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CASE REPORT **OPEN ACCESS**

MICROBIOLOGICAL EFFICACY OF INTRAVENOUS IMMUNOGLOBULINS IN THE COMPLEX TREATMENT OF TRACHEOBRONCHITIS IN PREMATURE INFANTS

***Maria Vasilievna Kushnareva**

Doctor of biological sciences, Academician Yu.E.Veltishchev Research Clinical Institute of Pediatrics, N.I.Pirogov Russian National Research Medical University, Moscow, Russian Federation

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***Corresponding author:**
Maria Vasilievna Kushnareva

ABSTRACT

***Material and methods*:** We investigated the microbiological efficacy of intravenous immunoglobulins (IVIG) in 34 premature newborns (birth weight was from 960 to 2750 g) with respiratory distress syndrome, those who were on hardware artificial ventilation of the lungs. The infectious complications did not develop in 20 infants (group I), and tracheobronchitis developed in 14 infants (group II). The infants in group II, along with basic therapy, received IVIG from the second day of life for three consecutive days. ***Results*:** The use of IVIG showed a high microbiological efficiency, which was in 86% of patients within a day from the start of treatment. The greatest inhibition of growth is observed in relation to bacterial microflora and intracellular microorganisms. The lowest effect was shown in relation to Candida albicans. A stable effect of IVIG was observed in all newborns within three days after the course of immunotherapy.

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INTRODUCTION

Currently, much attention is paid to the problem of treating infectious and inflammatory diseases in premature newborns. The use of hardware artificial lung ventilation (HALV) in infants with respiratory distress syndrome (RDS) often leads to the development of ventilator-associated tracheobronchitis (TB). The treatment with antibiotics does not always allow you to get a quick and lasting effect, since many pathogens have multiple resistance to these drugs (Cernada, M *et al*., 2014; Kolls, JK. 2017; Kushnareva MV, *et al*, 2019). The etiology of TB in newborns is represented often by a combination of bacteria and intracellular microorganisms: *Mycoplasma pneumonia*, *Mycoplasma hominis* (*M.hominis*), *Ureaplasma urealyticum* (*U. urealyticum*). However, the intracellular localization of microorganisms significantly limits the effect of antibiotics on them (Rakovskaya IV, 2008). The intravenous immunoglobulins (IVIGs) are used for the treatment of infection in newborn infants, but their effectiveness and expediency of use in the neonatal period is controversial (Antonov, A G, *et al*, 2007; Aronskind, E V, *et al*, 2007; Zwiers, C *et al*, 2018).

In particular, the question remains open about the use of IVIG for the treatment and prevention of infection in infants with RDS and those on the HALV.

Aim: To determine the microbiological effectiveness of intravenous immunoglobulins in the complex treatment of premature infants with RDS, who are on the HALV, complicated by tracheobronchitis.

MATERIALS AND METHODS

We examined 34 premature newborns with RDS who were on hardware artificial lung ventilation. The body weight at birth was from 960 to 2750 g, the gestational age was from 28 to 37 weeks. The group I included 20 premature newborns with RDS and without infectious and inflammatory complications. The duration of HALV in them was 2-4 days. TBA cultures were performed twice in these infants: on the 1-2 and 3-5 days of life. We used the immunoglobulin preparations for intravenous administration of different generations (6 infants received Octagam ®; 4 infants received Pentaglobin ® ; 4 infants received Intraglobin ®) for the treatment of infants with RDS

and subsequent development of tracheobronchitis (group II). The IVIG was administered from 2 days of life until the development of clinical symptoms of TB. All IVIGs were administered by slow intravenous infusions, three consecutive days, once a day. We used the dose of the IVIG recommended for use in newborns (Formular on the use of drugs of intravenous immunoglobulins in neonatology, 2006/2007; Instructions for the use of intravenous immunoglobulins): the dose of Octagam ® ("OCTAPHARMA AG", Austria) was 500 mg/kg; the dose of Pentaglobin ® ("BIOTEST PHARMA GMBH", Germany") was 250 mg/kg (5 ml/kg); the dose of Intraglobin ® ("BIOTEST PHARMA GMBH", Germany) was 6 - 8 ml /kg per day.(Antonov, A G, *et al*, 2007). The tracheobronchitis developed on 3-6 days of life in these infants. The duration of HALV was from 3 to 6 days. The TBA cultures were carried out on 1-2 days of life before IVIG administration, one day after the first infusion of immunoglobulin, and three days after the course of immunotherapy. The groups were representative of body weight and gestational age at birth.

