammatory diseases in the neonatal period and accounts for 46% of all neonatal pathology (1). According to a number of authors, ventilator-associated pneumonia (VAP) develops in 21-51% of newborns on mechanical ventilation of the lungs (MVL) (2,3). The greatest risk of death from pneumonia in childhood occurs during the neonatal period. Pneumonia is estimated to cause between 750,000 and 1.2 million neonatal deaths each year, accounting for 10% of global child mortality (4). According to Backhaus E, et al., (2016), the mortality rate from pneumonia is 1.2%, which is the highest among all neonatal infectious diseases. Thus, pneumonia is a serious problem threatening the health of newborns, which determines the need to optimize the treatment and prevention of this disease. A number of authors recommend including intravenous immunoglobulin (IVIg) preparations in the treatment of VAP in newborns (5,6,7).

The rationale for immune therapy is the incomplete development of the immune system in newborns, especially in premature infants, low levels of immunoglobulins in the blood, reduced phagocytosis of neutrophils and macrophages (8,9), and weak nonspecific protection of the mucous membranes against infection (10). However, debates about the advisability of using IVIg in neonatology continue to this day (6,11,12). In addition, the optimal timing for starting immunotherapy in infants with VAP has not been established.

Objective: To increase the effectiveness of complex treatment of VAP in premature infants onmechanical ventilationof the lungs, based on a comparative analysis of the clinical course of the disease in infants who received immunocorrection with IVIg drugs from the 2nd day of life, in the acute period of infection and in newborns who did not receive IVIg.

PATIENTS AND METHODS

We examined 112 premature newborns with respiratory distress syndrome (RDS), who were on mechanical ventilation from birth. Tracheobronchitis developed in 14 infants (group I), VAP developed in 98 infants on the 4th – 8th day of life. All infants with pneumonia received basic therapy, which included antibiotics, probiotics, syndrome therapy, oxygen support, infusion therapy, enteral nutrition, correction of water-electrolyte balance, neurological and cardiovascular disorders. We conducted clinical observation of newborns, laboratory and instrumental examinations (ultrasound, chest X-ray), microbiological cultures of tracheobronchial aspirates. All newborns were divided into 4 groups depending on the use of IVIg in the treatment regimen and the timing of their administration. Group I included 14 newborns with RDS who were on mechanical ventilationof the lungs and who received IVIg prophylactically from the 2nd day of life. These infants did not develop VAP. Sixteen premature infants with RDS who were mechanically ventilated of the lungs received intravenous immunoglobulins from the second day of life. However, clinical and radiographic signs of pneumonia were noted in them on the 4th to 7th day of life. These infants constituted the second group (II) in the main study. The third group (III) was represented by 47 premature infants with VAP, who, along with basic therapy, were treated with IVIg preparations in the presence of a clinical and radiological picture of pneumonia and severe intoxication in the acute period of the disease, starting from the 5th to 8th day from its onset.

The fourth group (IV) consisted of 35 patients with VAP who were not treated with immunoglobulins. These infants received only basic therapy. The indicators of body weight and length, the severity of the newborn's condition according to the Apgar scale at birth did not differ significantly in the study groups (Table 1). Immunotherapy in infants with RDS in groups I, II and III was carried out with IVIg preparations of different generations. All preparations were administered by slow intravenous infusions, once a day for three days in a row.We used doses recommended for use in neonates in the instructions for these drugs: Octagam® (OCTAPHARMA Pharmazeutika Produktionsges, m.b.H., Austria) at a dose of 500 mg/kg; Pentaglobin® (BIOTEST PHARMA GMBH, Germany) at a dose of 250 mg/kg; normal human immunoglobulin for intravenous administration liquid (Russia) at a dose of 400 mg/kg; Intraglobin® (BIOTEST PHARMA GMBH, Germany) at a dose of 6-8 ml/kg per day. IVIg was administered in groups I and II from the 2nd day of life until the development of clinical symptoms of pneumonia and tracheobronchitis, and in group III in the acute period of the disease, starting from 5-8 days from its onset.