All infants received basic treatment. It included oxygen therapy, antibacterial therapy, as well as syndromal and symptomatic treatment. Microbiological cultures of tracheobronchial aspirates (TBA) were carried out by qualitative and quantitative methods using a standard set of nutrient media. (Labinskaya, A S,,*et al*, 2015; Rakovskaya IV, 2008). The determination of the sensitivity to antibiotics of bacteria was carried out by the method of standard disks (Methodical instructions, 2004), The determination of the sensitivity to antibiotics of *M. hominis* and *U. urealyticum* was carried out in a liquid nutrient medium (Waites KB. *Et al*, 1999; Rakovskaya IV. 2008). The causative agents of the disease were strains of conditionally pathogenic microorganisms with a total microbial number (TMN) of more than lg3 colony-forming units in 1 ml of TBA (CFU / ml), and the accompanying microflora were strains with a TMN of less than lg4 CFU/ml (Labinskaya, A S,, *et al*, 2015). *Statistics*. Statistical processing of the results was carried out using the Statistica 7 computer software package. We determined the frequency of occurrence of microorganisms in % in infants in each group. The percentage of small numbers was calculated to compare the indicators between groups and in the dynamics of observation.

RESULTS AND DISCUSSION

The microorganisms were isolated from all the samples of TBA and were conditionally pathogenic microorganisms in terms of their species composition in premature newborns with RDS and without infection (group I). These were *Enterobacteriaceae* (in 17 infants), *Staphylococcus epidermidis* (*S. epidermidis*) (in 17 infants), *Streptococcus viridans*, *Streptococcus pyogenes*, *Enterococcus faecalis* (2 strains each), *Peptococcus spp.*, *Peptostreptococcus spp*., *Candida spp*., non-pathogenic *Corynebacterium* spp. and non-pathogenic *Neisseria spp*., (2-4 strains each). A single pathogen was found in the trachea in 8 infants. Several pathogens (from 2 to 4) were isolated in the remaining 12 infants. The degree of microbial colonization of the trachea was different: from lg1 to lg4 CFU/ml. The distribution of infants by TMN value at the first examination was as follows: TMN lg1-2 CFU / ml was in 17 newborns, TMN lg3 CFU/ml was in 2 and TMN lg4 CFU/ml was in 1 infant. The composition of microflora and TMN did not change in 2-4 days after the first examination in 13 infants of this group (37%). A decrease in TMN by 1-2 orders of magnitude and a decrease in the number of species from 3-4 to 1-2 were observed in the remaining infants. These changes appeared to be related to preventive antibacterial therapy, which usually included 1 or 2 antibiotics. The pathogens of tracheobronchitis were isolated in all examined group II newborns. The spectrum of TB pathogens is presented in Table 1. As can be seen from Table 1, the etiology of tracheobronchitis is represented by a wide range of microorganisms. Gram-positive and gram-negative pathogens were found with the same frequency. These were most often representatives of *Enterobacteriaceae* (*E. coli* and *Klebsiella pneumoniae*), *Enterococcus faecalis*, *Candida albicans*. *U. urealyticum* was found most often among intracellular microorganisms. Attention is drawn to the high frequency of mixed infection (86%), which was very diverse in its spectrum. Associations of bacteria with intracellular microorganisms and / or *Candida albicans* were quite common.

Table 1. The etiological structure of tracheobronchitis in infants who received IVIG (the number of microorganisms in TBA is lg4 and above CFU / ml)

N	Pathogens	Group II (n=14)	
		n	%
1	*E.coli*	4	29
2	*Klebsiella pneumoniae*	3	21
3	*S.epidermidis (h+)*	3	21
4	*Streptococcus A* (*Streptococcus pyogenes*)	1	7
5	*Enterococcus faecalis*	6	43
6	*Haemophylus influenzae*	2	14
7	*Candida albicans*	10	71
8	*M.hominis*	2	14
9	*U.urealyticum*	6	43
10	*Acinetobacter baumanii*	1	7
11	*Pseudomonas aeruginosa*	2	14
12	Monoinfection	2	14
13	Mixed infection (2 or more pathogens)	12	86
14	Bacteria + *Candida spp. + U. urealyticum or M. hominis*	8	57
15	Bacteria + *Candida spp*.	2	14
16	Two types of bacteria	2	14

Pathogens of secondary infection were isolated from TBA in 2 premature infants with tracheobronchitis 7 days after eradication of the first pathogen. The first association (*Ps. aeruginos*a + *Candida albicans*) was isolated in one infant and the second association (*Ps.aeruginosa + Candida albicans + Enterococcus faecalis*) was also isolated in one infant. Along with the pathogens of tracheobronchitis, concomitant conditionally pathogenic microflora in the amount of 10 – 100 CFU/ml (lg1-2 CFU/ml) was seeded from TBA. It was mainly represented by *S. epidermidis*, *Enterococcus spp*, *Str. Viridians.*, *Candida spp*., *Neisseria sicca*, and *Corynebacterium xerosis*. The low titer of pathogens, the absence of pathogenicity factors, and a single detection did not allow them to be attributed to the pathogens of the disease. The frequency of occurrence of these microorganisms ranged from 7 to 14%.

The study of the sensitivity of tracheobronchitis pathogens to antibiotics showed the following results. All *E. coli* strains were sensitive to amikacin, gentamicin, carbapenems, cefotaxime, and ceftazidime, 2 strains were also sensitive to kanamycin, neomycin, streptomycin, azithromycin, and azlocillin, and one strain was also sensitive to chloramphenicol and ampicillin. All strains of *Klebsiella pneumoniae* were resistant to ampicillin and carbenicillin and remained sensitive to amikacin, cephalosporins of the III-IV generation (cefotaxime, ceftazidim, cefaclor, cefepim), two strains were sensitive to carbapenems, netilmycin and gentamicin, one strain was sensitiv to chlormafenicol. The *Ps.aeruginosa* strain was hospital-acquired. It was sensitive to amikacin, piperacillin+ tazobactam, and colistin, resistant to ceftazidime, imipenem/cilastatin, meropenem, carbenicillin, chloramphenicol, netilmycin, streptomycin, and kanamycin. *The Acinetobacter baumanii* strain was sensitive to aminoglycosides and cefotaxime. All *Enterococcus faecalis* strains were susceptible to vancomycin and linezolid, three strains were susceptible to chloramphenicol, ampicillin, and rifampicin, and two strains were susceptible to cefotaxime and imipenem/celastatin. All *Enterococcus faecalis* strains were susceptible to vancomycin and linezolid, three strains were susceptible to chloramphenicol, ampicillin, and rifampicin, and two strains were susceptible to cefotaxime and imipenem/celastatin. *The Streptococcus* strain of group A was sensitive to benzylpenicillin, oxacillin, macrolides, cefazolin, cephalexin, azlocillin, vancomycin, linezolid. All strains of *S. epidermidis* with hemolytic properties were sensitive to vancomycin, linezolid, amikacin and gentamicin, two strains were sensitive to kanamycin, streptomycin, chloramphenicol, cephalexin, cefazolin, azithromycin, one strain was

Table 2. Microbiological efficacy of intravenous immunoglobulins in newborns with tracheobronchitis one day after the first infusion of the drug and 3 days after the course of treatment. Group II (n=14)

N	Performance indicators	Survey period: This is a day after the first infusion of the drug		Survey period: This is 3 days after the course of treatment	
		n	%	n	%
1	Reducing the titer of pathogens	12	86	11	79
2	Complete eradication	0	0	3	21
3	No effect:	2	14	0	0
4	The titer of the pathogen has not changed	1	7	0	0
5	Increase in the titer of the pathogen	1	7	0	0

sensitive to fusidin, benzylpenicillin and oxacillin. All *S. epider*midis strains were resistant to ampicillin and lincomycin. The strain of *Haemophylus influenzae* was sensitive to amoxicillin, cefixime, cefuroxime, azithromycin, chloramphenicol. *M. ho*minis and *U. urealiticum* remained sensitive to 2 or 3 antibiotics: all strains were sensitive to midekamycin, 20% of the strains were sensitive to amikacin and gentamicin. In addition, *M. hominis* strains were selectively highly sensitive to josamycin, and *U. urealitycum* strains were selectively sensitive to clarithromycin. It should be assumed that the early use of IVIG drugs in premature newborns, in which the respiratory tract was contaminated with intracellular pathogens, prevented massive colonization of the respiratory tract mucosa and the development of pneumonia. As can be seen from the above results of the study, most bacterial pathogens had acquired (*Enterobacteriaceae*, *S. epidermidis*, *Pseudomonas aeruginisa*) or natural (*Enterococcus faecalis*) resistance to antibiotics. *M. hominis* and *U. urealiticum*, in addition to their natural resistance to antibiotics, are poorly accessible to the effects of these drugs due to the intracellular localization of pathogens. These circumstances significantly complicate the treatment of infectious and inflammatory diseases in this category of patients. In this regard, the use of intravenous immunoglobulins, which have a broad antimicrobial effect, increases the possibility of successful treatment. The dynamics of changes in the respiratory tract microflora in infants with tracheobronchitis is presented in Table 2. In most infants with tracheobronchitis (86%), a decrease in the number of microorganisms in the respiratory tract occurred one day after the start of treatment with immunoglobulins. This indicated a rapid IVIG effect. In addition, the microbiological effect was stable. Thus, three days after the IVIG course, pathogens were detected in low titers (lg1-2 CFU/ml) in most infants (79%), and pathogens were not isolated in the remaining infants (21%). Thus, the positive microbiological effect of IVIG was observed in all infants with tracheobronchitis. The degree of reduction in the titer of bacteria and intracellular microorganisms was very high in all infants in 8-100 times, and Candida spp. in 2-4 times compared to the initial indicator. The microbiological effect of IVIG can be associated with an increase in the content of immunoglobulins in the mucosa and lumen of the respiratory tract, where they have an antimicrobial effect, as well as stimulate phagocytosis in the focus of inflammation (Antonov, A G, *et al*, 2007; Kushnarea , MV et Vetrova, EV. 2021).