RESULTS

At the preliminary stage, we studied the incidence of VAP in 30 premature infants of groups I and II with RDS, who received prophylactic IVIg from the second day of life due to the presence of several (2 or more) risk factors for the development of infectious and inflammatory diseases (prematurity, birth weight less than 1500 g, a complicated infectious history of the mother, especially in the third trimester; complicated labor, severe asphyxia suffered during delivery, MVL; deterioration in the infant's condition during the first two days of life in the presence of adequate syndrome-based therapy). The 14 premature infants (Group I) (47% of the number of newborns who received prophylactic IVIg) had infectious and inflammatory changes in the respiratory tract mucosa in the form of tracheobronchitis against the background of mechanical ventilation, but VAP did not develop. Thus, the prophylactic effect of IVIg administration in premature infants with a high risk of VAP development was 47%. At the same time, despite the immunocorrective treatment, clinical and radiological signs of pneumonia were noted in 16 premature infants (53%). As noted above, these infants constituted the second group (II) in the main study. Gram-negative pathogens predominated representatives of *Enterobacteriaceae* (*E. coli*, *Klebsiellaspp*., *Proteusmirabilis*, *Proteusvulgaris*, *Enterobactercloacae*, *Citrobacterdiversus*, *Serratiamarcescens*, *Erviniaamilovora*), *Ps. Aeruginosa* and *Stenotrophomonasmaltophilia* in the etiology of ventilator-associated pneumonia, which were found in 72% of infants. Among gram-positive microorganisms, the most common were *Staphylococcus epidermidis* with hemolytic properties and *Enterococcus spp*., while *Streptococcus spp*. and *Staphylococcus aureus* were encountered much less frequently. *Candida albicans* and *Candid krusei* were isolated from the respiratory tract in 18% of newborns in combination with bacteria. Intracellular pathogens (*Mycoplasma*, U*reaplasmaspp*., and *Chlamydia spp.*) were found in 58%. Mixed infection was detected in 80 infants (82%). It was very diverse in its spectrum. Most pathogens were resistant to 11-15 antibiotics, which made it difficult to select and implement adequate antimicrobial therapy and necessitated the inclusion of replacement immunotherapy with IVIg drugs in the treatment complex. The inclusion of these drugs in the treatment of RDS allowed us to prevent the development of VAP in half of the infants, as our clinical studies showed.

The results of the comparative analysis of the clinical course of VAP in the studied groups of infants are presented in Table 2.
As follows from the data presented in Table 2, the use of IVIg in the acute period of RDS led to a decrease in the prevalence of inflammatory lesions of the respiratory organs. Also, reliable differences were noted in infants of group II in the duration of artificial ventilation of the lungs, including in critical modes, antibacterial therapy, the frequency of development of pulmonary edema, atelectasis and bronchopulmonary dysplasia compared with infants of groups III and IV. Infants in Group II showed a faster resolution of the infectious and inflammatory process than those in the compared groups: clinical signs of severe toxicosis in the form of microcirculation disorders, edema, jaundice, changes in skin color, hepatosplenomegaly, and pathological changes in the peripheral blood.

A decrease in the incidence of sepsis and acute heart failure was also noted. Pneumonia did not cause death in any of the infants in this group (both deaths occurred as a result of progression of hydrocephalus, which developed against the background of massive intraventricular hemorrhages), while in infants with pneumonia in the other groups, infectious lesions were the cause of death in most cases. A more favorable course of VAP was observed in neonates of group III compared to neonates of group IV. Thus, the frequency of outcome in sepsis and development of BPD decreased almost 2 times, the duration of pneumonia and antibacterial therapy decreased on average by 3-4 days, the frequency of formation of atelectasis decreased by 10%, and mortality decreased by 2.2 times.