CONCLUSION

Thus, the use of intravenous immunoglobulins in infants with RDS and those on a mechanical ventilator complicated by tracheobronchitis is characterized by high microbiological efficiency, which occurs quickly and is registered in most patients within a day after the start of treatment. The greatest inhibition of growth was observed in relation to bacterial microflora and intracellular microorganisms. To a lesser extent, the effect was shown in relation to Candida spp. The spread of the inflammatory process and the development of pneumonia were prevented in infants with tracheobronchitis.

The bulleted key points:

1. IVIG actively inhibit the growth of TB pathogens (*bactria, M. hominis and U. urealiticum, Candida albicans)* in the respiratory tract a day after the first administration of the drug.

2. The antimicrobial effect of IVIG is long-lasting. Low titer of microorganisms or their absence occurs at least three days after the course of immunotherapy.

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REFERENCES

Cernada, M, Bruga, M, Colombek *et al*. 2014. Ventilator – associated pneumonia in neonatal patients: an update. Neonatology. 105:98-107.

Kolls, JK. 2017. Commentary: Understanding the Impact of Infection, Inflammation and Their Persistence in the Pathogenesis of Bronchopulmonary Dysplasia. 2017. Front Med (Lausanne). 2;4:24. doi: 10.3389/fmed.2017.00024. eCollection 2017. 9837.

Kushnareva, MV, Shabelnikova E I., Balashova E D, Keshishyan E S. 2019. Etiological structure of "fan-associated" pneumonia complicated by bronchopulmonary dysplasia in premature newborns. Pediatrician's practice. 3: 3-9. https://medi.ru/pp/ 2019/04/16405/

Rakovskaya IV. 2008 . Mycoplasms and mycoplasmal infections. Vestn Dermatol Venerol . 5: 60–6. https://www. vestnikdv.ru/ jour/issue/viewIssue/81/30 .

Zwiers, C, Scheffer-Rath, MEA, Lopriore , E, Masja de Haas, G, Liley HG. Immunoglobulin for alloimmune hemolytic disease in neonates. 2018. Cochrane Database Syst Rev. 3:

Antonov, A G, Ashitkova, N V, Biryukova, T V. *et al*. 2007. Form for the use of immunoglobulin preparations for intravenous administration in neonatology. Questions of practical pediatrics. 2:2:56-65. https://www.elibrary.ru/ item.asp?id=9552990 CD003 313. Published online 2018 Mar 18. doi: 10.1002/ 14651858 .CD003313.pub2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6494160/ .

Aronskind, E V, Tuzankina, I A, Kovtun, OP, Shershnev, V N. Mukhamedzyan, MN, Ufimtseva, O A. 2007. Effect of pentaglobin use in the neonatal period on the dynamics of immunological parameters of premature infants during the first year of life. Pediatrics. 86:1:40-45. https://pediatria journal.ru/ files/upload/mags/262/2007_1_1130.pdf

Labinskaya, A S, Kostyukova, N N, Ivanova, S M. Guide to medical microbiology: a textbook for the system of postgraduate professional education of doctors. Book 2: Private medical microbiology and etiological diagnosis of infections. Moscow: BINOM, 2015: 1151 p. https://search.rsl.ru/ru/record/0100 7944 470

Methods of control: Biological and microbiological factors. The definition of sensitivity of microorganisms to antibacterial preparations. Methodical instructions. HOWTO. MOOK 4.2. 1890-04 2004; Moscow (Russia): Medicina; 2004: 86. http://docs.cntd.ru/document/1200038583 (In Russ.)

Waites KB, Taylor-Robinson D. Mycoplasma and Ureaplasma In: P.R. Murray, *et al*., editors. *Manual of Clinical Microbiology. American Society for Microbiology Press;* 1999: 782—94.

Kushnareva MV, Vetrova EV. Effect of intravenous immunoglobulins on phagocytic activity of neutrophils in premature infants with respiratory distress syndrome and pneumonia. *International Journal of Current Research*. 2021; Vol. 13: Issue, 01: 15582-15585.

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