Table 1. The condition of the examined infants at birth

№	Infanthealthindicators	Groups of infants (tracheobronchitis, pneumonia)			
		Group I (Infants with tracheobronchitis)	Group II (pneumonia)	Group III (pneumonia)	Group IV (pneumonia)
1	Numberofinfants	14	16	47	35
2	Gestational age (weeks, M±m)	33.2±2.7	32.4±1.7	31.5±1.2	30.4±0.9
3	Birth weight (grams, M±m)	1901±505	1836±390	1585±192	1574±145
4	Body length at birth (cm, M±m)	41.8±2,3	42.2±2,9	40.5±1,7	39.9±1,4
5	Apgar at 1 minute (points, M±m)	4.5±0.8	4.2±0.7	4.3±0.6	4.2±0.6
5	Apgar at 5th minute (points,M±m)	5.6±0.9	5.9±0.7	5.6±0.5	5.8±0.4
7	Infants born in severe asphyxia (%) (Apgar at 1 minute < 3 points)	43	50	34	40
8	Infants born with moderate asphyxia (%) (Apgar at 5 minutes 3-6 points)	67	50	66	60

Table 2. Clinical course of mechanical ventilation-associated pneumonia in premature infants in the study groups

Clinicalindicators	Group II (n=16)	Group III (n=47)	Group IV (n=35)
Duration of respiratory support (days, M±m)	6.8±0.7*	15.8±0.99	13.6±2.11
Duration of mechanical ventilation in "rigid" modes (days, M±m)	3.7±0.4*	7.9±0.55	6.3±0.44
Frequency of inotropic support use (%)	18.8	37.1	36.1
Inflammatory changes in peripheral blood (%)	37.5	51.4	46.8
Common lung lesions according to radiography (%)	19*	51.0	50.4
Frequency of infectious complications (%), including those resulting in sepsis (%)	12.5 0	29.8 6.4	31.5 11.4
Frequency of Atelectasis Development (%)	31.3*	53.2	62.9
Frequency of pulmonary edema development (%)	31.3*	70.0	74.0
Duration of pneumonia (days, M±m)	18.6±1.12*	24.5±1.30	28.7±0.80
Duration of antibacterial therapy (days, M±m)	26.3±1.90*	36.2±0.70	39.2±0.85
Mortality (%)	12.5***	10.6	22.8
Frequency of bronchopulmonary dysplasia formation (%)	18.8**	27.6	45.6
Notes: 1) «*»-reliable difference with groups III and IV (p<0,05); 2) «**» – significant difference compared to group IV (p<0.05); 3)«***» -all fatal outcomes in group II were due to massive intraventricular hemorrhages.			

DISCUSSION

IVIg preparations are normal human immunoglobulins of class G, obtained from the blood plasma of healthy adult donors. The pharmacological action of IVIg preparations is provided by immunoglobulins, mainly of class G (IgG), which have the activity of antibodies of various specificities. IVIg contains antibodies against all major pathogens of human infectious diseases. The mechanism of immunomodulatory action of IVIg preparations is identical to the multicomponent mechanism of action of natural endogenous human immunoglobulins and consists of the following. Immunoglobulins recognize, neutralize and remove pathogens from the body through the effects of opsonization, precipitation, agglutination, activation of complement-dependent lysis of the immune complex "antigen-antibody" and stimulation of cellular effector mechanisms (9,10,13). The IVIg preparations have been shown to provide rapid elimination of pathogens from the respiratory tract in premature infants with VAP. Titers of bacterial pathogens of the *Enterobacteriaceae*y, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcu spp*., *Pseudomonas aeruginosa*, *Haemophilusinfluenzae*, *Streptococcus* groups *A* and *B*, *Pneumococcus*, *Bacteroidesfragilis*, *Mycoplasma hominis*, *Micoplasma pneumonia*, *Ureaplasmaurealyticum*, *Chlamidiatrahomatis* decrease in tracheobronchial aspirate by 10-100 times, and fungi of the genus *Candida* - by 1.5-2 times already one day after intravenous administration of IVIg(14). The antimicrobial effect of immunoglobulins is also associated with increased phagocytic activity of blood neutrophils against *Staphylococcus aureus*, *E. coli*, *Klebsiella pneumonia*, *Staphylococcus epidermidis*, and *Enterococcus faecalis*. Administration of immunoglobulins increased the pool of activated phagocytes from 35.6% to 48%, the average number of microbes absorbed by one neutrophil from 2.5 to 3.3, and increased the cytotoxic and digestive function of neutrophils by 1.5 times in newborns with pneumonia (13).The activity of such neutrophil enzymes as acid phosphatase, alkaline phosphatase, myeloperoxidase increased by 25-50%, and the number of neutrophils active in the NST- test increased by 25% in the tracheobronchial aspirate. In addition, the percentage of neutrophils in the cellular composition of the tracheobronchial aspirate increased from 33.3±3.35% to 52.7±3.15% and the number of CD-4 lymphocytes increased from 21.6±1.19% to 26.9±0.71%(15). It is important to note that IVIg is active against both bacterial and intracellular microorganisms, which often form associations in premature infants as causative agents of VAP. Stimulation of phagocytic activity allows to eliminate *Mycoplasmasspp*. and *Chlamydiaspp.*, which vegetate intracellularly and are difficult to access for most antibiotics. (13).

In addition, IVIg provide an anti-infective effect against pathogens that are multi-resistant or weakly sensitive to antibiotics and can be used simultaneously with other drugs, including antibiotics, which enhances the clinical effect(7, 11, 12). Early administration of IVIg suppresses massive contamination by microorganisms in the respiratory tract of infants, which prevents or weakens the inflammatory process, reduces its prevalence, and ultimately has a good preventive effect on the development of severe infection. The duration of action of IVIg drugs is on average 3-4 weeks, and the half–life $T_{1/2}$ for most drugs is more than 20 days (7, 12). The average concentration of immunoglobulins in the blood plasma of premature infants 2-3 weeks after treatment with IVIg preparations is 4.1±0.41 g/l for IgG, 0.62±0.11 g/l for IgM, and 0.22±0.10 g/l for IgA (15). This circumstance makes it possible to reduce the frequency or prevent secondary infection and the development of complications in infants.

CONCLUSION

Thus, the clinical effectiveness of prescribing IVIg in premature infants with RDS was obvious and significantly exceeded that in infants treated with immunoglobulins in the acute period of pneumonia and in newborns with the same pathology on basic therapy. The inclusion of IVIg in the treatment of infants with RDS on mechanical ventilation on the second day of life allows for a significant (2-fold) reduction in the risk of developing pneumonia, the duration and severity of the disease, including the outcome in sepsis, mortality (2-fold) and the frequency of BPD development compared to newborns who received IVIg in the acute period of pneumonia and to infants who did not receive immunotherapy. The above allows us to consider the early administration of immunoglobulins as the most appropriate in the complex treatment of RDS in infants with a high risk of developing pneumonia. The clinical criteria for prophylactic administration of IVIg are the absence of positive clinical dynamics or deterioration of the condition during 1-2 days of life (respiratory failure requiring respiratory support in "harsh" modes and tightening of mechanical ventilation parameters; the need for long-term inotropic support) with adequately administered syndrome-based therapy.

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Key words: Newborns, respiratory distress syndrome, intravenous immunoglobulins, pneumonia, tracheobronchitis.

KEY POINTS

1. Early administration of the intravenous immunoglobulins to preterm infants with RDS receiving mechanical ventilation reduces the incidence of ventilator-associated pneumonia.
2. Early administration of the immunoglobulins to preterm infants with RDS undergoing mechanical ventilation reduces the severity of ventilator-associated pneumonia and the development of complications.
3. This study is of great importance for public health, as it enables a reduction in mortality among premature infants with ventilator-associated pneumonia, as well as a decrease in the length of hospital stay and treatment costs.

GLOSSARY OF ABBREVIATIONS

BPD – the bronchopulmonary dysplasia
IgA– the immunoglobulins, mainly of classA
IgG – the immunoglobulins, mainly of class G
IgM– the immunoglobulins, mainly of class M
IVIg -intravenous immunoglobulins
MVL - mechanical ventilation of the lungs
RDS- respiratory distress syndrome
VAP -ventilator-associated pneumonia

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